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Original Paper

Prevalence and Prognostic Significance of Epilepsy in Patients with Gliomas

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The aim of this study was to evaluate the prevalence and prognostic significance of epilepsy in 1028 patients diagnosed in the computer tomography (CT) era with histological low- or high-grade intracranial gliomas. Survival analysis included Kaplan–Meier plots, log-rank tests, logistic regression and Cox's analysis as implemented in the SPSS statistical package. Epilepsy was a positive univariate ($P < 0.0001$) and multivariate, ($P < 0.03$) prognostic factor for survival in the total patient group ($n = 1028$, relative risk of death 0.83, 95% confidence interval (CI) 0.70–0.98) as well as in the high-grade patient group ($n = 649$, relative risk of death 0.80, 95% CI 0.66–0.96), but not in the group of low-grade glioma patients ($P > 0.2$). The prevalence of epilepsy in glioblastoma patients was 251/512 (49%), 95/137 (69%) in anaplastic gliomas, and 322/379 (85%) in patients with low-grade gliomas, with 97 of the 102 T1 low-grade subgroup (95%) having epilepsy, indicating that the presence of epilepsy may select patients for early radiological diagnosis. The frequency of epilepsy at presentation decreased with age in high-grade glioma patients, and increased with age in low-grade glioma patients to a plateau in the fourth decade of life ($P < 0.01$). The prevalence of epilepsy in patients with histological intracranial gliomas varied with patient age and tumour histology, with low-grade patients having the highest prevalence. Epilepsy was a significant positive prognostic factor except in patients with low-grade gliomas, and may select low-grade patients for early diagnosis. © **1998 Elsevier Science Ltd.**

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INTRODUCTION

EPILEPTIC SEIZURES are common in patients with primary brain tumours [1–3], and those who present with seizures may have a better prognosis [4–15]. A prevalence of epilepsy in a larger series of high-grade gliomas ranging from 22 to 37% has been reported [4–6]. In previous reports of astrocytomas or low-grade gliomas, the prevalence of epilepsy has ranged from 50 to 78% [7–11]. An exceptionally high value of 90% in patients with astrocytoma was found in Piepmeier's study [12]. Oligodendroglioma patients are generally thought to have the highest probability of epilepsy, with a prevalence of 72% in two recent series [13, 14]. However, most published papers reporting the prevalence and prognostic significance of epilepsy in patients with intracranial gliomas are fairly small [2, 6, 8–12], report on selected patients [4, 5, 9, 12, 14, 16], accrued before the computer tomography (CT) era [2, 9, 13, 17], or include many patients with unknown histology [7, 15]. Such studies may not reliably describe the true prevalence and prognostic implications of epilepsy in patients with gliomas.

Therefore, we investigated the prevalence and prognostic implications of epilepsy in 1028 consecutive patients with intracranial gliomas of known histology accrued at a single regional centre during the CT era.

PATIENTS AND METHODS

Data from 1028 patients with histologically verified primary intracranial tumours seen at the Norwegian Radium Hospital between 1980 and 1995 were examined. Together with two regional neurosurgical departments, the hospital provides the only neuro-oncological service to a population of 1.6 million living in south-eastern Norway outside Oslo. Between 1980 and 1987, the hospital also provided radiotherapy for brain tumour patients from the five northernmost counties of Norway.

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Hospital records were available for all patients. Variables registered in the database included month and year of first symptom, type of symptoms experienced before admittance, date of radiological diagnosis, CT or magnetic resonance imaging (MRI) findings, histological diagnosis according to the WHO classification system [18], WHO functional status [19] at first stay in our hospital, as well as details with regard to tumour localisation, tumour T-category and stage [20] as derived from the initial radiological diagnostic report, and patient management. All patients were followed until death or to 31 December 1995. The dates of death for deceased patients were obtained either from case records or from the Census Bureau.

A total of 1028 patients had histological diagnoses of glioblastoma, anaplastic astrocytoma, astrocytoma, oligodendroglioma or mixed glioma. Only 28 of these 1028 histologically verified gliomas were localised in the brain stem, cerebellum or the pineal region. Initial radiological diagnosis was based on CT and/or MRI in 1016 patients. In 12 patients, initial tumour diagnosis was made by other methods, usually cerebral angiography. Tumour contrast enhancement was considered present if described by the radiologist on initial routine diagnostic computer tomography, or present on re-evaluation of original CT images. Reliable data with regard to contrast enhancement was obtained in 903 out of 1028 patients. The major prognostic factors, age, WHO performance status, and low- or high-grade histology, were within the limits of 1–2% equally distributed between patients with reliable CT data ($n = 903$) compared with all patients with histologically verified intracranial gliomas ($n = 1028$) (Table 1). Reliable data on patient age, histology, presence of seizures and presence of mental changes were obtained in all patients, while data on WHO performance was lacking in one patient. The recorded presence of any emotional or cognitive tumour-related symptoms as described by the patient, relatives or doctor were registered as 'mental changes'.

Epilepsy was defined as any grand mal, petit mal, focal, sensory or psychomotoric attack registered in the patient's hospital records. We also noted whether epilepsy was a presenting symptom, i.e. apparent prior to radiological diagnosis, or during later follow-up. No retrospective classification of the type of seizure disorder was attempted, and a clinical diagnosis of epilepsy stated in the patient's hospital records was accepted at face value. Epilepsy prevalence was defined as the percentage of patients with histological intracranial gliomas registered with epilepsy during their entire illness.

The prediagnostic period was calculated from the month of first symptom to radiological diagnosis. Survival was calculated from the date of radiological diagnosis to death or to the date of the last observation. Generally, patients had tumour resection or biopsy performed at either of the two regional neurosurgical units and then received postoperative radiotherapy and/or chemotherapy at the Norwegian Radium Hospital.

Statistics

The SPSS statistical package [21] was used for data evaluation and presentation. Tables were tested for statistical significance by the chi-square test. Survival curves were produced according to the Kaplan–Meier method and differences in survival tested for statistical significance by the log-rank test. Multiple logistic regression analysis was used to test the predictive value of variables possibly associated with development of epilepsy in each tumour group (age, performance status, tumour contrast enhancement on CT, duration of prediagnostic period, presence of emotional or cognitive mental changes). Cox's proportional hazards model was used to investigate the effect of epilepsy as a covariate for survival together with age, histological grade, performance status, tumour contrast enhancement on CT, or presence of emotional or cognitive mental changes. A P value less than 0.05 was regarded as statistically significant. Throughout, two-sided P values are reported.

RESULTS

Median patient age and survival in each main histological subgroup are presented in Table 2. Only 61 patients were younger than 20 years, 20 had high-grade and 41 had low-grade tumours. A total of 190 patients, 170 with high-grade and 20 with low-grade tumours, were over 60 years of age. WHO performance status was 0–1 in 807 patients and 2–4 in 220 patients with histological intracranial glioma. Overall, 669 out of these 1028 patients (65.1%) experienced epileptic seizures during their neuro-oncological illness, 571 patients (55.5%) prior to radiological diagnosis.

The number of patients and the prevalence of epilepsy within each main histological subgroup are given in Table 3. The prevalence of epilepsy during the neuro-oncological illness decreased significantly with increasing histological grade ($P < 0.001$, chi-square). Within the high-grade group, patients with glioblastoma had a significantly lower prevalence than patients with anaplastic gliomas. Patients with low-grade tumours had by far the highest prevalence.

Patient age and histology influenced the probability of presenting with seizures prior to radiological diagnosis. Only the few patients younger than 10 years with high-grade tumours ($n = 8$) or older than 70 years with low-grade tumours ($n = 2$) did not fit this general pattern. In patients

Table 1. *Relative distribution of main prognostic factors in the group of patients with registered CT data* (n = 903) *and in the total patient population* (n = 1028)

Prognostic factor	Reliable CT data group	All patients
Median (mean) age	44 (44.2) years	45 (44.7) years
WHO performance status 0–1	80.6% ($n = 728$)	79.1% ($n = 812$)
WHO performance status 2–4	19.4% ($n = 175$)	20.9 ($n = 215$)
Low-grade histology	39.1% ($n = 353$)	36.9% ($n = 379$)
High-grade histology	60.9% ($n = 550$)	63.1% ($n = 649$)

Table 2. *Histological diagnosis, median age and median survival with* 95% *confidence intervals (CI) in* 1028 *patients with intracranial gliomas treated between* 1980 *and* 1995

Histology	Median age (years, range)	Median survival (95% CI)
Glioblastoma ($n = 512$)	51 (1–75)	12 months (11–13)
Anaplastic gliomas ($n = 137$)	43 (7–75)	33 months (22–44)
Low-grade gliomas ($n = 379$)	37 (3–72)	100 months (87–113)

Table 3. Prevalence of epilepsy in the main histological subgroups of 1028 intracranial gliomas treated between 1980 and 1995

Histology	Epilepsy prevalence*
Glioblastoma ($n = 512$)	252 (49%)
Anaplastic gliomas ($n = 137$)	95 (69%)
Low-grade gliomas ($n = 379$)	322 (85%)

*$P < 0.001$, chi-square.

with high-grade tumours ($n = 649$), the probability of epilepsy prior to radiological diagnosis declined with increasing patient age ($P < 0.01$, logistic regression). Conversely, in patients with low-grade gliomas ($n = 379$), the probability of epilepsy prior to radiological diagnosis increased with age ($P < 0.01$) and plateaued in patients 40 years of age or older (Figure 1).

In univariate survival analysis on all patients with histological diagnoses of intracranial gliomas ($n = 1028$), the presence of epilepsy in patients presenting with epilepsy prior to radiological diagnosis ($n = 571$) as well as epilepsy in the group of patients registered with epilepsy at any time point during their neuro-oncological illness ($n = 669$) emerged as a highly significant ($P < 0.0001$, log-rank) positive prognostic factor. The data in Figure 2 include all patients with a diagnosis of epilepsy ($n = 669$).

When the significance of epilepsy during the entire neuro-oncological illness as a prognostic factor for mortality was tested in Cox's multivariate analysis against age, performance status, tumour contrast enhancement on computer tomography, emotional or cognitive mental changes, and histological grade, epilepsy again proved a significant although weak positive prognostic factor in patients with intracranial gliomas (relative risk 0.83, 95% confidence interval 0.70–0.98, $P < 0.03$). In patients presenting with epilepsy prior to radiological diagnosis, the corresponding relative risk was 0.88 (95% confidence interval (CI) 0.81–0.96, $P < 0.01$).

High-grade Gliomas

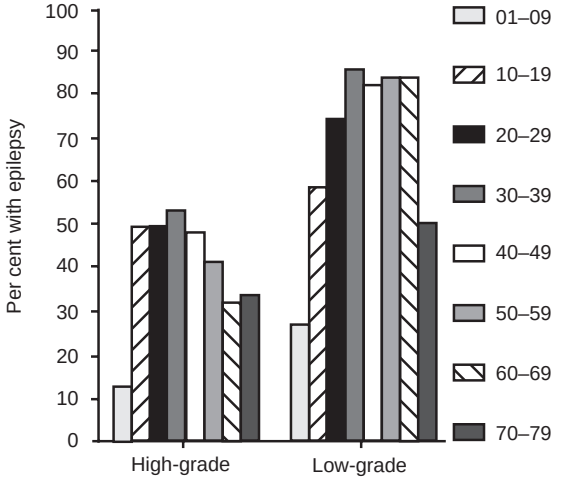

Figure 1. Frequency of epilepsy as a presenting symptom prior to radiological diagnosis in 10-year cohorts of patients with high-grade gliomas ($n = 649$) and low-grade gliomas ($n = 379$). The frequency of epilepsy decreased with age in high-grade gliomas. In contrast, the frequency of epilepsy increased with age in low-grade gliomas to reach a plateau in the fourth decade of life ($P < 0.01$, logistic regression).

Epilepsy (whether in the group of patients presenting with epilepsy prior to radiological diagnosis ($n = 276$), or in all high-grade patients with a diagnosis of epilepsy ($n = 347$) was a positive prognostic factor when tested by univariate analysis for all patients with high-grade glioma ($P < 0.0001$, log-rank). The data in Figure 3 include all patients with a high-grade glioma and epilepsy ($n = 347$). When the presence of epilepsy at any time during the neuro-oncological illness was tested as a prognostic factor for mortality in the multivariate Cox model together with age, CT enhancement, the presence of emotional or cognitive mental changes and WHO performance status, epilepsy emerged as a significant independent positive prognostic factor in the high-grade glioma group (relative risk 0.80, 95% CI 0.66–0.96, $P < 0.02$). In patients presenting with epilepsy prior to radiological diagnosis, the corresponding relative risk was 0.86 (95% CI 0.78–0.95, $P < 0.01$).

Low-grade Gliomas

Epilepsy (whether in the group of patients presenting with epilepsy prior to radiological diagnosis ($n = 295$), or in all low-grade patients with a diagnosis of epilepsy ($n = 322$)) was of no statistical significance (a positive prognostic factor when tested by univariate analysis in patients with low-grade glioma; $P > 0.2$, log-rank). The data in Figure 4 include all patients with low-grade glioma and epilepsy ($n = 322$). The overall prevalence of epilepsy in patients with low-grade tumours was 85% (Table 3). No significant difference in epilepsy prevalence was seen in patients with astrocytoma ($n = 268$, prevalence 84.7%) compared with patients with oligodendroglioma or mixed gliomas ($n = 111$, prevalence 85.6%). The percentages of patients presenting with epilepsy prior to radiological diagnosis increased for each age decade and plateaued in patients 40 years or older (Figure 1).

According to the UICC T category system [20], T1 tumours are less than 5 cm in diameter and may not cross the midline or impinge on the ventricular system. The prevalence of epilepsy as a presenting symptom was unequally distributed between T categories, with 93/102 (91.2%) in T1 patients compared with 202/277 (72.9%) in patients of all other T categories in the low-grade group ($P < 0.0001$, chi-square). The prevalence of epilepsy in T1 patients was 95%. Low-grade patients with T1 tumours had median survival of

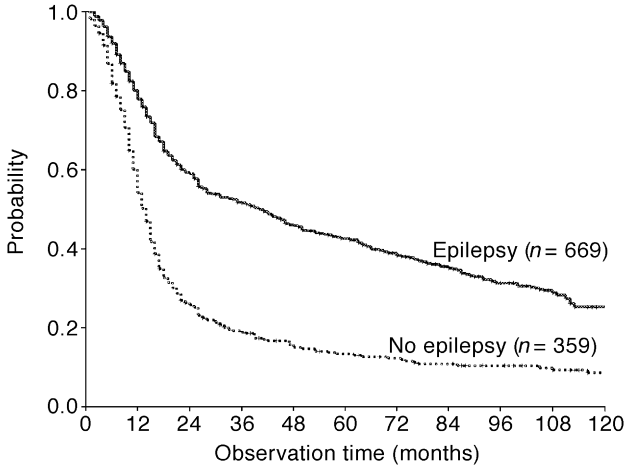

Figure 2. Survival for patients with a diagnosis of epilepsy during neoplastic illness in 1028 patients with intracranial low- ($n = 379$) or high-grade ($n = 649$) gliomas. The difference in survival was highly significant ($P < 0.0001$).

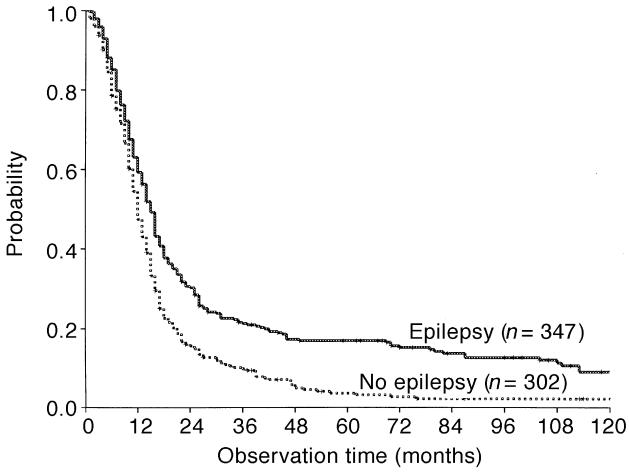

Figure 3. Survival by a diagnosis of epilepsy during the neoplastic illness in 649 patients with high-grade intracranial gliomas. The difference in survival is highly significant ($P < 0.0001$).

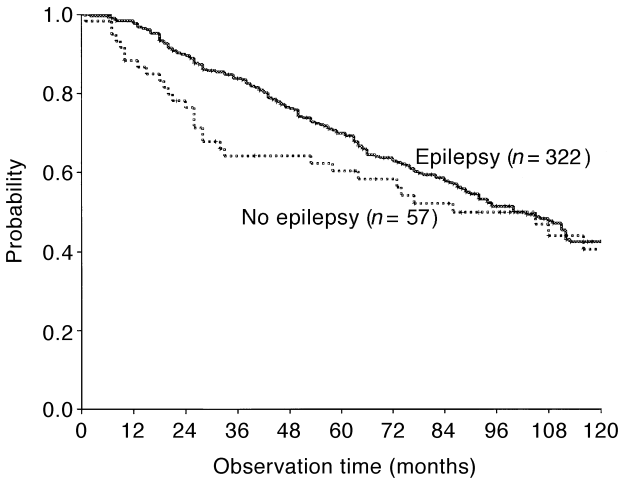

Figure 4. Survival by a diagnosis of epilepsy during the neoplastic illness in 379 patients with intracranial low-grade gliomas. There was an initial trend which did not reach statistical significance ($P > 0.2$, log-rank) towards better survival in patients with epilepsy.

130 months (95% CI 91–169 months) compared with 100 months in the entire low-grade group (n.s.). When epilepsy was assessed as a prognostic factor for survival by univariate analysis in the entire low-grade group, a non-significant trend towards initially better survival in patients with epilepsy was found (Figure 4).

DISCUSSION

The reported prevalence of epilepsy in patients with gliomas ranges from 30 to 90% [4–8, 12–15, 17, 22, 23], with low-grade glioma patients having the highest prevalence [7–9, 11, 12, 22]. In an unselected patient group containing high-grade aggressive tumours as well as indolent low-grade gliomas, epilepsy clearly can be expected to be a positive prognostic factor [7, 16, 17, 23].

Our findings, based on a very large single institution regionally and consecutively accrued patient sample, with over 94% adult patients, generally corroborate these earlier reports. However, we found at least a 10–15% higher epilepsy prevalence within each of the subgroups low-grade, anaplastic and glioblastoma patients than most previous studies. Our definition of epilepsy included patients presenting with epilepsy following diagnosis, so at least part of the observed higher prevalence could be explained by the more complete or longer follow-up possible in our regional patients. Also, the better diagnostic neuroimaging methods now available to diagnose gliomas in patients with seizures compared to reports from the pre-CT/MRI era may have increased the prevalence of epilepsy in glioma patients by revealing gliomas in patients who prior to the CT/MRI era would have been diagnosed with idiopathic epilepsy.

Furthermore, the exceptionally high percentage of T1 low-grade patients presenting with epilepsy (91.2%) may indicate that epilepsy as a presenting symptom also selects patients for early diagnosis. Compared with the pre-CT/MRI era, the prognostic implications of epilepsy may now be changing due to better diagnostic imaging. Very small tumours may cause epilepsy years before any other symptoms, and patients diagnosed with smaller tumours may be expected to live longer. In fact, median survival in our low-grade patients was almost doubled compared with the 2–5 years commonly reported in low-grade patient series accrued prior to the CT era [17, 22–25], although comparable to survival in two recent reports [11, 26]. Survival in low-grade patients with T1 tumours was even better, with 50% of such patients alive 130 months after diagnosis. However, diagnosis in contemporary patients who do not present with seizures is probably now also made at earlier disease stages compared to the pre-CT/MRI era. This may explain why the presence of epilepsy did not qualify as a statistically significant positive prognostic factor in our low-grade patients.

We consistently found an association between patient age, tumour grade and the presence of epilepsy. The probability of epilepsy as a symptom prior to radiological diagnosis increased with age to a plateau in the fourth decade in patients with low-grade gliomas, and decreased with age in patients with high-grade gliomas. A possible explanation is that the slow tumour evolution generally seen in low-grade gliomas will put these patients at prolonged risk of seizures, while patients with high-grade gliomas generally have short disease duration which leaves less time to develop epilepsy. Alternatively, high-grade gliomas in younger patients may be more prone to have transformed from a pre-existing low-grade tumour, partly retaining a less aggressive tumour biology, while high-grade gliomas in older patients more often may arise *de novo*. Such a hypothesis may also explain why we found the statistically strongest association between epilepsy and prolonged survival in patients with high-grade gliomas. We agree with previous investigators [4, 5, 7] that epilepsy is a marker for less aggressive tumour biology within the high-grade glioma group.

Single institution low-grade glioma series often include a large proportion of children [10, 22, 27–29] with excellent prognosis [22, 28–30], and survival plots in such reports generally show a plateau after 5–15 years [10, 22, 27–29]. In our adult low-grade glioma patients, as also reported by other investigators [11, 23], no plateau phase in survival was reached even after 10 years from diagnosis. Nor was epilepsy a statistically significant positive prognostic factor in our low-grade patients, in contrast to findings in the recent report by Leighton and associates [11].

In conclusion, the prevalence of epilepsy in intracranial gliomas varied with patient age and histological grade of the glioma. Epilepsy was a positive although weak positive prognostic factor in the total glioma patient population and in patients with high-grade gliomas, but did not reach statistical significance as a prognostic factor in patients with low-grade gliomas.

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