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Treatment approach and survival of glioblastoma: results from a population-based study

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ABSTRACT

Objectives: To evaluate treatment and survival of glioblastoma in a real-world setting.

Setting: A population-based retrospective cohort study including all ten hospitals in a predefined geographical area.

Participants: All patients aged 18 years or older diagnosed with glioblastoma between 1/1/2007 and 31/12/2014 were enrolled, both patients with histologically confirmed glioblastoma and patients with diagnosis based solely on typical MRI pattern. Patients from outside the region and patients with recurrent glioma, synchronous malignancies, or lack of informed consent were excluded, resulting in a cohort of 363 patients.

Primary and secondary outcome measures: Median overall survival and survival rates. Associations between radiological and clinical characteristics and treatment approach measured by unadjusted and adjusted odds ratio.

Results: Median overall survival was 10.2 months (95% CI 9.1-11.3). Resection was performed in 221 patients (60.9%), and was inversely associated with age over 70 years, deep-seated tumour, tumour invasion of the corpus callosum, and multifocality. Median survival was 13.7 months (95% CI 12.1-15.4) in patients having performed resection, 8.3 months (95% CI 6.6-9.9) in patients undergone biopsy, and 4.5 months (95% CI 4.0-5.1) in patients where no surgical intervention was performed. Chemoradiotherapy according to the Stupp protocol was given to 157 patients (43%). Age over 70 years, cognitive impairment, and

tumour invasion of the corpus callosum were associated with less intensive chemoradiotherapy. Median survival was 16.3 months (95% CI 14.1-18.5), 7.9 months (95% CI 6.7-9.0), and 2.0 months (95% CI 0.9-3.2) in patients treated according to the Stupp protocol, less intensive chemoradiotherapy and best supportive care, respectively.

Conclusions: In a real-world setting, less than half of the patients received full-course chemoradiotherapy, with a median survival comparable to results from clinical trials. Survival was considerably worse in patients receiving less intensive treatment. Our results point out a risk of undertreating glioblastoma, especially in elderly patients.

STRENGTHS AND LIMITATIONS OF THE STUDY

- This population-based study provides knowledge on treatment and survival of glioblastoma in a real-world setting, including the establishment of long-term survival rates.
- To our knowledge, this is the first study to use a standardized score in the assessment of comorbidity burden in patients with glioblastoma.
- Detailed information on treatment and complications were available in all patients, within a common patient record system throughout the region.
- We included both patients with histologically confirmed glioblastoma and patients with MRI-based diagnosis, to counteract the exclusion of elderly, frail patients and patients with deep-seated tumours where biopsy were considered not feasible.
- Among the limitations of this study were the lack of molecular analysis and standardized performance assessment.

INTRODUCTION

Glioblastoma (GBM) is the most frequent of the malignant primary brain tumours in adults.[1 2] Prognosis is poor, with a median overall survival of approximately 11 months and a five-year survival of less than 6% reported from population-based materials.[1 3] Standard diagnostic procedures in patients with primary brain tumours include neuroimaging and histopathological and molecular classification.[4] However, when clinicians consider a biopsy unsafe or not feasible, i.e. in patients with poor functional status or patients harbouring a deep-seated tumour, the diagnosis is based solely on radiological characteristics. Advanced Magnetic Resonance Imaging (MRI) modalities have resulted in a high ability to differentiate GBM from other intracranial lesions.[5 6]

Standard of care is maximal safe resection or biopsy followed by chemoradiotherapy (CRT).[4 7] Implementation of the Stupp protocol, i.e. radiation therapy given as 60 Gy in 2 Gy fractions with concomitant Temozolomide (Tmz) followed by six courses of Tmz monotherapy, improved overall survival in patients in good performance status and age up to 70 years, and is currently standard of care.[4 8] Clinical trials have demonstrated that hypofractionated radiation therapy with or without Tmz, or Tmz alone if O^6-methylguanine-DNA methyl transferase (MGMT) promoter is methylated, are beneficial treatment options in elderly patients.[9-11] Best supportive care may be an appropriate approach in elderly and very frail patients, particularly in patients with multifocal or large tumours.[4] Elderly patients, patients with poor performance status, and patients lacking histological confirmation of the diagnosis, are excluded from most clinical trials. This may result in selection bias and impact on survival rates.

We aimed to determine overall survival from GBM in an unselected cohort of consecutive patients diagnosed with GBM during an eight years period in a geographically

defined area of Western Norway. Furthermore, to analyse clinical and radiological characteristics associated with treatment approach, and the association between treatment intensity and survival.

METHODS

This was a population-based, retrospective cohort study of patients diagnosed with glioblastoma (GBM) between 1/1/2007 and 31/12/2014. Patients aged 18 years or older, diagnosed with International Classification of Diseases 10th Revision (ICD-10) code C71 (malignant neoplasm of brain) or C72 (malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system) in the Western region of Norway, were identified through electronic medical records. Both patients with histologically verified GBM and patients where the GBM diagnosis was based solely on typical MRI characteristics were enrolled. Patients from outside the region and patients with recurrent glioma, synchronous malignancies, or lack of informed consent were excluded. Ten hospitals in the predefined geographical region served population of approximately 1.020.000 in the study period [12]. All hospitals provided medical treatment and supportive care in patients with GBM. Neurosurgical treatment of patients with brain tumour was centralized to one hospital, while radiation therapy was centralized to two hospitals in the region.

Demographics and patient characteristics were identified (table 1). Time of diagnosis was defined as the date of first MRI detecting the primary brain tumour. The follow-up period was at least five years or until death. We defined patients aged 70 years and older as elderly, based on the cut-off value in relevant studies and clinical practice in the region.[9 13-16] Comorbidity was classified according to Charlson comorbidity index, and we defined a cut-off score of seven or more as a high comorbidity burden.[17] We registered any cognitive impairment described by clinicians, regardless of severity and causation. Radiological

characteristics were obtained from MRI reports. MGMT promoter methylation and IDH mutation were not implemented as routine analyses in the study period.

Information regarding primary treatment, complications, and survival were collected from medical records. Surgery was categorized into resection, biopsy, and no surgical intervention. Primary CRT was categorized into full-intensive treatment according to the Stupp protocol, less intensive CRT, and best supportive care. Treatment according to the Stupp protocol was defined as a delivered radiation dose of 60 Gy (and optional additional boost), concomitant Tmz throughout the entire radiation therapy period, and at least one out of six planned Tmz monotherapy courses fulfilled, in concordance with a previous and comparable study.[18] Less intensive CRT was further classified into i) full-course radiation therapy (60 Gy in 2 Gy fractions) and Tmz to a less extent than the Stupp protocol, ii) short-course radiation therapy with concomitant and at least one Tmz monotherapy course, iii) short-course radiation therapy with Tmz to a less extent or no Tmz, and iv) Tmz monotherapy without radiation therapy.

Adverse events and complications including infections, bone marrow suppression grade 3-4 according to CTCAE (Common Terminology Criteria for Adverse Events) Version 5.0, venous thromboembolism, epileptic seizures, and osteoporosis (defined as low-energy fracture or bone density below -2.5 standard deviation measured by bone density scan) were identified. We calculated survival rates from time of diagnosis, and defined long-term survival as survival of more than five years.

Patient and public involvement

Patients or the public were not involved in this study.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (no. 2014/1931). Informed consent was obtained from patients alive at the time of inclusion. A waiver of consent was approved for deceased patients.

Statistics

We used Chi-square Test or Fisher's Exact Test as appropriate for categorical variables. Continuous variables were compared using t-test for normally distributed data, otherwise by Mann-Whitney U test. Verification of normality was done by quantile-quantile (Q-Q) plots. Clinical and radiological characteristics and their associations with treatment approach were analysed using binomial logistic regression, in which variables considered reasonably likely to influence on management approach were included in the model. Survival analyses were performed using Kaplan Meier plot and log-rank test. Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed in IBM SPSS Statistics version 24 (SPSS Inc., Chicago, IL, USA).

RESULTS

We identified 381 patients diagnosed with GBM in the predefined geographical region between 1/1/2007 and 31/12/2014. Among these, 16 patients were excluded according to exclusion criteria (non-resident (n=1), previous low-grade or anaplastic glioma (n=10), synchronous cancer (n=4), and lack of informed consent (n=1)). One patient was lost to follow-up and one patient was excluded due to disproved GBM diagnosis by autopsy. Finally, 363 patients diagnosed with GBM in the predefined period were included. None of these patients were included in clinical trials. Histological confirmation of the diagnoses was lacking in 90 patients (24.8%), including two patients with non-representative biopsies, where

the diagnosis was based on typical MRI characteristics. Among patients aged over 70 years, 65 of 127 patients (51.2%) lacked histological confirmation of the diagnosis, compared to 25 of 236 patients (10.6%) aged under 70 years.

Tumour and patient characteristics

Median age at time of diagnosis was 64.6 years (range 18.1-94.9). Median age in patients with histologically confirmed GBM was 61.5 years (range 18.1-86.1), compared to 77.0 years (range 35.0-94.9) in patients with MRI-based diagnosis (p<0.0001). Mean Charlson comorbidity score was 3.9 (standard deviation (SD) 1.4) in patients with histologically confirmed GBM, compared to 5.7 (SD 1.6) in patients with MRI-based GBM diagnosis (p<0.0001). Male/female ratio was 1.39. Additional patient and tumour characteristics are outlined in table 1.

Table 1. Patient and tumour characteristics in adults diagnosed with glioblastoma between January 2007 and December 2014

	Total cohort n=363	Histological confirmed GBM n=273	MRI-based diagnosis of GBM* n=90	p-value
Patient characteristics				
Male gender	211 (58%)	155 (57%)	56 (62%)	0.364
Age ≥ 70 years	127 (35%)	62 (23%)	65 (72%)	**<0,001**
Charlson comorbidity score ≥7	41 (11%)	15 (5%)	26 (29%)	**<0.001**
Initial symptoms				
Cognitive impairment	171 (47%)	126 (46%)	45 (50%)	0.526
Headache	159 (44%)	134 (49%)	25 (28%)	**<0.001**
Mono-/hemiparesis	122 (34%)	85 (31%)	37 (41%)	0.089
Epilepsy at initial diagnosis	110 (30%)	97 (36%)	13 (14%)	**<0.001**
Central facial palsy	96 (26%)	65 (24%)	31 (34%)	0.047
Dysphasia	85 (23%)	63 (23%)	22 (24%)	0.790
Severe gait dysfunction‡	61 (17%)	32 (12%)	29 (32%)	**<0.001**
Dizziness	62 (17%)	38 (14%)	24 (27%)	**<0.001**
Visual field loss	54 (15%)	38 (14%)	16 (18%)	**0.044**
Previous radiation therapy to brain	4 (1%)	4 (1%)	0	0.486

First-degree relative with GBM	3	(1%)	3	(1%)	0	0.318
Tumour characteristics						
Tumour localization						
Frontal	88	(24%)	67	(25%)	21 (23%)	0.897
Temporal	82	(23%)	68	(25%)	14 (16%)	0.080
Parietal	28	(8%)	23	(8%)	5 (6%)	0.403
Occipital	9	(2%)	6	(2%)	3 (3%)	0.526
Overlapping	108	(30%)	89	(33%)	19 (21%)	0.050
Deep seated‡	46	(13%)	20	(7%)	26 (29%)	**<0.001**
Corpus callosum invasion	100	(28%)	65	(24%)	35 (39%)	**0.005**
Radiologic sign of gliomatosis cerebri	8	(2%)	7	(3%)	1 (1%)	0.425
Multifocality	90	(25%)	68	(25%)	22 (24%)	0.930
MRI contrast enhancement						
Circular (central necrosis)	263	(73%)	194	(71%)	69 (77%)	0.458
Irregular/patchy	27	(7%)	21	(8%)	6 (7%)	0.673
No enhancement	3	(1%)	3	(1%)	0 -	0.546
Information not available	45	(12%)	35	(13%)	10 (11%)	0.670

Results presented in absolute numbers and % of total. Comparison between groups (histological confirmed GBM and MRI based GBM diagnosis) was performed by Chi-square Test (Fisher's Exact Test when expected cell count <5).

* Highly suspected GBM based on typical MRI characteristics, biopsy not performed; † Inability to walk without support; ‡ Thalamus, basal ganglia, internal capsula, splenium corpus callosum, mesencephalon, brain stem, and cerebellum.

GBM=glioblastoma; MRI=magnetic resonance imaging.

Headache and epilepsy were more frequent in patients with histologically confirmed GBM compared to patients with MRI-based diagnosis, while dizziness and gait dysfunction were more frequent among patients with MRI-based diagnosis. Classification of performance status by validated screening tools (e.g. ECOG and Karnofsky score) was not applicable due to insufficient description of performance status in the medical files.

Treatment and complications

Treatment approach in the total cohort is described in figure 1. Resection was performed in 221 of 363 patients (60.9%). Radiation therapy was given to 323 patients (89.0%), where full-course radiation therapy (60 Gy or 60Gy with additional boost) was planned or commenced in 218 patients. Among these 218 patients, 14 patients (6.4%) had the treatment cancelled (n=1),

discontinued (n=5), or converted to a short-course regimen (n=8). Change in radiation therapy plan was due to poor general condition or rapid clinical deterioration (n=11), patient preferences (n=2), or acute complications (n=1). Further, 120 patients were allocated to short-course radiation therapy. Among these, the treatment was cancelled (n=13) or discontinued (n=11) in 24 patients (20.0%), due to poor general condition (n=14), acute complications (n=7), or patient preferences (n=3).

Chemoradiotherapy (CRT) according to the Stupp protocol was prepared or commenced in 185 patients, whereas the treatment plan was changed or prematurely interrupted in 28 of these (15.1%). Consequently, 157 patients (43.3% of the total cohort) received CRT according to the Stupp protocol. Nine of the 11 patients receiving CRT according to the Stupp protocol, despite the lack of histological confirmation, had deep-seated tumours. In patients receiving adjuvant Tmz, regardless of radiation therapy dose, the mean number of Tmz courses was 4.6 (range 1-14). Nine of the patients who underwent resection were not eligible for CRT, due to complications, rapid progression, or poor general condition. Among 236 patients aged under 70 years, 144 (61.0%) received CRT according to the Stupp protocol, 85 patients (36.0%) received less intensive CRT, and 7 patients (3.0%) received best supportive care. In the cohort of 127 patients aged over 70 years, 13 (10.2%) received CRT according to the Stupp protocol, 82 patients (64.6%) received less intensive CRT, and 32 patients (25.2%) received best supportive care.

[Figure 1 near here]

Associations between patient and tumour characteristics and treatment approach are presented in table 2. Elderly patients, patients with multifocal or deep-seated tumour, and patients with tumour invasion of the corpus callosum were less likely to undergo surgical resection. Elderly patients, patients with cognitive impairment, and patients with tumour

invading the corpus callosum were less likely to receive CRT according to the Stupp protocol.

Table 2. Associations between patient and tumour characteristics and treatment approach in 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

	No resection				CRT less intensive than Stupp protocol†			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Male gender	0.9	(0.6-1.4)	1.1	(0.6-1.9)	**0.6**	(0.4-0.9)*	0.6	(0.4-1.0)
Age ≥70 years	**4.5**	(2.9-7.2)***	**6.1**	(3.3-11.1)***	**13.7**	(7.3-25.8)***	**12.9**	(6.5-26.0)***
Cognitive impairment	1.2	(0.8-1.8)	1.1	(0.7-1.9)	**1.8**	(0.6-1.7)**	**1.8**	(1.1-3.1)*
Charlson comorbidity score ≥7	**4.5**	(2.2-9.1)***	2.1	(0.9-4.9)	**11.6**	(3.5-38.4)***	2.9	(0.8-11.1)
Multifocal tumour	**1.9**	(1.2-3.1)**	**2.7**	(1.5-4.9)*	1.2	(0.7-1.9)	1.7	(0.9-3.0)
Deep seated tumour‡	**7.3**	(3.5-15.3)***	**9.4**	(4.0-21.7)***	1.4	(0.7-2.6)	1.2	(0.6-2.6)
Tumour invasion of the corpus callosum	**3.7**	(2.3-6.0)***	**5.0**	(2.8-8.9)***	**2.3**	(1.4-3.8)**	**2.8**	(1.6-5.0)***

OR, 95% CI and p-values calculated by binomial logistic regression. No resection (=1) compared to resection (=0). No CRT or less-intensive CRT (=1) compared to Stupp protocol (=0).

Two-sided p-values <0.05 were considered statistical significant; *p<0.05; **p<0.01; ***p<0.001; p-values not marked by an asterix are not significant.

† Stupp protocol = Radiation therapy 60 Gy in 2 Gy fractions (delivered), fulfilled concomitant Tmz, and fulfilled at least one out of six planned Tmz monotherapy courses

‡ Thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, brain stem, and cerebellum.

CI=confidence interval; CRT=chemoradiotherapy; Gy=Gray; OR=odds ratio.

In total 188 patients (51.8%) had at least one epileptic seizure, the majority at the time of diagnosis. Venous thromboembolism (deep venous thrombosis of extremity, pulmonary embolism, or sinus vein thrombosis) occurred in 75 patients (20.7%), while 26 patients (7.2%) were diagnosed with osteoporosis. Among 247 patients receiving initial chemotherapy, CTCAE grade 3-4 bone marrow suppression, i.e. platelet count < 50.0 x 10^9/L and/or neutrophil count <1.0 x 10^9/L, occurred in 37 patients (15.0%). Fifty-eight patients (23.5%) had bacterial or viral infections, while 11 patients (4.5%) experienced septicaemia or neutropenic fever.

Survival

Median overall survival was 10.2 months (95% CI 9.1-11.3 months). One-year, two-year, three-year and five-year survival rates were 41.3%, 17.3%, 9.1% and 4.1%, respectively. Kaplan Meier curves on median survival according to age, surgery and CRT are presented in figure 2. Median survival in patients aged under 70 years was 13.5 months (95% CI 12.1-14.9), compared to 5.2 months (95% CI 4.1-6.3) in patients aged over 70 years. Median survival in patients undergone resection was 13.7 months (95% CI 12.1-15.4), compared to 8.3 months (95% CI 6.6-9.9) and 4.5 months (95% CI 4.0-5.1) in patients undergone biopsy or no surgical intervention, respectively. Median survival in patients receiving CRT according to the Stupp protocol was 16.3 months (95% CI 14.1-18.5), compared to 7.9 months (95% CI 6.7-9.0) and 2.0 months (95% CI 0.9.3.2) in patients treated with less intensive CRT or best supportive care, respectively. In patients aged over 70 years and receiving CRT according to the Stupp protocol, median survival was 21.4 months (95% CI 7.5-35.3), compared to 6.0 months (95% CI 4.7-7.7) and 2.0 months (95% CI 0.7.3.4) in those treated with less intensive CRT or best supportive care. Among 157 patients receiving CRT according to the Stupp protocol, 49 patients (31.2%) survived for longer than two years, and 14 patients (8.9%) survived for more than five years.

[Figure 2 near here]

An alluvial diagram visualizes the consecutive treatment modalities and the association with median survival (figure 3). In the total cohort, 15 patients (4.1%) achieved long-term survival of more than five years. Twelve of these patients underwent surgical resection, whereas three had a biopsy alone. Moreover, 14 out of 15 long-term surviving patients completed the Stupp protocol, while one patient received hypofractionated radiation therapy followed by Tmz monotherapy. All 15 long-term surviving patients completed at least six maintenance Tmz courses (range six to nine).

[Figure 3 near here]

DISCUSSION

Median overall survival in our cohort of 363 consecutive patients diagnosed with glioblastoma was approximately 10 months. Surgical resection and full-course chemoradiotherapy (CRT) were strongly associated with improved survival. However, only two thirds of the patients underwent resection, and less than half of the patients received CRT according to the Stupp protocol. Both those aged over and those aged under 70 years, and who received treatment according to the Stupp protocol, had a favourable prognosis with a median survival and long-term survival rates as seen in clinical trials. Survival was considerable worse in elderly patients and patients receiving less intensive treatment. A significant number of patients received best supportive care, thus the survival was poorer in this population-based study compared to results from clinical trials.

Histological confirmation of the diagnosis was lacking in approximately 25% of the patients in our cohort. There are limited real-world data describing the frequency of omitting biopsy in patients with highly suspected GBM according to MRI. A previous Norwegian study reported that 12% of the patients diagnosed with GBM had the diagnosis based solely on radiological pattern or autopsy.[19] Conversely, an English population-based study reported that less than 10% of patients aged under 70 years, and 40% of patients aged over 70 years, lacked histological confirmation of the diagnosis, comparable to our result.[20] We found that patients with MRI-based diagnosis were older and had a higher comorbidity burden, and they had more often deep-seated tumours. In addition, they more often presented with dizziness and gait disturbances, which are vague and often slowly progressing symptoms that may have led to a delay in diagnosis compared to patients presenting with epileptic seizure or headache. It is likely to assume that established experiences and traditions among clinicians may

influence the choice of intervention, e.g. emphasizing the risk of complications related to neurosurgery in elderly or frail patients, and patients with deep-seated tumours. The dismal prognosis of patients not undergoing resection is another possible contributing factor to the choice of this diagnostic approach. A further reason may be the improvement of MRI techniques, including perfusion-weighted imaging and diffusion-weighted MRI, facilitating the distinction of GBM from other intracranial lesions.[21 22] However, in order to increase the diagnostic accuracy, biopsy should also be recommended in patients considered not to benefit from resection, when considered feasible and safe.

Surgical resection was performed in 61% of the patients in this cohort, in line with the above mentioned study from England.[20] However, the resection rate was lower than reported in other previous population-based studies, where 74% of patients underwent resection.[3 18] A possible explanation is our inclusion of patients with MRI-based GBM diagnosis, with a higher number of patients with deep-seated tumours and tumours invading the corpus callosum. Patients who underwent resection had a significant better survival than those who underwent biopsy or no surgical intervention.

Nearly 90% of the patients in our cohort received radiotherapy, the majority in combination with Tmz. However, less than half of the patients received CRT according to the Stupp protocol, similar to the findings of Lwin and colleagues.[18] We assume that the frequency of elderly patients, patients with a significant comorbidity burden, and patients with extensive symptoms including cognitive impairment influence the choice of therapeutic intensity, and the capability for patients to complete commenced treatment. Patients aged over 70 years received less intensive treatment compared to younger patients, in concordance with previous studies of elderly patients with GBM.[3 13 14 20]

Median overall survival in our cohort was approximately 10 months. This is comparable with results from previous population-based studies after the implementation of

the Stupp protocol, where median survival ranged from 6.1 to 15.3 months.[3 18-20 23 24] A recent systematic review reported a median overall survival of 15.6 months after implementation of combined CRT.[25] However, nearly one third of the studies included in this review were clinical trials, with an expected superiority in survival rates compared to population-based materials. In our cohort, five-year survival rate was approximately 4%, equal to that reported in large population-based materials.[1 20] Survival was considerable better in patients receiving CRT according to the Stupp protocol, with a median survival of approximately 16 months and a five-year survival rate of 8.9%, similar to the results from previous population-based studies.[3 18 19] These survival rates are also in line with the results from the randomized clinical trial by Stupp and colleagues, where median survival in the CRT arm was 14.6 months, and five-year survival was 9.8%.[8 26] Our results highlight the gap between the survival rates reported from clinical studies and those observed in a real-world setting.

Median overall survival in patients aged over 70 years was 5.2 months in our cohort, in line with previous population-based studies where median survival ranged from less than three to four months.[13 14 16 20] Survival in elderly patients in our cohort was strongly associated with CRT treatment approach, and ranged from two months in patients receiving best supportive care to 21 months in patients receiving CRT according to the Stupp protocol. This was comparable to results from previous population-based studies on elderly patients.[3 27] As expected, median overall survival in elderly patients was lower in our unselected cohort than demonstrated in prospective clinical trials, where median survival ranged from 5.2 months to 9.6 months depending on CRT.[9-11 15] A recent Cochrane analysis concluded that CRT improved survival compared to radiation therapy alone in elderly patients capable of self-caring.[28] The improved survival in elderly patients receiving combined CRT, both in our cohort and previous studies, demonstrates a potential benefit from intensive treatment in this group.[3 10 27 29] A disregard of this issue may cause a potential risk of undertreating elderly

patients. Nevertheless, in patients of advanced age or suffering from extensive disabilities, best supportive care may be an appropriate approach.

As concerns the methodology of our study, we find that the population-based design is a strength. The long-term follow-up of an unselected cohort provide knowledge on treatment and survival of GBM, including the establishment of long-term survival rates, and the inclusion period ensured that all included patients were diagnosed with GBM after the implementation of the current standard treatment. Other strengths were the low dropout rate of only one patient (0.3%), and the detailed clinical information on treatment and complications available in all patients, within a common patient record system throughout the region. Among the limitations of the study was the lack of molecular analyses. Further, performance status was not sufficiently described in medical records and not applicable to validated screening tools. To counteract this, comorbidity burden, cognitive impairment and gait dysfunction were included in the analyses. In addition, surgical resection was not classified into degree of resection; hence, the survival curves do not differentiated between macroscopic complete and partial resection. The inclusion of patients with MRI-based diagnosis can be considered both a disadvantage and an advantage. To reduce the risk of incorrect inclusion of non-GBM patients, we included only patients when clinicians and radiologists unequivocally considered GBM the most likely diagnosis. Even though biopsy is highly recommended and standard of care, it is not always considered feasible and safe. Therefore, the inclusion of these patients provides knowledge on the diagnostic approach and survival of all patients with highly suspected GBM based on MRI.

In conclusion, the prognosis of GBM was considerably worse in a real-world setting compared to results from clinical trials. In patients receiving treatment according to the Stupp protocol, survival rates were comparable to that achieved in clinical trials. However, only two thirds of the patients in our cohort underwent resection, and less than half of the patients

received treatment according to the Stupp protocol. Our results point towards a risk of undertreating patients with GBM, and a potential benefit from choosing a more aggressive treatment approach.

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Disclosure of interest

The authors report no conflicts of interest.

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Contributors

LSB, OF and EF initiated the study and were responsible for study design and data collecting. LSB was responsible for statistical analyses, contributed by OF, BG, RM and EF, with support from statistician AU. All co-authors participated in the interpretation of the results. LSB and OF designed the figures. LSB drafted the initial manuscript, and all co-authors reviewed and edited the paper.

Data sharing

Deidentified participant data are prohibited from distribution.

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FIGURE LEGENDS:

Figure 1. Treatment approach in a population-based cohort diagnosed with glioblastoma between January 2007 and December 2014.

Median age (range) and median survival (95% CI) in the respective treatment groups.

*RT delivered 60 Gy in 2 Gy fractions (n=152) and optionally additional boost (n=5), concomitant Tmz throughout the entire RT period, and completed at least one of six planned monotherapy Temozolomide courses. †60 Gy delivered (n=45) and additional boost (n=2). ‡39 Gy in 3 Gy fractions (n=85); 20 Gy in 4 Gy fractions (n=1); stereotactic radiosurgery (n=2); whole brain RT 30-36 Gy in 3 Gy fractions (n=9); 50-54 Gy in 2 Gy fractions (n=3); 40.05 Gy in 2.67 Gy fractions (n=1); discontinued 60 Gy or hypofractionated regimens (n=18).

CRT=chemoradiotherapy; RT=radiation therapy; Gy=Gray; Tmz=Temozolomide; SD=Standard deviation; CI=Confidence Interval

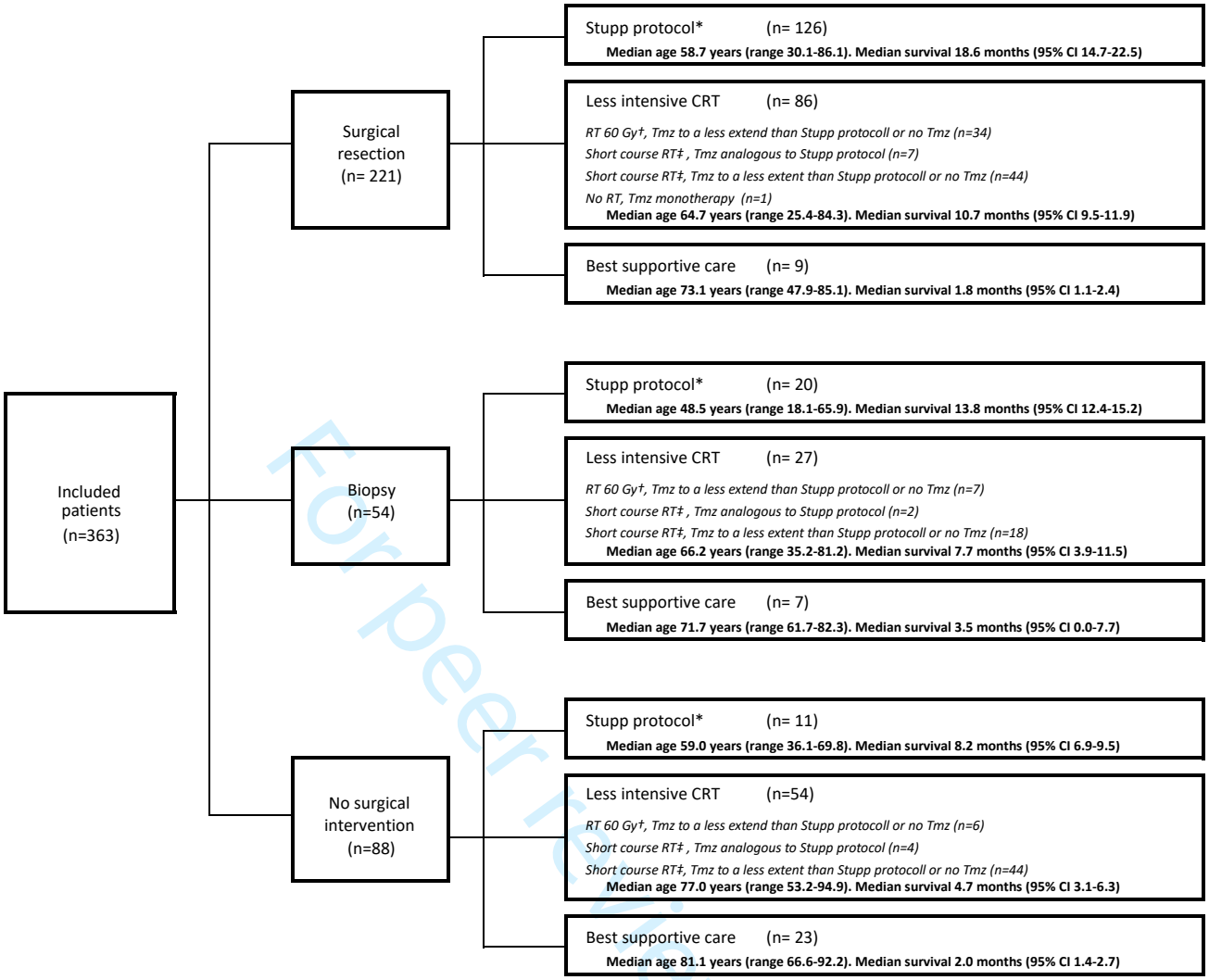
Figure 2. Overall survival in 363 adults diagnosed with glioblastoma between January 2007 and December 2014.

a) Survival by age. b) Survival by surgical treatment. c) Survival by chemoradiotherapy. d) Survival by chemoradiotherapy in patients aged 70 years or older.

Stupp protocol is here defined as completed radiation therapy in total dose of 60 Gy in 2 Gy fractions, concomitant Temozolomide in the entire radiation therapy period, and completed at least one out six planned Temozolomide monotherapy courses. Cumulative survival in months with 95% Confidence Interval (CI) bands. Groups compared with log rank test.

Figure 3. Alluvial diagram visualising associations between combination of treatment modalities and median survival in an unselected cohort of 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

The width of the curves represents the absolute number of patients. The colours of the curves correspond to median survival in months.



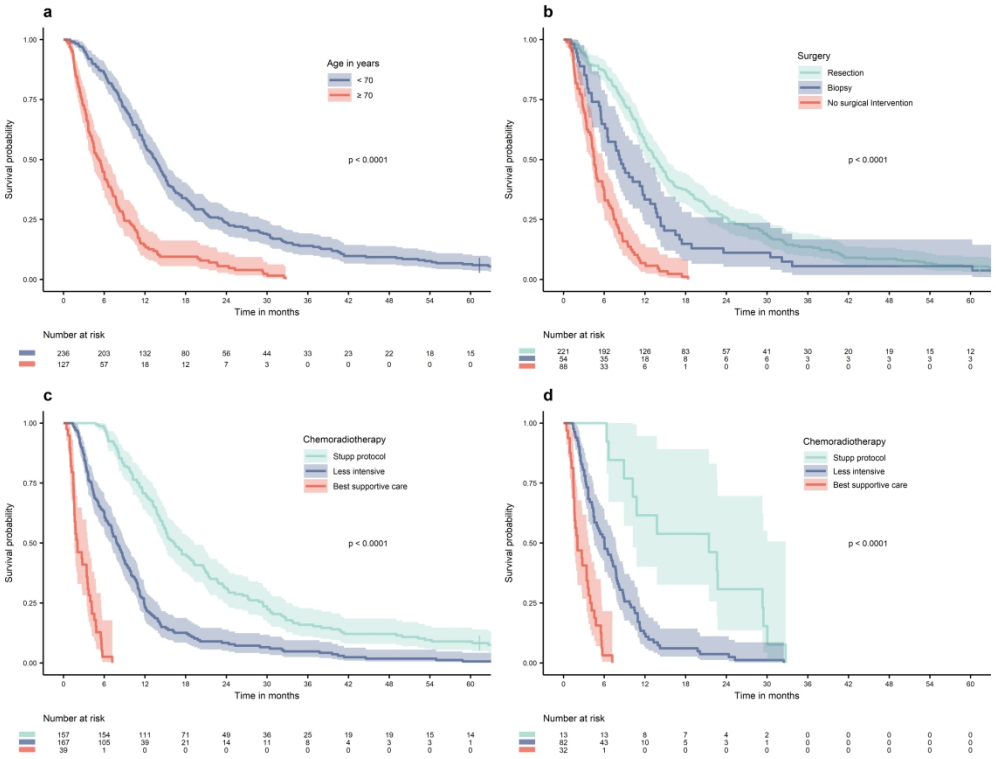


Figure 2. Overall survival in 363 adults diagnosed with glioblastoma between January 2007 and December 2014.

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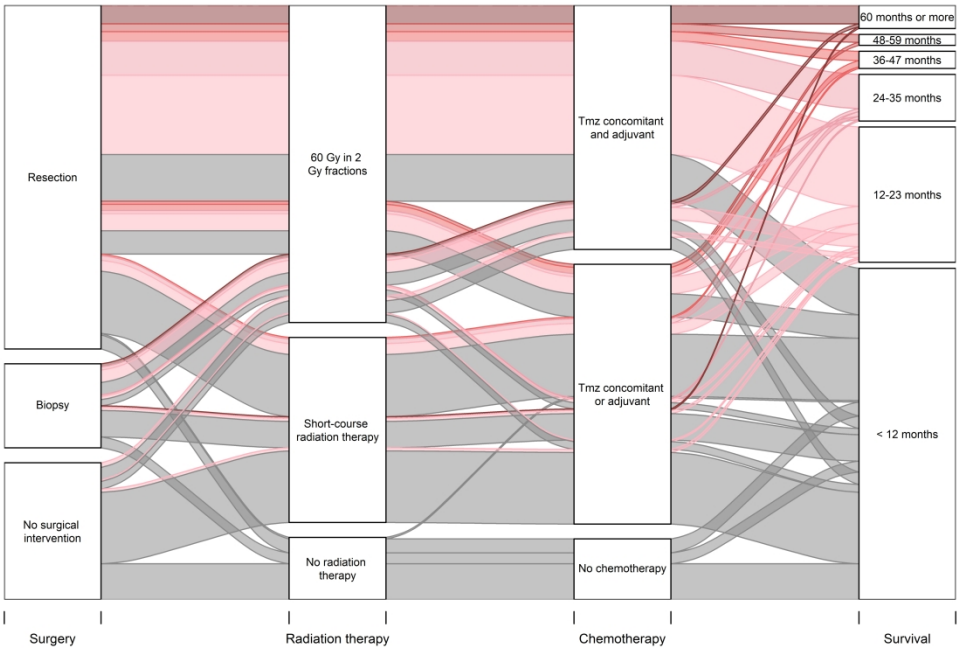

Figure 3. Alluvial diagram visualising associations between combination of treatment modalities and median survival in an unselected cohort of 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

209x139mm (600 x 600 DPI)

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Treatment approach and survival from glioblastoma: results from a population-based retrospective cohort study from Western Norway

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Treatment approach and survival from glioblastoma: results from a population-based retrospective cohort study from Western Norway

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ABSTRACT

Objectives: To evaluate treatment and survival from glioblastoma in a real-world setting.

Design and settings: A population-based retrospective cohort study from Western Norway.

Participants: 363 patients aged 18 years or older diagnosed with glioblastoma between 1/1/2007 and 31/12/2014.

Primary and secondary outcome measures: Overall survival and survival rates determined by Kaplan Meier method, groups compared by log rank test. Associations between clinical characteristics and treatment approach assessed by logistic regression. Associations between treatment approach and outcome analysed by Cox regression.

Results: Median overall survival was 10.2 months (95% CI 9.1-11.3). Resection was performed in 221 patients (60.9%), and was inversely associated with age over 70 years, higher comorbidity burden, deep-seated tumour localisation, and multifocality. Median survival was 13.7 months (95% CI 12.1-15.4) in patients undergoing tumour resection, 8.3 months (95% CI 6.6-9.9) in patients undergoing biopsy, and 4.5 months (95% CI 4.0-5.1) in patients where no surgical intervention was performed. Chemoradiotherapy according to the Stupp protocol was given to 157 patients (43%). Age over 70 years, higher comorbidity burden, and cognitive impairment were associated with less intensive chemoradiotherapy. Median survival was 16.3 months (95% CI 14.1-

18.5), 7.9 months (95% CI 6.7-9.0), and 2.0 months (95% CI 0.9-3.2) in patients treated according to the Stupp protocol, with less intensive chemoradiotherapy and with best supportive care, respectively. Surgical resection (hazard ratio (HR) 0.61 (95% CI 0.47-0.79) and chemoradiotherapy according to the Stupp protocol (HR 0.09 (95% CI 0.06-0.15) were strongly associated with favourable overall survival, when adjusted for clinical variables.

Conclusions: In a real-world setting, less than half of the patients received full-course chemoradiotherapy, with a median survival comparable to results from clinical trials. Survival was considerably worse in patients receiving less intensive treatment. Our results point out a substantial risk of undertreating glioblastoma, especially in elderly patients.

STRENGTHS AND LIMITATIONS OF THE STUDY

- This population-based study provides knowledge on treatment and survival from glioblastoma in a real-world setting, including the establishment of long-term survival rates.
- To our knowledge, this is the first study to use a standardized score in the assessment of comorbidity burden in patients with glioblastoma.
- Detailed information on treatment and complications were available in all patients, within a common patient record system used throughout the region.
- We included both patients with histologically confirmed glioblastoma and patients with an MRI-based diagnosis to counteract the exclusion of elderly, frail patients and patients with deep-seated tumours where biopsy was considered not feasible.

- Limitations of this study included the lack of molecular analysis and standardized performance assessment.

INTRODUCTION

Glioblastoma WHO grade IV is the most frequent of the malignant primary brain tumours in adults.[1 2] Prognosis is poor, with a median overall survival of approximately 11 months and a five-year survival of less than 6% reported from population-based materials.[1 3] Standard diagnostic procedures in patients with primary brain tumours include neuroimaging and histopathological and molecular classification.[4] However, when clinicians consider a biopsy unsafe or not feasible, e.g. in patients with poor functional status or patients harbouring a deep-seated tumour, the diagnosis is based solely on radiological characteristics. Advanced magnetic resonance imaging (MRI) modalities have resulted in a greater ability to differentiate glioblastoma from other intracranial lesions.[5 6]

Gold standard management of glioblastoma is maximal safe resection or biopsy followed by chemoradiotherapy (CRT).[4 7] The implementation of the Stupp protocol, i.e. radiation therapy given as 60 Gy in 2 Gy fractions with concomitant temozolomide (TMZ) followed by six courses of TMZ monotherapy, improved overall survival in patients with good performance status and age up to 70 years, and is currently the gold standard of care.[4 8] Several targeted therapies have been evaluated in clinical trials, however currently not implemented in standard care.[9] Clinical trials have demonstrated that hypofractionated radiation therapy with or without TMZ, or TMZ alone if O^6-methylguanine-DNA methyl transferase (MGMT) promoter is methylated, are beneficial treatment options in elderly patients.[10-12] Best supportive care may be an appropriate approach in the elderly and very frail patients, particularly in patients with multifocal or large tumours.[4] Elderly patients, patients

with poor performance status, and patients lacking histological confirmation of the diagnosis, are excluded from most clinical trials. This may result in selection bias and impact survival rates.

We aimed to determine overall survival from glioblastoma in an unselected cohort of consecutive patients diagnosed with glioblastoma during an eight-year period in a geographically defined area of Western Norway. Furthermore, we analysed clinical and radiological characteristics associated with treatment approach, and the association between treatment intensity and survival.

METHODS

This was a population-based, retrospective cohort study of patients diagnosed with glioblastoma between 1/1/2007 and 31/12/2014. Patients aged 18 years or older, diagnosed with International Classification of Diseases 10th Revision (ICD-10) code C71 (malignant neoplasm of brain) or C72 (malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system) in the Western region of Norway, were identified through electronic medical records. Both patients with histologically verified glioblastoma and patients where the glioblastoma diagnosis was based solely on typical MRI characteristics were enrolled. Patients from outside the region and patients with recurrent glioma, synchronous malignancies, or lack of informed consent were excluded. During the study period, the predefined geographical region served a population of approximately 1.020.000. [13] All hospitals provided medical treatment and supportive care to patients with glioblastoma. Neurosurgical treatment of patients with brain tumour was centralized to one hospital, while radiation therapy was centralized to two hospitals in the region.

Demographics and patient characteristics were identified (table 1). Time of diagnosis was defined as the date of the first MRI detecting the primary brain tumour. The follow-up

period was at least five years, or until death. We defined patients aged 70 years and older as elderly, based on the cut-off value in relevant studies and clinical practice in the region.[10 14-17] Comorbidity was classified according to the Charlson comorbidity index.[18] We registered any cognitive impairment described by clinicians, regardless of severity and causation. Radiological characteristics were obtained from MRI reports. MGMT promoter methylation and IDH mutation were not implemented as routine analyses in the study period.

Information regarding primary treatment, complications, and survival were collected from medical records. Surgery was categorized into resection, biopsy, and no surgical intervention. Primary CRT was categorized into fullintensive treatment according to the Stupp protocol, less intensive CRT, and best supportive care. Treatment according to the Stupp protocol was defined as a delivered radiation dose of 60 Gy (and optional additional boost), concomitant TMZ throughout the entire radiation therapy period, and at least one out of six planned TMZ monotherapy courses fulfilled, in concordance with a previous and comparable study.[19] Less intensive CRT was further classified into i) full-course radiation therapy (60 Gy in 2 Gy fractions) and TMZ to a lesser extent than the Stupp protocol, ii) short-course radiation therapy with concomitant TMZ and at least one monotherapy TMZ course, iii) short-course radiation therapy with TMZ to a lesser extent or no TMZ, and iv) TMZ monotherapy without radiation therapy.

Adverse events and complications including infections, bone marrow suppression grade 3-4 according to CTCAE (Common Terminology Criteria for Adverse Events) Version 5.0, venous thromboembolism, epileptic seizures, and osteoporosis (defined as low-energy fracture or bone density below -2.5 standard deviations measured by bone density scan) were identified. We calculated survival rates from time of diagnosis, and defined long-term survival as survival of more than five years.

Patient and public involvement

Patients and the public were not involved in this study.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (no. 2014/1931). Informed consent was obtained from patients alive at the time of inclusion. A waiver of consent was approved for deceased patients.

Statistics

We used Chi-square test or Fisher's exact test as appropriate for categorical variables. For continuous variables, we used a t-test for normally distributed data, otherwise the Mann-Whitney U test. Verification of normality was done by quantile-quantile (Q-Q) plots. Clinical and radiological characteristics and their associations with treatment approach were analysed using binomial logistic regression. We applied the univariate and multivariate Cox proportional hazards regression models to evaluate the effect of treatment on overall survival. Cox proportional hazard assumption was tested for all variables. Clinical and radiological variables considered reasonably likely to influence the management approach and outcome were included in the models. Survival probabilities were calculated using a Kaplan Meier plot and groups compared by log-rank testing. Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 24 (SPSS Inc., Chicago, IL, USA).

RESULTS

We identified 381 patients diagnosed with glioblastoma in the predefined geographical region between 1/1/2007 and 31/12/2014. From these, 16 patients were excluded according to exclusion criteria (non-resident (n=1), previous low-grade or anaplastic glioma (n=10),

synchronous cancer (n=4), and lack of informed consent (n=1)). One patient was lost to follow-up and one patient was excluded due to disproved glioblastoma diagnosis by autopsy. The remaining 363 patients diagnosed with glioblastoma in the predefined period were included. None of these participated in clinical trials. Histological confirmation of the diagnosis was lacking in 90 patients (24.8%), including two patients with non-representative biopsies, in whom the diagnosis was based on typical MRI characteristics. Amongst the 127 patients aged over 70 years, 65 (51.2%) lacked histological confirmation of the diagnosis, compared to 25 of the 236 patients (10.6%) aged under 70 years.

Tumour and patient characteristics

Median age at the time of diagnosis was 64.6 years (range 18.1-94.9). Median age in patients with histologically confirmed glioblastoma was 61.5 years (range 18.1-86.1), compared to 77.0 years (range 35.0-94.9) in patients with an MRI-based diagnosis (p<0.0001). Mean Charlson comorbidity score was 3.9 (standard deviation (SD) 1.4) in patients with histologically confirmed glioblastoma, compared to 5.7 (SD 1.6) in patients with an MRI-based diagnosis (p<0.0001). Male/female ratio was 1.39. Additional patient and tumour characteristics are outlined in table 1.

Table 1. Patient and tumour characteristics in adults diagnosed with glioblastoma between January 2007 and December 2014

	Total cohort n=363	Histologically confirmed glioblastoma n=273	MRI-based diagnosis of glioblastoma* n=90	p-value
Patient characteristics				
Male gender	211 (58%)	155 (57%)	56 (62%)	0.364
Age ≥ 70 years	127 (35%)	62 (23%)	65 (72%)	**<0,001**
Initial symptoms				
Cognitive impairment	171 (47%)	126 (46%)	45 (50%)	0.526
Headache	159 (44%)	134 (49%)	25 (28%)	**<0.001**

Mono-/hemiparesis	122	(34%)	85	(31%)	37	(41%)	0.089
Epilepsy at initial diagnosis	110	(30%)	97	(36%)	13	(14%)	**<0.001**
Central facial palsy	96	(26%)	65	(24%)	31	(34%)	0.047
Dysphasia	85	(23%)	63	(23%)	22	(24%)	0.790
Severe gait dysfunction‡	61	(17%)	32	(12%)	29	(32%)	**<0.001**
Dizziness	62	(17%)	38	(14%)	24	(27%)	**<0.001**
Visual field loss	54	(15%)	38	(14%)	16	(18%)	**0.044**
Previous radiation therapy to brain	4	(1%)	4	(1%)	0		0.486
Glioblastoma in first-degree relative	3	(1%)	3	(1%)	0		0.318
Tumour characteristics							
Tumour localisation							
Frontal	88	(24%)	67	(25%)	21	(23%)	0.897
Temporal	82	(23%)	68	(25%)	14	(16%)	0.080
Parietal	28	(8%)	23	(8%)	5	(6%)	0.403
Occipital	9	(2%)	6	(2%)	3	(3%)	0.526
Overlapping	108	(30%)	89	(33%)	19	(21%)	0.050
Deep-seated‡	46	(13%)	20	(7%)	26	(29%)	**<0.001**
Corpus callosum invasion	100	(28%)	65	(24%)	35	(39%)	**0.005**
Radiological signs of gliomatosis cerebri	8	(2%)	7	(3%)	1	(1%)	0.425
Multifocality	90	(25%)	68	(25%)	22	(24%)	0.930
MRI contrast enhancement							
Circular (central necrosis)	263	(73%)	194	(71%)	69	(77%)	0.458
Irregular/patchy	27	(7%)	21	(8%)	6	(7%)	0.673
No enhancement	3	(1%)	3	(1%)	0	-	0.546
Information not available	45	(12%)	35	(13%)	10	(11%)	0.670

Results presented in absolute numbers and % of total. Comparison between groups (histologically confirmed glioblastoma and MRI based glioblastoma diagnosis) was performed by Chi-square test (Fisher's exact test when expected cell count <5).

* Highly suspected glioblastoma based on typical MRI characteristics, biopsy not performed; † Inability to walk without support; ‡ Thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, brain stem, and cerebellum.

MRI=magnetic resonance imaging.

Headache and epilepsy were more frequent in patients with histologically confirmed glioblastoma compared to patients with an MRI-based diagnosis, whilst dizziness and gait dysfunction were more frequent among patients with an MRI-based diagnosis. Classification of performance status by validated screening tools (e.g. ECOG and Karnofsky score) was not applicable due to insufficient documentation of performance status in the medical records.

Treatment and complications

Surgical resection was performed in 221 of 363 patients (60.9%). Radiation therapy was given to 323 patients (89.0%), where full-course radiation therapy (60 Gy or 60Gy with additional boost) was planned or commenced in 218 patients. Among these 218 patients, 14 (6.4%) had the treatment cancelled (n=1), discontinued (n=5), or converted to a short-course regimen (n=8). Change in radiation therapy plan was due to poor general condition or rapid clinical deterioration (n=11), patient preferences (n=2), or acute complications (n=1). Further, 120 patients were allocated to short-course radiation therapy. Among these, the treatment was cancelled (n=13) or discontinued (n=11) in 24 patients (20.0%), due to poor general condition (n=14), acute complications (n=7), or patient preferences (n=3).

Chemoradiotherapy (CRT) according to the Stupp protocol was prepared or commenced in 185 patients, while the treatment plan was changed or prematurely interrupted in 28 of these (15.1%). Consequently, 157 patients (43.3% of the total cohort) received CRT according to the Stupp protocol, including 11 patients without histological confirmation. Nine of these 11 patients had deep-seated tumours. In patients receiving adjuvant TMZ, regardless of radiation therapy dose, the mean number of TMZ courses was 4.6 (range 1-14). Nine of the patients who underwent resection were not eligible for CRT, due to complications, rapid progression, or poor general condition. Among 236 patients aged under 70 years, 144 (61.0%) received CRT according to the Stupp protocol, 85 patients (36.0%) received less intensive CRT, and 7 patients (3.0%) received best supportive care. In the cohort of 127 patients aged over 70 years, 13 (10.2%) received CRT according to the Stupp protocol, 82 patients (64.6%) received less intensive CRT, and 32 patients (25.2%) received best supportive care.

Associations between patient and tumour characteristics and treatment approach are presented in table 2. Elderly patients, patients with multifocal or deep-seated tumours, and

patients with higher comorbidity burden were less likely to undergo surgical resection, according to adjusted logistic regression analyses. Elderly patients, patients with cognitive impairment, patients with increasing comorbidity burden, and females were less likely to receive CRT according to the Stupp protocol.

Table 2. Associations between patient and tumour characteristics and treatment approach in 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

	No resection				CRT less intensive than Stupp protocol†			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Female gender	1.1	(0.7-1.6)	1.0	(0.6-1.7)	**1.7**	(1.1-2.5)*	**1.8**	(1.1-3.1)*
Age ≥ 70 years	**4.5**	(2.9-7.2)***	**3.0**	(1.5-6.3)**	**13.7**	(7.3-25.8)***	**5.1**	(2.2-11.8)***
Cognitive impairment	1.2	(0.8-1.8)	1.2	(0.8-2.1)	**1.8**	(0.6-1.7)**	1.8	(1.1-3.0)*
Charlson comorbidity score	**1.5**	(1.3-1.8)***	**1.3**	(1.0-1.6)*	**2.2**	(1.8-2.6)***	**1.6**	(1.2-2.0)***
Multifocal tumour	**1.9**	(1.2-3.1)**	**2.6**	(1.5-4.6)*	1.2	(0.7-1.9)	1.6	(0.9-2.9)
Deep seated tumour‡	**7.3**	(3.5-15.3)***	**10.0**	(4.4-22.3)***	1.4	(0.7-2.6)	1.5	(0.7-3.2)

OR, 95% CI and p-values calculated by binomial logistic regression. No resection (=1) compared to resection (=0). No CRT or less intensive CRT (=1) compared to Stupp protocol (=0).
Two-sided p-values <0.05 were considered statistically significant; *p<0.05; **p<0.01; ***p<0.001; results not marked by an asterix are not significant.
† Stupp protocol = Radiation therapy 60 Gy in 2 Gy fractions (delivered), fulfilled concomitant TMZ, and fulfilled at least one out of six planned TMZ monotherapy courses
‡ Thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, brain stem, and cerebellum.
CI=confidence interval; CRT=chemoradiotherapy; Gy=Gray; OR=odds ratio; TMZ=Temozolomide.

In total 188 patients (51.8%) had at least one epileptic seizure, the majority at the time of diagnosis. Venous thromboembolism (deep venous thrombosis of extremity, pulmonary embolism, or sinus vein thrombosis) occurred in 75 patients (20.7%), while 26 patients (7.2%) were diagnosed with osteoporosis. Among 247 patients receiving initial chemotherapy, CTCAE grade 3-4 bone marrow suppression, i.e. platelet count < 50.0 x 10^9/L and/or neutrophil count <1.0 x 10^9/L, occurred in 37 patients (15.0%). Fifty-eight patients (23.5%) had bacterial or viral infections, whilst 11 patients (4.5%) experienced septicaemia or neutropenic fever.

Survival

Median overall survival was 10.2 months (95% CI 9.1-11.3 months). One-year, two-year, three-year and five-year survival rates were 41.3%, 17.3%, 9.1% and 4.1%, respectively. Median survival amongst patients with histologically confirmed glioblastoma was 12.6 months (95% CI 11.4-13.8), compared to 4.5 months (95% CI 4.0-5.1) in patients with an MRI-based diagnosis ($p<0.0001$). In total, 354 of the 363 included patients (97.5%) died during the study period, and one patient was lost to follow-up. Kaplan Meier curves of survival according to age, surgery and CRT are presented in figure 1. Median survival in patients aged under 70 years was 13.5 months (95% CI 12.1-14.9), compared to 5.2 months (95% CI 4.1-6.3) in patients aged over 70 years. Median survival in patients who underwent resection was 13.7 months (95% CI 12.1-15.4), compared to 8.3 months (95% CI 6.6-9.9) for those who underwent biopsy, and 4.5 months (95% CI 4.0-5.1) in patients with no surgical intervention. Median survival in patients receiving CRT according to the Stupp protocol was 16.3 months (95% CI 14.1-18.5), compared to 7.9 months (95% CI 6.7-9.0) and 2.0 months (95% CI 0.9.3.2) in patients treated with less intensive CRT or best supportive care, respectively. In patients aged over 70 years and receiving CRT according to the Stupp protocol, median survival was 21.4 months (95% CI 7.5-35.3), compared to 6.0 months (95% CI 4.7-7.7) and 2.0 months (95% CI 0.7.3.4) in those treated with less intensive CRT or best supportive care. Among 157 patients receiving CRT according to the Stupp protocol, 49 patients (31.2%) survived for longer than two years, and 14 patients (8.9%) survived for more than five years.

[Figure 1 near here]

Univariate and multivariate Cox proportional hazards regression models of overall survival are presented in table 3. Resection compared to no resection was strongly associated with improved overall survival according to multivariate analyses (HR 0.61, $p<0.001$). CRT

according to the Stupp protocol (HR 0.09, p<0.001) and less intensive CRT (HR 0.17, p<0.001) were strongly associated with better outcomes.

Table 3. Univariate and multivariate Cox regression analysis of overall survival in 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

	Univariate analysis			Multivariate analysis		
Variables	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Female gender	1.04	(0.784-1.29)	0.71	**0.91**	(0.73-1.14)	0.40
Age ≥70 years	3.00	(2.38-3.77)	**<0.001**	**1.32**	(0.93-1.87)	0.12
Cognitive impairment	1.25	(1.01-1.54)	**0.04**	**1.06**	(0.84-1.32)	0.64
Charlson comorbidity	1.44	(1.34-1.54)	**<0.001**	**1.22**	(1.10-1.35)	**<0.001**
Deep seated tumour†	1.78	(1.30-2.44)	**<0.001**	1.54	(1.09-2.19)	**0.02**
Multifocality	1.53	(1.20-1.95)	**<0.01**	1.42	(1.09-1.84)	**<0.01**
Surgical treatment						
No resection	Ref			Ref		
Resection	0.39	(0.31-0.48)	**<0.001**	0.61	(0.47-0.79)	**<0.001**
Chemoradiotherapy						
No CRT	Ref			Ref		
Less intensive CRT	0.12	(0.08-0.18)	**<0.001**	0.17	(0.11-0.26)	**<0.001**
Stupp protocol‡	0.05	(0.03-0.07)	**<0.001**	**0.09**	(0.06-0.15)	**<0.001**

HR, 95% CI and p-values calculated by univariate and multivariate Cox proportional hazards regression model. P-values <0.05 considered statistically significant.

†thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, brain stem, and cerebellar vermis.

‡Radiation therapy 60 Gy in 2 Gy fractions (delivered), fulfilled concomitant TMZ, and fulfilled at least one out of six planned TMZ monotherapy courses

HR=hazard ratio; CI=confidence interval; CRT=chemoradiotherapy; Gy=Gray

An alluvial diagram visualizes the consecutive treatment modalities and the association with median survival (figure 2). In the whole cohort, 15 patients (4.1%) achieved long-term survival of more than five years. Twelve of these patients underwent surgical resection, whereas three had a biopsy alone. Moreover, 14 out of 15 long-term surviving

patients completed the Stupp protocol, whilst one patient received hypofractionated radiation therapy followed by TMZ monotherapy. All 15 long-term surviving patients completed at least six maintenance TMZ courses (range six to nine).

[Figure 2 near here]

DISCUSSION

Median overall survival in our cohort of 363 consecutive patients diagnosed with glioblastoma was approximately 10 months. Surgical resection and full-course chemoradiotherapy (CRT) were strongly associated with improved survival, as demonstrated by multivariate Cox regression. However, only two thirds of the patients underwent resection, and less than half of the patients received CRT according to the Stupp protocol. Age over 70 years was strongly associated with less intensive treatment, both surgery and CRT. Irrespective of age, those who received treatment according to the Stupp protocol, had a favourable prognosis with median survival and long-term survival rates comparable to those observed in clinical trials. Survival was considerably worse in elderly patients and patients receiving less intensive treatment. A significant number of patients received best supportive care only, thus the overall survival was poorer in this population-based study compared to results from clinical trials.

Histological confirmation of the diagnosis was lacking in approximately 25% of the patients in our cohort. There are limited real-world data describing the frequency of omitting biopsy in patients with a high suspicion of glioblastoma according to MRI. A previous Norwegian study reported that 12% of the patients diagnosed with glioblastoma had a diagnosis based solely on radiological pattern or autopsy.[20] Conversely, an English population-based study reported that less than 10% of patients aged under 70 years, and 40% of patients aged over 70 years, lacked histological confirmation of the diagnosis, comparable to our findings.[21] We found that patients with MRI-based diagnoses were older and had a

higher comorbidity burden, and they more often had deep-seated tumours. In addition, they more commonly presented with dizziness and gait disturbances, which are vague and often slowly progressing symptoms that may have led to a delay in diagnosis compared to patients presenting with epileptic seizure or headache. It is reasonable to assume that established experiences and traditions among clinicians may influence the choice of intervention, e.g. emphasizing the risk of complications related to neurosurgery in elderly or frail patients, and patients with deep-seated tumours. The dismal prognosis of patients not undergoing resection is another possible contributing factor to the choice of this managment. A further reason may be the improvement of MRI techniques, including perfusion-weighted imaging and diffusion-weighted MRI, facilitating the distinction of glioblastoma from other intracranial lesions.[22 23] However, in order to increase the diagnostic accuracy, biopsy should also be recommended in patients considered unlikely to benefit from resection, when considered feasible and safe.

Resection was performed in 61% of the patients in this cohort, in line with the aforementioned study from England.[21] However, the resection rate was lower than reported in other previous population-based studies, where 74% of patients underwent resection.[3 19] A possible explanation is our inclusion of patients with an MRI-based glioblastoma diagnosis, and a higher number of patients with deep-seated tumours. Patients who underwent resection had a significantly better survival than those who underwent biopsy or no surgical intervention.

Nearly 90% of the patients in our cohort received radiotherapy, the majority in combination with TMZ. Multivariate Cox regression, with adjustment for age and other clinical variables, demonstrated improved overall survival in patients receiving CRT according to the Stupp. However, less than half of the patients received CRT according to the Stupp protocol, similar to the findings of Lwin and colleagues.[19] We assume that the frequency of elderly patients, patients with a significant comorbidity burden, and patients with

extensive symptoms including cognitive impairment, influence the choice of therapeutic intensity and the capacity of patients to complete commenced treatment. Patients aged over 70 years received less intensive treatment compared to younger patients, in concordance with previous studies of elderly patients with glioblastoma.[3 14 15 21]

Median overall survival in our cohort was approximately 10 months, comparable with results from previous population-based studies with median survival ranging from 6.1 to 15.3 months.[3 19-21 24 25] A five-year survival rate of approximately 4% was equal to that reported in large population-based materials.[1 21] A recent systematic review reported a superior median overall survival of 15.6 months in the post-Stupp era.[26] However, nearly one third of the studies included in this review article were clinical trials, with an expected superiority in survival rates compared to population-based materials. In our cohort, outcome was considerably better in patients receiving CRT according to the Stupp protocol, with a median survival of approximately 16 months and a five-year survival rate of 8.9%. This was in line with the results from the randomized clinical trial by Stupp and colleagues, where median survival in the CRT arm was 14.6 months, and five-year survival was 9.8%.[8 27] Our results highlight the gap between the survival rates reported from clinical studies and those observed in a real-world setting.

Median overall survival in patients aged over 70 years was 5.2 months in our cohort, in line with previous population-based studies where median survival ranged from less than three upto four months.[14 15 17 21] Survival in elderly patients in our cohort was strongly associated with a CRT treatment approach, and ranged from two months in patients receiving best supportive care to 21 months in patients receiving CRT according to the Stupp protocol. This was comparable to results from previous population-based studies in elderly patients.[3 28] As expected, median overall survival in elderly patients was lower in our unselected cohort than that demonstrated in prospective clinical trials, where median survival ranged from 5.2 to

9.6 months depending on CRT.[10-12 16] A recent Cochrane analysis concluded that CRT improved survival compared to radiation therapy alone in elderly patients capable of self-care.[29] The improved survival in elderly patients receiving combined CRT, both in our cohort and previous studies, demonstrates a potential benefit from intensive treatment in this group.[3 11 28 30] A disregard of this issue may risk potentially undertreating elderly patients. Nevertheless, in patients of advanced age, or suffering from extensive disabilities, best supportive care may be an appropriate approach.

As concerns the methodology of our study, we regards the population-based design as a strength. The long-term follow-up of an unselected cohort provides knowledge on treatment and survival from glioblastoma, including the establishment of long-term survival rates, and the inclusion period ensured that all included patients were diagnosed with glioblastoma after the implementation of the current standard treatment. Other strengths were the low dropout rate of only one patient (0.3%), and the detailed clinical information on treatment and complications available in all patients within a common patient record system throughout the region. Among the limitations of the study was the lack of molecular analyses. Further, performance status was not sufficiently described in medical records and not applicable to validated screening tools. To counteract this, comorbidity burden, cognitive impairment and gait dysfunction were included in the analyses. In addition, surgical resection was not classified into degree of resection; hence, the survival curves do not differentiated between macroscopic complete and partial resection. The inclusion of patients with MRI-based diagnosis can be considered both a disadvantage and an advantage. To reduce the risk of incorrect inclusion of non-glioblastoma patients, we included only patients when clinicians and radiologists unequivocally considered glioblastoma the most likely diagnosis. Even though biopsy is highly recommended and standard of care, it is not always considered feasible and safe. Therefore, the inclusion of these patients provides knowledge on the

diagnostic approach and survival of all patients with highly suspected glioblastoma based on MRI.

In conclusion, the prognosis of glioblastoma was considerably worse in a real-world setting compared to results from clinical trials. In patients receiving treatment according to the Stupp protocol, survival rates were comparable to that achieved in clinical trials. Multivariate Cox regression demonstrated that both resection and CRT were strongly associated with better outcome. However, only two thirds of the patients in our cohort underwent resection, and less than half of the patients received treatment according to the Stupp protocol. Our results point towards a substantial risk of undertreating patients with glioblastoma, especially in elderly patients, and a potential benefit from choosing a more aggressive treatment approach.

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Disclosure of interest

The authors report no conflicts of interest.

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Contributors

All co-authors have contributed to the design of the work and, are accountable for all its aspects. LSB, OF and EF initiated the study and were responsible for study design and data collecting. LSB was responsible for statistical analyses, contributed by OF, BG, RM and EF,

with support from statistician AU. All co-authors participated in the interpretation of the results. LSB and OF designed the figures. LSB drafted the initial manuscript, and all co-authors reviewed and edited the paper. All co-authors approved the final version of the manuscript.

Data sharing

No data are available

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FIGURE LEGENDS:

Figure 1. Overall survival in 363 adults diagnosed with glioblastoma between January 2007 and December 2014.

a) Survival by age. b) Survival by surgical treatment. c) Survival by chemoradiotherapy. d) Survival by chemoradiotherapy in patients aged 70 years or older.

Stupp protocol is here defined as completed radiation therapy in total dose of 60 Gy in 2 Gy fractions, concomitant Temozolomide in the entire radiation therapy period, and completed at least one out six planned Temozolomide monotherapy courses. Cumulative survival in months with 95% Confidence Interval (CI) bands. Groups compared with log rank test.

Figure 2. Alluvial diagram visualising associations between combination of treatment modalities and median survival in an unselected cohort of 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

The width of the curves represents the absolute number of patients. The colours of the curves correspond to median survival in months.

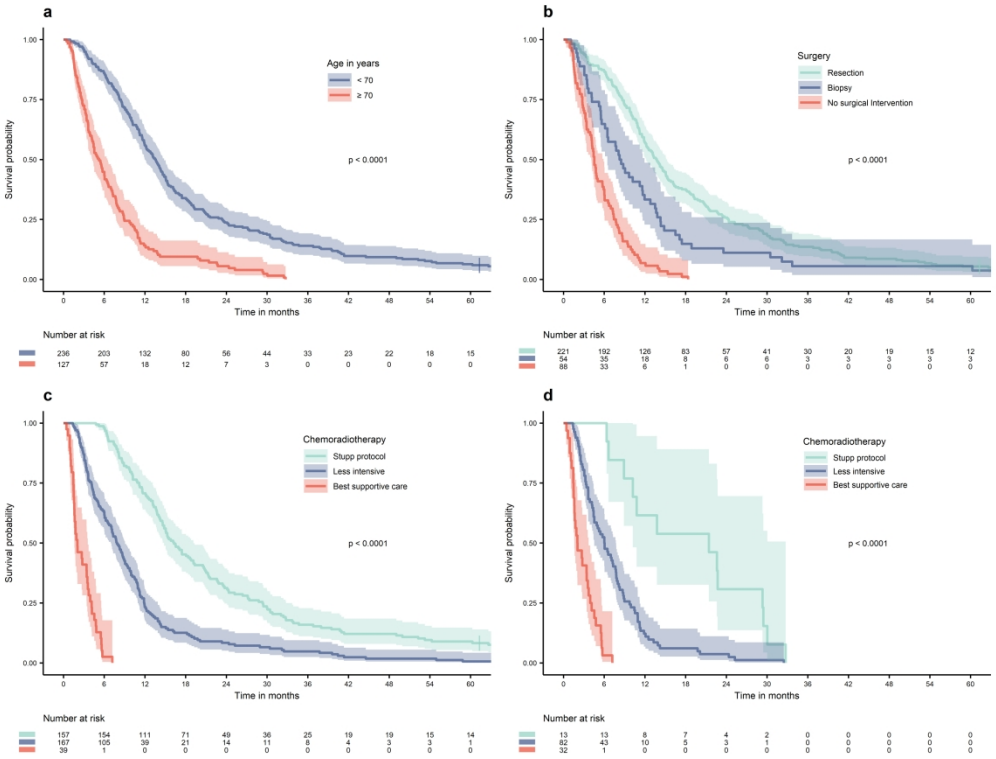

Figure 1. Overall survival in 363 adults diagnosed with glioblastoma between January 2007 and December 2014.

299x229mm (300 x 300 DPI)

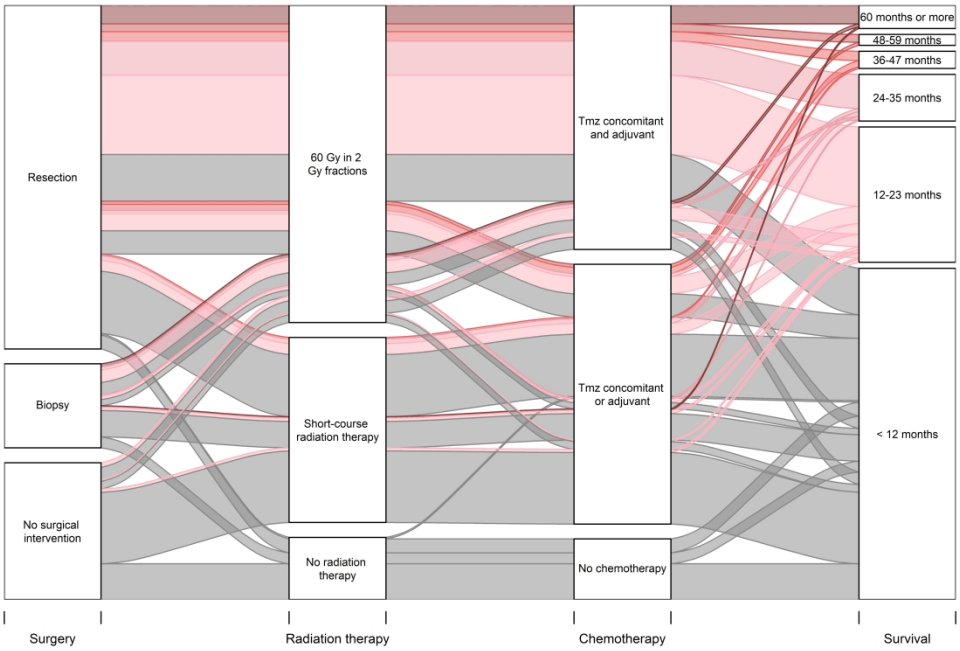

Figure 2. Alluvial diagram visualising associations between combination of treatment modalities and median survival in an unselected cohort of 363 patients diagnosed with glioblastoma between January 2007 and December 2014.

209x139mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 (title page), 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6 Table 1 and 2 (page 8 and11)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5, 9, 17
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	17
		(*d*) If applicable, explain how loss to follow-up was addressed	17
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each	Table 1

		variable of interest	(page 8-9)
		(c) Summarise follow-up time (eg, average and total amount)	5, 12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7 Table 2 (page 11) Table 3 (page 13)
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.