Is the Long-Term Survival of Patients with Intracranial Glioblastoma Multiforme Overstated?

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BACKGROUND. The 5-year survival rate for intracranial glioblastoma multiforme (GBM) has remained at 4–5% for the last 30 years, in spite of multiple randomized prospective trials. The authors hypothesized, based on the literature, that even this remarkably poor survival rate is an overstatement. They investigated this hypothesis using the the Duke University Medical Center Tumor Registry.

METHODS. The authors reviewed all patients with the diagnosis of intracranial GBM recorded in the Duke University Medical Center Tumor Registry from the registry's inception in 1976 through 1996. This search identified a population of patients with a minimum of 5 years of follow-up. Each of the long-term survivors was assigned a code number for clinical information. The pathology slides were provided to a neuropathologist in a coded fashion so that the patients could not be identified. The neuropathologist reviewed the slides to analyze the presence or absence of nine histologic factors. A match technique was used to identify a control population of patients with GBM who were not 5-year survivors and were all deceased. The control population was compared with the study population to ascertain if there are histologic correlates associated with long-term survivorship.

RESULTS. The authors identified 766 patients recorded by the tumor registry as having an intracranial GBM with a minimum of 5 years of follow up. Of the total population, 32 patients initially appeared to be 5-year survivors (4%). Upon review of the medical records for these 32 patients, however, the authors found only 17 patients who were truly 5-year survivors. The most common reason for miscoding was the presence of a low-grade astrocytoma that subsequently dedifferentiated into GBM. The 17 long-term survivors included 11 males and 6 females. Their mean age at diagnosis was 40.2 years. Therapy consisted of a macroscopic total resection in 4 patients (22%), a biopsy in 1 patient (6%), a subtotal resection in 10 patients (56%), and unknown extent of resection in 2 patients (11%). All patients received partial brain irradiation (mean dose, 62.6 Gy) and chemotherapy. Thirteen different single-agent or combination chemotherapy programs were used. Two patients also received I-131 monoclonal antibody therapy. Analysis of the nine histopathologic factors studied showed that intermediate fibrillary elements were more common and small anaplastic elements were less common in the long-term survivors than in the control population.

CONCLUSIONS. Survival data on intracranial GBM, based on tumor registry data, should be interpreted cautiously. Reliable conclusions can only be drawn when such data are supplemented with clinical information and the histopathology is reviewed carefully. The group of long-term survivors in the current study were younger than the typical GBM population. Conventionally treated patients with GBM, chosen from an unselected population from a tumor registry, have a smaller chance of long-term survival than is generally believed. ***Cancer* 2003;98:1745–8.**

KEYWORDS: glioblastoma multiforme, gliomas, radiotherapy, histologic factors.

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The prognosis for patients with intracranial glioblastoma multiforme (GBM) is very poor. The median survival period, with best available treatment, is 10–12 months. The reported 5-year survival rate, in spite of multiple randomized trials, has remained at 4–5% for the last 30 years.[1–9]

Recent studies from tumor registries in Canada and Sweden suggested that the long-term survival rate may, in fact, be less than 3%.[10,11] These studies raise the question of whether or not the reported long-term survival rate of patients with GBM, based on registry data, is overstated. We elected to further investigate this issue in a detailed study of the Duke University Medical Center Tumor Registry. In addition, we conducted a clinicopathologic investigation of 5-year survivors of intracranial GBM. We recorded information about the cytologic composition of these tumors, which generally is not specified in the routine pathology reports. To determine whether there are specific cytopathologic characteristics associated with long-term survivors, we performed a case–control study.

MATERIALS AND METHODS

We reviewed the computer records of all patients with a diagnosis of intracranial GBM recorded in the Duke University Medical Center Tumor Registry from its inception in 1976 through 1996. This search generated a population of patients with a minimum of 5 years of follow-up. We postulated that if this population is similar to patients with GBM in the general published literature, approximately 4–5% of the patients would be listed as survivors of 5 or more years.

Having identified a group of patients who were 5-year survivors, we recorded the following information: age at diagnosis, gender, details of the pathology diagnosis contained in the medical record, the extent of surgery (biopsy, subtotal resection, or total resection) based on the operative report and postoperative imaging, the dose of external beam radiotherapy administered, whether radiotherapy was administered to the whole brain or to a more limited field, the use of radiolabeled monoclonal antibodies, chemotherapeutic agents administered, the date of last follow-up, and whether the patient was alive or dead.

Each of the long-term survivors was assigned a code number for clinical information. The pathology slides were provided to a neuropathologist in a coded fashion so that the patients could not be identified. The neuropathologist reviewed the slides to analyze the presence of vascular endothelial proliferation, gliosarcoma, rhabdoid elements, gigantocellular elements, large gemistocytic cells, intermediate fibrillary cells, small fibrillary cells, small anaplastic cells, or an oligodendroglioma component. A match technique was used to identify a control population of patients with intracranial GBM who were not 5-year survivors and were all deceased. These individuals were matched to the study population by year of diagnosis, age, and gender.

Statement Regarding Consent

The Duke University Medical Center institutional review board issued a waiver for obtaining informed consent from the few remaining living subjects. The reasons for the waiver were 1) the risk of the study was minimal, 2) the privacy and confidentiality of the data were well protected, and 3) obtaining informed consent from the few remaining long-term survivors of GBM would be impractical and potentially psychologically distressing.

RESULTS

The tumor registry identified 766 patients who had had at least 5 years of follow-up, i.e., the diagnosis was made in 1996 or earlier. Of these 766 patients, 32 were identified initially by the registry computer as 5-year survivors. After reviewing the charts, only 17 were determined to be truly 5-year survivors (2%). The most common reason for inappropriate entry into the tumor registry as a long-term survivor of intracranial GBM was a diagnosis of low-grade astrocytomas that subsequently dedifferentiated into GBM.

The clinicodemographic characteristics of the 17 long-term survivors are shown in Table 1. The mean age at diagnosis was 40.2 $\pm$15.9 years. The mean age at diagnosis for the remaining 749 patients was 54.7 $\pm$ 18.0 years (difference between means, $P < 0.0001$).

The 2:1 match technique identified 34 patients to compare with the 17 study patients. Of these 34 control patients, however, original pathology slides could not be located for 5 patients. Therefore, we compared a control population of 29 patients with 17 study population patients. Intermediate fibrillary elements were more common and small anaplastic elements were less common in the long-term survivors compared with the control population. ($P < 0.05$, Table 2).

DISCUSSION

A study from the Alberta Cancer Registry identified 29 long-term survivors from a total population of 689 patients with GBM.[10] This indicated a long-term survival rate, consistent with the published literature, of 4%. However, on histologic review, only 15 of the 29 patients were confirmed as having GBM. This lowered the long-term survival rate to approximately 2.2% in the Canadian study.

The Stockholm Regional Cancer Registry conducted a similar review of 39 patients who were be-

TABLE 1
Clinicodemographic Characteristics of the 17 Long-Term Survivors of Intracranial Glioblastoma Multiforme

Characteristic	No. of patients
Gender	
Male	11
Female	6
Race	
Caucasian	17
Age (yrs)	
Mean ± SD (range)	40.2 ± 15.9 (12–70)
Type of surgery	
Biopsy	1
Subtotal resection	10
Total resection	4
Not described	2
Type of external beam radiotherapy	
Limited field	12
Whole brain	0
Field size not specified	5
Radiotherapy dose (Gy)	
Mean (range)	62.6 ± 7.9 (60–76.8)
Other therapy (20 programs in 17 patients)	
BCNU	6
Timezolomide	3
I-131	2
Other chemotherapy programs	9

SD: standard deviation; Gy: Gray; BCNU: N,N′- bis (2-chloroethyl)-N-nitrosourea.

TABLE 2
Histologic Evaluation of Long-Term Survivors of Intracranial Glioblastoma Multiforme Compared with a Group of Control Patients Matched for Age, Gender, and Date of Diagnosis

Characteristic elements present	Study population (n = 17) (%)	Controls (n = 29) (%)
Gliosarcoma	0	2 (7)
Rhabdoid	0	1 (3)
Gigantocellular	5 (29)	6 (21)
Large gemistocytic	5 (29)	4 (14)
Intermediate fibrillary[a]	15 (88)	20 (69)
Small fibrillary	2 (12)	3 (10)
Small anaplastic[a]	0	5 (17)
Oligodendroglioma component	3 (18)	4 (14)
Vascular proliferation	10 (59)	17 (59)

[a] $P < 0.05$ by χ^2 analysis with 1 degree of freedom.

lieved to be long-term survivors of high-grade supratentorial malignant gliomas.[11] Only 19 patients were confirmed to have this diagnosis on histopathologic review. The Canadian and Swedish studies raised the question of whether or not the true reported long-term survival rate of patients with GBM is overstated. Similarly, in the current review, the initial long-term survival rate was believed to be 4%. On more careful study, the rate was detrmined to be 2%.

We found that long-term survivors of GBM were younger at clinical presentation than the patients who did not survive as longpopulation. In general, the mean age at onset for patients with GBM is 53 years, which is older than the mean age for patients with anaplastic astrocytoma (i.e., 40 years).[9] At the Duke University Medical Center, the mean age at onset for patients with GBM is 54.7 years. The finding that our mean age at diagnosis in long-term survivors of GBM was 40 years suggests that we have identified a population that is already known to have a better prognosis on the basis of young age. Two histologic characteristics differed between the study and control populations. For example, the presence of intermediate fibrillary cells were more common in the long-term survivors and small anaplastic cells were entirely absent in the long-term survivors.

A limitation of the current study was that it was conducted using a single institution's tumor registry rather than a broad-based population registry. Even with 766 patients in the initial study group, only 17 long-term survivors were identified. Thus, the number of patients available for histopathologic comparison with a control group was small. Nonetheless, our inability to find distinguishing histopathologic criteria appears to be consistent with previously published literature.[12]

In the future, studies should be devoted to the use of molecular panels and monoclonal antibody labeling in an attempt to identify the characteristics predictive of long-term survivorship in GBM. An analysis of the molecular biology of GBM offers some initial clues as to which patients might be long-term survivors.[9,13,14]

The current study was undertaken to establish the 5-year survival rate of patients with GBM at a major institution treating a large number of patients near the end of the 20th century. The results, taken from the tumor registry at the Duke University Medical Center, are unbiased with regard to therapeutic protocol. Admission criteria such as age, performance score, and completion of radiotherapy are factors known to influence not only the selection of patients to protocols but also long-term survival.[3–6,9] Molecular studies into DNA repair, chemotherapeutic resistance, telomere lengthening, and growth factor expression could identify additional factors that may influence survival.[13–15] As we enter the 21st century, one would ultimately hope to identify a population of patients appropriate for more aggressive therapy to engender a higher proportion of long-term survivors.

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