as the corona radiata. Interruption of blood flow to these long insular arteries during the resection of intrinsic insular tumor may result in hemiparesis; thus, these arteries should be preserved to prevent infarction of the corona radiata.[6,10,19,20]

Data in the present study demonstrated that, in addition to the long insular arteries, the long medullary arteries from the opercular and cortical segments of the MCA passing over the frontoparietal operculum contribute to the arterial supply to the corona radiata. Although the vascular supply can show individual variations, these long medullary arteries can be impaired during the resection of a pure opercular glioma. Adequate collateral blood supply would not be expected[13] because intraparenchymal arterioles such as the lateral striate arteries, long insular arteries, and long medullary arteries are all end arteries without substantial anastomoses with other arteries except in pathological cases like moyamoya disease. If the impaired arteries supply most of the descending motor pathway, resection of opercular glioma is likely to result in hemiparesis.

The long insular arteries are mostly located in the posterior region of the insula,[20] most commonly on the posterior half of the central insular sulcus and on the long gyri.[19] Thus, subcortical resection around the upper limiting sulcus of the posterior region of the insula carries a higher risk of sacrifice of the long insular arteries, which may lead to extensive corona radiata infarction, and ultimately critical damage to the descending motor pathway. Similarly, a wide resection in the anteroposterior and cephalocaudal directions of the opercular region could damage a large number of medullary arteries from the opercular and cortical segments of the MCA over the frontoparietal operculum. In our experience, these two maneuvers appeared to be risk factors for critical infarction in the corona radiata after resection of an opercular glioma. However, reliable methods for avoiding damage to the long insular and medullary arteries are not available. Limited resection of the operculum as well as sparing of the posterior region of the insula may be the only measures presently available to avoid injury to a large number of long insular arteries and long medullary arteries. The development of new surgical devices to remove an opercular glioma with preservation of thin blood vessels like these arteries is to be expected in the future.

Conclusions

In the present study we found that ischemic complications occurring beneath the resection cavity including the pyramidal tract within the corona radiata are caused by damage to the distributing arteries—in particular, the long insular arteries and/or medullary arteries from the opercular and cortical segments of the MCA passing over the frontoparietal operculum—after resection of glioma in the frontoparietal opercular region inferolateral to the hand/digit sensorimotor area. Surgeons should be aware of the risk of ischemic complications during resection of opercular glioma and the possibility of permanent motor deficits.

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Brief Report of Special Case

Primary CNS lymphoma treated with combined intra-arterial ACNU and radiotherapy

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Summary

Object. To assess whether nimustine (ACNU), a drug that can cross the blood brain barrier, combined with radiotherapy, improved the survival of patients with primary central nervous system lymphoma (PCNSL).

Clinical materials and methods. Between 1995 and 2005, we treated 63 immunocompetent PCNSL patients with combination therapy consisting of intra-arterial ACNU (100 mg/m^2) and whole brain radiotherapy (36–50 Gy). Their median age was 60 years (range 28–81). The median follow-up was 24 months.

Findings. With this regimen we achieved a complete response rate of 75% (43 of 57 patients). Kaplan–Meier estimates for median progression-free survival and median overall survival were 26 and 39 months, respectively. The 3- and 5-year survival rates were 51% (95% confidence interval [CI], 36–65%) and 32% (95% CI, 17–47%), respectively. By multivariate analysis, age (<60 vs. ≥60 years) was the only statistically significant prognostic factor; the WBRT dose, sex, and number of tumors were not significant prognostic factors in this study. Myelosuppression was the most frequent side effect, 60% of patients experienced grade 3–4 leukopenia. Late neurotoxicity as a result of treatment was observed in 14 of 43 patients (34%) and higher age (>60) was associated with a high risk of neurotoxicity.

Conclusion. The intra-arterial administration of ACNU combined with radiation therapy yielded a high response rate at acceptable toxicity levels in younger patients with PCNSL. However, late neurotoxicity was a serious complication in patients above 60 years of age.

Keywords: Lymphoma; intra-arterial administration; ACNU; central nervous system.

Abbreviations

ACNU	nimustine
BBB	blood brain barrier
BCNU	carmustine
CNS	central nervous system
ECOG	Eastern Cooperative Oncology Group
HIV-1	human immunodeficiency virus type 1
MRI	magnetic resonance imaging
MTX	methotrexate
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NHL	non Hodgkin's lymphoma
OS	overall survival
PCNSL	primary CNS lymphoma
PFS	progression-free survival
WBRT	whole brain radiotherapy
WHO	World Health Organization

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Introduction

The incidence of primary central nervous system lymphoma (PCNSL) has been increasing steadily, and its optimal treatment remains to be established [5]. Although radiotherapy (RT) alone produced a complete tumor response and symptom improvement in most patients, the median survival was only 12–18 months and the 5-year survival rate was less than 5% [9, 24]. Combination chemotherapy with cyclophosphamide, doxorubicine, vincristine, and predonisone (CHOP) constitutes the best treatment for comparable systemic non-Hodgkin's lymphoma (NHL). However, large multicenter trials that delivered combined CHOP and cranial irradiation for PCNSL failed to yield better survival rates than RT alone, suggesting that systemic chemotherapy, effective in NHL, is not efficacious against PCNSL, possibly because these drugs are capable of only limited blood brain barrier (BBB) penetration [21, 23, 26].

As the BBB prevents hydrophilic compounds, including most chemotherapeutic agents, from entering cerebral tissues, the delivery of compounds such as methotrexate (MTX) requires high doses. Because the addition of high-dose MTX (MTX > 1 g/m^2) to RT has substantially improved the median survival of PCNSL patients, this combination therapy represents the current standard treatment for PCNSL [2, 13, 16]. However, due to delayed drug clearance, high-dose MTX is associated with acute toxicity and may result in renal compromise, and delayed neurotoxicity has been reported in patients receiving combined MTX-RT [1].

Because they can cross the BBB, nitrosoureas have been added to regimens to treat PCNSL [3, 4, 6, 28]. In Japan, nimustine (ACNU), one of the chloroethylnitrosoureas, has been widely used in glioma patients [30]. However, in early pilot studies that treated PCNSL patients with ACNU, its effectiveness could not be proven [15, 33].

In this study, we examined whether the addition of intra-arterially delivered ACNU improved the survival of PCNSL patients subjected to RT.

Patients and methods

Patient characteristics

In this study, we evaluated the treatment outcomes in 63 newly diagnosed PCNSL patients who were treated between 1995 and 2005, at Miyagi Cancer Center Hospital. Their clinical data were retrospectively evaluated. There were 33 men and 30 women ranging in age from 28 to 81 years (median 60 years); none presented with clinical evidence of human immunodeficiency virus type 1 (HIV-1) infection. All underwent magnetic resonance imaging (MRI) of the brain and spinal cord, cytologic study of cerebrospinal fluid (CSF) taps, chest and abdominal computed tomography (CT), and ophthalmologic evaluation including slit lamp examination. The diagnosis was histologically proven in 55 patients; in 53, the immunophenotype was of B-cell origin, the other 2 patients had T-cell NHL (Table 1).

Table 1. *Patient characteristics*

	No. of patients	%
Age (years)		
Median	60	
Range	28–81	
<60 years	30	48
≥60 years	33	52
Sex		
Male	33	52
Female	30	48
Surgical procedure		
Stereotactic biopsy	45	71
Tumor resection	10	16
None	8	13
Immunophenotype ($n = 55$)		
B-cell origin	53	96
T-cell origin	2	4
Ocular involvement ($n = 63$)	4	6
Performance status at diagnosis ($n = 63$)		
Median	1	
0	4	6
1	29	46
2	15	24
3	7	11
4	8	13

Performance status

The performance status was scored according to the Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) grading system. The median score of the 63 patients at the time of diagnosis was 1 (range 0–4).

Intra-arterial infusion of ACNU

Patients received intra-arterial ACNU (100 mg/m^2) once during radiotherapy. Using Seldinger's method, a parent catheter was introduced through the right femoral artery and advanced to the target parent arteries. A microcath-

eter was then advanced in the parent artery until it reached the desired drug delivery site. To cover as much brain parenchyma as possible, ACNU was delivered via the bilateral internal carotid arteries and the left vertebral artery, with the catheter tip immediately distal to the ophthalmic artery and at the V3 and V4 portion, respectively. For the reason that with this method, the territory perfused by the right posterior cerebellar artery does not receive ACNU irrigation, one-third of the total ACNU dose was infused into each artery. The drug was diluted with distilled water (total volume 10 ml); the infusion time was 1–2 min.

Radiation therapy

Of the 63 patients, 36, ranging in age from 27 to 76 years (median 60 years), received 36–50 Gy whole-brain irradiation in 18–25 fractions during a 4- to 5-week period plus a boost to the lesion site. The other 27 patients, ranging in age from 49 to 82 years (median 60 years), were treated with 30 Gy of whole-brain irradiation delivered in 15 fractions during a 3-week period and a boost to the lesion site(s). One patient with a spinal lesion and positive CSF cytology underwent additional spinal radiotherapy (40 Gy in 25 fractions delivered over the course of 5 weeks.

Assessment of response and toxicity

MRI study was performed before and after the initial therapy. Patients were followed clinically (scoring of performance status) and by MRI every 3 months, for the first 3 years after treatment, and then every 6 months. Complete response was defined as the total disappearance of the enhancing tumor, partial response as a more than 50% reduction in the product of the perpendicular diameters of the area of contrast enhancement without the appearance of new lesions [22]. Acute toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). Worsening of cognitive function related to delayed neurotoxicity was defined as performance status deterioration in patients who survived longer than 1 year without recurrence.

Statistical methods

Actuarial survival curves were estimated using the method of Kaplan and Meier [19]. The patients were subcategorized according to sex (male vs. female), age (<60 years vs. ≥60 years), RT dose (30 Gy vs. ≥36 Gy), and number of tumors at presentation (unifocal vs. multifocal disease). We performed univariate analysis of these 4 variables and the log-rank test [27]. The 4 covariates were then analyzed using the multivariate Cox proportional hazards model.

Results

Radio-chemotherapy and acute and subacute toxicities

Of the 63 patients, 62 completed the protocol. Myelosuppression was the most frequent side effect; NCI-CTC grade 4 leukopenia occurred in 8 (13%) patients, grade 3 leukopenia and thrombocytopenia in 29 (47%) and 16 (26%), respectively. Other grade 3 and 4 toxicities included pulmonary embolism in 1 patient and pneumonia in 8 patients; 1 patient died from interstitial pneumonia during therapy. There were no other deaths attributable to toxicity. None of the patients experienced ophthalmologic aggravation due to the intra-arterial infusion.

Response to therapy

The therapeutic response could not be determined in 6 patients; 5 had undergone complete tumor resection prior to therapy, and one patient died of interstitial pneumonia during therapy. Consequently, 57 patients were assessable; of these, 43 (75%) achieved complete-remission and 14 (25%), partial.

Post-treatment change in performance status

Of the 63 patients treated with our protocol, one died during therapy, and 4 manifested no change from their pre-treatment performance status of 0. Among the remaining 58 patients with a pre-treatment performance status of 1–4, 29 (50%) showed grade improvement, 6 (10%) worsened, and 23 (40%) exhibited no change.

Survival

Follow-up ranged from 3 to 99 months (median 23 months). Of the 63 patients originally entered in this study, 31 (49%) died during follow-up. The Kaplan–Meier estimate for median progression-free survival (PFS) was 26 months (95% CI, 17–34 months); median overall survival (OS) was 39 months (95% CI, 28–48 months) (Fig. 1). In 55 patients who have biopsy proof of lymphoma, median OS was also 39 months (95% CI, 29–49 months) (Fig. 1).

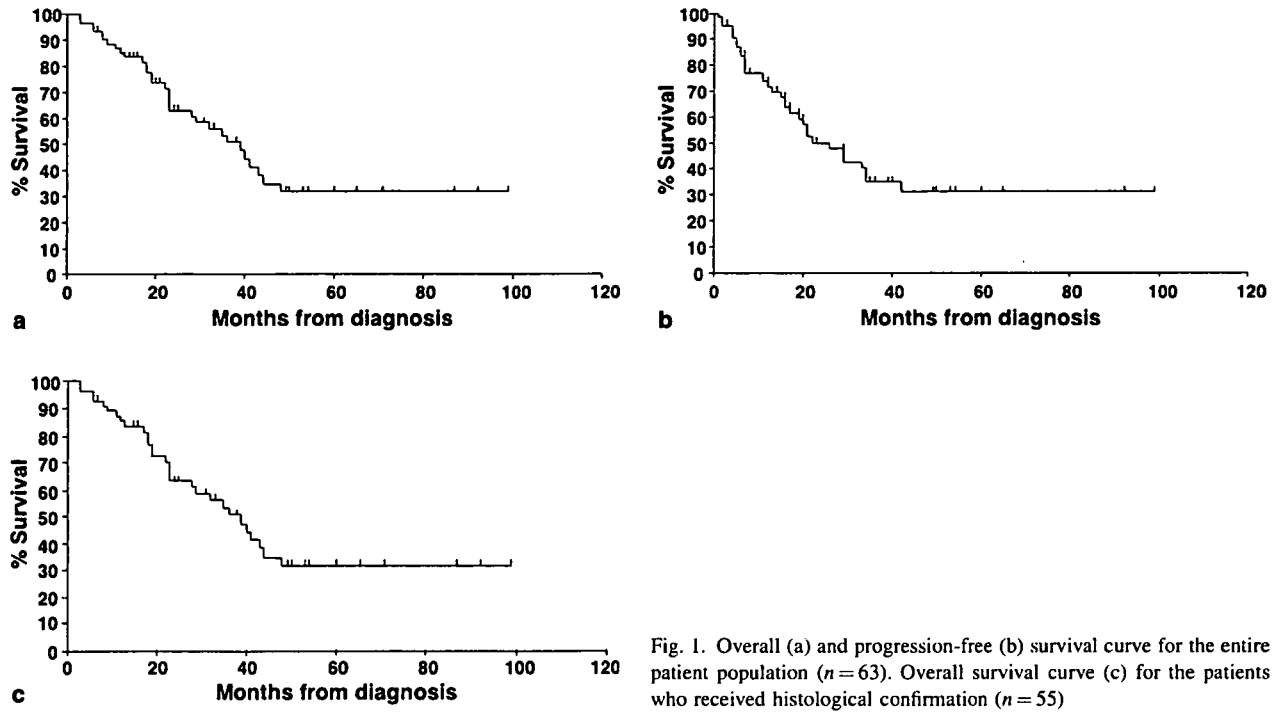

Fig. 1. Overall (a) and progression-free (b) survival curve for the entire patient population ($n = 63$). Overall survival curve (c) for the patients who received histological confirmation ($n = 55$)

The 3- and 5-year OS rates were 51% (95% CI, 36–65%) and 32% (95% CI, 17–47%), respectively. Of the patients who died, one succumbed to interstitial pneumonia during therapy, 3 died after treatment without evidence of lymphoma due to pneumonia ($n = 2$) and cerebral infarction ($n = 1$). Another 21 died from lymphoma after clinical relapse; their median survival after relapsing was 6 months (range 2–19 months). In the remaining 6 patients, the main cause of death was dementia with no clinical or radiographic evidence of disease recurrence. When we analyzed the baseline features for OS, we found that patients younger than 60 years and

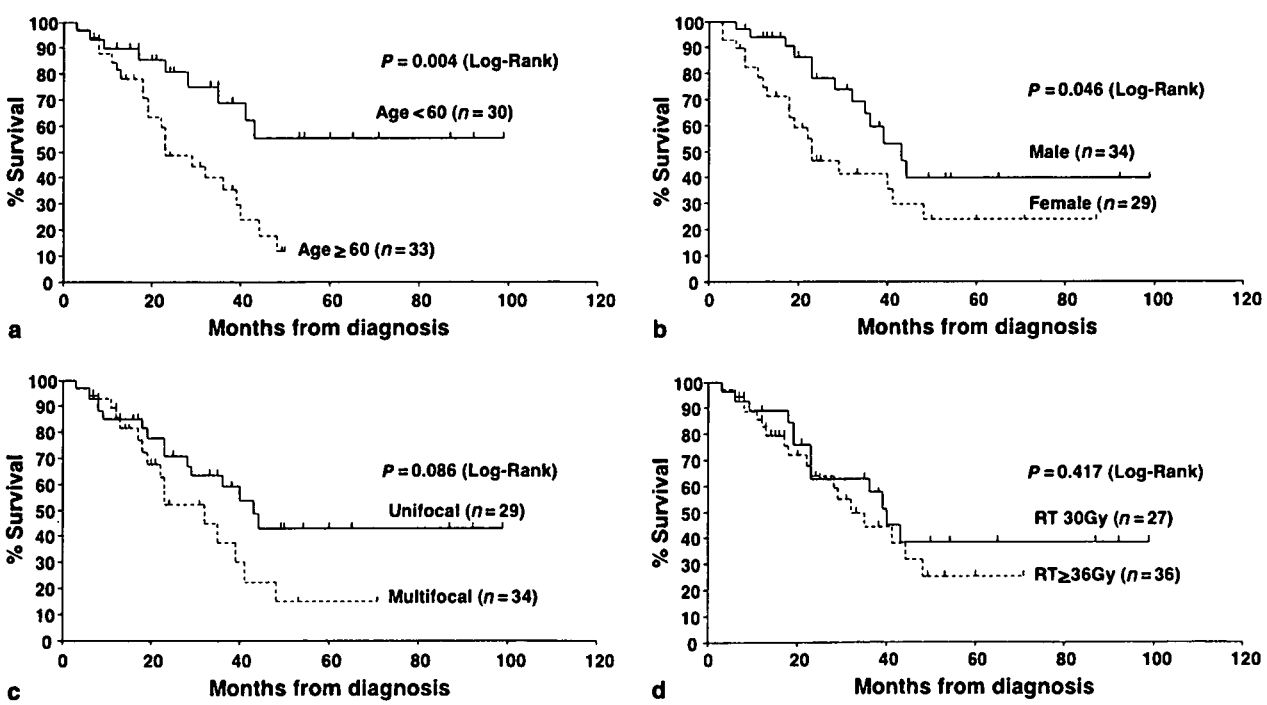

Fig. 2. (a) Overall survival based on patient age. (b) Overall survival based on patient sex. (c) Overall survival based on the number of tumors at presentation. (d) Overall survival based on the RT dose

Table 2. *Multivariate analysis*

Variables	HR	95% CI
Age (years)		
<60	1.0	
≥60	2.8	1.3–6.1
Sex		
Male	1.0	
Female	1.7	0.8–3.6
Whole-brain radiation dose		
30 Gy	1.0	
≥36 Gy	1.0	0.4–2.2
Number of tumors		
Unifocal	1.0	
Multifocal	1.8	0.8–3.9

males tended to have a favorable treatment outcome ($p = 0.004$ and $p = 0.046$, respectively) (Fig. 2a, b). Patients with multiple lesions tended to exhibit a trend for poor survival ($p = 0.086$) (Fig. 2c). The RT dose was not predictive of OS (Fig. 2d). By multivariate analysis, only the patient age (<60 vs. ≥60 years) had a statistically significant effect on OS (hazard ratio, 2.8; 95% CI, 1.3–6.1) (Table 2). In 30 patients younger than 60 years, the median OS has not been reached at the time of writing this article. In this subgroup, the estimated 3- and 5-year survival rate was 70% (95% CI, 50–89%), and 56% (95% CI, 32–79%), respectively. Among patients aged 60 years and above, median OS was 23 months (95% CI, 19–39 months); their estimated 3- and 5-year survival rate was 35% (95% CI, 17–54%), and 12% (95% CI, 0–27%), respectively (Fig. 2a).

Late neurotoxicity

Performance status changes from the pretreatment baseline were analyzed after completion of the initial therapy and at 3-month intervals thereafter until relapse or death unrelated to PCNSL. Of the 41 patients who survived longer than 1 year, 14 (34%) manifested a decline in the performance status that was associated with late neurotoxicity. Only 2 (8%) of 25 patients younger than 60 years at the time of diagnosis manifested neurotoxicity; 12 (75%) of 16 patients aged 60 years and above developed dementia.

Discussion

In this retrospective study, we assessed whether the addition of intra-arterially delivered ACNU improved the survival of PCNSL patients subjected to RT.

At present, the addition of MTX alone or of MTX-based chemotherapy to whole-brain irradiation therapy is the only regimen that extends the overall survival of PCNSL patients compared to historical series treated with whole-brain RT alone [2, 8, 11, 13, 16]. Reportedly, the overall response rate ranged between 65 and 95%; the 3- and 5-year survival rate was between 45 and 58%, and 30 and 56%, respectively [2, 11, 12, 25]. At present, it appears that high-dose MTX, a folate antagonist that can cross the BBB, is the most effective drug in patients with PCNSL.

With regard to nitrosoureas, carmustine (BCNU, 100 mg/m^2, i.v.) has been added to high-dose MTX based regimens to treat PCNSL [3, 28]. The 3- and 5-year survival rates were 55–58 and 36%, respectively. However, experimental studies indicated that the intra-arterial delivery of BCNU yields pharmacokinetic advantages over i.v. infusion and clinical trials showed the drug to be effective and safe [14, 18]. ACNU is water-soluble and more suitable for intra-arterial administration than BCNU which is dissolved in absolute ethanol and diluted in water. While intra-arterial ACNU has been used for adjuvant therapy in patients with newly diagnosed malignant glioma [7, 29, 32], in patients with newly diagnosed glioblastoma, intra-arterial delivery did not increase survival and progression-free survival compared to i.v. infusion, possibly because although ACNU can cross the BBB, its activity against glioblastoma is modest [20]. For these reasons, we chose intra-arterial infusion of ACNU in an effort to improve the efficacy of the drug and to increase its concentration in the tumor. Our patient characteristics did not differ substantially from those of most published series (median age 60 years). The tumor response rate of 100% in our series and the 3- and 5-year survival estimates of 51 and 32%, respectively, are comparable to previously published results when PCNSL was treated with MTX or MTX-based chemotherapy combined with whole-brain radiotherapy [2, 3, 11, 13, 16, 28], suggesting that a single dose of intra-arterial ACNU produced a substantial improvement in survival. This regimen may represent a good alternative therapy in PCNSL patients with renal failure.

Leukocytopenia was the primary acute chemotherapy-induced toxicity we encountered. With the exception of one patient who died of interstitial pneumonia, none of the others, including patients in the older age group, manifested serious acute complications. There was no ocular toxicity due to the intra-arterial administration of ACNU in any of our patients.

PCNSL patients treated with combined high-dose MTX chemotherapy and radiotherapy became vulnera-

ble to late neurotoxicity. The risk of toxicity was directly related to age. Patients aged 60 years and above at the time of diagnosis and treatment manifested a 100% incidence of late neurotoxicity at 24 months after diagnosis whereas those younger than 60 years had a maximal risk of 30% at 96 months [10]. In PCNSL patients subjected to an ACNU-based regimen, only 2 (8%) of 25 patients younger than 60 years at the time of diagnosis developed neurotoxicity; 12 (75%) of 16 patients aged 60 years and above developed dementia. The incidence of late neurotoxicity was almost the same as reported in PCNSL patients treated with the high-dose MTX regimen. Some patients with malignant glioma treated with intra-arterial ACNU did, while others did not, develop late neurotoxicity [7, 29, 31, 32]. However, PCNSL patients also received whole-brain irradiation while those with malignant glioma were usually treated with local brain irradiation. In addition, since the survival of patients with malignant glioma is shorter than that of PCNSL patients, there may not have been enough time for the manifestation of late neurotoxicity in this group [29].

As in NHL, we found that the patient age was the most important prognostic factor; multivariate analysis showed that only the age at diagnosis was an independently significant covariate.

Among patients 60 years and older, median OS was 23 months; their estimated 3- and 5-year survival rate was 35, and 12%, respectively. Although the addition of intra-arterially delivered ACNU improved survival even in older patients subjected to RT, late neurotoxicity was a major serious complication. Based on the results of a multicenter phase II study, Hoang-Xuan *et al.* [17] recommended MTX-based chemotherapy alone for PCNSL patients older than 60 years because this group is at highest risk for radiation-related neurotoxicity. We suggest that to decrease the incidence of late neurotoxicity, the intra-arterial administration of ACNU and the addition of chemotherapy with, for example, high-dose MTX without radiotherapy may be a viable alternative to treat PCNSL patients older than 60 years. On the other hand, as the estimated 3- and 5-year survival rate was 70 and 56%, respectively, in patients younger than 60 years, the intra-arterial administration of ACNU combined with whole-brain irradiation may yield a high response rate at acceptable toxicity levels in this group of PCNSL patients.

Conclusions

The addition of intra-arterially delivered ACNU improved the survival of PCNSL patients subjected to RT. Median overall- and progression-free survival was 39 and 26 months, respectively. However, as late neurotoxicity was a serious complication in patients older than 60 years, we recommend that the dose of RT be reduced, or RT delayed, and that combined chemotherapy with intra-arterial infusion of ACNU be considered in older PCNSL patients. We found that younger patients, in particular, fared well with the chemoradiotherapy regimen. Although MTX-based chemotherapy continues to be the standard regimen to treat PCNSL, in our younger PCNSL patients, the intra-arterial administration of ACNU combined with whole-brain irradiation yielded a high response rate at acceptable toxicity levels.

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Comment

This is an interesting study in that it takes a very different approach to the management of primary CNS lymphoma as compared to the conventional lead with high dose methotrexates. The paper is clear and well presented and the number of patients is substantial given the rarity of this disease. The spectrum of patients, including as it does substantial numbers over the age of 60, is comparable to many such series in the literature. It appears to show that on using a single dose of intra-arterial ACNU and whole brain radiotherapy, survivals equivalent to those achieved with high-dose intravenous methotrexate can be achieved. The results are particularly good in patients under sixty years of age. However, the claim that there is very little neurological damage may well reflect a failure to look for and report on detailed cognitive assessments.

On the other hand, the results in the older population show the same devastating consequences of survival in these patients. The assumption is that the radiation is responsible for the high rate of late dementia and the argument that this regimen is not acceptable in patients over 60 years of age is well received.

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Anaplastic astrocytoma and anaplastic oligodendroglioma occurring 6 years after subtotal resection of a central neurocytoma

Case report

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✓The authors present the case of a 51-year-old man who presented with an anaplastic astrocytoma and anaplastic oligodendroglioma that developed 6 years after subtotal resection of a central neurocytoma in his right lateral ventricle. He had received neither radiation therapy nor chemotherapy after the original resection. On readmission, neuroimaging revealed a mass in the right parietal lobe and a diffuse lesion in the right temporal lobe, insula, and corona radiata. Because both lesions extended to the right lateral ventricle wall, they were regarded as recurrent rather than metachronous tumors. Histological examination revealed anaplastic oligodendroglioma in the parietal lobe and anaplastic astrocytoma in the insula. One year later, the anaplastic astrocytoma was found to have transformed into a glioblastoma multiforme. Fluorescence in situ hybridization analysis and immunohistochemical examinations detected deletions of the 1p36 and 19q13 loci, and nuclear accumulation of TP53 protein in the anaplastic oligodendroglioma but not in the glioblastoma multiforme. These findings suggest that central neurocytoma or progenitor cells have the potential for oligodendrocytic and astrocytic transformation with different genetic aberrations. *(DOI: 10.3171/JNS-07/07/0185)*

KEY WORDS • **anaplastic astrocytoma** • **anaplastic oligodendroglioma** • **central neurocytoma**

CENTRAL neurocytomas are a recently described[8] rare neoplasm type that accounts for approximately 0.25% of tumors of the CNS.[16] In general, central neurocytomas are regarded as having benign biological behavior and a favorable prognosis.[9,27] However, cases of recurrence and rapid progression have been reported.[2,15,17,18,22,23] Interestingly, the recurrent tumors exhibit various histological features[5,7,21,22,29] such as less differentiated central neurocytomas,[22] more differentiated central neurocytomas occurring as gangliocytomas,[21] and central neurocytomas with glial differentiation and craniospinal dissemination.[1,5]

In our patient, anaplastic astrocytoma and anaplastic oligodendroglioma developed 6 years after resection of the central neurocytoma.

Case Report

History and First Presentation. This 45-year-old man presented to our institution after suffering a head injury in October 1994. On admission, no neurological deficits were identified. However, on computed tomography a calcified lesion was revealed in the right lateral ventricle (Fig. 1A). On T1-weighted MR imaging with Gd-DTPA enhancement and on T2-weighted MR imaging, a heterogeneous mass was revealed in the right lateral ventricle (Fig. 1B). The patient underwent subtotal resection via the transcallosal approach.

First Histological Examination. Histological examination of the surgical specimen revealed small round cells with clear cytoplasm and uniform round nuclei embedded in a fibrillary background. Honeycomb architecture and anuclear zones were observed. No cellular pleomorphisms, mitotic cells, vascular proliferations, or necrotic cells were found (Fig. 1D). Immunohistochemical studies revealed diffuse expression of synaptophysin in the cytoplasm in a neuropil pattern (Fig. 1E) but no expression of GFAP (Fig. 1F). Monoclonal antibody staining with MIB-1 showed expression of Ki 67 antigen in 0.5% of cells. The histological diagnosis was central neurocytoma.

Postoperative MR imaging showed residual tumor, but no radiation therapy or chemotherapy was administered. The residual tumor had disappeared spontaneously 6 months af-

Abbreviations used in this paper: CNS = central nervous system; DTPA = diethylenetriaminepentaacetic acid; GFAP = glial fibrillary acidic protein; MR = magnetic resonance.

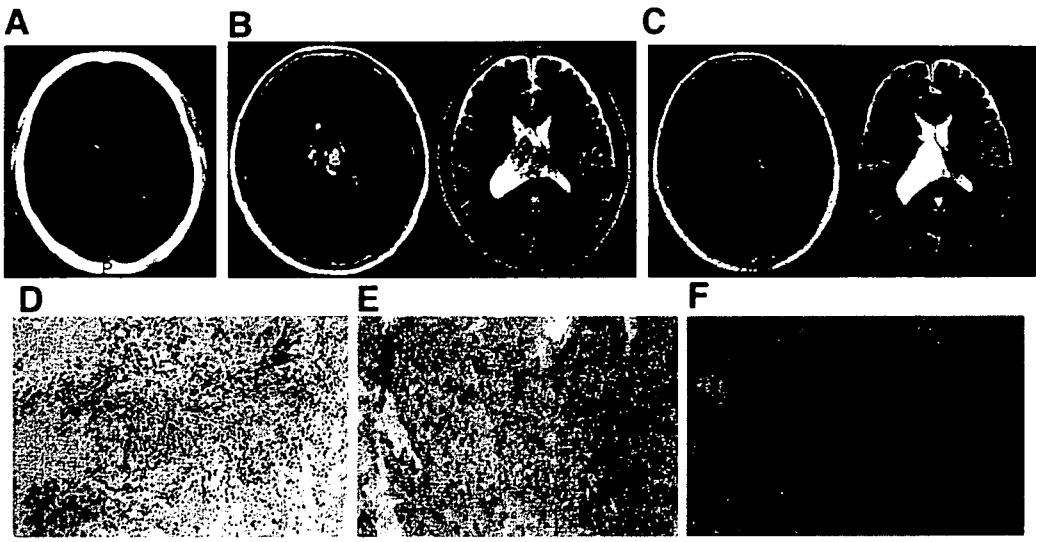

FIG. 1. A: Axial computed tomography scan obtained at admission demonstrating an intraventricular mass lesion with calcification. B: Axial T1-weighted MR image with Gd-DTPA *(left)* and axial T2-weighted MR image *(right)* obtained at admission demonstrating a mixed intensity mass in the right lateral ventricle. C: Axial T1-weighted MR image with Gd-DTPA *(left)* and a T2-weighted MR image *(right)* obtained 5 years after initial resection demonstrating no enhanced lesions or abnormal areas of high intensity. D: Photomicrograph showing tumor cells with round nuclei and clear cytoplasm proliferating in a honeycomb architecture. H & E, original magnification × 100. E: Immunohistochemical staining showing synaptophysin expression in the cytoplasm. Original magnification × 200. F: Immunohistochemical staining showing no detectable expression of GFAP, except in reactive astrocytes. Original magnification × 200.

ter subtotal resection. No evidence of recurrence was detected on follow-up MR images obtained in March 2000 (Fig. 1C).

Second Presentation. When he was 51 years of age, the patient presented again with a deep sensation disturbance in the left upper limb in October 2000. On T1-weighted MR imaging with Gd-DTPA, an enhanced lesion was revealed in the right parietal lobe, and on T2-weighted MR imaging a diffuse lesion in the right temporal lobe, insula, and corona radiata could be seen (Fig. 2A–C). Axial and coronal T2-weighted MR imaging demonstrated that the high-intensity areas of both lesions were in contact with the right lateral

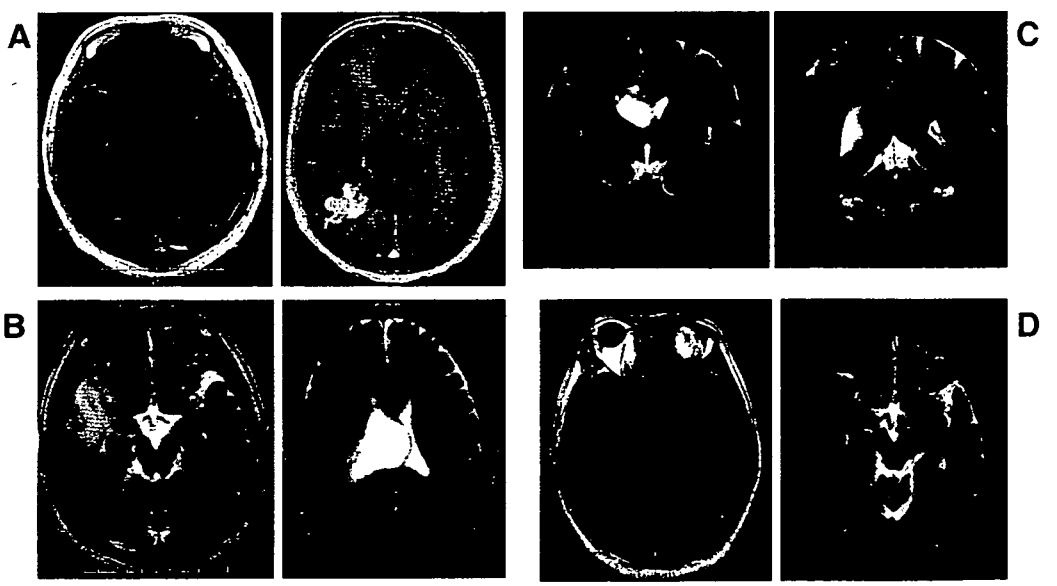

FIG. 2. A: Axial T1-weighted MR images with Gd-DTPA obtained at the first recurrence showing an enhanced lesion in the right parietal lobe and an unenhancing low-intensity lesion in the right temporal lobe. B and C: Axial (B) and coronal (C) T2-weighted MR images demonstrating a diffuse lesion in the right temporal lobe, insula, and corona radiata, and high intensity areas of both lesions in contact with the right lateral ventricle wall. D: Axial T1-weighted MR image with Gd-DTPA enhancement *(left)* and T2-weighted MR image *(right)* at second recurrence showing the enhanced lesion in the right temporal lobe.

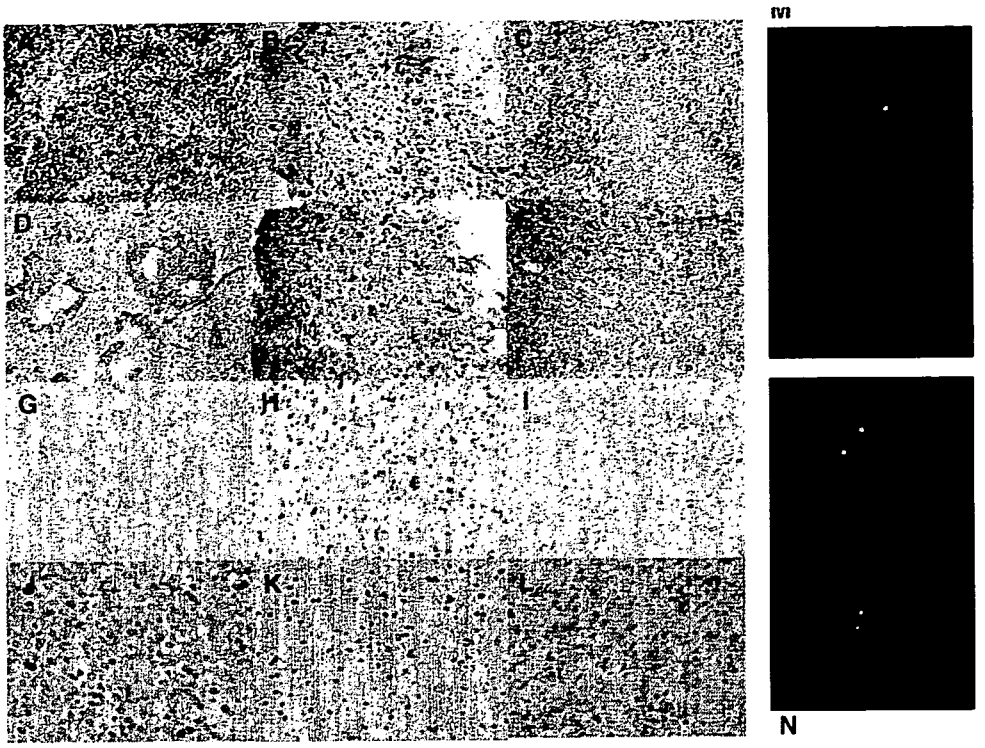

FIG. 3. A, D, G, and J: Photomicrographs of right parietal anaplastic oligodendroglioma tissue demonstrating compact proliferation of tumor cells with round nuclei and clear cytoplasm within a fibrous matrix. High cellularity, pleomorphism, high mitotic activity, microvascular proliferation, and necrosis were observed (A; H & E, original magnification × 200). Immunohistochemical staining showed no expression of GFAP (D, × 400), but expression of nestin (G, × 400). Nuclear accumulation of TP53 protein was found (J, × 400). B, E, H, and K: Photomicrographs of right insula anaplastic astrocytoma tissue demonstrating diffuse proliferation of spindle-shaped cells in a loose fibrous matrix. Mitosis and nuclear atypia were present (B; H & E, original magnification × 200). There was expression of both GFAP (E, × 400) and nestin (H, × 400), but nuclear accumulation of TP53 protein was not found (K, × 400). C, F, I, and L: Photomicrographs of right temporal glioblastoma tissue demonstrating diffuse proliferation of pleomorphic cells and pseudopalisading necrosis (C; H & E, original magnification × 200). There was expression of GFAP (F, × 400) and nestin (I, × 400), but no nuclear accumulation of TP53 protein (L, × 400). M: Fluorescence in situ hybridization analysis of tissue from the right parietal anaplastic oligodendroglioma showing allelic loss of 1p36 *(upper panel)* and 19q13 loci *(lower panel)*. The *green areas* show the SpectrumGreen-labeled probe for 1q25 *(upper panel)* or 19p13 *(lower panel)*. The *red areas* show the SpectrumOrange-labeled probe for 1p36 *(upper panel)* or 19q13 *(lower panel)*. N: Fluorescence in situ hybridization analysis of tissue from the right temporal glioblastoma multiforme showing no allelic loss of 1p36 *(upper panel)* or 19q13 *(lower panel)* loci. The *green areas* show the SpectrumGreen-labeled probe for 1q25 *(upper panel)* or 19p13 *(lower panel)*. The *red areas* show the SpectrumOrange-labeled probe for 1p36 *(upper panel)* or 19q13 *(lower panel)*.

ventricle wall (Fig. 2B and C). Gross-total resection of the mass in the right parietal lobe and stereotactic biopsy of the diffuse lesion in the right insula were performed.

Second Histological Examination. Histological examination showed that the specimen obtained from the right parietal lesion consisted of round small cells with clear cytoplasm, proliferating with a lobar pattern in a fibrous matrix. Atypical histological features including high cellularity, pleomorphism, high mitotic activity, microvascular proliferation, and areas of necrosis were noted (Fig. 3A). Immunohistochemical examination revealed no expression of synaptophysin or GFAP (Fig. 3D), but detected expression of OLIG2, myelin-binding protein, and nestin (Fig. 3G). Nuclear accumulation of TP53 protein was found in more than 20% of cells (Fig. 3J), and staining with MIB-1 monoclonal antibody demonstrated expression of Ki 67 antigen in 35.0% of cells. Fluorescence in situ hybridization analysis revealed allelic loss of 1p36 and 19q13 loci (Fig. 3M). The histological diagnosis of the parietal lesion was anaplastic oligodendroglioma.

Histological examination of a biopsy specimen from the right insula revealed diffuse proliferation of spindle-shaped cells within a loose fibrous matrix. One or two mitotic cells per 10 hpfs and nuclear atypia were also found (Fig. 3B). Immunohistochemical examination revealed no expression of synaptophysin, but expression of GFAP and nestin was detected (Fig. 3E and H). Nuclear accumulation of TP53 protein was found in less than 5% of cells (Fig. 3K). Expression of Ki 67 antigen in 27.8% of cells was noted on staining with MIB-1 monoclonal antibody. The histological diagnosis of the diffuse lesion in the right insula was anaplastic astrocytoma.

Treatment. Chemotherapy with nimustine hydrochloride (100 mg/m^2) and radiation therapy to the right hemisphere and bilateral lateral ventricles were administered. As a result, the diffuse lesion in the right temporal lobe disap-

peared. One year later, however, MR imaging with Gd-DTPA demonstrated a new enhanced lesion in the right temporal lobe (Fig. 2D). The patient underwent a right temporal lobectomy.

Histological examination of the specimen from the temporal lobectomy revealed poorly differentiated pleomorphic cells of a high cellularity with significant areas of mitosis, vascular proliferation, and pseudopalisading necrosis (Fig. 3C). Immunohistochemical examination revealed expression of GFAP and nestin (Fig. 3F and I). Nuclear accumulation of TP53 protein was found in less than 5% of cells (Fig. 3L). The histological diagnosis of the recurrent temporal lesion was glioblastoma multiforme. Retention of both 1p36 and 19q13 loci (Fig. 3N) was revealed on fluorescence in situ hybridization analysis.

Discussion

There are two proposed mechanisms to explain the development of two histologically distinct tumors 6 years after complete remission of a central neurocytoma. First, the tumors could have developed independently of the central neurocytoma as metachronous tumors. Metachronous gliomas are known to develop spontaneously, especially in the presence of neurofibromatosis Type 1, multiple sclerosis, or previous irradiation.[14,20,24] In a previously reported case, an anaplastic astrocytoma developed in the right basal ganglia and temporal lobe of a patient 8 years after partial resection and irradiation of a central neurocytoma.[26] However, the patient in the present study did not have a history of any of these predisposing factors.

Second, central neurocytoma or its progenitor cells may migrate and transform into astrocytic and oligodendrocytic tumors in the temporal and parietal lobes. Immunohistochemical, electron microscopy, and electrophysiological studies have demonstrated that central neurocytoma exhibits astrocytic, oligodendrocytic, and neuronal characteristics.[11,13,19,28] These findings suggest that central neurocytomas could originate from multipotential progenitor cells located in the subventricular zone and retain the capacity for multipotent differentiation.[5,11,19] In our patient, the anaplastic oligodendroglioma and anaplastic astrocytoma had developed in contact with the ventricle wall, suggesting that the tumor progenitor cells in the ventricle wall could migrate into the parietal and temporal regions.

Nestin is a commonly used marker for undifferentiated cells in the developing CNS and for dedifferentiated cells in CNS tumors.[3,4,10] Therefore, we performed immunohistochemical staining for nestin expression to evaluate the involvement of undifferentiated progenitor cells in the development of the anaplastic oligodendroglioma and anaplastic astrocytoma. Considering that both of the recurrent tumors expressed nestin, dedifferentiated or undifferentiated progenitor cells may have migrated from the ventricle wall to the parietal and temporal lobes and then transformed into astrocytic and oligodendroglial cells. In addition, nuclear accumulation of TP53 protein was overexpressed only in the anaplastic oligodendroglioma cells. Unfortunately we could not analyze *p53* expression in the specimen of central neurocytoma tissue because the biopsy sample was insufficient; however, inactivation of the *p53* pathway is unusual in the development of a central neurocytoma.[18] Therefore, inactivation of *p53* may have been involved in the transformation of the progenitor cells into oligodendroglioma in this case.

Allelic loss of the 1p and 19q loci were found in the anaplastic oligodendroglioma, but not in the glioblastoma in this case. Similarly, synchronous oligodendroglioma in the frontal lobe and pilocytic astrocytoma in the cerebellum have been reported with allelic loss of the 1p36 locus in oligodendroglioma, but not in pilocytic astrocytoma cells.[12] We were not able to analyze the status of 1p36 and 19q13 loci in the central neurocytoma because of an insufficient sample; however, allelic loss of 1p and 19q loci have not been detected in other cases of central neurocytomas reported in the literature.[6,25]

We speculate that allelic loss at 1p or 19q loci in the progenitor cells and inactivation of *p53* are involved in the development of oligodendroglial tumors from progenitor cells, and that distinct unknown genetic aberrations are involved in astrocytic or neuronal differentiation. Further detailed molecular analysis may clarify the mechanisms of transformation and differentiation in these tumors.

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Prognostic significance of surgery and radiation therapy in cases of anaplastic astrocytoma: retrospective analysis of 170 cases

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Object. The purpose of this retrospective study was to estimate the prognostic impact of treatment parameters for 170 patients with anaplastic astrocytoma (AA).

Methods. Survival outcome and prognostic factors were analyzed for 170 patients with AA. In the multivariate analysis, site of lesion (frontal or parietal lobe, $p = 0.002$), extent of surgery (total or subtotal resection, $p = 0.001$), Karnofsky Performance Scale status (0–2, $p = 0.021$), age ($\leq$ 50 years, $p = 0.024$), and total dose of radiation therapy ($>$ 60 Gy, $p = 0.029$) were significant favorable prognostic factors.

In the analysis of groups according to extent of surgery, patients who underwent total or subtotal resection had a significantly more favorable prognosis than did patients who underwent partial resection or biopsy (5-year survival rate 54.0% for total or subtotal resection compared with 17.5% for partial resection or biopsy; median survival time [MST] 62.6 months compared with 22.9 months [$p < 0.0001$, log-rank test]; hazard ratio [HR] 0.67; and 95% confidence interval [CI] 0.52–0.85 [$p = 0.001$]).

In the analysis of groups according to total radiation dose, the group of patients who received doses greater than 60 Gy had a significantly more favorable prognosis than did the group who received 60 Gy or less (5-year survival rate 45.0% for patients who received doses greater than 60 Gy compared with 21.1% for those receiving 60 Gy or less; MST 48.9 months compared with 21.6 months [$p = 0.0006$, log-rank test]; HR 0.96; 95% CI 0.93–0.99 [$p = 0.029$]).

Conclusions. The most important parameter in the treatment of AA was extent of surgery, and total radiation dose was the second most important factor. Resection of as much of the tumor as possible and delivery of a total radiation dose of greater than 60 Gy seem to be required for local control of AA.

KEY WORDS • **anaplastic astrocytoma** • **surgery** • **radiation therapy** • **survival analysis** • **multivariate analysis**

MALIGNANT gliomas and astrocytomas account for approximately 50% of primary CNS tumors in adults: glioblastomas multiforme account for approximately 30%, AAs for approximately 10%, and low-grade astrocytomas for approximately 10%. It has been reported that the median survival period of patients with AA is 10 to 40 months (~ 20–30 months on average).[6,16,20,22]

It has been reported as well that the major prognostic factors for patients with AA are age, KPS status, and extent of surgery. In some studies investigators have also shown that the presence of ringed contrast enhancement, score on the Ki 67 labeling index, total radiation dose, the presence of convulsion, microvascular density, and expression of vascular endothelial growth factor are prognostic factors.[1,2,5,6,8,16,20,22]

Despite the availability of combined multimodality treatment, AA has an unfavorable prognosis. Surgery and radiation therapy are essential for radical treatment of malignant astrocytoma, but an optimal treatment regimen has not yet been established. The purpose of this study was to evaluate the outcome of treatment in 170 patients with AA and to estimate the prognostic factors and contribution of each parameter of treatment by using multivariate analysis.

Abbreviations used in this paper: AA = anaplastic astrocytoma; CI = confidence interval; CNS = central nervous system; CT = computed tomography; EBRT = external-beam radiation therapy; HR = hazard ratio; IORT = intraoperative radiation therapy; KPS = Karnofsky Performance Scale; MR = magnetic resonance; MST = median survival time; WBRT = whole-brain radiation therapy.

Clinical Material and Methods

Patient Population

Data were obtained in 170 consecutive patients with AA (109 men and 61 women; median age 44 years) who were treated between May 1981 and March 2002. The median follow-up period was 37.9 months (range 2.2–189 months). The characteristics of the patients in this study are shown in Table 1. All patients had intracranial primary tumor(s) for

which the histopathological diagnosis was Grade III astrocytoma (Grade III oligoastrocytoma or other Grade III gliomas were excluded). The histopathological diagnosis was determined based on the findings of at least one pathologist and one neurosurgeon. Histopathological grading was determined on the basis of the latest World Health Organization classification. The final follow-up date was May 23, 2003. Astrocytomas that were initially treated as Grade III lesions and changed to Grade IV during the course of follow up were included in this study. Astrocytomas that were not Grade III at the time of initial treatment were excluded.

The KPS status was determined according to the criteria of the Eastern Cooperative Oncology Group before treatment.[12] This was accomplished using enhanced CT scans and/or T_2-weighted or enhanced T_1-weighted MR images. Preoperative and postoperative MR imaging was routinely performed after 1987. The size of the tumor was measured as accurately as possible by more than one radiologist and neurosurgeon. Because of the difficulty in measuring tumor volume in cases treated early in the study, the methods for assessing the size of the tumor were unified into measurement of its long axis.

Surgery and Chemotherapy

The extent of surgery was evaluated on postoperative MR images and/or CT scans obtained within 72 hours postsurgery. Comparing these with preoperative MR and/or CT images, gross-total resection of the tumor was defined as resection with no macroscopic residual tumor, subtotal resection was defined as more than 75% resection, and partial resection was defined as less than 75% resection. Biopsy (including open procedures and needle biopsy) that was performed only for the purpose of histological diagnosis was defined as less than 10% resection. Although there was uncertainty in evaluating the extent of surgery before the advent of MR imaging, this factor was assessed based on CT findings and the surgeon's judgment as far as possible. Surgery (or biopsy) was performed before radiation therapy and chemotherapy in almost all cases. Chemotherapy was routinely combined as much as possible. Patients who had renal dysfunction, hepatic dysfunction, or poor KPS status or who did not give consent for chemotherapy did not receive it. Nimustine hydrochloride (2–3 mg/kg weekly) was mainly used in adjuvant chemotherapy.

Radiation Therapy

All patients were treated with 4- to 10-MV photons (almost all of them with 10-MV photons) by using a linear accelerator, and all were immobilized in a resinous shell during the treatment. The standard dose of WBRT was 30 Gy in 15 fractions (plus local boost irradiation of 30 Gy in 15 fractions). The WBRT field included the cerebrum, cerebellum, and brainstem (above the posterior cranial fossa), and parallel-opposed lateral fields were used. The extended local irradiation field included the whole T_2-weighted high-intensity region visualized on MR images or a 2- to 3-cm margin around the tumor, and usually more than two fields were used. The fractionation regimen was as follows: 1) conventional fractionation (2 Gy/day with a total of 10 Gy delivered in five fractions within 1 week); 2) uneven fractionation (a combination of high-dose and low-dose fractions [4–5 Gy on Day 1 and 1–1.5 Gy/day between Days 2–5] with a total of 7–9 Gy delivered in three–five fractions/week); and 3) hyperfractionation (1.2 Gy/fraction, two fractions/day for a total of 12 Gy delivered in 10 fractions within 1 week). The conventional fractionation regimen was mainly used from 1981 through 1985, the uneven fractionation regimen from 1986 through 1995, and the hyperfractionation regimen from 1995 through 2003. A single dose of 15 Gy delivered using 8- to 10-MeV electrons was used for IORT.

TABLE 1

*Characteristics in 170 patients with AA who underwent surgery and radiation therapy**

Characteristic	No. of Patients
sex	
male	109
female	61
histological findings of tumor: AA (Grade III)†	170
site of lesion	
frontal lobe	74
parietal lobe	17
temporal lobe	36
occipital lobe	5
basal ganglia or thalamus	13
cerebellum	8
brainstem	3
other	14
extent of resection	
total	56
subtotal	20
partial	43
biopsy only	51
chemo	
nimustine hydrochloride	117
none	53
fractionation regimen	
conventional	49
uneven	76
HF	45
completion of tx	
completed	161
suspended	9

* Chemo = chemotherapy; HF = hyperfractionation; tx = treatment.
† According to the World Health Organization revised classification.

Treatment-Related Toxicity

Toxicity was clinically diagnosed on the basis of common toxicity criteria (version 2.0). Patients in whom radiographically confirmed changes without recurrence were demonstrated (such as ≥ Grade 3 leukoencephalopathy-associated radiological findings, or brain necrosis that was diagnosed on the basis of changes seen on follow-up CT or MR images, clinical examination, and/or histopathological findings) were classified as suffering treatment-related toxicity.

Statistical Analysis

Survival time was calculated from the date of first treatment to the date of death. Progression-free survival was calculated from the date of first treatment to the date of first progression (local recurrence or distant metastasis). Survival curves were analyzed using the Kaplan–Meier method and the log-rank test. The Cox proportional hazards model

and a stepwise method were used for multivariate analysis of prognostic factors. The patient's sex, age, KPS status, site of lesion, tumor size, treatment with or without chemotherapy, extent of surgery, treatment with or without IORT, total dose of radiation therapy, period of EBRT, irradiation field (combination of WBRT or extended local irradiation alone), fractionation regimen of radiation therapy, and period of treatment were used as continuous or discrete variables in multivariate analysis (Table 2). Analyses of prognostic factors were performed for all patients whose tumor diagnosis was Grade III glioma. Statistical relationships between significant prognostic factors were analyzed using the chi-square test.

Results

Data from patients with AA treated between May 1981 and March 2002 at our institution were analyzed. At least two cases of Grade III astrocytoma (1.1%) were histologically proven to be Grade IV astrocytoma at the time of recurrence. One hundred sixty-one patients completed the course of treatment, but nine did not because of deterioration of their general condition due to uncontrolled tumor growth. At the final follow-up date, 110 patients (64.7%) were dead and 60 (35.3%) were alive. Of the patients who had died, 102 (92.7%) died of primary disease and eight (7.3%) died of intercurrent disease.

Survival analysis of the 170 patients showed that the MST was 33.6 months and that the 2- and 5-year survival rates were 57.1 and 33.8%, respectively (Fig. 1). Two-year and 5-year progression-free survival rates were 49.3 and 30.2%, respectively.

Table 3 shows the results of univariate and multivariate analyses of prognostic factors for the 170 patients. In the multivariate analysis, site of the lesion ($p = 0.002$), extent of surgery ($p = 0.001$), KPS status ($p = 0.021$), age ($p = 0.024$), and total dose of radiation therapy ($p = 0.029$) were significant prognostic factors. Patient sex, tumor size, treatment with or without chemotherapy, treatment with or without IORT, period of EBRT, irradiation field, fractionation regimen of radiation therapy, and period of treatment were not statistically significant in multivariate analysis.

The patients in whom primary lesions were located in the frontal or parietal lobe had a significantly more favorable prognosis than did the patients who had primary lesions in other sites (MST 48.9 months compared with 22.6 months [$p < 0.0001$, log-rank test]). The patients who had a good KPS score before treatment had a significantly more favorable prognosis than did those in whom a poor KPS score was noted (MST 41 months compared with 10 months [$p < 0.0001$, log-rank test]). The patients who were 50 years of age or younger had a significantly more favorable prognosis than did the patients who were older than 50 years of age (MST 44.9 months compared with 19.0 months [$p < 0.0001$, log-rank test]).

Figure 2 shows survival curves according to extent of surgery. The patients who underwent total or subtotal resection of the tumor showed a significantly more favorable prognosis than did those who underwent partial resection or biopsy only (5-year survival rate 54.0% compared with 17.5%; MST 62.6 months compared with 22.9 months [$p < 0.0001$, log-rank test]; HR 0.67; 95% CI 0.52–0.85 [$p = 0.001$]). In the survival analysis based on fine distinctions, the MSTs of patients in the total resection, subtotal resection, partial resection, and biopsy-only groups were 86.4, 61.6, 22.9, and 23.4 months, respectively ($p < 0.0001$, log-rank test [data not shown]). The prognosis of

TABLE 2

*Parameters of variables in univariate and multivariate analyses in 170 patients with AA**

Variable	Value
sex (D)	
male	109
female	61
mean age in yrs (C)	43.1 ± 17.5
KPS status (D)	
0–2	136
3–4	34
site of lesion (D)	
frontal or parietal lobe	91
other	79
mean tumor size in cm (C)	5.1 ± 2.0
tx w/ chemo (D)	
yes	117
no	53
extent of resection (D)	
total or subtotal	76
partial or biopsy only	94
tx w/ IORT (D)	
yes	28
no	142
irradiation field (D)	
combination of WBRT	39
extended local	131
fractionation regimen (D)	
conventional	49
uneven	76
HF	45
mean total dose in Gy (C)	63.0 ± 11.0
mean period of EBRT in days (C)	49.9 ± 14.1
period of tx (D)	
1981–1992	85
1992–2002	85

* Means are expressed ± standard deviations. Abbreviations: (C) = continuous variable; (D) = discrete variable.

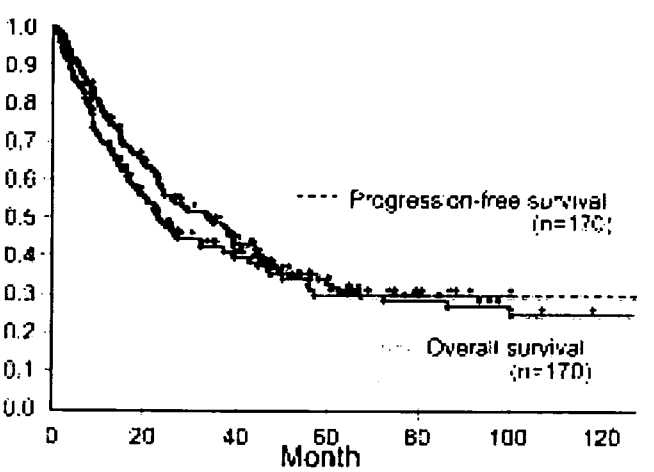

FIG. 1. Graph showing overall and progression-free survival in 170 patients with AA. In this and subsequent graphs, values on the y axis denote the percentage of survival.

TABLE 3

*Results of univariate and multivariate analyses of data in 170 patients with AA**

Variable	Univariate Analysis			Multivariate Analysis		
	HR [Expβ]	χ^2	p Value	HR [Expβ]	χ^2	p Value
sex (D)	0.921	0.671	0.413	NS	NS	NS
age (C)	0.980	11.43	<0.001	0.986	5.078	0.024
KPS status (D)	0.596	19.73	<0.001	0.748	5.314	0.021
site (D)	0.672	16.74	<0.001	0.717	9.873	0.002
tumor size (C)	0.930	2.397	0.122	NS	NS	NS
chemo (D)	0.849	2.553	0.110	NS	NS	NS
extent of op (D)	0.591	27.73	<0.001	0.665	10.71	0.001
IORT (D)	0.839	2.066	0.151	NS	NS	NS
irradiation field (D)	0.723	8.922	0.003	NS	NS	NS
fractionation regimen (D)	0.600	9.922	0.007	NS	NS	NS
total dose (C)	0.962	14.56	<0.001	0.960	4.763	0.029
period of EBRT (C)	0.994	0.531	0.466	NS	NS	NS
period of tx (D)	0.576	30.80	<0.001	NS	NS	NS

* Exp = exponential; NS = not significant.

patients in the total resection group was the most favorable, and significantly so, whereas the prognosis of those in the subtotal resection group was slightly worse, although the difference was not significant (p = 0.55, log-rank test). Nevertheless, the prognosis of the patients in the subtotal resection group was significantly more favorable than for those in the partial resection and biopsy-only groups (p = 0.007, log-rank test).

Figure 3 shows survival curves according to the total dose of radiation therapy. The group treated with a high dose (> 60 Gy, 91 patients) showed a significantly more favorable prognosis than did the one treated with a low dose (≤ 60 Gy, 79 patients) (5-year survival rate in the high-dose group was 45.0% compared with 21.1% in the low-dose group; MST was 48.9 months compared with 21.6 months ([p = 0.0006, log-rank test]; HR 0.96; 95% CI 0.93–0.99 [p = 0.029]).

Figure 4 shows survival curves according to extent of

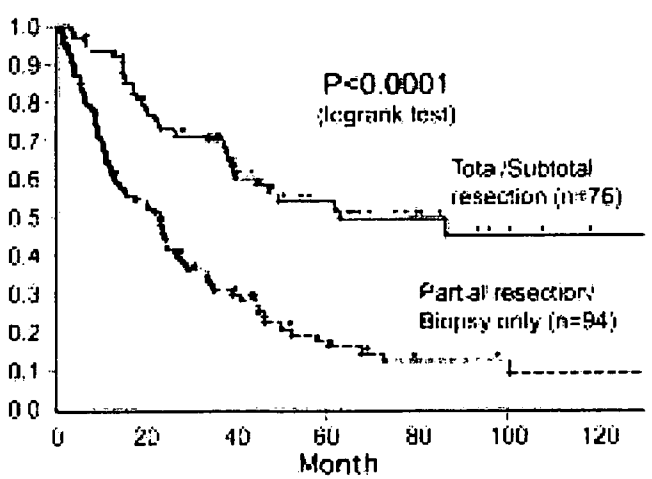

FIG. 2. Survival curves plotted according to extent of surgery (total or subtotal resection compared with partial resection or biopsy only) in 170 patients with AA.

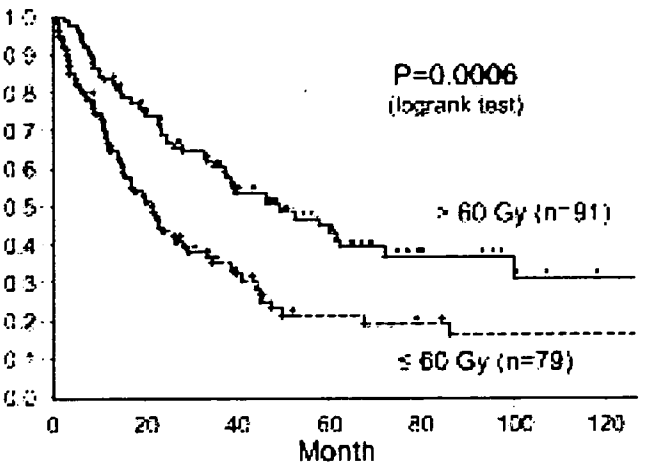

FIG. 3. Survival curves plotted according to total radiation dose (> 60 Gy or ≤ 60 Gy) in 170 patients with AA.

surgery (≥ subtotal resection or ≤ partial resection) and total radiation dose (> 60 Gy or ≤ 60 Gy). Patients were divided into three categories (Group A, those who underwent ≥ subtotal resection and received a > 60-Gy radiation dose; Group B, those who underwent ≤ partial resection and received a > 60-Gy radiation dose, or ≥ subtotal resection and ≤ 60 Gy; and Group C, those who underwent ≤ partial resection and received a ≤ 60-Gy radiation dose). The prognosis of the patients in Group A was significantly more favorable than that of patients in Group B or C (5-year survival rates: Group A, 66.2%; Group B, 25.7%; and Group C, 14.8% [p < 0.0001, log-rank test]; HR 0.40, 95% CI 0.28–0.56 for Group A, and HR 1.27, 95% CI 0.98–1.67 for group B [p < 0.0001]). The groups in which either surgery or radiation dose was insufficient showed significantly poor prognosis.

Figure 5 shows survival curves according to total radiation dose in the 56 patients who underwent gross-total resection of tumor. The patients treated with a high dose (> 60 Gy, 33 patients) showed a significantly more favorable prognosis than the ones treated with a low dose (≤ 60 Gy, 23 patients). The 5-year survival rate in the high-dose group was 65.6%, compared with 38.3% in the low-dose group ([p = 0.04, log-rank test]; HR 0.67; 95% CI 0.44–1.00 [p = 0.05]).

Treatment-associated brain necrosis was seen in 10 (5.9%) of the 170 patients (Table 4). The median period before brain necrosis occurred was 28.3 months (range 8.2–76.2 months). The mean total radiation dose for patients with brain necrosis was 70.6 ± 12.9 Gy, and that for patients without brain necrosis was 62.5 ± 10.7 Gy (mean ± standard deviation, p = 0.02). The total radiation dose was significantly higher in patients in whom brain necrosis was noted. In the group of patients who underwent chemotherapy, five (4%) of 117 had brain necrosis, and in the group of patients who underwent IORT, three (11%) of 28 had brain necrosis. No significant relationships were found between brain necrosis, use of IORT, and use of chemotherapy. Four of the 10 patients with brain necrosis died; however, as shown in the table, no patient died of radiation-induced brain necrosis. Most of the patients with brain necrosis showed few neurological symptoms.

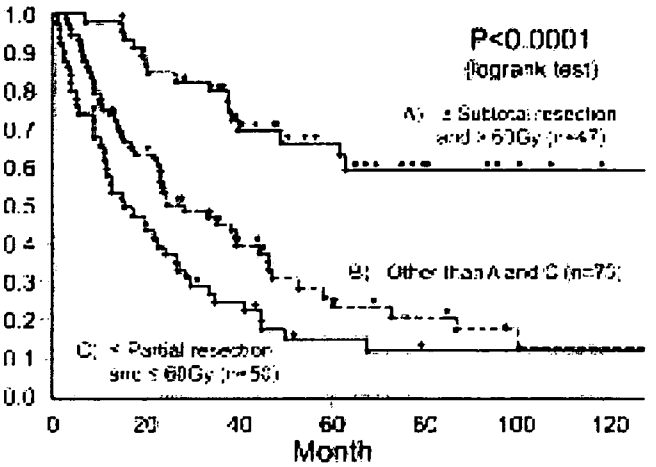

FIG. 4. Survival curves plotted according to extent of surgery and total radiation dose (Group A, ≥ subtotal resection and > 60 Gy [47 patients]; Group B, ≥ subtotal resection and ≤ 60 Gy, or ≤ partial resection and > 60 Gy [73 patients]; and Group C, ≤ partial resection and ≤ 60 Gy [50 patients]).

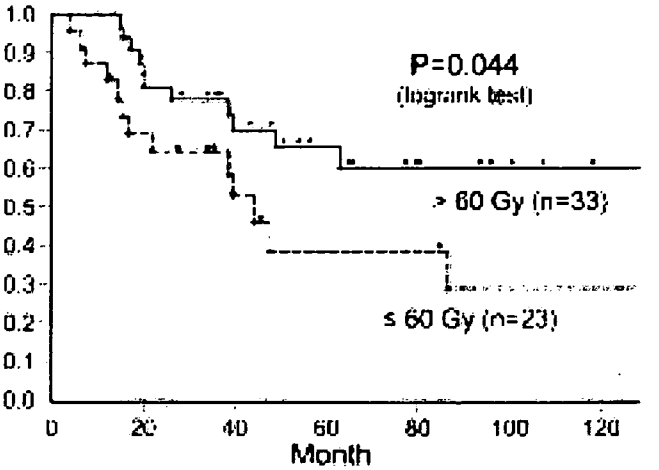

FIG. 5. Survival curves plotted according to total radiation dose (> 60 Gy or ≤ 60 Gy), limited to the patients who underwent gross-total tumor removal (56 patients).

Discussion

Significant prognostic factors for patients with AA in multivariate analysis were as follows: site of the lesion, extent of surgery, KPS status, patient's age, and total dose of radiation therapy. According to these results, factors on the patient's side, such as site, KPS, and age, account for the majority of prognostic factors. As shown in previous studies, these factors have a great impact on the prognosis of patients with high-grade glioma.[2,6,8,11,16,20,22]

Extent of surgery was the most powerful prognostic factor in the treatment parameters, and total dose of radiation therapy was the second most important prognostic factor. Several authors have reported that extent of surgery has a strong correlation with the prognosis of patients, and the results of our study are compatible with those of the other studies.[11,16] Curran et al.[3] suggested that resection did not have a great impact on prognosis in patients with glioblastoma multiforme located in the supratentorial area compared with the impact of radiation alone. However, in this study of AAs located in the supratentorial area (132 tumors), the prognosis of patients who underwent total or subtotal resection was significantly more favorable than that of patients who underwent partial resection or biopsy only (MST 86.4 compared with 24.7 months, $p < 0.0001$). Although there are various opinions about the significance of surgery,[1,6,20] the results of the aforementioned study imply that surgery is an essential modality and that the extent of resection has a great impact on prognosis in patients with AA.

It is known that malignant glioma is a radioresistant tumor both in vitro and in vivo, and it is difficult to control the lesion by using irradiation alone.[14,16,19] The results of our study also support the suggestion that resection of as much of the tumor as possible is a precondition for a favorable prognosis. According to our results, total radiation dose was the second most significant prognostic factor in the parameters of treatment. This finding has no relation to the presence of postoperative residual tumor: patients in the higher total dose group, even those who underwent total or subtotal resection, showed a significantly more favorable prognosis (80 patients, 5-year survival rates 63.1% compared with 31.7% [p = 0.003, log-rank test; data not shown]). Also, as shown in Fig. 5, a radiation dose of more

TABLE 4

*Characteristics in 10 patients with treatment-associated brain necrosis**

Case No.	Fractionation Regimen	Dose of EBRT (Gy)	IORT	Chemo	Extent of Resection	Site of Lesion	Time to Brain Necrosis (mos)	Status at Final FU
1	uneven	58	no	no	biopsy	multiple	8.2	disease-specific death
2	uneven	54	no	yes	biopsy	frontal	9.6	disease-specific death
3	uneven	61.5	no	no	total	frontal	23.4	alive
4	uneven	63	no	yes	total	frontal	55.5	alive
5	uneven	63	no	no	partial	frontal	33.2	alive
6	HF	72	no	no	total	frontal	12.8	alive
7	HF	72	yes	no	total	frontal	76.2	alive
8	HF	72	no	yes	subtotal	frontal	35.4	alive
9	HF	72	yes	yes	subtotal	frontal	11.6	dead of intercurrent disease
10	HF	72	yes	yes	partial	temporal	34.7	disease-specific death

* biopsy = biopsy alone; FU = follow up; total = gross-total resection.

than 60 Gy significantly contributes to improvement in the patients' prognosis, even in cases in which gross-total resection of the tumor was successfully performed. This result supports the suggestion that postoperative radiation therapy at an insufficient dose leads to local recurrence, even if the primary lesion has been totally resected, and that combined radiation therapy is essential for treatment of AA.

Malignant glioma often spreads microscopically beyond the macroscopic margin visualized on MR or CT images.[7,9] It is therefore thought to be difficult to resect microscopic malignant cells invading peripheral tissue around the tumor. On the other hand, malignant glioma is radioresistant,[14,16] and it is therefore difficult to eliminate macroscopic tumor by using radiotherapy alone. It seems that the role of surgery is removal of the bulk of the tumor, and that the role of radiation therapy is elimination of residual microscopic malignant cells. Surgery and radiation therapy have distinct roles, and both modalities seem to be essential for the treatment of Grade III glioma. Results of survival analysis taking into account the combination of these modalities seem to support this opinion (Fig. 4).

Miller et al.[8] reported that total radiation dose was one of the significant prognostic factors. The results of our study are consistent with their results in that total radiation dose had an impact on the prognosis of patients with malignant glioma. However, these authors reported that no additional benefit could be obtained for doses greater than 60 Gy, whereas the results of our study are quite different in this point. This difference may be due to the number of patients in the Miller study (16 with AA and 66 with glioblastoma multiforme) who received radiation therapy at that time. In the present study, which includes a much larger cohort (170 patients with only AAs), we suggest that postoperative radiation therapy at a dose of more than 60 Gy is required for local control, and this speculation seems to be valid from the viewpoint of biological and clinical radiosensitivity of malignant glioma cells.[14,19]

Use of chemotherapy was not a significant prognostic factor in this study, either in univariate or multivariate analysis, and its use was not significantly related to brain necrosis. The role of chemotherapy in high-grade glioma is controversial. Nevertheless, several investigators have reported a small but significant benefit for survival in patients with high-grade glioma.[4,21] Although the impact of chemotherapy is not superior to that of surgery and radiotherapy, further investigation of optimal timing, dose intensity, and the optimal drug combination is required. Use of IORT was also not a significant prognostic factor in multivariate analysis, and the significance of IORT for treatment of high-grade glioma is controversial. Several investigators have suggested that there is no significant benefit of IORT,[10] whereas others have suggested that IORT is effective for patients with high-grade glioma, but the survival benefit has not been clarified.[13,15] The prognostic significance of IORT in patients with Grade III astrocytoma was not shown in this study.

One of the problems is occurrence of toxicity, such as brain necrosis. Five of the 10 patients with brain necrosis in our study underwent uneven fractionation of radiotherapy. Brain necrosis occurred in those five despite relatively low doses of total radiation without IORT. A large single-fraction size (4–5 Gy/fraction) was used in this regimen. It is known that irradiation with a large single-fraction size is one of the risk factors of late toxicity, especially in the CNS.[23] Care should be taken when using a large single-fraction size for treatment of CNS tumors. Hyperfractionated radiation therapy uses a small single-fraction size (1.2 Gy/fraction); nevertheless, the standard dose is relatively high. Therefore, the use of IORT should be determined with caution. In our study, the significance of the fractionation regimen of radiotherapy combined with the use of IORT has not been shown in the multivariate analysis of patient survival. However, a large fraction size for EBRT or IORT seemed to be one of the causes of late toxicity.

The difference in influence of fraction size between malignant glioma and healthy CNS tissue may come from the difference between alpha/beta values in malignant tissue and those in healthy tissue from the viewpoint of radiation biology. It is reported that the alpha/beta value of malignant glioma is high (usually $\geq$ 10 Gy), whereas the alpha/beta value of healthy CNS tissue is low (usually $<$ 5 Gy).[17,18,24] This difference between alpha/beta values in tumor and healthy tissue means that healthy CNS tissue is more sensitive to an increase in the fraction size of irradiation. Based on these results, it seems that to avoid late toxicity a large fraction size of EBRT or IORT should not be routinely used for treatment of CNS tumors. However, as shown in Table 4, there was no treatment-related death in patients in our study. It is therefore thought that irradiation of more than 60 Gy will not lead to dangerous and intolerable toxicity. As shown by survival curves in Fig. 3, the survival benefit of irradiation with more than 60 Gy seems to exceed the risk of radiation-induced toxicity.

Conclusions

The results of this retrospective study showed significantly better survival in patients who underwent surgery and radiation therapy for treatment of AA. As complete a tumor resection as possible and combining surgery with high-dose irradiation seem to improve the prognosis of patients with these lesions. The MST of patients with AA has been extended by approximately one and a half times in recent decades, but the optimum dose, field of radiation therapy, fractionation regimen, and regimen of chemotherapy have not yet been established. Further investigation of treatment parameters is required for improvement of treatment protocols for AA.

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