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Prognostic significance of contrast-enhancing anaplastic astrocytomas in adults

Clinical article

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Object. Patients harboring anaplastic astrocytomas (AAs) typically have a poor prognosis, with median survival times of approximately 3 years following resection. However, a significant variability in individual outcomes remains, with some patients surviving for a few months and others for several years. The ability to predict patient outcomes based on preoperative variables would help prognosticate survival and may also guide treatment strategies. The prognostic implications of a preoperative contrast-enhancing AA remain poorly understood.

Methods. The medical records of all patients who underwent a craniotomy for a hemispheric AA from 1996 to 2006 at a single institution were retrospectively reviewed. Multivariate proportional hazards regression analysis was used to identify independent associations with recurrence and survival. The Kaplan-Meier method and log-rank analysis were used to plot and compare outcomes for patients with and without preoperative contrast enhancement.

Results. One hundred sixty-five patients were available for analysis. The AAs were contrast enhancing in 102 patients (62%), and nonenhancing in 63 patients (38%). There were no significant differences in clinical and treatment-related variables between patients with and without contrast enhancement. After multivariate analysis, contrast enhancement was independently associated with decreased survival ($p = 0.02$) and increased recurrence ($p = 0.04$). The 5-year overall survival rates for patients with contrast-enhancing versus nonenhancing tumors were 31 and 38.5%, respectively. The 3-year rates of progression-free survival for patients with contrast-enhancing versus nonenhancing tumors were 32 and 56%, respectively. Interestingly, heterogeneously enhancing tumors appear to result in poorer outcomes as compared with other types of enhancement (such as ring enhancing, nodular, and others). Among patients with contrast-enhancing AAs, gross-total resection significantly delayed recurrence ($p = 0.05$) but did not significantly prolong survival ($p = 0.52$).

Conclusions. This study may provide insights into risk-stratifying patients with AAs, and most specifically those with AAs that enhance with contrast administration. *(DOI: 10.3171/2010.2.JNS091010)*

Key Words • **anaplastic astrocytoma** • **contrast enhancement** • **outcome** • **recurrence** • **survival**

Patients harboring AAs typically have dismal prognoses, with median survival times of approximately 3 years following resection. Some patients have AAs that recur within months of surgery and they die shortly thereafter from progressive disease, whereas other patients harbor tumors that remain indolent for several years.[10,19] These differences in outcomes have placed an emphasis on ascertaining risk factors associated with recurrence and survival for patients undergoing resection of AAs. An understanding of these factors will help predict outcomes and may also guide treatment strategies.

Studies attempting to ascertain factors associated with recurrence and survival for patients with AAs are few and limited. The only factors that have been consistently shown to be associated with survival are patient age, preoperative neurological status, and extent of resection.[8,12,19] However, the ability to predict how an AA behaves based on preoperative neuroimaging is limited. Anaplastic astrocytomas that exhibit preoperative contrast enhancement on neuroimaging may behave more

Abbreviations used in this paper: AA = anaplastic astrocytoma; GTR = gross-total resection; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky Performance Scale; PFS = progression-free survival; STR = subtotal resection.

This article contains some figures that are displayed in color online but in black and white in the print edition.

aggressively, similar to low-grade gliomas.[3] However, the consequences of a contrast-enhancing AA remain controversial, with some studies showing either a negative association or no association with patient survival.[6,8,17,22] These studies are limited by small patient sample sizes, lack of multivariate analyses, failure to include uniform pathologies, or inclusion of patients undergoing biopsy procedures, among others.[6,8,17,22] The prognostic implication of a contrast-enhancing AA therefore remains poorly understood. In this study we have evaluated the effects of preoperative contrast enhancement on survival and recurrence for adult patients harboring supratentorial AAs. An understanding of tumor behavior may lead to individualized treatment strategies aimed at maximizing patient outcomes.

Methods

Patient Selection

The records of all adult patients undergoing surgery for an AA at a single academic tertiary care institution (Johns Hopkins Hospital) between 1996 and 2006 were retrospectively reviewed. Patients at least 18 years old with a tissue-proven diagnosis of a hemispheric WHO Grade III AA[16] were included in the study. Patients with prior lower-grade tumors, oligodendroglial components to their tumor, infratentorial location, without pre- and postoperative MR imaging, and/or who underwent diagnostic needle biopsy only, were excluded from the analysis. Tumor pathology was determined by a senior neuropathologist, and based on WHO criteria.[16] The criteria for identifying the pathology of recurrent AAs were also based on the WHO classification scheme, including cellular pleomorphism, mitoses, and absence of necrosis.

The clinical, operative, and hospital course records of the patients were reviewed. Information collected from neurosurgery and neurooncology clinical notes included patient demographics, presenting symptoms, pre- and postoperative neuroimaging, postoperative neurological function, and adjuvant therapy. Preoperative KPS scores[18] were assigned by the clinician at the time of evaluation and available in the chart for review in all patients. Tumor characteristics on pre- and postoperative MR imaging were assessed at the time of surgery by a neuroradiologist blinded to patient outcomes.

In general, the aim of surgery was to achieve a GTR of the tumor when possible. Subtotal resection was performed mainly when the tumor involved eloquent brain as confirmed by intraoperative mapping and/or monitoring (awake/speech language mapping, direct cortical motor stimulation, and motor evoked or somatosensory evoked potentials). Motor and somatosensory evoked potentials were routinely used in the majority of cases. Surgical navigation (CT and/or MR imaging wand) was used in all cases after 2001. The use of motor mapping or electrocorticography largely depended on the preference of the surgeon. The degree of resection was determined from neuroradiology reports. Subtotal resection and GTR were defined as having residual and no residual enhancement noted on postoperative MR imaging obtained < 48 hours after resection, respectively. In the subset of AAs that did not demonstrate preoperative enhancement, the extent of resection was determined by comparing preoperative FLAIR signal abnormality with postoperative MR imaging obtained within 48 hours of resection. Perioperative mortality was defined as death within 30 days of surgery.

Imaging Characteristics and Criteria

Preoperative MR imaging with and without contrast administration was available for review in all patients. All patients underwent the same preoperative MR imaging protocol, which consisted of a 3-plane localizer sequence (TR 8.5 msec, TE 1.6 msec), an axial FLAIR sequence (TR 10,000 msec, TE 148 msec, TI 2200 msec), an axial T2-weighted fast spin echo sequence (TR 3000 msec, TE 102 msec, echo train length 16, matrix 256 × 196 mm), axial diffusion weighted imaging (TR 10,000 msec, TE 99 msec, b = 1000 sec/mm^2), and a postcontrast 3D spoiled-gradient recalled-acquisition in the steady-state (TR 34 msec, TE 8 msec) T1-weighted sequence. Gadolinium was administered intravenously (1 ml/4.5 kg), and postcontrast axial images were obtained 4 minutes after infusion.

The date of death was recorded according to the public US Social Security Death Index database (http://ssdi.rootsweb.ancestry.com/). Patients who were not confirmed as having died were classified as lost to follow-up at the time of the last clinic visit. Additionally, patients with tumors that were not confirmed as having recurred were classified as lost to follow-up at the time of the last MR imaging. Tumor recurrence was defined as evidence of either tumor recurrence or progressive growth on MR imaging. As such, patient survival is a more reliable outcome measure as compared with tumor recurrence. Also, it is inherent that it is easier to detect tumor progression for contrast-enhancing tumors as compared with nonenhancing tumors. Thus, FLAIR imaging was primarily used to detect tumor recurrence to minimize this inherent limitation. Nonetheless, although these factors may be interrelated, examining the role of contrast enhancement as it relates to patient survival and tumor recurrence are important outcome variables that provide insight into tumor biology and patient outcomes.

Statistical Analysis

Summary data were presented as means ± SDs for parametric data and as median (IQR) for nonparametric data. Percentages were compared using the Fisher exact test. For intergroup comparisons, the Student t-test was used for continuous data and the Mann-Whitney U-test for categorical data. The independent association between preoperative tumor enhancement and factors known to be associated with survival (age,[19,22] KPS score,[8,19] extent of resection,[8,12] postoperative radiation,[9] temozolomide,[14] and carmustine wafer implantation[1]) was assessed using multivariate proportional-hazards regression analysis (JMP version 7, SAS Institute). This same model was also used to identify independent associations for tumor recurrence. Survival and recurrence as a function of time after resec-

tion were expressed as estimated Kaplan-Meier plots. Survival and recurrence between patients with and without MR imaging contrast-enhancing tumors were compared using log-rank analysis. Probability values < 0.05 in all analyses were considered statistically significant.

Results

Patient Population

The pre- and postoperative patient information is summarized in Table 1. Of 181 patients who underwent craniotomies for an AA, 165 met inclusion/exclusion criteria. Average patient age was 42 ± 14 years. One hundred twenty-five patients (76%) underwent surgery for primary resection of an AA and 40 (24%) underwent surgery for secondary resection of a recurrent AA. Median KPS score (IQR) at presentation was 80 (80–90). Eighty-four patients (51%) presented with seizures, 60 (36%) with signs of increased intracranial pressure (headache, nausea, vomiting), 22 (13%) with speech or language difficulty, 22 (13%) with mental status changes, 11 (7%) with visual deficits, 29 (18%) with motor deficits, and 22 (13%) with sensory deficits. The average tumor size was 4.0 ± 1.8 cm, and the tumor occurred primarily in the frontal lobe in 91 patients (55%), temporal lobe in 41 (25%), parietal lobe in 29 (18%), and occipital lobe in 4 patients (2%). The tumor primarily involved the cortex in 73 patients (44%), and involved the language cortex in 4 (2%) and the motor/sensory cortex in 12 (7%). Gross-total resection was achieved in 78 patients (47%). There was 1 case of perioperative death, which was secondary to a myocardial infarction. Thirty-one patients (19%) received carmustine wafer implantation, 110 (67%) received temozolomide chemotherapy, and 125 (76%) received radiation therapy. At last follow-up, 79 (48%) of the tumors had recurred and 90 (55%) patients had died. For the 75 surviving patients (45%), the median (IQR) follow-up time was 33.6 (12–54) months. The median overall survival was 34.5 months, and the 1-, 2-, 5-, and 10-year survival rates were 80.3, 63.3, 34.2, and 18.7%, respectively. The median PFS was 33.1 months, and the 1-, 2-, 5-, and 10-year PFS rates were 71.7, 58.7, 34.7, and 0%, respectively.

TABLE 1: Summary of pre- and postoperative characteristics in 165 patients with hemispheric AAs*

Characteristic	Group		p Value
	Tumor Enhancement	Tumor Non-enhancement	
no. of patients	102	63	
mean age ± SD	43.7 ± 14.9	39.6 ± 14.7	0.10
male	66 (65)	36 (57)	0.41
median KPS score (IQR)	80 (80–90)	80 (80–90)	0.76
symptom duration (mos)	2 (1–5)	2 (1–4)	0.61
symptoms			
seizures	52 (51)	32 (51)	0.99
headache/nausea/vomiting	33 (32)	27 (43)	0.19
motor deficit	19 (19)	10 (16)	0.68
sensory deficit	14 (14)	8 (13)	0.99
language deficit	16 (16)	6 (10)	0.35
visual deficit	7 (7)	4 (6)	0.99
gait deficit	5 (5)	3 (5)	0.99
cognitive deficit	16 (16)	6 (10)	0.35
primary resection	74 (73)	51 (81)	0.26
tumor size (cm)	3.8 ± 1.7	4.4 ± 1.9	0.10
tumor location			
frontal	55 (54)	36 (57)	0.75
temporal	24 (24)	17 (27)	0.71
parietal	20 (20)	9 (14)	0.41
occipital	3 (3)	1 (2)	0.99
cortical	45 (44)	28 (44)	0.99
eloquence	10 (10)	6 (10)	0.99
language cortex	3 (3)	1 (2)	0.99
motor/sensory cortex	7 (7)	5 (8)	0.77
GTR	45 (44)	33 (52)	0.34
new postoperative deficit			
motor deficit	5 (5)	3 (5)	0.99
language deficit	0 (0)	0 (0)	0.99
visual deficit	1 (1)	2 (3)	0.56
carmustine wafer implantation	21 (21)	10 (16)	0.54
temozolomide chemotherapy	69 (68)	41 (65)	0.74
postop radiation therapy	78 (76)	47 (75)	0.85

* All data given as number of patients (%) unless otherwise indicated.

Contrast-Enhancing AAs

One hundred and two patients (62%) presented with a contrast-enhancing AA (Fig. 1). Of these contrast-enhancing AAs, 45 (44%) demonstrated nodular enhancement, 47 (46%) heterogeneous enhancement, and 18 (18%) ring enhancement. There were no clinical, radiographic, or treatment variables that were significantly different between patients with and without contrast-enhancing tumors, respectively (Table 1).

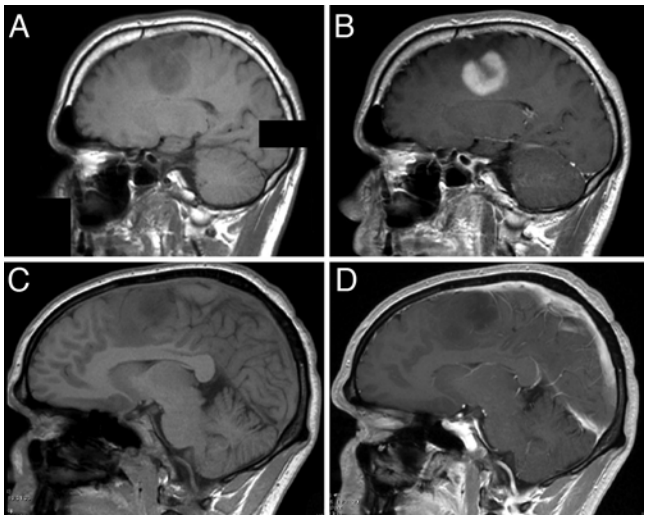

Fig. 1. Precontrast **(A and C)** and postcontrast **(B and D)** administration T1-weighted MR images demonstrating representative patients with a contrast-enhancing **(A and B)** and nonenhancing **(C and D)** AA. The AA is left frontal in the first patient **(A and B)**, and right frontal in the second patient **(C and D)**.

Contrast Enhancement and Survival

Tumor contrast enhancement was associated with survival according to the univariate analysis (HR 1.628, 95% CI 1.059–2.556; p = 0.02). After controlling for all factors previously shown to be associated with survival (age,[19,22] KPS score,[8,19] extent of resection,[8,12] postoperative radiation,[9] temozolomide,[14] and carmustine wafer implantation[1]), contrast enhancement remained independently associated with survival after multivariate analysis (HR 2.370, 95% CI 1.031–3.162; p = 0.02). Among the different types of enhancement, patients with heterogeneous enhancement had the most significant association with poor survival (HR 1.720, 95% CI 1.094–2.655; p = 0.02). However, there was no significant association between patient survival and the presence of nodular enhancement (p = 0.16) or ring enhancement (p = 0.82). In terms of GTR, there was no significant difference in the extent of resection between patients with and without nodular enhancement (p = 0.27).

The median survival duration for patients with enhancing AAs was 26.7 months, compared with 48.0 months for patients with nonenhancing AAs (p = 0.01). The 1-, 2-, 3-, and 5-year survival rates were 75.4, 55.4, 41.2, and 31.3%, respectively, for patients with enhancing AAs as compared with 88.0, 75.5, 60.4, and 38.5, respectively, for patients with nonenhancing AAs (Fig. 2). After matching patients with and without contrast enhancement by age, patients with contrast-enhancing tumors showed poorer overall survival rates as compared with patients without contrast-enhancing tumors (p = 0.02). The median survival duration was 27.4 months for patients with contrast enhancement as compared with 47.9 months for patients without contrast enhancement.

Contrast Enhancement and Recurrence

Similar to the results for patient survival, tumor contrast enhancement was significantly associated with recurrence in the univariate analysis (HR 1.571, 95% CI 1.002–2.543; p = 0.04). After controlling for all factors previously shown to be associated with recurrence (age,[19,22] KPS score,[8,19] extent of resection,[8,12] postoperative radiation,[9] temozolomide,[14] and carmustine wafer implantation[1]), contrast enhancement remained independently associated with recurrence in the multivariate analysis (HR 1.590, 95% CI 1.005–2.447; p = 0.04). However, there was no significant association between type of enhancement and recurrence (nodular, p = 0.27; heterogeneous, p = 0.10; ring enhancement, p = 0.29). The presence of heterogeneous enhancement trended toward, but did not reach, statistical significance (HR 1.502, 95% CI 0.974–2.404; p = 0.10).

The median PFS for patients with enhancing AAs was 22.0 months, compared with 52.9 months for patients with nonenhancing AAs (p = 0.001). The 1-, 2-, 3-, and 5-year PFS rates were 61.6, 48.1, 31.9, and 27.8%, respectively, for patients with enhancing AAs, as compared with 85.4, 70.8, 55.9, and 43.2%, respectively, for patients with nonenhancing AAs (Fig. 3). After matching patients with and without contrast enhancement by age, patients with contrast-enhancing tumors had poorer PFS rates compared with patients without contrast-enhancing tumors (p = 0.02). The median survival duration was 28.7 months for patients with contrast enhancement as compared with 52.9 months for patients without contrast enhancement.

Contrast-Enhancing Tumors and Extent of Resection

The effects of the extent of resection on recurrence and survival for patients with contrast-enhancing AAs were then analyzed. With regard to recurrence, the median PFS for patients with GTR of their enhancing AAs was 30.9 months, compared with 16.6 months for patients with STR. This difference was statistically significant in the log-rank analysis (p = 0.05). With regard to survival, the median overall survival for patients with GTR of their enhancing AAs was 33.8 months, compared with 25.9 months for patients with STR. However, this difference was not statistically significant in the log-rank analysis (p = 0.52).

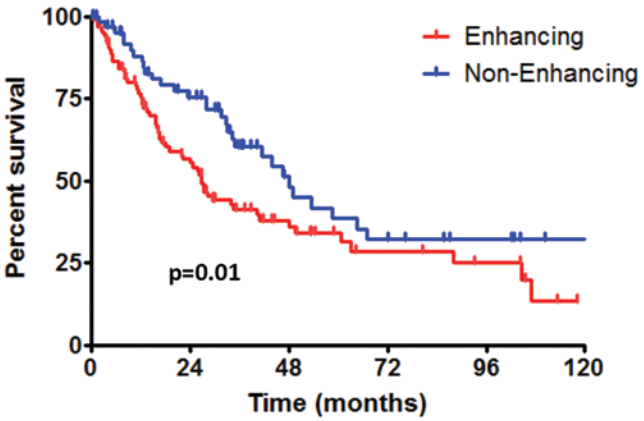

Fig. 2. Graph of the percentage of overall survival for adult patients with contrast-enhancing versus nonenhancing AAs. The median survival for patients with contrast-enhancing AAs was 26.7 months versus 48.0 months for patients with nonenhancing AAs (p = 0.01). The 1-, 2-, 3-, and 5-year survival rates were 75.4, 55.4, 41.2, and 31.3%, respectively, for patients with contrast-enhancing AAs, compared with 88.0, 75.5, 60.4, and 38.5%, respectively, for patients with nonenhancing AAs.

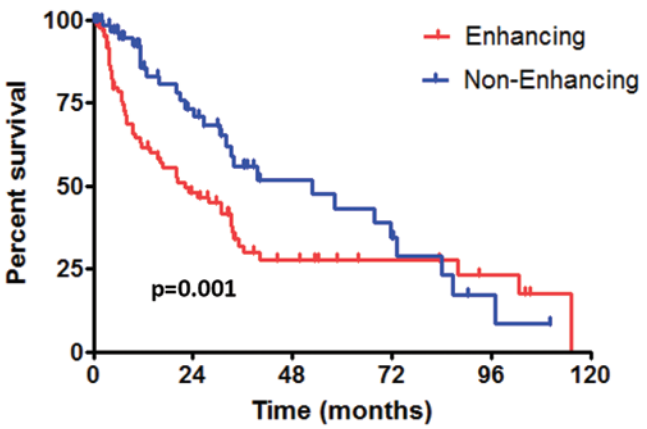

Fig. 3. Graph of the percentage of PFS in adult patients with contrast-enhancing versus nonenhancing AAs. The median PFS for patients with contrast-enhancing AAs was 22.0 months versus 52.9 months for patients with nonenhancing AAs (p = 0.001). The 1-, 2-, 3-, and 5-year PFS rates were 61.6, 48.1, 31.9, and 27.8%, respectively, for patients with contrast-enhancing AAs, compared with 85.4, 70.8, 55.9, and 43.2%, respectively, for patients with nonenhancing AAs.

Discussion

In this present study of 165 adult patients with hemispheric AA, 102 (62%) and 63 (38%) patients had contrast-enhancing and nonenhancing tumors, respectively. There were no significant differences in clinical and treatment-related variables between patients with and without contrast enhancement. Preoperative contrast enhancement was independently associated with decreased survival and increased recurrence in multivariate and log-rank analyses. The 5-year overall survival rates for patients with contrast-enhancing versus nonenhancing tumors were 31 and 38.5%, respectively. The 3-year rates of PFS for patients with contrast-enhancing versus nonenhancing tumors were 32 and 56%, respectively. Patients with heterogeneously enhancing tumors appear to have poorer outcomes as compared with patients with different types of enhancement (such as ring enhancing, nodular, and others). Among patients with contrast-enhancing AAs, GTR significantly delayed recurrence but did not significantly prolong survival.

Anaplastic astrocytomas are relatively rare tumors, with an annual incidence of 0.5 to 0.7 per 100,000 people.[21] Patients with AAs have a median PFS and overall survival of approximately 24 and 30 months, respectively.[8,12,21,22] Although the median PFS and overall survival times remain poor, individual survival is variable, with some patients surviving for a few months and others for several years.[8,12,21,22] This heterogeneity has placed an emphasis on understanding factors associated with delayed recurrence and prolonged survival. This understanding may not only help physicians and patients predict outcomes, but may also help guide treatment strategies.

The prognostic implication of an AA that enhances with contrast administration remains controversial. Among AAs, 50 to 70% of these tumors enhance with contrast administration.[8,17,22] Contrast enhancement typically occurs when contrast extravasates from the tumor vasculature, which typically lacks endothelial tight junctions.[2,4] The presence of contrast enhancement usually portends a more malignant tumor. In fact, the majority of malignant astrocytomas (AAs and glioblastomas) display contrast enhancement, while lower-grade tumors typically lack contrast enhancement.[2,4] However, it is not unusual for high-grade tumors to lack enhancement and for low-grade tumors to display enhancement.[2–4] The prognostic implication of contrast enhancement among AAs is poorly understood.

Previous studies evaluating the effects of contrast enhancement on patient outcomes are few and limited.[8,17,22] Tortosa et al.[22] studied 95 patients with anaplastic tumors, including oligodendrogliomas and oligoastrocytomas, and found that the absence of ring enhancement was associated with longer survival. In 2005 Pope et al.[17] studied the MR imaging of patients with both WHO Grade III and IV gliomas and found a possible association between contrast enhancement and survival, but only evaluated 42 patients with anaplastic tumors. Keles et al.[8] studied 102 patients with AAs, and found that preoperative contrast enhancement was not significantly associated with survival, but did find that the volume of residual contrast following surgery predicted overall survival. However, these studies consisted of small patient sample sizes, included patients with mixed pathologies and pathological grades, and incorporated patients who underwent needle biopsy procedures, which is subject to sampling errors.[17,22] These factors may confound the ability to understand the effects of preoperative contrast enhancement on recurrence and survival for patients with AAs.

The findings of this study may help guide treatment strategies and physician-patient discussions for patients with AAs, but are currently speculative. The only preoperative factors that have been found to be associated with outcomes are patient age and functional status, in which younger age and improved neurological function were associated with improved outcomes.[17,22] This study also shows the importance of preoperative contrast enhancement. Patients with preoperative contrast-enhancing tumors may experience increased recurrence and shortened survival. Among patients with contrast-enhancing AAs, those tumors with heterogeneous enhancement may be particularly prone to progress. Furthermore, extensive resection may delay recurrence, but may not affect overall survival for patients with contrast-enhancing AAs, as it has with all AAs regardless of contrast enhancement.[12] The presence of preoperative contrast enhancement may identify a more malignant subset of AA that behaves more like a glioblastoma, or the subgroup of tumors closer to glioblastoma (at the time of diagnosis), in their hypothesized biological transformation. The advent of newer imaging modalities including diffusion and perfusion-weighted imaging, vascular space occupancy, and cerebral metabolic rate of oxygen consumption also provide useful prognostic information for patients with AAs as well as other tumors.[5,7,11,23,24]

A different argument can be made for the noncontrast-enhancing AA. Because AAs are often grouped with glioblastomas in the way they are treated, AAs regardless of enhancement will typically be treated with radiation therapy and temozolomide chemotherapy.[21] However, the subset of AAs that do not enhance appear to be different and in some cases behave more like lower-grade tumors. Patients with these tumors may benefit from a different treatment regimen similar to what is reserved for patients with low-grade gliomas. This is obviously speculative, but may support the need for targeted therapy, where different treatments are aimed at the unique aspects of individual tumors. This study also shows the limitations of the current WHO grading system. In fact, AAs may actually represent a continuum between low-grade (WHO Grade II) and malignant (WHO Grade IV) astrocytomas, in which nonenhancing tumors behave more like Grade II tumors and contrast-enhancing tumors behave more like Grade IV tumors. This understanding may lead to more effective targeted therapies. In addition, the presence of contrast enhancement may provide more of an argument for re-resection, a need for prompt adjuvant chemotherapy and radiotherapy, and closer surveillance protocols.

This study is inherently limited by its retrospective design, and as a result, it is not appropriate to infer direct causal relationships. The patient population in this study cohort did not undergo standardized treatment paradigms,

which makes it difficult to study the effects of specific treatment modalities. One cannot discard the possibility that although extensive tissue was sent to the pathologist, the tissue that may identify a tumor as a glioblastoma may not be part of the sample undergoing analysis for diagnosis. Also, recurrence may be easier to detect with contrast-enhancing tumors as compared with nonenhancing tumors. To minimize this limitation with recurrence as an outcome measure, we relied on MR imaging, and especially FLAIR imaging, to detect tumor recurrence. Furthermore, the percentage of resection was not consistently recorded, which makes it difficult to ascertain gradations in outcomes. However, we tried to create a uniform patient population by utilizing strict inclusion criteria, thus providing more relevant information for adult patients with hemispheric AA. We included only patients who underwent resection of their tumor, and excluded variants known to effect survival including pediatric patients,[13] infratentorial tumors,[20] and biopsy procedures.[15] In addition, we used multivariate analyses to control for variables previously shown to have a strong clinical relationship with survival and recurrence in patients with AAs. We realize, however, that not all biases can be controlled for in this context, which is evident when the differences between patients with and without contrast-enhancing AA are marginally similar. Studies analyzing factors associated with recurrence and malignant degeneration have been limited. Given these statistical controls and a relatively precise outcome measure, we believe our findings may offer useful insights into the treatment of patients with AA. However, prospective studies are needed to provide better data for guiding clinical decision making.

Conclusions

Patients harboring AAs may have a dismal prognosis and it is understood that their individual survival is variable. The ability to identify preoperative risk factors associated with patient outcomes is limited. The presence of preoperative contrast enhancement, namely heterogeneous enhancement, may predict a more malignant subset of AAs that are associated with increased recurrence and decreased patient survival.

Disclosure

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