World Neurosurgery: X 22 (2024) 100331

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Impact of remoteness and rurality on the treatment and survival of patients with glioblastoma in the north of Scotland

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ARTICLE INFO

Keywords:
Neurosurgery
Glioblastoma
Health services Accessibility

ABSTRACT

Background: The geographical catchment area served by the Neurosurgical Unit in Aberdeen, Scotland is the largest in the United Kingdom. We examined whether a distance-decay effect on survival exists for patients diagnosed with glioblastoma, who have to travel substantial distances for neurosurgical and oncological treatment in the north of Scotland.

Methods: Electronic medical records of adult patients with glioblastoma, referred for treatment between 2007 and 2018, who underwent surgical resection were reviewed. Travel time by car (as a measure of distance travelled) was calculated from the patients' home to their general practice (GP) and to their main neuro-oncological centre.

Results: There were 122 patients; 71 (58.2%) were male and the mean age was 57.8 years. The urban-rural split was 61.5% and 38.5%, respectively. Median driving time to the neuro-oncological centre was 36 min and to the GP this was 6 min. Most patients underwent either sub-total (49.6%) or gross total (46.3%) surgical resection. Post-operative treatments included: radiotherapy only (15.6%), chemotherapy only (6.6%), and chemotherapy with radiotherapy (63.1%). Temozolomide was used in 70.5% of patients. Seventeen patients did not receive any post-operative chemo-radiotherapy. The median survival time was 345 days. There was no statistically significant association between distance travelled and survival time in days. MGMT methylation status, extent of resection, Charlson co-morbidity index and treatment received significantly affected survival.

Conclusions: There was no evidence of disadvantage on survival time for patients living further from their neuro-oncological centre compared to those who live nearer.

1. Introduction

Glioblastoma is the most common malignant primary brain tumour. Gold-standard management includes maximally safe surgical resection followed by radiotherapy and/or chemotherapy which is led by the neuro-oncology team.[1] Temozolomide is the chemotherapeutic agent of choice and is known to be more effective in patients whose tumour expresses a methylated form of the promoter of the gene encoding for the repair enzyme O-6-methylguanine-DNA methyltransferase (MGMT). The median survival time is 15 months.[2] A study in England found that sex, socio-economic status and geographic variation are independent factors, in addition to tumour characteristics, which determine survival in adults with glioma.[3] Epidemiological studies evidence a distance-decay effect, whereby patients who live further away from a healthcare facility have poorer health outcomes.[4]

The catchment population served by the Neurosurgical Unit at Aberdeen Royal Infirmary (ARI) is ~800,000 people which is relatively smaller compared to other units in the United Kingdom (UK). However,

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https://doi.org/10.1016/j.wnsx.2024.100331
Received 2 November 2022; Accepted 21 February 2024
Available online 25 February 2024

this population is spread across the UK's largest geographical catchment area.[5] This extensive area covers the part of Scotland north of a line drawn between Fort William in the West and Montrose in the East, in addition to the Highlands and the Northern Islands of Orkney and Shetland. Patients who visit ARI for neurosurgical treatment and follow-up appointments may fly, drive or take a ferry, however, road links are relatively slow.[6] Given that 98% of Scotland's land mass is rural and 17% of the population are resident there, it is important to consider how this rurality affects patients undergoing treatment for aggressive cancers such as glioblastoma which require timely diagnosis and treatment.[7] To this end, the authors aimed to understand whether the unique rurality and remoteness of the north of Scotland impacted the survival of patients with glioblastoma.

2. Methods

The study was registered with the NHS Grampian Quality Improvement and Assurance Team (Project ID 5067) as well as the local Caldicott Guardian (ca/2019/01). The NHS Grampian Cancer Care Pathway (CCP) database was used to search for patients referred to ARI for neurological and CNS cancer treatment between 1st January 2007 to 31st December 2018. The CCP is an electronic clinical database that records information about individual patients' cancer care and the accuracy of this database has been previously validated.[8,9] Adult patients (greater than or equal to 18 years of age) with histopathologically-confirmed glioblastoma who underwent surgical resection for whom there was sufficient data were included. The electronic medical records of patients were reviewed to collect data including MGMT methylation status, extent of resection, and post-operative treatment (chemotherapy, radiotherapy, and re-operation). The radiological extent of surgical resection was independently assessed by two authors (AG and JW) using post-operative MRI or CT scans, and graded as partial, sub-total or gross total surgical resection.

Survival time (in days) was calculated from the date of operation until either the date of death, the date that the patient was lost to follow-up, or the end of the data collection period. The travel time (in minutes) by car from the patient's home to their general practice (GP), and to Aberdeen Royal Infirmary, were calculated using a standard route planner (Google Maps®, Mountain View, CA, USA). Travel by car was used as a proxy measure of distance travelled as it has been shown that 87% of patients undergoing cancer treatment in Northern England travelled to hospital by car.[10] For patients who received their post-operative chemo-radiotherapy at more than one location or whose GP changed, the main GP and neuro-oncology centre where the patient attended for most of their treatment and follow-up was used when calculating travelling time. Each patient was assigned the Scottish Index of Multiple Deprivation (SIMD) and the Scottish Government Urban-Rural Classification using their home post code. Patients' electronic records were reviewed for past medical history and the Charlson Morbidity Index was calculated. Each patient's Eastern Cooperative Oncology Group (ECOG) Status of Performance at presentation was determined.

2.1. Statistical analysis

Pearson correlation co-efficients were used to determine the association between the logarithm of distance to the neuro-oncological centre/GP and survival time. A log rank test with travel time (as a proxy measure of distance travelled) to the neuro-oncological centre (group 1: 30 min or less; group 2: more than 30 min) and to the GP (group 1: 5 min or less; group 2: more than 5 min) was performed. These travel time limits were selected based on a large, data-linkage study which found that Scottish cancer patients living less than 5 min from their GP were more likely to start their cancer treatment sooner, and patients living more than 30 min from their oncology centre were less likely to survive to 1 year.[9] Kaplan-Meir curves were generated for gender, MGMT status, urban-rural two-fold index, urban rural six-fold index, SIMD decile, SIMD quintile, extent of resection, ECOG performance status, Charlson co-morbidity index, and treatment received. The Kruskal–Wallis test statistic was used to assess the distance travelled between groups of patients categorised by the treatment received. Results were analysed using the log-rank test and were considered significant if the p-value was below 0.05. Analyses were adjusted for age, sex, SIMD, and urban/rural index. Statistical analysis was performed using SPSS Version 27 (SPSS Inc, IBM, NY, USA).

3. Results

A total of 122 patients, for whom there was sufficient data available, were included in the analysis (see Table 1). The mean age of patients was 57.8 years (SD ± 12.4). There were 71 males (58.2%) and 51 females (41.8%). Most patients (66.1%) had a pre-operative ECOG performance status score of one followed by two (23.1%). Data was missing for one

Table 1
Key patient demographics and characteristics. Data presented are mean (SD) and median (IQR) for normally and non-normally distributed continuous variables and number (%) for categorical data.

Key demographics and patient characteristics	N (%)	
Mean age (years)	57.8	SD ± 12.4
Gender		
Male	71 (58.2)	
Female	51 (41.8)	
Charlson co-morbidity index		
0	26 (21.3)	
1	30 (24.6)	
2	39 (32.0)	
3	13 (10.7)	
4	6 (4.9)	
5	4 (3.3)	
6	3 (2.5)	
13	1 (0.8)	
Pre-operative ECOG score		
0	6 (4.9)	
1	80 (65.6)	
2	28 (23)	
3	6 (4.9)	
4	1 (0.8)	
Six-fold urban-rural index	35 (28.7%)	
Large urban	26 (21.3%)	
Other urban area	7 (5.7%)	
Accessible small town	7 (5.7%)	
Remote small town	30 (24.6%)	
Accessible rural	17 (13.9%)	
Remote rural	17 (13.9%)	
Median driving time – home to neuro-oncological centre (minutes)	36	IQR 14.8–60.3
Median driving time – home to GP (minutes)	6	IQR 4–9
MGMT methylation status		
Methylated	43 (48.9)	
Unmethylated	45 (51.1)	
Extent of resection		
GTR	56 (46.3)	
STR	60 (49.6)	
Partial	5 (4.1)	
Post-operative treatment		
None	17 (13.9)	
Radiotherapy only	19 (15.6)	
Chemotherapy only	8 (6.6)	
Chemotherapy and radiotherapy	77 (63.1)	
Median survival (days)	345	IQR 183–641

Abbreviations: GP; General practice, MGMT; O-6-methylguanine-DNA methyltransferase, GTR; gross total resection, STR; subtotal resection.

patient. Most patients had a Charlson co-morbidity index of two (32%), followed by one (24.6%) and zero (21.3%). Data was missing for one patient. The methylation status was available for 88 patients (72.1%). Of these, 43 patients (48.9%) had a tumour which was MGMT methylated. Based on a two-fold urban-rural index, 75 patients (61.5%) lived in an urban area versus 47 patients (38.5%) who lived rurally. A six-fold urban-rural index showed a bimodal distribution: large urban (28.7%), other urban area (21.3%), accessible small town (5.7%), remote small town (5.7%), accessible rural (24.6%) and remote rural (13.6%). The distribution of patients across the SIMD-2016 quintiles (five denotes the least deprived and one the most deprived) was: fifth quintile (32.8%), fourth quintile (26.2%), third quintile (19.7%), second quintile (14.8%), and first quintile (6.6%). Travel times from the patients' home to their neuro-oncological centre ranged from 5 min to 427 min. There were 30 patients whose travel time from their home to the oncological centre was longer than 60 min, and 18 of these patients had a travel time longer than 90 min. The median driving time from patients' home to their main oncological centre was 36 min (IQR 14.8–60.3). The median driving team from patients' home to their general practitioner was 6 min (IQR 4–9).

Most patients underwent either sub-total (49.6%) or gross total (46.3%) surgical resection. Partial surgical resection was achieved in 4.1% of patients. Extent of resection data was missing for one patient. Post-operative treatments included: post-operative radiotherapy only (15.6%), post-operative chemotherapy only (6.6%), post-operative chemotherapy and radiotherapy (63.1%). Post-operative treatment data was missing for one patient. Temozolomide was used in 70.5% of patients. Seventeen patients did not receive any post-operative chemo-radiotherapy. Reasons for this included death (n = 11), not being medically fit (n = 5), patient choice (n = 1), and leaving the country (n = 1). Thirteen patients (10.8%) underwent re-operation. Re-operation data was missing for two patients. At the close of the study, the outcomes for patients were alive (13 patients), dead (107 patients) and lost to follow-up (two patients). The median survival time (in days) was 345 (IQR 183–641).

Based on the Pearson correlation co-efficients and the log rank test, there was no statistically significant association between either distance travelled to the neuro-oncological centre or distance travelled to the GP and survival time (or loss to follow-up). No difference in statistical significance was observed when higher travel time limits (60 min for home to neuro-oncological centre and 10 min for home to GP) were used instead. Survival analysis using Kaplan–Meier curves and the log-rank test revealed that MGMT methylation status (p = 0.002), extent of resection (p = 0.009; see Fig. 1), Charlson co-morbidity index (p = 0.000) and treatment received (p = 0.000; see Fig. 2) were statistically significant. However, gender (p = 0.199), urban-rural 2-fold index (p = 0.853; see Fig. 3), urban-rural 6-fold index (p = 0.109), SIMD decile (p = 0.739), SIMD quintile (p = 0.709), and ECOG performance status pre surgery (p = 0.127) were not statistically significant. Based on the Kruskal–Wallis test statistic, there was no statistically significant difference between treatment received and distance to the neuro-oncological centre or GP.

4. Discussion

In this retrospective analysis of 122 glioblastoma patients living in the north of Scotland, we found no statistically significant disadvantage on survival for patients who live further from the neuro-oncological centre compared to those who live nearer. The demographic findings of our study are comparable to those from a study of patients with glioblastoma who underwent surgical resection.[11] Our finding of increasing incidence of glioblastoma with age and decreasing age-stratified survival which is similar to the findings from a large study of patients with glioblastoma in England.[12]

Epidemiological studies have shown evidence of a distance-decay effect, whereby patients who live further from a healthcare facility have poorer health outcomes compared to those who live closer.[4] A large data-linkage study of cancer patients undertaken in Scotland found that mainland patients living more than 60 min from their cancer treatment center and island dwellers commenced their treatment more quickly following referral by their GP and their diagnosis compared to those who lived within 15 min.[9] However, it was found that increased travelling time to the cancer treatment center was associated with an increased one-year mortality rate.

In our study, there was no statistically significant association between either distance travelled to the neuro-oncological centre or

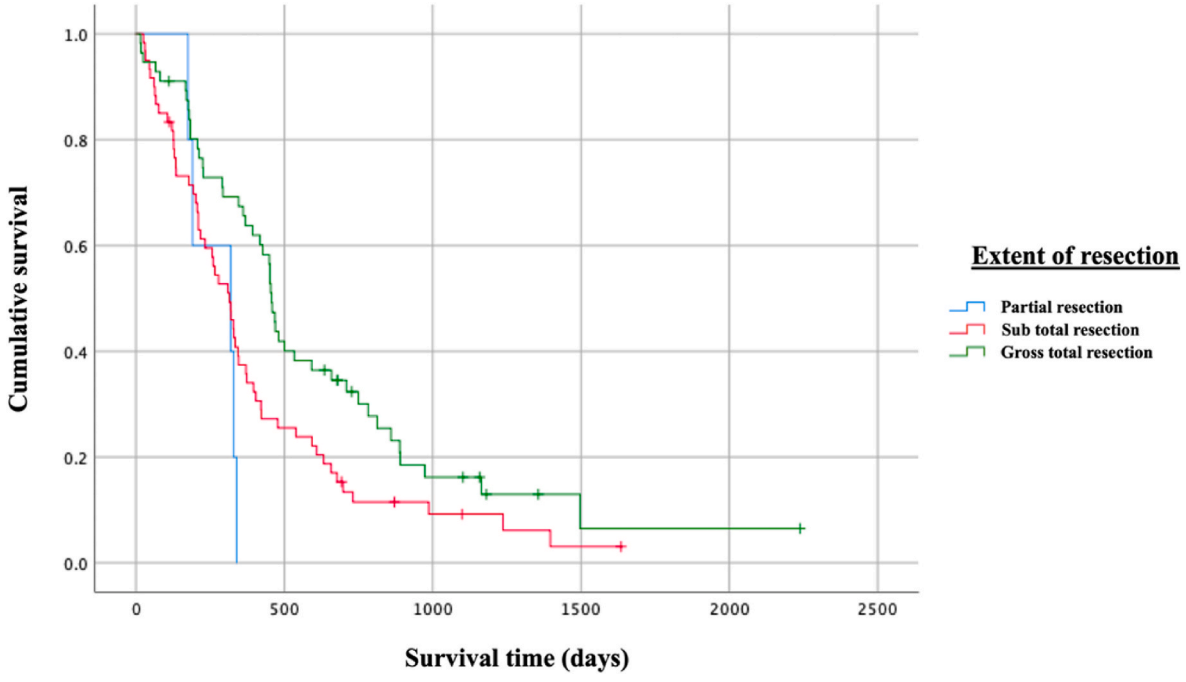

Fig. 1. Kaplan–Meier curve comparing survival time (in days) between groups categorised by extent of resection.

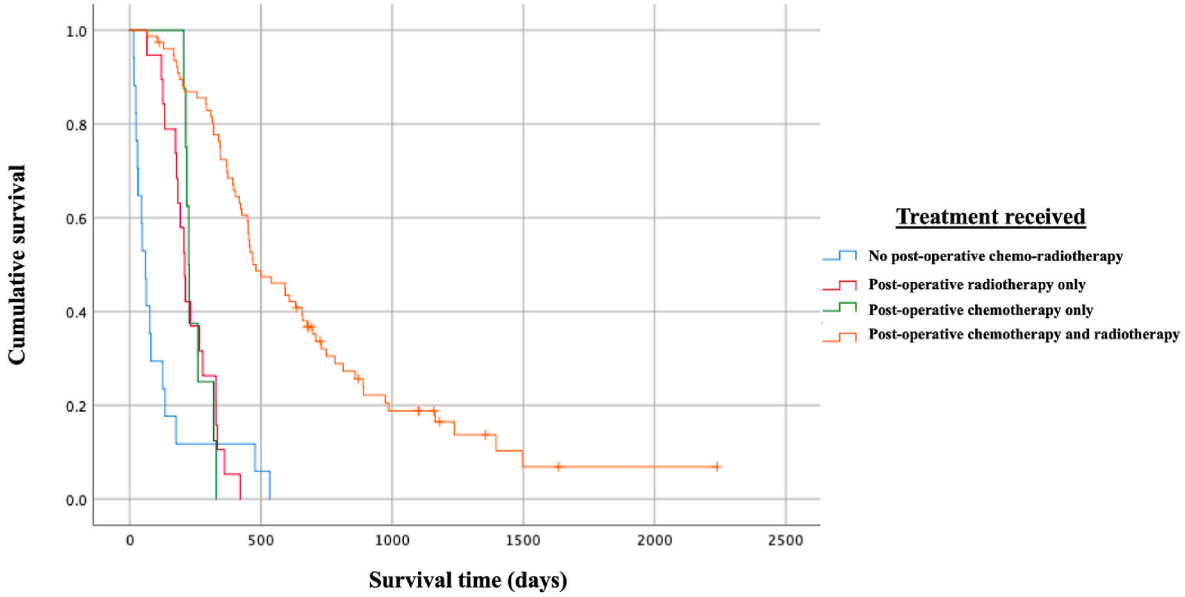

Fig. 2. Kaplan–Meier curve comparing survival time (in days) between groups categorised by treatment received.

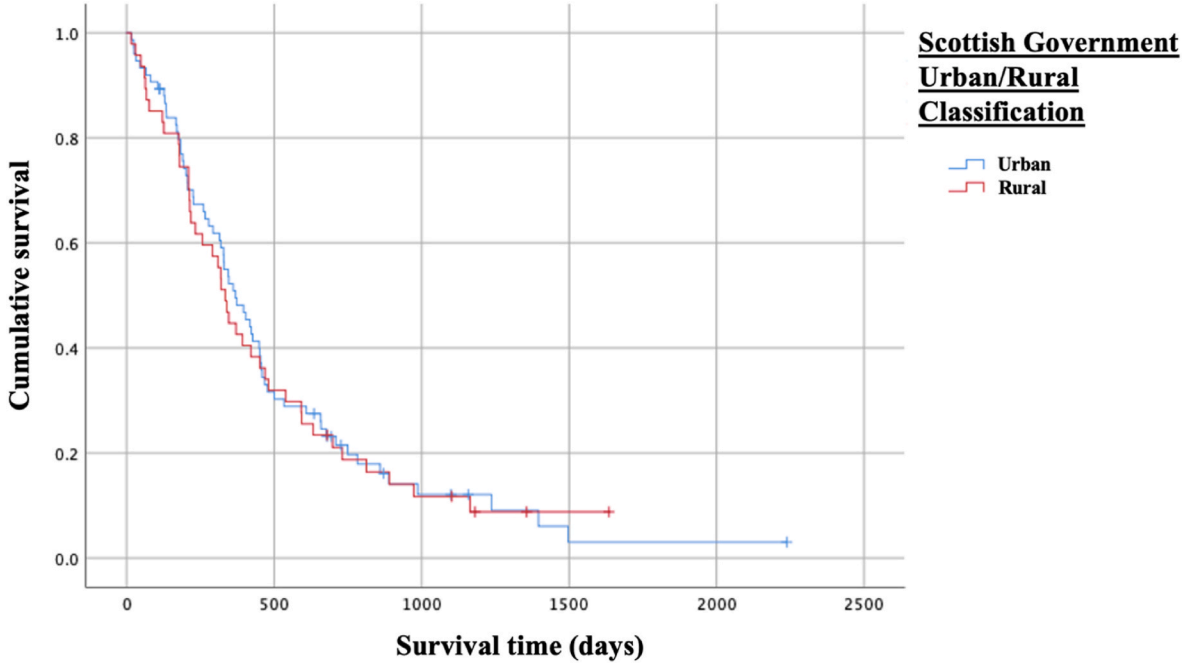

Fig. 3. Kaplan–Meier curve comparing survival time (in days) between groups categorised by the Scottish Government Urban/Rural Classification.

distance travelled to the GP and survival time in days. A retrospective analysis of 208 patients with glioblastoma who underwent surgical resection and adjuvant therapy over a 19-year period encompassing the pre-temozolomide and temozolomide-era found that the distance from the patients' home to the neuro-oncological center had a significant negative influence on overall survival in the pre-temozolomide era.[11] However, there was no statistically significant effect in the sub-group of patients who received temozolomide treatment. Patients living further from the neuro-oncological center were significantly less often treated with adjuvant treatment other than radiotherapy,[11] although, there was no such correlation in patients treated with concomitant and adjuvant temozolomide. Kerschbaumer et al proposed that this disparity in timely diagnosis and treatment in the rural population was due to the increased side–effect profile of the adjuvant chemotherapeutic agents used at that time, such as procarbazine, lomustine and vincristine (PCV) and other nitrosourea-based drugs.

Concomitant radiochemotherapy and adjuvant temozolomide was established as the standard of treatment in 2005.[1] Our study analysed patients who received treatment in the temozolomide-era between 2007 and 2018. The explanation proposed by Kerschbaumer et al may explain our study's finding of no statistically significant relationship between travel time (as a measure of distance) to the neuro-oncological center and overall survival. The choice and amount of chemo-radiotherapy depends on multiple factors, including the patient's fitness to undergo treatment and the methylation status of their tumour.[13] In our study, fourteen percent of patients did not receive any post-operative chemo-radiotherapy and the reasons for this included death, not being medically fit, patient choice, and leaving the country. In the north of

Scotland, the sole neurosurgical center is based at Aberdeen Royal Infirmary. However, the neurosurgical consultants travel to the more northernly Raigmore Hospital in Inverness on an *ad hoc* basis to undertake outpatient clinics for patients with glioblastoma living in that region.

Patients travelling to ARI from the more distant Highland Health Board area (which is out with the local Grampian Health Board where ARI is located) can claim financial support for their travel and accommodation costs.[14] This may offset some of the geographical access difficulties of being resident in an area that is distant to the neuro-oncological center facilitating travel to receive treatment and follow-up which may help to explain the findings of this paper.

This study has a number of strengths which add to the body of evidence on glioblastoma. This study included patients identified from a validated database with histopathologically-diagnosed glioblastoma. The studied cohort is valid because the demographic findings are similar to previous studies of patients with glioblastoma and because it was found that MGMT status, extent of resection and treatment received impacted survival time in days. Due to the use of electronic medical records, data on a comprehensive array of relevant variables was included with very little missing data. This study also has several limitations. As a retrospective review of medical records, the possibility of selection bias in the included sample population could not be excluded and cases that were incorrectly coded may not have been included in the data set. Travel time by car was used as the measure of distance travelled and the actual travel time of patients may vary significantly depending on the choice of transportation and travel conditions. As a single-centre service evaluation, this limits the generalizability of the findings.

5. Conclusion

To the best of our knowledge, this is the first study evaluating the impact of rurality and remoteness on the provision of neurosurgical and oncological services for patients diagnosed with glioblastoma in the north of Scotland. This study found that there was no statistically significant relationship between travel time (as a measure of distance) to the neuro-oncological center and survival time. The findings of this study add to the body of evidence on the impact of rurality and remoteness on patients with glioblastoma and it will be of interest to centers which provide neurosurgical and oncological care for patients diagnosed with glioblastoma who reside in remote and rural regions.

CRediT authorship contribution statement

Damjan Veljanoski: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Raphae Barlas:** Formal analysis, Methodology, Validation, Writing – review & editing. **Aimun A.B. Jamjoom:** Methodology, Writing – review & editing. **James Walkden:** Validation, Writing – review & editing. **Graham Horgan:** Formal analysis, Methodology, Validation, Writing – review & editing. **Rafael Moleron:** Methodology, Writing – review & editing. **Phyo Kyaw Myint:** Methodology, Supervision, Writing – review & editing. **Anastasios Giamouriadis:** Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996. https://doi.org/10.1056/NEJMOA043330/SUPPL_FILE/987SA1.PDF.
2. Thakkar JP, Dolecek TA, Horbinski C, et al. Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol Biomarkers Prev*. 2014;23(10):1985–1996. https://doi.org/10.1158/1055-9965.EPI-14-0275/68016/AM/EPIDEMIOLOGIC-AND-MOLECULAR-PROGNOSTIC-REVIEW-OF.
3. Tseng JH, Merchant E, Tseng MY. Effects of socioeconomic and geographic variations on survival for adult glioma in England and Wales. *Surg Neurol*. 2006;66(3):258–263. https://doi.org/10.1016/J.SURNEU.2006.03.048.
4. Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. *BMJ Open*. 2016;6(11), e013059. https://doi.org/10.1136/BMJOPEN-2016-013059.
5. Managed Service Network (MSN) Neurosurgery. Aberdeen Royal Infirmary. https://www.[msn-neuro.com/about/centres-aberdeen/].
6. Carter D. *Review of Neurosurgical Units in Scotland*. 2000.
7. Scottish Government. *National Statistics. Rural Scotland Key Facts 2021*. 2021.
8. Murchie P, Campbell N, Smith S, et al. Is current GP referral practice for cancer in Scotland optimal? A detailed exploration of cancer referral pathways using primary care records and a cancer care pathway database. Commissioned research protocol from the Detect Cancer Early Programme of the. *Eur J Cancer Care*. 2013;24.
9. Turner M, Fielding S, Ong Y, et al. A cancer geography paradox? Poorer cancer outcomes with longer travelling times to healthcare facilities despite prompter diagnosis and treatment: a data-linkage study. *Br J Cancer*. 2017;117(3):439–449. https://doi.org/10.1038/BJC.2017.180.
10. Haynes R, Jones AP, Sauerzapf V, Zhao H. Validation of travel times to hospital estimated by GIS. *Int J Health Geogr*. 2006;5. https://doi.org/10.1186/1476-072X-5-40.
11. Kerschbaumer J, Freyschlag CF, Bauer R, et al. Distance to the neurooncological Center: a negative prognostic factor in patients with glioblastoma multiforme. An epidemiological study. *Anticancer Res*. 2012;32(12):5515–5520.
12. Brodbelt A, Greenberg D, Winters T, Williams M, Vernon S, Collins VP. Glioblastoma in England: 2007–2011. *Eur J Cancer*. 2015;51(4):533–542. https://doi.org/10.1016/J.EJCA.2014.12.014.
13. Greenberg MS. Astrocytomas. In: *Handbook of Neurosurgery*. 2015.
14. NHS Grampian. Paying Out Patient Travel Claims..

List of abbreviations

ARI: Aberdeen Royal Infirmary
CCP: Cancer Care Pathway
CT: Computerised Tomography
DNA: Deoxyribonucleic acid
ECOG: Eastern Cooperative Oncology Group
GP: General practice
GTR: Gross Total Resection
IQR: Interquartile Range
MGMT: O-6-methylguanine-DNA methyltransferase
MRI: Magnetic Resonance Imaging
PCV: procarbazine, lomustine and vincristine
SD: Standard deviation
SIMD: Scottish Index of Multiple Deprivation
STR: Subtotal resection
UK:: United Kingdom