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LONG-TERM SURVIVAL AFTER MALIGNANT GLIOMA

A clinical and histopathological study on the accuracy of the diagnosis in a population-based cancer register

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Abstract

The Stockholm Regional Cancer Register (SRCR) contains 1 002 patients with malignant glioma reported between 1958 and 1977. A total of 49 patients had a minimum survival time of 4 years and of these 48 were studied in search for histological characteristics that might explain the unexpectedly good prognosis. In only 8 of the 48 patients (17%) could the diagnosis of malignant glioma of high malignancy grade be verified at histopathological reexamination. All 8 were grade III tumors according to WHO and no primary glioblastomas were found. The explanation for the erroneous registration was either incorrect initial pathological diagnosis or incorrect registration. No common morphological features could be found among the correctly registered long-term survivors. Survival data on gliomas based on original histopathological diagnoses derived from information in population-based cancer registers should be cautiously interpreted. Reliable conclusions can only be drawn when such data are supplemented with clinical information and the histopathology is reviewed.

Key words: Brain neoplasms, glioblastoma, anaplastic astrocytoma, survival, cancer registration.

Patients with anaplastic astrocytomas and glioblastomas usually have a poor prognosis regardless of treatment modality (1). However, a small number of patients survive for a long time (2). In the present study patients with malignant glioma were examined for prognostically favorable factors. A cohort of long-term surviving glioma patients in the Stockholm Regional Cancer Registry (SRCR) were studied. Cancer registration and histopathology were reviewed.

Material and Methods

Nationwide cancer incidence registration was established in Sweden in 1958. The SRCR is one of the six regional registries with a coverage of 1.5 million inhabitants. The Regional Cancer Registry collects data which are sent annually to the National Swedish Cancer Registry. Every physician is obliged by law to report a new cancer diagnosis to the regional cancer registry. This entails a double notification procedure from both clinicians and pathologists/cytologists. To obtain information on deaths and causes of death, the cancer registry files are matched annually with the nationwide Swedish Cause of Death Register at the National Central Bureau of Statistics. This record-linkage is made possible by the unique identification number which every Swedish resident is given at birth or on taking up permanent abode.

In the SRCR the coding of tumor site had been performed according to ICD-7 (International Classification of Diseases, 7th revision). Patients with malignant glioma according to the original histopathological classification were selected. The following diagnoses were included in the study: astrocytoma grade III or IV (3), glioblastoma, malignant oligodendroglioma, and spongioblastoma.

From 1958 through 1977, 1 002 patients (mean age 56 years) with malignant glioma were reported to the SRCR. Since the length of long-term survival conventionally reported in malignant gliomas is two years, a minimum of 4 years' survival was chosen as a selection criteria.

Of the 1 002 patients, 49 had a survival time of 4 years or longer after the primary diagnosis. These 49 'long-term survivors' constituted the study group. The histological specimen of one patient could not be found, leaving 48 patient specimens for re-examination (30 men and 18

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women; mean age 35 years). The patients in the study group were followed in the Cause of Death Register until December 31, 1981, the last year the Cause of Death Register was updated at the time of the study. Patients still alive in 1981 were followed-up to July 31, 1986, via population registers.

Since it could be suspected that apparent long-term surviving glioma patients in the cancer register could, at least in part, represent erroneous diagnoses and/or registration errors, the patients studied were compared with the total material of 1 002 patients. A random sample of 50 patients (26 men and 24 women; mean age 60 years) was selected from the total material. These patients constituted the control group and they were examined in the same way as the patients in the study group as to histopathology and accuracy of registration.

The information on the original Cancer Registry notifications, and Cancer Registry codings were investigated for patients in both the study group and the control group. All original histological slides were re-examined, and in a few cases they were supplemented with material from paraffin blocks, with or without immunohistochemistry. Reclassification was done according to the current WHO classification (1, 4).

Results

All 48 cases in the study group should have been malignant gliomas with long-term survival, if the original histopathological diagnosis, the initial cancer notification with histopathological and/or clinical findings, and registration had been correct. However, only 8 of them had had a true anaplastic glioma (malignancy grade III, according to WHO) and no patient had a glioblastoma (malignancy grade IV according to WHO, see also reference 1). The remaining 40 patients had either an inaccurate diagnosis or had been erroneously registered. In many cases more than one type of error was found in the multistep procedure from clinical diagnosis to final registration at the Cancer Registry.

Histopathological reevaluation. In the study group the morphological re-examination resulted in 16 diagnoses without change in histopathology at review (Table 1). Among these were the 8 cases with long-term survival (Table 2). However, some of the 16 cases were not correctly registered due to other causes. A change in the histopathological diagnosis was observed in 20/48 cases (42%; Table 1). Eleven of these 20 patients had an astrocytoma or an oligodendroglioma grade I or II at review, in 8 instances the tumor was of non-neuroepithelial origin at review, and one was notified but not operated on primarily (specimens existed from a later operation). The three glioblastomas mentioned in Table 1 refer to tumor diagnoses at autopsy (n = 2) or surgery (n = 1). The remaining 9 patients either had a low-grade glioma histopathologically correctly diagnosed (n = 7), had a non-glial tumor (n = 1), or no tumor tissue in the surgical specimen (n = 1).

Table 1

Original histopathological diagnosis and corresponding reviewed diagnosis according to the WHO classification in the study group of 48 long-term survivors

Reviewed histopathological diagnosis	Original histopathological diagnosis		
	Glioma, grade III or IV	Glioma, grade I or II	No tumor tissue
Glioma, grade III or IV	16	–	–
Glioblastoma	3*	–	–
Glioma, grade I or II	11	7	–
Other	8	1	–
No tumor tissue	1**	–	1**
Total	39	8	1

* Registration based on autopsy findings in 2 cases and on neuroradiological findings/clinical data in 1 case.
** Registration based on neuroradiological/clinical data.

Notification data and registration. Twenty cases were incorrectly registered due to altered histopathological diagnoses (see above). The explanation of erroneous registration of 20 cases was as follows (Table 3): incomplete information in the notification forms (n = 5) and coding errors (n = 3) occurred in 8/48 patients (17%). Due to non-notification of the primary diagnosis, 5 cases were first reported to the Cancer Registry after autopsy. Since no information on the primary diagnosis was available, cases of primarily low malignancy grade came to be registered with their autopsy diagnosis of higher malignancy grade, which was predated to their first presentation. Progression of the tumor and change in the malignancy grade of the recurrence, had led to an incorrect change in the Cancer Registry coding in 7 instances.

Characteristics of the 8 long-term survivors. Eight patients had either an anaplastic astrocytoma or an anaplastic mixed oligoastrocytoma (Table 3). These were correctly diagnosed, notified, coded and registered.

There was no case of a glioblastoma at primary diagnosis (Table 2). The median age was 40 years at diagnosis. Nothing exceptional in the tumor localization or treatment was evident. All but one eventually developed a recurrence. Three of the recurrences were of the same malignancy grade as the original tumor and 4 patients had developed a glioblastoma (malignancy grade IV) at recurrence. Survival after recurrence was limited (Table 2).

Control group. No case of a notification or coding error was found among the random sample of 50 patients drawn from the original cohort (Table 3). In one case registration error occurred due to a code alteration. This was performed when malignant progression was notified. Since the

Table 2

Clinical and histopathological characteristics of the 8 long-term survivors correctly registered as malignant glioma

Reviewed primary diagnosis	Age	Localization lobe (R = right, L = left)	Treatment	Interval to recurrence, months	Recurrence			Total survival, months
					Reviewed pathological diagnosis	Treatment	Survival after recurrence, months	
Anaplastic astrocytoma	42	R. parietal	Surgery, radiotherapy	58	Anaplastic oligodendroglioma and astrocytoma component	Surgery	21	79
Anaplastic mixed oligoastrocytoma	46	L. frontal, corpus callosum basal ganglia	Surgery, radiotherapy	84	Anaplastic mixed oligoastrocytoma	Surgery, chemotherapy	19	103
Anaplastic mixed oligoastrocytoma	39	R. temporal	Surgery, radiotherapy	46	Glioblastoma	Surgery	3	49
Anaplastic astrocytoma	38	R. frontal	Surgery, radiotherapy	84	Glioblastoma	Surgery	8	92
Anaplastic astrocytoma	10	L. temporal	Surgery, radio- and chemotherapy	46	1. Anaplastic astrocytoma	Surgery	18	
				60	2. Glioblastoma	Surgery	4	64
Anaplastic astrocytoma	47	L. temporal	Surgery, radiotherapy	61	Anaplastic astrocytoma	No treatment	11	72
Anaplastic astrocytoma	41	Frontal	Surgery, radio- and chemotherapy	–	–	–	Alive	>144
Anaplastic astrocytoma and oligodenroglial component	29	R. frontal parietal	Surgery, radio- and chemotherapy	87	Glioblastoma	Surgery, chemotherapy	8	95
Median	40			Median 61			Median 14.5	85.5+

Table 3

Correctness of cancer registration of patients with malignant glioma in a cancer register. The study group represents long-term survivors in a cohort of 1 002 patients, and the control group a random sample from the same cohort

Cause	No. of patients	
	Study group	Control group
Altered histological diagnosis at review	20	2
Incomplete notification causing erroneous registration	5	–
Incorrect coding	3	–
Autopsy notification only, primary diagnosis not available	5	–
Malignant progression and altered histology coding	7	1
Correct diagnosis and registration	8	47
Total	48	50

recurrent tumor was of higher malignancy grade, the original primary diagnosis in the register was eradicated. At histopathological review the original diagnosis of a high malignancy glioma could not be verified in 2 cases (4%). The majority of control patients were dead within 2 years and only 3/50 (6%) were long-term survivors (9, 11 and 14+ years respectively).

Discussion

Survival in malignant glioma is usually short and long-term survivors are rare. Survival data for patients with primary brain tumors, derived from the information in the current population-based cancer register, were found not to be absolutely reliable, since many of the long-term survivors had been reported with an erroneous diagnosis by the pathologist or were incorrectly registered by the Cancer Registry.

Since the median ages in the control group and the total material were similar (60 and 56 years) and the survival figures in the control group corresponded to those

reported in the literature (1, 2), an estimate of the correctly registered cases with malignant glioma indicated 94% correctly registered in the SRCR. However, in the study group of long-term survivors only 8/48 (17%) were correctly registered. These 8 patients had lower median age (40 years) than the controls. The strong impact of age on prognosis has been reported in many studies (5–7). Median survival among the 8 patients with grade III tumors was 85.5+ months. The median survival of patients with glioblastoma at recurrence was approximately 6 months, while patients with grade III tumors at recurrence survived an average of 18 months. At the end of the follow-up period 7 patients were dead and 1 was still alive after 12 years.

No case of primary glioblastoma was found among the 8 long-term survivors. Gliomas are well known to undergo malignant progression (8, 9). The registration system used is not designed to take this biological fact into consideration. As recurrences are not usually registered in cancer registries, only the primary tumor will be documented. When an initially low malignant tumor recurred and the histopathology showed progression to a higher malignancy grade then, if reported, it was erroneously re-registered by the cancer register, replacing the primary diagnosis. Such cases were found both in the study group (n = 7) and in the control group (n = 1). A thorough analysis of patients showing tumor progression can only be performed in a special study and the information required cannot be drawn from a cancer registry. Blindly linking cancer registry data and data from the Cause of Death Register will yield incorrect data on long-term survival.

A discrepancy of 42% between the original and the review histopathological diagnoses was found in the study group as compared to 4% in the control group.

Since the first descriptions of gliomas during the middle of the last century, many classifications and grading systems have been proposed (3, 4, 8, 10). Primarily, they have been designed to provide clinicians with information to assist in choosing treatment and predicting outcome. The different classification systems used during the last decades have caused problems in cancer registration, due to their variable acceptance by the different professional groups involved in patient care. An internationally standardized and accepted classification system is thus to be recommended.

Survival data for patients with brain tumors thus have to be carefully interpreted when derived from the information in a population-based cancer registry. Our findings demonstrate that survival information on malignant gliomas is liable to be misinterpreted, in particular due to incorrect classification and erroneous registration. By selecting all long-term survivors with registered malignant brain tumors we selected many forms of mistakes in the registration. The few errors in the control group confirmed this conclusion. Our findings could help to improve and adjust histopathological diagnosis and registration routines at the SRCR and make them more consistent with the biology of brain tumors.

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REFERENCES

1. Burger PC, Vogel FS, Green SB, Strike TA. Glioblastoma multiforme and anaplastic astrocytoma. Pathologic criteria and prognostic implication. Cancer 1985; 56: 1106–11.
2. Salcman M. The morbidity and mortality of brain tumors. A perspective on recent advances in therapy. Neurol Clin 1985; 3: 229–57.
3. Kernohan JW, Mabon RF, Svien HJ, Adson AW. A simplified classification of gliomas. Proc Staff Meet Mayo Clin 1949; 24: 71–5.
4. Zülch KJ. Histological typing of tumours of the central nervous system. International histological classification of tumours, No. 21. Geneva: World Health Organization, 1979: 43.
5. Burger PC, Green SB. Patient age, histological features, and length of survival in patients with glioblastoma multiforme. Cancer 1987; 59: 1617–25.
6. Piepmeier JM. Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. J Neurosurg 1987; 67: 177–81.
7. Walker DM, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 1980; 303: 1323–9.
8. Russel DS, Rubinstein LJ. Pathology of tumours of the nervous system. Edition 4. Edinburgh: Edward Arnold Publishers Ltd, 1977: 146.
9. Scherer HJ. Cerebral astrocytomas and their derivatives. Am J Cancer 1940; 40: 159–98.
10. Ringertz N. Grading of gliomas. Acta Pathol Microbiol Scand 1950; 27: 51–64.