**Objective:** To compare the clinical presentation, time elapsed to diagnosis, and survival of elderly patients (≥65 years) with that in younger patients with malignant primary brain tumors.

**Design:** Retrospective cohort study.

**Setting:** Four hospitals in Minneapolis, Minn.

**Patients:** Seven hundred fourteen patients diagnosed as having and treated for primary malignant brain tumors between 1980 and 1995; 230 (32%) were 65 years or older.

**Main Outcome Measures:** The type and duration of the chief presenting symptom, the time elapsed to diagnosis, the treatment modalities used, and patient survival were analyzed.

**Results:** Time elapsed from onset of symptom to diagnosis was not longer for elderly patients than younger ones, with the exception of patients aged 18 to 24 years, who had a significantly longer delay in diagnosis ($P = .004$). Elderly patients were significantly less likely to present with headache or seizure ($P < .001$), and more likely to present with confusion, aphasia, or memory loss (for each, $P < .001$). With the single exception of confusion, the duration of all other presenting symptoms was not significantly longer for patients 65 years and older compared with younger patients. Survival is significantly reduced in older patients, and appears to worsen significantly in patients 45 years and older ($P < .001$). A significantly higher proportion of patients 65 years and older with glioblastoma multiforme received no treatment ($P = .004$) if diagnosed after 1990.

**Conclusions:** Elderly patients (≥65 years) with malignant brain tumors are diagnosed as promptly as younger patients, although they have a markedly different constellation of symptoms. Since diagnosis of brain tumors continues to improve in the elderly, it may be more difficult to ascribe the steady increase in incidence to artifactual factors.

**Arch Neurol. 1998;55:922-928**

During the last 3 decades, major increases in mortality due to and incidence rates of primary brain tumors have been observed in the United States and other industrialized countries; in the United States, recorded incidence of cancer of the brain and central nervous system has increased by 1.2% per year since 1973, and the death rate has increased by 0.7% per year. These increases have been particularly marked among individuals 65 years or older; in this age group, incidence rates have increased 2.5% per year since 1980. Based on data from the Surveillance, Epidemiology, and End Results registry, the incidence of malignant brain tumors rose between 1973 and 1985: 200% for the 75- to 79-year age group; 400% for the 80- to 84-year age group; and 500% for those 85 years or older. Among histological types, aggressive tumors of glial origin, particularly glioblastoma multiforme and astrocytoma, were most common among the elderly.

There has been considerable controversy regarding whether the increase in the elderly is largely artifactual, due to improvement in detection and diagnosis of brain tumors, along with an increased awareness of neurologic disease in the elderly, or whether a true increase in malignant brain tumors has occurred during this period. The introduction of computed tomography (CT) in the early 1970s and magnetic resonance imaging in the 1980s together with stereotactic needle biopsy considerably reduced the morbidity associated with prior diagnostic procedures, which may have been deferred in older patients. Dramatic increases in these diagnostic modalities have been documented for patients 65 years or older since the late 1970s, and strong positive correlations have been noted between reported death rates from brain tumors and...
METHODS

We reviewed medical records on all patients diagnosed as having primary malignant brain tumors between 1980 and 1995 at 4 major hospitals: Abbott-Northwestern Hospital, Methodist Hospital, Fairview-Southdale Hospital, and Hennepin County Medical Center. All these hospitals provide full diagnostic and treatment facilities for patients with brain tumors, are located in Hennepin County, Minnesota, and are of varying sizes: Abbott-Northwestern Hospital, 597 beds; Methodist Hospital, 426 beds; Hennepin County Medical Center, 507 beds; and Fairview-Southdale Hospital, 390 beds. Two of the hospitals, Abbott-Northwestern Hospital and Hennepin County Medical Center, have academic affiliations with the University of Minnesota Medical School. Cases were defined as adults aged 18 years or older with primary malignant brain tumor according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code 191, and diagnosis was confirmed using tissue examination. Patients were included if their diagnosis occurred between January 1, 1980, and December 31, 1995. We defined elderly as individuals 65 years or older; for portions of the analysis, individuals in this age group were further subdivided into individuals 75 years or older, and 85 years or older.

The following data were abstracted from medical records: demographic information including the patient's sex, race, age at diagnosis, and city and state of residence; medical history including presence and year of onset of psychiatric illnesses, history of head trauma, or seizure disorder; family history of cancer; tobacco use and duration of use; the patient's occupation; and types of insurance carried. The following clinical data were collected: chief symptom and duration, secondary symptoms and duration(s), initial diagnostic evaluation, including biopsy, CT, or magnetic resonance imaging scans, the tissue type and location of the tumor, therapeutic modalities used, and types and dates of follow-up treatments. Death dates were determined with the cooperation of tumor registries at each of the 4 hospitals. Hospital tumor registries used hospital discharge information, death listings from the Minnesota Department of Health, obituary notices, as well as correspondence with 23 area hospitals via the cancer program database of the Alliance Medical Registries Inc, Boston, Mass.

Data were entered using Epi Info, Version 6.04b7 and transferred to SAS statistical software Version 6.11 (SAS Institute Inc, Cary, NC). Trend analyses were performed using Kendall tau-b (τ) test. Trend analysis was not performed if the average number of patients in a category was fewer than 5. Comparison of medians was performed using the Wilcoxon rank sum test or Kruskal-Wallis test as appropriate. Survival analyses were performed using PROC LIFETEST in SAS statistical software, using the Kaplan-Meier method of estimating the survival function. Survival curves were generated using S-PLUS (Mathsoft Inc, Seattle, Wash).

RESULTS

DEMOGRAPHIC DATA

During 1980-1995, medical records were reviewed for a total of 714 patients. The proportions of patient records reviewed by the hospitals are as follows: Abbott-Northwestern Hospital, 318 (44.5%); Methodist Hospital, 233 (32.6%); Fairview-Southdale Hospital, 118 (16.5%); and Hennepin County Medical Center, 45 (6.3%). Fifty-five percent of patients were male. The mean age at diagnosis was 53.3 years (age range, 19-91 years). Nearly one third of patients (32.2%) were 65 years or older.
Table 1. Diagnosis of Primary Malignant Brain Tumor by Type of Tumor and Age of Patient, Minnesota Cohort Study, 1980-1995

<table>
<thead>
<tr>
<th>Tumor Types</th>
<th>18-24</th>
<th>25-44</th>
<th>45-64</th>
<th>65-74</th>
<th>≥75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astroglial neoplasms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma multiforme*</td>
<td>7 (23)</td>
<td>50 (23)</td>
<td>140 (58)</td>
<td>91 (65)</td>
<td>66 (73)</td>
<td>254 (49)</td>
</tr>
<tr>
<td>Anaplastic astrocytomas</td>
<td>2 (6)</td>
<td>39 (18)</td>
<td>46 (19)</td>
<td>27 (19)</td>
<td>13 (14)</td>
<td>127 (18)</td>
</tr>
<tr>
<td>Astrocytoma (grades I-II)*</td>
<td>13 (42)</td>
<td>63 (30)</td>
<td>23 (10)</td>
<td>8 (6)</td>
<td>1 (1)</td>
<td>108 (15)</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>2 (6)</td>
<td>29 (14)</td>
<td>17 (7)</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>52 (7)</td>
</tr>
<tr>
<td>Gangliomas</td>
<td>1 (3)</td>
<td>3 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>2 (6)</td>
<td>10 (5)</td>
<td>1 (0)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>1 (3)</td>
<td>10 (5)</td>
<td>9 (4)</td>
<td>8 (6)</td>
<td>7 (8)</td>
<td>35 (5)</td>
</tr>
<tr>
<td>Medulloblastomas</td>
<td>2 (6)</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>6 (5)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (100)</td>
<td>213 (100)</td>
<td>240 (100)</td>
<td>140 (100)</td>
<td>90 (100)</td>
<td>714 (100)</td>
</tr>
</tbody>
</table>

*P < .001 for trend, for increasing or decreasing age at diagnosis by tumor type, when contrasting with other tumor types, using the t test.

Table 2. Duration of Symptoms (Median Days) by Age Category, Patients With Malignant Primary Brain Tumors, Minnesota Cohort Study, 1980-1995

<table>
<thead>
<tr>
<th>Symptom</th>
<th>18-44*</th>
<th>45-64</th>
<th>≥65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>21.0</td>
<td>21.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Seizure</td>
<td>3.0</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Confusion‡</td>
<td>2.0</td>
<td>7.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Aphasia</td>
<td>4.0</td>
<td>5.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>10.5</td>
<td>14.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Focal motor weakness</td>
<td>102.5</td>
<td>21.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Personality change</td>
<td>193.0</td>
<td>27.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Memory loss</td>
<td>60.0</td>
<td>30.0</td>
<td>30.0</td>
</tr>
</tbody>
</table>

* Fewer than 5 patients in this age category with the following symptoms: aphasia (3), personality change (4), and memory loss (3).
‡ P = .03 by Kruskal-Wallis rank sum test.

**AGE AT DIAGNOSIS AND TYPE OF TUMOR**

The median ages of patients diagnosed as having various types of tumors ranged from 62 years (age range, 24-84 years) for glioblastoma multiforme to 30 years (range, 22-36 years) for ganglioglioma. The proportion of patients diagnosed as having glioblastoma multiforme increased progressively by age group, ranging from 23% of patients aged 18 to 24 years to 73% of patients 75 years or older (P < .001, t test) (Table 1). Among patients 85 years or older, 8 (89%) of 9 had glioblastoma multiforme. The diagnosis of astrocytoma grade I or II occurred significantly less frequently among elderly patients; only 1% of patients 75 years or older had this type of tumor, compared with 42% of patients aged 18 to 24 years (P < .001, t test) (Table 1). Trend analysis did not reveal other significant associations between age at diagnosis and specific type of tumor.

**AGE AT DIAGNOSIS AND PRESENTATION**

Headache was significantly more common as the main presenting symptom in younger age groups, decreasing from 44% in patients aged 18 to 24 years to 8% in patients 75 years or older (P < .001, t test). Similarly, seizure was significantly more common among younger patients; seizure occurred in 33% and 35% of patients aged 18 to 24 years and 25 to 44 years, respectively, compared with only 8% of patients 75 years or older (P < .001, t test). Elderly patients were more likely to experience a variety of other symptoms, such as confusion, aphasia, memory loss, personality change, hemiplegia, and focal motor weakness. No single symptom or symptoms predominated; confusion or aphasia were the most common presenting symptoms among patients 65 years or older, but each was experienced by only 12% of individuals in this age group. Trend analysis revealed that confusion, aphasia, and memory loss were most clearly associated with advancing age (P < .001, t test) (Table 2).

**TYPE OF TUMOR AND PRESENTATION**

Among the 5 most commonly diagnosed types of tumors, the proportion of patients presenting with headache ranged at the time of diagnosis. The breakdown of patients by race was as follows: 698 (98%) white, 10 (1%) Asian, 5 (1%) black, and 1 (<1%) Native American. Patients resided in Minnesota (94%), Wisconsin (2%), and 14 other states. Among patients residing in Minnesota, 102 (14%) and 12 (2%) listed their residence as Minneapolis or St Paul, respectively; however, an additional 311 (44%) lived in the Twin Cities metropolitan area.

**TYPES OF TUMOR**

Fourteen types of malignant primary neoplasms were diagnosed among patients during this period. The following tumors were diagnosed in order of frequency: glioblastoma multiforme (49.6%), anaplastic astrocytoma (17.8%), astrocytoma, grade 1 or II (15.1%), oligodendroglioma (7.3%), lymphoma (4.9%), ependymoma (2.3%), and medulloblastoma (1.0%). The following tumor types were diagnosed in fewer than 5 patients: ganglioglioma (4 patients), mixed polygodendroglioma and astrocytoma (4 patients), oligoastrocytoma (2 patients), sarcomatous meningioma (1 patient), pleomorphic xanthroastrocytoma (1 patient), papillary carcinoma (1 patient), and gliosarcoma (1 patient).
from a high of 26% for those with astrocytoma (grade I or II) to a low of 14% for those with lymphoma; there was no significant association between headache and any specific type of tumor. However, the presentation of seizure was significantly more common for patients with astrocytoma (grade I or II) than patients with other types of tumors (45% vs 18%; \( P < 0.001, \) \( t \) test). Conversely, patients with lymphoma were significantly less likely to present with a seizure compared with patients with other types of tumors (3% vs 23%; \( P < 0.001, \) \( t \) test). A relatively high proportion of patients with lymphoma presented with a gait change, compared with those with other types of tumors (17% vs 3%; \( P = 0.003, \) \( t \) test). Except for seizure and gait change, there were no other significant associations between specific presenting symptoms and type of tumor.

**AGE AT DIAGNOSIS AND DURATION OF SYMPTOMS**

The time elapsed between the onset of symptoms and diagnosis was significantly longer for the youngest group of patients (aged 18-24 years): the median interval was 45.0 days, compared with a median of 14.0 days for all older patients (\( P = 0.004, \) Wilcoxon 2-sample test). This difference was largely attributable to the longer duration of seizure symptoms in patients aged 18 to 24 years, which was 232.5 days, compared with 2.0 days for all older patients (\( P = 0.01, \) Wilcoxon 2-sample test). The median symptomatic period before diagnosis was 14.0 days for patients aged 25 to 44 years and 45 to 64 years, 21.0 days for patients aged 65 to 74 years, 17.5 days for patients aged 75 to 84 years, and 30.0 days for patients 85 years or older.

The duration of the chief presenting symptom did not vary significantly between patient age groups except for the symptom of confusion. The duration of confusion increased from a median of 2.0 days in patients aged 18 to 44 years to a median of 20.5 days in patients 65 years or older (\( P = 0.03, \) Kruskal-Wallis rank sum test) (Table 2). With the exception of confusion and aphasia, the median time elapsed for other symptoms among patients 65 years or older was shorter than for patients aged 18 to 44 years (Table 2).

**SURVIVAL ANALYSIS**

In an analysis of survival for patients with all types of tumors, older patients had markedly reduced survival. The survival pattern of patients aged 45 to 64 years more closely resembled that of older rather than younger patients (Figure 1). Patients aged 18 to 44 years survived significantly longer than patients 45 years or older (\( P < 0.001, \) log rank and Wilcoxon tests). Median survival by age group was as follows: 75 years or older, 4.0 months; 65 to 74 years, 8.0 months; 45 to 64 years, 12.0 months; and 25 to 44 years, 84.0 months. Median survival could not be calculated for those aged 18 to 24 years, because 54% were still alive at the censor date.

**PATIENTS WITH GliOBLASTOMA MULTIFORME**

For patients with glioblastoma multiforme, the median time elapsed from onset of symptoms to diagnosis was longest for patients aged 18 to 24 years (median, 28.0 days), and exceeded the duration of symptoms when analyzed either for patients 65 years or older (median, 20.0 days) or 75 years or older (median, 20.5 days). Headache was the most common symptom; the proportion of patients with headache decreased significantly with age, from a high of 43% among patients aged 18 to 24 years, to a low of 9% among patients 75 years or older (\( P < 0.001, \) \( \tau \) test) (Table 3). Seizure was the second most common symptom, and decreased from a high of 29% for patients aged 25 to 44 years to 9% among patients 75 years or older (\( P < 0.001, \) \( \tau \) test) (Table 3).

The spectrum of symptoms was considerably greater for older than younger patients; only 14% of patients older than 65 years experienced confusion as the primary symptom of glioblastoma multiforme, but it was still the most common presenting symptom in this age category. In trend analysis of patients with glioblastoma multiforme, aphasia and hemiplegia were significantly associated with advancing age (\( P < 0.005 \) and \( P < 0.05 \), respectively, \( \tau \) test) (Table 3). Comparing the age categories 18 to 44 years, 45 to 64 years, and 65 years or older, there were no significant differences in the duration of headache, seizure, confusion, aphasia, hemiplegia, or any other specific symptom for patients with glioblastoma multiforme.

A subanalysis of treatment modalities used for patients 65 years or older revealed that patients diagnosed between 1990 and 1995 were significantly more likely to receive no treatment (18%) compared with patients diagnosed earlier (\( P = 0.004, \) \( \tau \) test) (Table 4). Elderly patients diagnosed between 1990 and 1995 were less likely to undergo surgery, radiation therapy, and chemotherapy than elderly patients diagnosed between 1980 and 1989 (\( P < 0.01, \) \( \tau \) test) (Table 4).

Survival analysis revealed that advanced age was associated with significantly lower survival (Figure 2). Median survival by age group was as follows: 75 years or older, 4.0 months; 65 to 74 years, 8.0 months; 45 to 64 years, 11.0 months; 25 to 44 years, 23.0 months; and 18 to 24 years, 47 months. Patients diagnosed between 1990
and 1995 did not have improved survival compared with patients diagnosed between 1980 and 1984, or 1985 and 1989.

**COMMENT**

Despite the increasing incidence of primary malignant brain tumors among the elderly, relatively few studies have addressed clinical trends among this age group, particularly in recent years. Our study confirmed that the clinical presentation of elderly patients is markedly different from their younger counterparts. Among patients 65 years or older, only 11% and 9% of patients presented with headache or seizure, respectively, compared with 30% and 35% of patients younger than 45 years. The reduced frequency of headache in older patients may be related in part to varying degrees of general brain atrophy, which leaves the subarachnoid space and ventricles larger, allowing for more expansion of space-occupying lesions.

Late-onset seizure is frequently considered to be a classic sign of brain tumor; however, seizure is a relatively unusual manifestation of brain tumor in the elderly. The frequency of seizure among patients 65 years or older was only 9% in our study, which confirms the findings of 2 older studies, in which 6% and 20% of elderly patients presented with seizure. Compared with elderly patients, we noted that younger patients had a higher frequency of seizure across each grade of astroglia, including glioblastoma multiforme. A low rate of seizure activity occurred among patients with lymp.
O

UR STUDY revealed that the spectrum of presenting symptoms among the elderly is distinctly different, and considerably more diverse than that for younger patients. Among patients 65 years or older, confusion and aphasia were the 2 most common presenting symptoms; however, given the variety of other presentations, the proportion of elderly patients with these symptoms was relatively small (12%). Changes in intellectual function, as manifested by memory loss or personality change, as well as focal or more generalized motor deficits, also occurred 2 to 4 times more frequently among elderly patients; however, less than 10% of elderly patients exhibited any one of these specific symptoms.

Compared with younger patients, the “relatively muted” symptoms of malignant brain tumor among the elderly have been previously discussed, and much emphasis has been placed on the difficulty of establishing the correct diagnosis. A review of these studies reveals the magnitude of the advantage conferred by the availability of neuroimaging studies. In a retrospective review of 34 tumors found at autopsy between 1950 and 1960, McLaurin and Helmer found that only 22 symptomatic cases were most frequently misdiagnosed as cerebrovascular thrombosis, carotid artery insufficiency, and subarachnoid hemorrhage, and most would have been correctly diagnosed if contrast studies had been performed. In another series published in 1972, more than 90% of 156 elderly patients found to have intracerebral tumors were misdiagnosed by their referring physicians; although 27 specific diagnoses were made, most were considered to have a variety of cardiovascular disease.

A striking finding in our study is the relatively short duration of symptoms for patients with brain tumor, particularly among the elderly, compared with other studies published within the last 15 years. In one study of 38 elderly patients, with a median age of 73 years, the average duration of symptoms was 11 weeks. In another investigation that did not report median times, the range of duration of symptoms for patients 65 years or older with glioma was 0 to 3 months for motor weakness, 1 week to 5 months for mental status changes, 3 months to 2 years for headache, and 3 weeks to 9 years for seizure. The considerably reduced duration of symptoms we documented suggests that diagnosis occurred earlier in the population of elderly patients we studied. Interestingly, the period between onset of symptoms and diagnosis was longest for the patients aged between 18 and 24 years (median age, 45 months). Although the number of patients in this group was relatively small, a relatively high proportion of patients with low-grade astrocytoma had a history of chronic seizure disorder, a phenomenon that has been well described. It is also possible that the index of clinical suspicion may be lower in the youngest patients, and they may undergo medical evaluation less frequently.

In our study, the proportion of patients with glioblastoma multiforme increased with each decade to a maximum of 89% among patients 85 years or older. The steady increase in the proportion of cases attributable to glioblastoma multiforme has been consistently documented in a variety of study settings, from Japan to Australia. Unfortunately, glioblastoma multiforme is the most biologically malignant astrocytic tumor, and the prognosis for most patients has not improved substantially in the last 30 years. Age has been widely cited as the most important prognostic factor, regardless of the type of treatment received. The outcome for older patients is particularly poor, and the range of median survivals we documented—4.0 months to 47 months for the oldest (≥75 years) and youngest (18-24 years) patients—is consistent with other recent studies.

The standard of care for glioblastoma multiforme is ordinarily considered to be maximal feasible surgical resection, followed by local field irradiation for 6 to 7 weeks, as well as chemotherapy. Support for the latter has been relatively weak, as only one phase 3 study in the era of modern neuroimaging shows increased survival as a result of adjuvant chemotherapy. Although surgical resection is generally practiced if possible, the role of surgery in prolonging survival has recently been questioned. Interestingly, in our study population the proportion of elderly patients receiving no treatment increased from 4% for those patients diagnosed between 1980 and 1989 to 18% for elderly patients diagnosed between 1990 and 1995. The proportion of elderly patients receiving surgery, radiation, and chemotherapy also significantly decreased during this period. These trends suggest that practitioners in Minnesota may be treating elderly patients with glioblastoma multiforme less aggressively, perhaps based on the limitations of available treatment options.

Our study reveals the extent to which elderly patients have a distinct and more varied presentation compared with younger patients; however, there was little evidence for a diagnostic delay, as has been described in a number of other studies. Unfortunately, earlier detection of malignant brain tumors, particularly glioblastoma multiforme, has had little impact on survival in elderly patients. As neuroimaging studies are performed with greater frequency in the elderly, and patients in this age group have better access to neurologic opinion, it will be most interesting to observe whether the incidence of brain tumors among the elderly will gradually plateau, or whether it will continue to increase dramatically. If the latter occurs, additional studies will clearly be needed to ascertain potential causes of this remarkable phenomenon.

Accepted for publication March 13, 1998.

We thank Chap Le, PhD, Division of Biostatistics, University of Minnesota, Rochester, for his advice regarding the statistical analysis of the data. We also thank Sue Koering, Lolly Naslund, Susan Blubaum, and Kirsti Taipale for their help in compiling information from the hospital tumor registries, as well as John Soler, MPH, of the Minnesota Cancer Surveillance System, Minnesota Department of Health, for his assistance in providing surveillance data.
REFERENCES


