BRAIN ASTROCYTOMAS : A STUDY OF EPIDEMIOLOGICAL FINDINGS, TREATMENT RESULTS AND PROGNOSTIC FACTORS IN TEHRAN CANCER INSTITUTE'S RADIOTHERAPY PATIENTS

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Abstract - Astrocytomas, including glioblastoma multiforme (GBM), are the most common brain tumors. Post-operative radiotherapy plays an important role in their treatment. Records of all patients with a pathologic diagnosis of astrocytoma referred for radiotherapy from 1987-1992 were reviewed and prognostic factors with regard to recurrences were analyzed.

During the study period, 162 astrocytoma patients were treated by radiation in our department. Male-to-female ratio was 1.4:1. The disease was most prevalent in the 3rd and 4th decades of life. Most tumors were in cerebral hemispheres and grade IV. In nearly all patients only CT scan had been used for diagnosis, and total resection had been performed.

Radiation dose was mostly 5,000-5,500 cGy by standard fractionation. Follow-up was available for 91 patients, and in these patients CCNU (lomustine) chemotherapy was prescribed for high-grade tumors. Three-year local control was 77% . Grade, extent of surgery, and use of CCNU were statistically significant as prognostic factors. Also 4 GBM long-term survivors were found. Treatment of brain astrocytomas by radiation in our department was concluded to be reasonably successful.

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Key Words: astrocytoma, glioblastoma multigorme, brain radiotherapy, chemotherapy, CCNU

INTRODUCTION

Brain tumor is the second most common cause of neurological death after cerebrovascular accidents. It is the most common solid tumor of childhood and the second most common cause of cancer death in children, after leukemias (1). Astrocytomas, including glioblastoma multiforme (GBM), are the most common primary brain tumors (2). Post-operative radiotherapy plays an important role in the treatment of astrocytomas and has led to significant improvements in their prognosis, but optimal therapy with a high rate of long-term disease - free survival is still not available (3).

Adjuvant chemotherapy too is used in high-grade tumors with some success (4), but no major advantage has been reported yet for this modality.

Considering the importance of brain tumors and the significant morbidity and mortality they cause, a retrospective study was undertaken to evaluate the epidemiological characteristics, radiotherapy details, treatment results, and prognostic factors of the brain astrocytoma patients treated in the Radiation Oncology Department of Cancer Institute, Tehran University of Medical Sciences.

MATERIAL AND METHODS

Records of all patients with a pathologic diagnosis of astrocytoma referred to our department for radiotherapy in the 5-year period of 1987-1992 were retrospectively studied. Epidemiological and treatment details were sought; patients' follow-up was checked and the number and time of tumor recurrences were evaluated. Prognostic factors (age, sex, tumor site, histologic grade, extent of surgery and use of chemotherapy) with regard to recurrence of disease were statistically analyzed by chi-square test and linear correlation.

RESULTS

During the study period, 162 patients with a pathologic diagnosis of astrocytoma were treated in our department. Ninety-five patients (57%) were male and 67(43%) female, with a male to female ratio of 1.4:1. The youngest patient was 2.5 and the oldest 83 years old with a mean age of 28 years. The disease was most prevalent in the 3rd and 4th decades of life, and 40% of the patients were in this age range. The second most common age group was 1-10 years (20%). The distribution of age in our patients has been shown in Fig. 1.

The tumor site was in the cerebral hemispheres in 112 patients (69%), cerebellum in 22(13%), thalamus, hypothalamus and optic chiasma in 15 (9%), brainstem

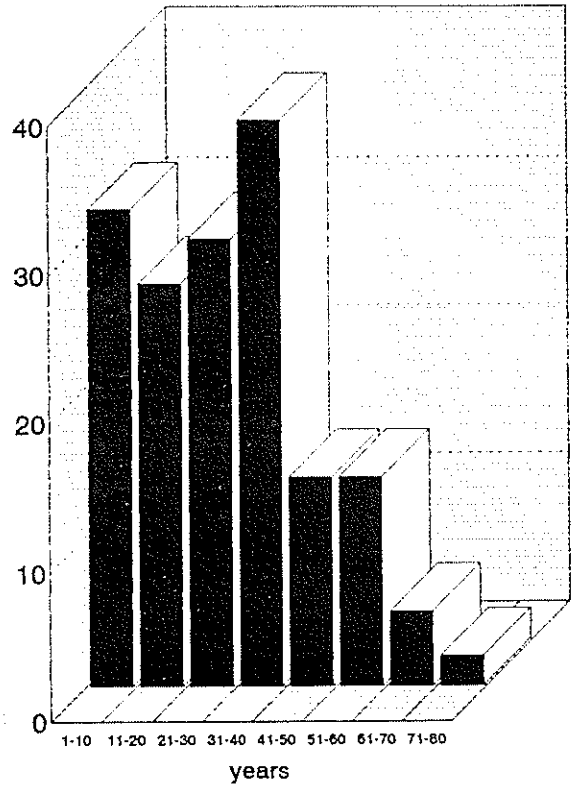

Fig. 1. Age distribution

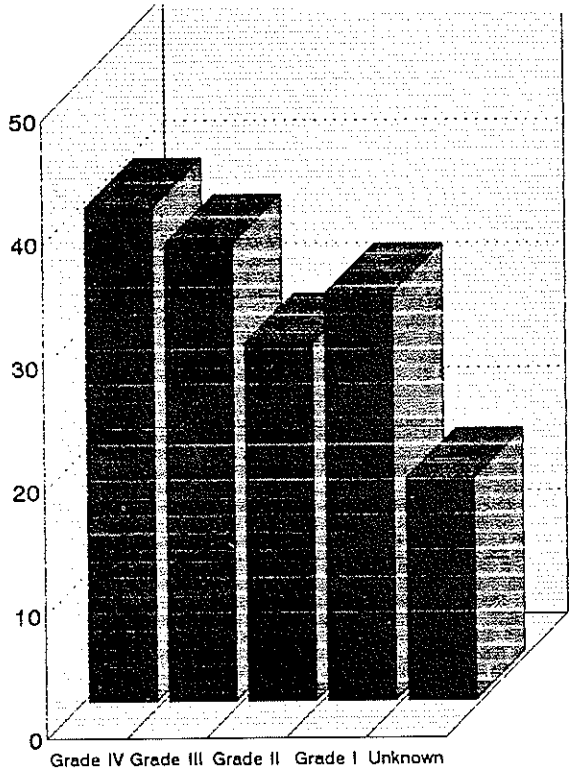

Fig. 3. Tumor grade

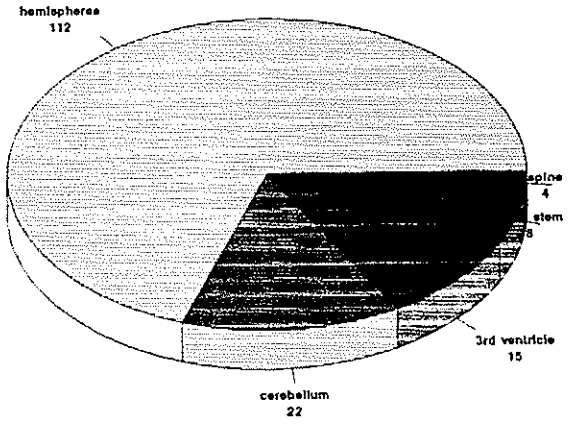

Fig. 2. Tumor site

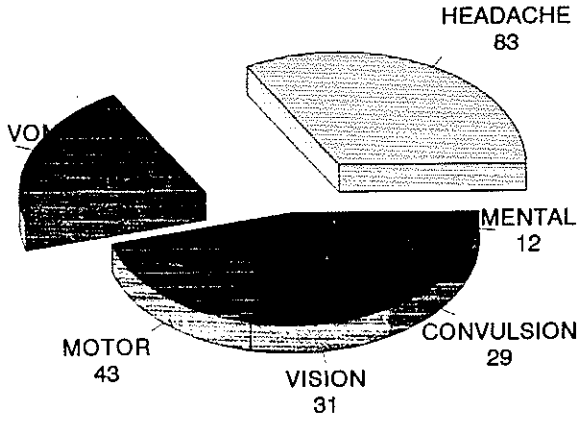

Fig. 4. Symptoms

in 8(5%) and spine in 4 (2%) (Fig. 2).

Grade IV astrocytoma was found in 40 patients and grade III in 37, totally including 49% of the patients. Twenty-nine patients (18%) had grade II tumors and 33 (23%) grade I. Grading had not been performed on tumors of 18 patients (Fig. 3).

The most common symptoms were headache, followed by nausea and vomiting, which were present in more than 50% of the patients. Less common were sensory and motor disturbances, vision dysfunctions, convulsions, and mental problems (Fig. 4).

All patients had been diagnosed by computed tomography (CT). Only one patient had been evaluated by magnetic resonance imaging (MRI), in addition to CT. Most tumors (119, 71%) had been removed by subtotal resection, and total resection had been performed in only 9 patients (5%). In 24% of the cases (41 patients) the tumors had only been biopsied. Eleven patients had a shunt operation.

All patients received their radiotherapy by two opposed lateral fields on cobalt-60 units. Nearly all recieved a dose of 5,000-5,500 cGy by treatment fractions of 200 cGy, five daily fractions each week. Radiation fields were local fields with suitable margins in grade I and II astrocytomas, and whole-brain fields up to 3,000-5,000 cGy with localized boost fields afterwards in grades III and IV astrocytomas. Spine fields were posterior direct local fields with suitable margins and a dose of 5,000 cGy in 25 fractions.

It should be mentioned that 16 patients (10%) did not complete their treatment, the reasons of which are not clear. Also, 4 children received their radiation to a dose of 4,400-4,600 cGy in 22-23 fractions, and two GBM patients received 6,000cGy in 30 fractions in the last year of the study period. From the 162 treated patients, only 91 (56%) returned for follow-up. In these patients the mean follow-up duration was 15 months, with a range of 3-60 months. Chemotherapy with CCNU (lomustine) was prescribed to 2/3 of the followed adult patients with grade IV tumors (14 out of 21) and nearly half of grade III patients (9 out of 21). Only one patient with a grade II tumor among the 49 followed grade I or II patients received CCNU. The decision for CCNU administration was only made by the judgment of the responsible radiation oncologist. Dose of CCNU was 100-130 mg/sq.m every 6 weeks.

Of the followed-up patients, 58 had follow-up for less than one year, 8 of whom suffered a local recurrence. Thirty-three patients were followed for more than one year, 13 of whom had a local recurrence. The total number of recurrences in the whole follow-up period was 21 (23%), which shows a local control of 77%.

The relationship of various patient variables, tumor, and treatment factors were evaluated for statistical significance. The highest significance was found for correlation of age and tumor grade, showing an increase of tumor grade with age. There was a significant association between grade and use of CCNU chemotherapy, showing more CCNU use in higher grades. Age had an effect on tumor site, with more hemispheric sites in older patients, and 3rd ventricle and spinal sites in younger ones. In addition, biopsy was often performed in 3rd ventricle and spinal tumors, with more complete surgeries in cerebral hemispheres and cerebellum.

The effect of various epidemiological and treatment factors on tumor recurrence and prognosis was statistically analyzed. These factors included age, sex, tumor site, tumor grade, extent of surgery, and use of chemotherapy (CCNU). Statistical significance was found only for grade (higher rate of recurrence with higher grades), surgical extent (lower rate of recurrence with more complete surgery), and CCNU use (lower recurrence).

It is noteworthy that after treatment with radiation and CCNU, four male GBM patients (out of 40 GBMs, 10%) survived for 4-4.5 years with no recurrence, and two of them were still disease- free at the last follow-up, 50-55 months after radiotherapy.

DISCUSSION

After surgical resection, radiation therapy is the single most effective treatment for malignant astrocytomas (4). Randomized trials of radiotherapy added to surgery have demonstrated a clear survival benefit (1,2). Dose escalation through radiosurgery (5) or brachytherapy boosts (6) in addition to standard external-beam treatment has been attempted, but application of these modalities is limited to approximately 20-30% of patients with malignant glioma. Another approach is the use of hyperfractionated (7) or accelerated radiotheapy (8) or concurrent use of chemotherapy with radiation (9,10), but to date these methods have not demonstrated a definite survival advantage (2).

Postoperative treatment of low-grade astrocytomas, especially in children, is controversial. Postoperative adjuvant therapy is clearly not indicated after complete surgical resection of pilocytic and other low-grade astrocytomas in children, but the use of radiotherapy following less than complete resection is reported in several series to result in better disease-free survival (11). The outcome of adult patients with total resection has been found in some series to be similar to that of patients undergoing less extensive surgery. Thus in adults postoperative radiation has been recommended after complete resection by some authors, whereas

others advise that radiotherapy be withheld until there is evidence of tumor recurrence (1).

Our study could not present epidemiological data representing the Iranian patient population with astrocytomas, as the study population includes only the patients referred for radiotherapy and does not include the patients with low-grade tumors solely observed after surgery. Nonetheless it could be informative in the absence of a population-based cancer registry.

In our study, the male-to-female ratio of 1.4:1 is in accordance with international literature showing preponderance among males for most brain tumor types (2,4). Peak age was in the 3rd and 4th decades of life. The most common tumor site was the cerebral hemispheres and the most common grade was grade IV (25%), though the patients were almost equally divided among the malignant (grades III and IV) and low-grade (grades I and II) groups. This is again in agreement with international literature.

All our patients had been diagnosed by CT scanning with only one MRI performed, although the recent widespread availability of MRI has replaced CT as the optimal method of imaging (12) and MRI is now considered to be the imaging modality of choice for most brain tumors (1,2,4). This is probably the result of difficult access and high cost of MRI during the study period in Iran, and of changing neuroimaging strategies.

Total resection had been performed for only 5% of our patients, and most had been treated by subtotal surgery. This demonstrates the difficulty of performing a complete resection in malignant astrocytomas, and is also a reflection of the referral nature of our patient population, as the totally resected low-grade astrocytomas might not have been sent for radiotherapy.

All patients in our study were treated by cobalt-60 radiotherapy units. It should be emphasized that brain irradiation presents no technical difficulties using either a cobalt-60 unit or a linear accelerator (13). The radiation fields included local (partial) brain fields in low-grade astrocytomas, and whole-brain fields with local boost fields after an initial dose in malignant astrocytomas. However, the use of localized fields for low-grade tumors has been the subject of dispute. Previously, whole-brain irradiation was recommended (13) and earlier trials of radiation therapy treated whole brain fields but recent trials of limited field irradiation have shown survival times comparable to those obtained with whole-brain therapy (4). Therefore, generous margins and inclusion of all radiographic evidence of tumor and associated edema is the rule today (1,2) and is the current treatment policy of our department.

Dose of radiation in our patients was mostly 5,000-5,500 cGy, but children tended to receive a lower dose and GBM patients received a dose of 6,000 cGy in the last year of study period. This again reflects the evolving treatment policies. Previously, doses like 4,500 cGy in 20 fractions were recommended for malignant astrocytomas (14), but the recent recommendation is 6,000 cGy in 30 fractions for GBM (1,2,4) and is the current dose of radiation in our department. Attempts for higher doses through radiosurgery or brachytherapy boosts or hyperfractionated radiotherapy continues, as mentioned before.

Only 56% of the patients came back for follow-up, and in these patients the mean follow-up time was 15 months (max. 60 months). Lack of long-term follow-up covering the maximum number of patients has always been a problem of the retrospective studies in our institute, and we believe of the Iranian studies in general. The reasons for this are multiple, and cannot be discussed here.

In the followed patients the rate of tumor recurrence was 13% in one year and 23% at the last follow-up, which shows a 3-year local control of 77%. Considering the relatively short and incomplete follow-up in our study, this local control rate cannot be very accurate. But keeping in mind its limitations, it is a measure of treatment success in our department and compares favoraby with international literature.

The statistical analysis of various patient, tumor and treatment factors showed significant relationships representing the increased incidence of high-grade tumors in older ages and the difficulty of more compelete surgeries in tumors around 3rd ventricle. It also showed the prevaling policy of using chemotherapy for high-grade tumors.

Increasing grades of malignancy within the astrocytoma group are generally associated directly with patient age. Low-grade astrocytomas are most common in patients 20-40 years old, anaplastic astrocytomas in 30-50 years, and GBM (the most malignant tumor) in patients who are 50 or older (15).

Also the analysis of prognostic factors demonstrated the effects of grade, extent of surgery, and use of CCNU to be statistically significant. It is recognized that higher grades of malignancy in gliomas are associated with a poorer patient prognosis (15). But the role of surgical extent in determining eventual outcome of patients with malignant glioma is somewhat controversial. To date, no prospective, randomized studies have critically evaluated this (16), though the trend in recent literature is to support the strategy of removing as much tumor as possible. It is believed that maximal surgical resection improves the results of treatment (1, 17), and our study is in agreement with this belief.

The chemotherapy prescribed to our patients was single-agent CCNU, and it was prescribed to more than half of the patients with grade III or IV tumors. The nitrosoureas, including carmustine (BCNU) and

lomustine (CCNU), appear to be the most active single agents for malignant astrocytomas (18). These drugs readily cross the blood-brain barrier. BCNU is the most active in this group, but it should be used intravenously while CCNU is used orally and is more convenient.

Our study showed a lower rate of recurrence with the use of adjuvant chemotherapy. Adjuvant chemotherapy after irradiation has modestly improved survival in GBM and more so in anaplastic astrocytoma (1,4,19). At least one study supports the use of three-drug combination of procarbazine, CCNU, and vincristine (PCV) over signle-agent BCNU (20) for this purpose, and because of this some authorities recommend PCV for the adjuvant chemotherapy of malignant astrocytomas (1) while others consider the treatment of 60 Gy radiation plus adjuvant BCNU to be the standard to which other therapies should be compared (4), still others consider either BCNU or PCV currently acceptable (21). Considering the above and considering the relative convenience of CCNU and its efficacy in our experience, the current policy in our department is to use CCNU as adjuvant to radiation in malignant astrocytomas. Also a randomized trial for comparison of adjuvant CCNU and PCV has been proposed by us, and will be hopefully launched soon in our department.

Chemotherapy has no established role in the treatment of low-grade astrocytomas (22), but it could be useful in infants and very young children for controlling the lesion while deferring irradiation until the child is older (4,23).

No mention has been made in this report of the adverse effects of radiation. This is because whithin the therapeutic doses, acute damage of radiation to CNS parenchyma is rare. Nausea and vomiting and occasionally a transient worsening of pretreatment symptoms may occur during the course of radiotherapy. But the significant side effects of CNS irradiation are late effects, which require long-term and accurate follow-up to discover and are generally difficult to diagnose and differentiate from tumor recurrence. The most serious late reaction to radiotherapy is radiation necrosis, which may appear years (peak at 3 years) after irradiation (2). We did not find any significant late effect of radiation in the study patients. However, considering the limitations mentioned before we may have remained ignorant of some late sequelae.

Despite all the efforts and the multimodality management of high-grade astrocytomas, unfortunately treatment is not ultimately successful and recurrence is the rule leading to death, especially in GBMs. Long-term survivors of GBM are reported in literature (24). In this study we found four GBM patients surviving without tumor recurrence for more than 4-4.5 years after irradiation and CCNU, two of them still disease-free at the last follow-up.

In conclusion epidemiologic findings in patients with brain astrocytomas referred to our department for radiotherapy were similar to those reported in international literature. Our treatment with irradiation plus CCNU chemotherapy in high-grade tumors had a 3-year local control of 77%, comparable to international literature. Statistically significant prognostic factors included grade, extent of surgery, and use of CCNU. Considering this, the current policy in our department is to use 5,000-5,500 cGy radiotherapy with local fields for incompletely resected low-grade astrocytomas, and to use 6,000 cGy radiation with wide margins plus adjuvant CCNU in GBM. Also a randomized trial is proposed to test combination chemotherapy (PCV) against stingle-agent CCNU.

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