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Regional and socio-economic variation in survival after glioblastoma in Denmark, 2013-2018

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ABSTRACT

INTRODUCTION. Glioblastoma is the most frequent primary brain tumour in adults. In Denmark, the treatment of glioblastoma is centralised to four neurosurgical and oncological departments located in four of the five Danish administrative regions. The aim of this study was to examine the regional and socioeconomic variation in survival after a diagnosis of glioblastoma in Denmark.

METHODS. We included 1,731 patients with histologically confirmed glioblastoma from 2013 to 2018 registered in the Danish Neuro-oncology Registry. The data sources were the Danish National Registries. The exposure was region of residence at diagnosis and household income in the year before diagnosis. Follow-up was initiated at diagnosis and concluded at death or end-of-follow-up on 15 July 2019. Cox regression was used to examine overall mortality by exposure.

RESULTS. With adjustment for age, sex, year of diagnosis and comorbidity, mortality rates of glioblastoma patients varied significantly between regions and were lowest in the Region of Southern Denmark and highest in the Capital Region (hazard ratio = 0.79; 95% confidence interval: 0.68-0.91, compared with the Capital Region). Further adjustment for surgical resection attenuated the regional differences in mortality. Income was not a predictor of survival.

CONCLUSIONS. We found significant regional variation in survival after a diagnosis of glioblastoma. Differences in treatment patterns between regions may explain part of this mortality variation. Household income and education level did not explain the regional differences.

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Glioblastoma carries a severe prognosis with a median survival of approximately 12 months [1]. The primary treatment of glioblastoma is surgical resection most often followed by chemotherapy and radiotherapy. Due to the intracerebral location of the tumour, surgical resection as the primary treatment is carefully balanced against the risk of complications in terms of impaired physical or cognitive function with a possible severe impact on the patient's quality of life. When surgical resection is not feasible, tissue-based diagnostics is performed by stereotactic biopsy [2, 3]. When the patient's condition is poor, no tissue diagnosis is obtained and palliative treatment is initiated. In Denmark, the treatment of glioblastoma is provided according to national guidelines [4].

The treatment of gliomas in Denmark is centralised to four hospitals located in four of the five Danish geographical regions: Rigshospitalet (Capital Region), Odense University Hospital (Region of Southern Denmark), Aarhus University Hospital (Central Denmark Region) and Aalborg University Hospital (North Denmark Region). Surgery, radiotherapy and chemotherapy are conducted in all four hospitals. Patients who live in Region Zealand are typically referred to Rigshospitalet for diagnostic workup and treatment.

In Denmark, healthcare and hospital services are provided to the residents by each of the five Danish administrative regions, and the evaluation of mortality rates across regions may reflect regional differences in treatment intensity or quality. Furthermore, it is of interest to examine the contribution of socio-economic factors to survival after a diagnosis of glioblastoma in the tax-financed Danish healthcare system [5].

The aim of this study was to examine regional differences in overall survival after a histologically verified diagnosis of glioblastoma in Denmark, and to evaluate the influence of the use of surgical resection and socio-economic factors on the prognosis.

METHODS

We collected data on all patients with histologically verified gliomas diagnosed in the 2013-2018 period registered in the Danish Neuro-oncology Registry (n = 2,435) (DNOR) [6]. Patients with missing data on tumour grade or socio-economic variables were excluded. These exclusions left 2,360 patients. The analysis was further restricted to 1,731 (73%) patients with grade IV glioma (glioblastoma) (SNOMED morphology codes: M94403; M94423). The date of diagnosis was the earliest date of diagnostic biopsy or surgical resection with corresponding histologically verified glioblastoma.

Data sources were the DNOR [6], the Danish Civil Registration System (CRS) [7] and the Danish National Patient Registry (NPR) [8]. Information about education and household income was extracted from the national registries at Statistics Denmark [9, 10]. The unique Danish ten-digit personal identification number (PIN) was used to link data across registers. The study was registered in accordance with the General Data Protection Regulation in the Central Denmark Region (Reg. no.: 1-16-02-823-17).

Region of residence at diagnosis, marital status and date of death were extracted from the CRS [7]. The Capital Region contributed with the highest number of patients and was used as the reference region in the analyses. Marital status was defined as 1) married or in a registered partnership, 2) other cohabiting persons and 3) single or widowed.

The highest attained formal education for each patient was classified as 1) basic school education (the compulsory school education only), 2) professional education (including, e.g., apprenticeships and including high-school only), 3) shorter further education and 4) longer further education.

Household income in the year before the cancer diagnosis was grouped into quartiles of the income distribution for the total population of glioblastoma patients.

Comorbidity up to three months prior to the date of diagnosis was calculated as the Charlson Comorbidity Index based on hospital discharge diagnoses in the NPR [11] from ten years before the date of diagnosis.

Tumour grade was defined according to the contemporary World Health Organization (WHO) Classification of Tumors of the Central Nervous System [12].

Surgical resection was a binary variable indicating that a resection (NOMESCO classification code AAB00 (gross total resection) or AAB10 (partial resection)) [13] was the primary treatment. Surgical resection registered within

90 days of an initial diagnostic biopsy was classified as the primary treatment.

The statistical analysis was conducted as a time-to-event analysis using death from any cause as outcome. Patients were followed up from the date of diagnosis until death, emigration or end-of-follow-up on July 15, 2019, whichever occurred first. The follow-up period ranged from six months to six years, depending on the time of diagnosis. We used a multivariable Cox regression model and reported the results as adjusted hazard ratios (HRs) with corresponding 95% confidence interval (95% CI). The basic model (Model 1) included age (quadratic function), sex, year of diagnosis and comorbidity as covariates. Each of the remaining covariates were then added to Model 1 separately in order to identify their individual contribution to the variation in mortality.

Trial registration: not relevant.

RESULTS

Table 1 characterises the study population of 1,731 glioblastoma patients by region of residence. The patients in the Capital Region were more often women, were better educated and had a higher income than patients in the other regions. Region Zealand had the highest proportion (12%) of patients with a high comorbidity (Charlson Comorbidity Index > 3). The highest proportion of patients of older age (≥ 70 years), lower education (school-based education only) and low income was seen in the Region of Southern Denmark. Surgical resection was initiated more frequently in the Region of Southern Denmark (83%) than in the other four regions. The lowest resection rate was observed in the North Denmark Region (59%).

Table 1 also includes results of the Cox regression analyses for each of the included covariates in the study. The basic model included adjustment for age, sex, year of diagnosis and comorbidity. Mortality increased significantly with higher age and high comorbidity but did not differ significantly between men and women; nor according to education or income. Patients with no surgical resection had significantly higher mortality.

TABLE 1 Overview of cohort of 1,731 patients with histologically verified glioblastoma, Denmark, 2013-2018.

	Region, n (%)							
	North Denmark Region	Central Denmark Region	Region of Southern Denmark	Region Zealand	Capital Region of Denmark	Total, n (%)	Hazard ratio[a] (95% CI)	p-value[b]
Total population	200 (12[c])	353 (20[c])	388 (22[c])	274 (16[c])	516 (30[c])	1,731 (100[c])		
Year of diagnosis (p = 0.79[d])								0.42
2013	40 (20)	54 (15)	69 (18)	45 (16)	87 (17)	295 (17)	1.00 (reference)	
2014	34 (17)	52 (15)	76 (20)	47 (17)	92 (18)	301 (17)	1.02 (0.87-1.21)	
2015	31 (16)	70 (20)	64 (16)	51 (19)	98 (19)	314 (18)	1.18 (1.00-1.38)	
2016	39 (20)	54 (15)	71 (18)	43 (16)	77 (15)	284 (16)	1.09 (0.92-1.29)	
2017	30 (15)	62 (18)	56 (14)	40 (15)	77 (15)	265 (15)	1.04 (0.87-1.25)	
2018	26 (13)	61 (17)	52 (13)	48 (18)	85 (16)	272 (16)	1.02 (0.83-1.26)	
Age group (p = 0.14[d])								< 0.0001
18-39 yrs	6 (4)	17 (5)	11 (3)	7 (3)	26 (5)	67 (4)	0.56 (0.41-0.75)	
40-49 yrs	13 (7)	31 (9)	23 (6)	16 (6)	37 (7)	120 (7)	0.70 (0.57-0.87)	
50-59 yrs	41 (21)	76 (22)	70 (18)	53 (19)	102 (20)	342 (20)	0.72 (0.62-0.84)	
60-69 yrs	71 (36)	127 (36)	115 (30)	91 (33)	152 (29)	556 (32)	1.00 (reference)	
70-79 yrs	55 (28)	84 (24)	138 (36)	82 (30)	159 (31)	518 (30)	1.34 (1.18-1.53)	
≥ 80 yrs	14 (7)	18 (5)	31 (8)	25 (9)	40 (8)	128 (7)	2.48 (2.03-3.04)	
Sex (p = 0.53[d])								0.60
Men	127 (64)	214 (61)	235 (61)	169 (62)	295 (57)	1,040 (60)	1.00 (reference)	
Women	73 (37)	139 (39)	153 (39)	105 (38)	221 (43)	691 (40)	0.97 (0.88-1.08)	
Charlson Comorbidity Index (p = 0.01[d])								< 0.0001
0	149 (75)	264 (75)	275 (71)	171 (62)	379 (73)	1,238 (72)	1.00 (reference)	
1-2	40 (20)	66 (19)	86 (22)	69 (25)	103 (20)	364 (21)	1.18 (1.04-1.34)	
≥ 3	11 (6)	23 (7)	27 (7)	34 (12)	34 (7)	129 (7)	1.52 (1.26-1.85)	
Civil status (p = 0.26[d])								0.05
Married	129 (65)	218 (62)	252 (65)	188 (69)	309 (60)	1,096 (63)	1.00 (reference)	
Cohabiting	36 (18)	74 (21)	81 (21)	54 (20)	124 (24)	369 (21)	1.14 (1.00-1.30)	
Single	35 (18)	61 (17)	55 (14)	32 (12)	83 (16)	266 (15)	1.16 (0.99-1.36)	
Education (p < 0.0001[d])								0.39
School	65 (33)	103 (29)	145 (37)	92 (34)	126 (24)	531 (31)	1.00 (reference)	
Professional education	99 (50)	159 (45)	136 (35)	123 (45)	216 (42)	733 (42)	0.92 (0.81-1.04)	
Shorter further education	26 (13)	69 (20)	88 (23)	41 (15)	114 (22)	338 (20)	0.89 (0.77-1.04)	
Longer further education	10 (5)	22 (6)	19 (5)	18 (7)	60 (12)	129 (7)	0.90 (0.73-1.12)	
Income (p < 0.0001[d])								0.46
Quartile 1	60 (30)	65 (18)	125 (32)	74 (27)	109 (21)	433 (25)	1.00 (reference)	
Quartile 2	64 (32)	94 (27)	87 (22)	72 (26)	116 (22)	433 (25)	1.07 (0.93-1.24)	
Quartile 3	47 (24)	98 (28)	99 (26)	65 (24)	123 (24)	432 (25)	0.97 (0.84-1.13)	
Quartile 4	29 (15)	96 (27)	77 (20)	63 (23)	168 (33)	433 (25)	0.96 (0.82-1.12)	
Resection within 90 days of diagnosis (p < 0.0001[d])								< 0.0001
Yes	118 (59)	238 (67)	321 (83)	202 (74)	372 (72)	1,251 (72)	1.00 (reference)	
No	82 (41)	115 (33)	67 (17)	72 (26)	144 (28)	480 (28)	2.26 (2.02-2.54)	

CI = confidence interval.
a) Estimates of the risk of death from any cause by the multivariable Cox regression model adjusted for age group, sex, year of diagnosis and Charlson Comorbidity Index.
b) From Wald tests for heterogeneity in the adjusted models.
c) Row %.
d) From χ^2-tests for heterogeneity.

Table 2 shows the regional variation in mortality using different adjustments. With adjustment for age, sex, year of diagnosis and comorbidity (Model 1), the Region of Southern Denmark had the lowest mortality, HR = 0.79 (95% CI: 0.68-0.91)); and the Capital Region had the highest (HR = 1.00; the baseline category in the model). The results were robust to further separate adjustment for civil status, education and income. When adjusted for surgical resection, the regional differences in mortality were attenuated, indicating that the variation in Model 1 was partly attributable to the varying use of surgical resection.

TABLE 2 Cox regression analyses of all-cause mortality by region of residence of 1,731 patients with glioblastoma, Denmark, 2013-2018. Sensitivity analyses for available covariates.

	Hazard ratio (95% confidence interval)				
Region of residence	Model 1[a] (p = 0.02[b])	Model 1 and civil status (p = 0.03[b])	Model 1 and education (p = 0.01[b])	Model 1 and income (p = 0.02[b])	Model 1 and resection (p = 0.48[b])
North Denmark Region	0.95 (0.80-1.13)	0.96 (0.80-1.14)	0.93 (0.78-1.11)	0.93 (0.78-1.10)	0.89 (0.75-1.06)
Central Denmark Region	0.90 (0.77-1.04)	0.90 (0.78-1.04)	0.88 (0.76-1.03)	0.89 (0.77-1.03)	0.90 (0.78-1.04)
Region of Southern Denmark	0.79 (0.68-0.91)	0.79 (0.69-0.91)	0.78 (0.67-0.90)	0.78 (0.68-0.90)	0.90 (0.79-1.04)
Region Zealand	0.88 (0.75-1.03)	0.89 (0.76-1.04)	0.86 (0.73-1.01)	0.87 (0.74-1.02)	0.95 (0.81-1.11)
Capital Region of Denmark	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

a) Model 1 includes age, year of diagnosis, sex and the Charlson Comorbidity Index.
b) From Wald tests for heterogeneity in the adjusted models.

Table 3 shows the adjusted hazard ratio estimates of mortality by household income. Model 1 showed no significant variation in mortality between income groups, and estimates were robust to the separate adjustment for included covariates.

TABLE 3 Cox regression analyses of all-cause mortality by income of 1,731 patients with histologically verified glioblastoma, Denmark, 2013-2018. Sensitivity analyses for available covariates.

	Hazard ratio (95% confidence interval)				
Income	Model 1[a] (p = 0.46[b])	Model 1 and civil status (p = 0.52[b])	Model 1 and education (p = 0.56[b])	Model 1 and region of residence (p = 0.35[b])	Model 1 and resection (p = 0.12[b])
Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	1.07 (0.93-1.24)	1.05 (0.91-1.21)	1.08 (0.94-1.25)	1.07 (0.92-1.23)	1.15 (0.99-1.33)
Quartile 3	0.97 (0.84-1.13)	0.95 (0.82-1.10)	0.99 (0.85-1.15)	0.96 (0.83-1.11)	0.99 (0.86-1.15)
Quartile 4	0.96 (0.82-1.12)	0.95 (0.81-1.11)	0.99 (0.84-1.17)	0.93 (0.80-1.09)	0.99 (0.84-1.15)

a) Model 1 is adjusted for age, sex, year of diagnosis and the Charlson Comorbidity Index.
b) From Wald tests for heterogeneity in the adjusted models.

DISCUSSION

We examined regional differences in mortality after a histologically confirmed glioblastoma diagnosis in 1,731 patients in Denmark. The median overall survival was 11.2 months.

When adjustment was made for year of diagnosis, age, sex and comorbidity, a 21% difference was observed in patient mortality between Southern Denmark (lowest) and the Capital Region (highest). In the age group 60-69 years (32% of the study population), the observed regional difference in mortality corresponded to a difference in median survival between Southern Denmark and the Capital Region of 2.6 months (Log-rank, p = 0.51). In the age group ≥ 70 years, the difference in median survival was 2.3 months (log-rank, p = 0.11), whereas in the age group 18-59 years the difference was only 0.2 months in favour of the Capital Region (log-rank, p = 0.36) (**Figure 1**).

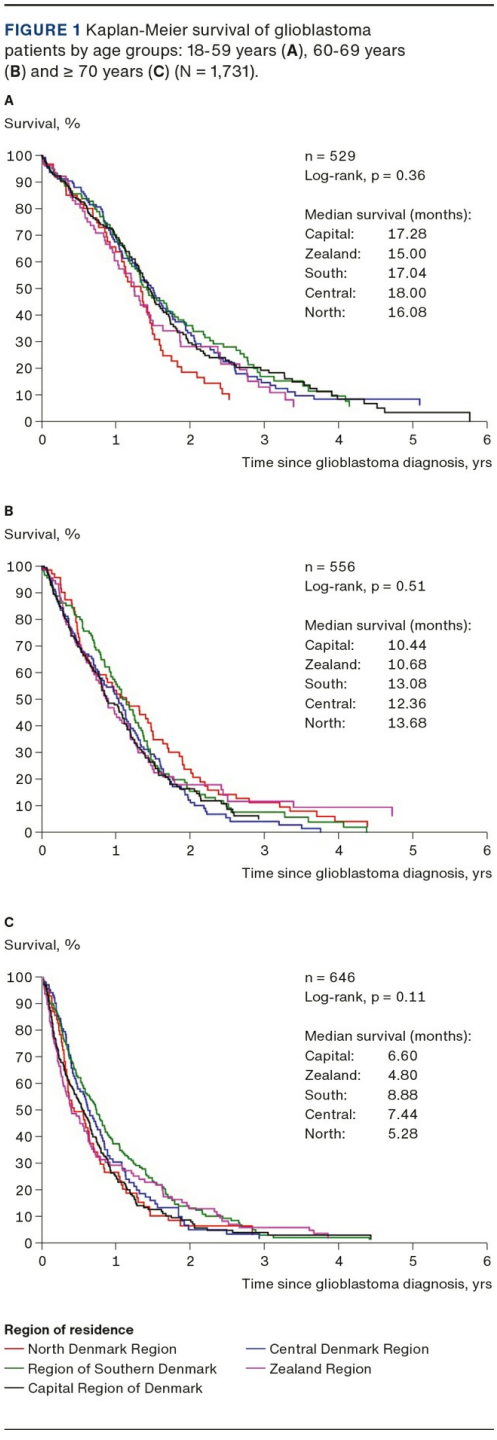

FIGURE 1 Kaplan-Meier survival of glioblastoma patients by age groups: 18-59 years (**A**), 60-69 years (**B**) and ≥ 70 years (**C**) (N = 1,731).

The variation between the five Danish regions in socio-economic variables did not explain the observed regional differences in mortality as revealed by the robust HR estimate for Southern Denmark after separate adjustments. The results were sensitive to adjustment for surgical resection, which varied from 83% in Southern Denmark to 59% in Northern Denmark. Surgical resection had an attenuating effect on the observed regional variation.

Only around 15% of glioblastoma patients survive two years after diagnosis [1]. Therefore, quality of life is of utmost importance when deciding the treatment strategy. The choice of treatment strategy also depends on

comorbidity and performance status, and on disease-related neurological deficits such as cognitive impairment, memory loss, apraxia and language disorders. Furthermore, the risk of adverse effects from surgery and other interventions needs to be considered to balance the expected survival benefit.

The resection rate ranged from 59% to 83% between the five Danish regions, although all treatment is centralised to four high-volume academic centres that follow the same national guidelines to perform resection as safely as possible [4]. This difference may be a result of patient selection because patients are selected for resection according to age, performance status and infiltration of the tumour into eloquent brain tissue. Moreover, with extended state or tumour growth at symptom presentation, some patients are not offered surgery and were thus not included in this analysis.

A national consensus exists on guidelines based on systematic reviews which conclude that a total resection improves survival [14], although the extent of resection remains controversial due to few randomised controlled trials [15]. Hence, surgical resection is the standard treatment in glioblastomas [2], but preventing neurological deficits has top priority when aiming to perform resection as safely as possible since postoperative deficits may reduce patient survival and quality of life [16]. Selection for surgery is therefore a complex risk-adapted strategy influenced by evaluation of prognostic data, patient-preferences and usability of surgical adjuncts. We do not have data on the regional variation in these surgical adjuncts, such as stereotactic navigation systems, intraoperative MRI, tumour visualisation by fluorescent aminolevulinic acid and awake monitoring with cortical stimulation, which can optimise the achievement of minimal residual postoperative tumour volume. The risk-adapted selection strategy is of utmost importance and may have influenced the regional variation in resection rate.

We used data from the population-based Danish national health registries and registries from Statistics Denmark that are renerally considered to be of high quality in terms of completeness and validity [7-10]. Since 2015, the DNOR has been based on registrations in the NPR combined with clinical validation of data and supplementary, manually registered variables that are not possible to obtain through the Danish registries. A previous validation study conducted before the DNOR was register based (2009-2014) showed that the population of glioma patients was nearly complete (92%) and the data of selected clinically important variables was of good validity [6].

Household income in the year before diagnosis was not a predictor of survival, a very positive finding in the Danish healthcare setting. Furthermore, socio-economic covariates did not contribute to explaining the variation in survival between the five Danish regions.

CONCLUSIONS

We found 21% variation in age-, sex- and comorbidity-adjusted patient mortality between the five Danish regions in patients with a histologically verified glioblastoma diagnosis. The observed differences in surgical treatment across the five Danish regions may explain part of the variation in mortality. Household income was not associated with survival, nor did socio-economic factors explain regional differences in survival after a glioblastoma diagnosis.

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