Glioblastoma treated with postoperative radio-chemotherapy:

Prognostic value of apparent diffusion coefficient at MR imaging

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Abstract

Purpose: To retrospectively evaluate whether the mean-, minimum-, and maximum apparent diffusion coefficient (ADC) of glioblastomas obtained from pretreatment MR images is of prognostic value in patients with glioblastoma.

Materials and Methods: The the institutional review board approved our study and waived the requirement for informed patient consent. Between February 1998 and January 2006, 33 patients (24 males, 9 females; age range 10 – 76 years) with supratentorial glioblastoma underwent pretreatment magnetic resonance (MR) imaging. The values of the mean-, minimum-, and maximum ADC (ADC_{mean}, ADC_{MIN}, and ADC_{MAX}, respectively) of each tumor were preoperatively determined from several regions of interest defined in the tumors. After surgical intervention, all patients underwent irradiation and chemotherapy performed according to our hospital protocol. The patient age, symptom duration, Karnofsky performance scale score, extent of surgery, and ADC were assessed using factor analysis of overall survival. Prognostic factors were evaluated using Kaplan-Meier survival curves, the log-rank test, and multiple regression analysis with the Cox proportional hazards model.

Results: Likelihood tests confirmed that ADC_{MIN} was the strongest among the 3 prognostic factors. Total surgical removal was the most important predictive factor for overall survival ($P < 0.01$). ADC_{MIN} was also statistically correlated with overall survival ($P < 0.05$) and could be used to classify patients into different prognostic groups. Interestingly, ADC_{MIN} was also the strongest prognostic factor ($P < 0.01$) in the group of patients in whom total tumor removal was not possible.

Conclusion: The ADC_{MIN} value obtained from pretreatment MR images is a useful clinical prognostic biomarker in patients with glioblastoma.

KEY WORDS: apparent diffusion coefficient, echo planar imaging, glioblastoma, magnetic resonance imaging, overall survival

Introduction

Glioblastoma is the most common malignant primary neoplasm of the central nervous system; median survival is approximately 1 year (1, 2). Conventional magnetic resonance imaging (MRI) can yield information on the gross anatomic structure of glioblastoma, but it provides little functional information. Diffusion-weighted (DW) MRI enables the volumetric intravoxel measurement of tissue characteristics based on the detection of changes in the random motion of water protons at the cellular or physiological level (3). Although the usefulness of DW-MRI for preoperative grading and postoperative assessment of glial tumors has been investigated (4-7), its value for predicting survival has not been fully addressed (8-10). Because the apparent diffusion coefficient (ADC) is inversely related to tumor cellularity and the glioma grade (4, 6, 11-14), we postulated that it reflects the biological viability and prognosis of glioblastomas. We therefore analyzed the ADC with respect to the surgical resection status and compared the mean-, minimum-, and maximum ADC (ADC_{mean}, ADC_{MIN}, and ADC_{MAX}, respectively) values as factors reflecting biological activity. We performed a retrospective study to determine whether these values obtained on

preoperative MRI scans are of prognostic value in patients with glioblastoma. We discovered that the ADC_{MIN} value is a prognostic factor for survival in patients with glioblastomas that are not totally resectable.

Materials and Methods

The institutional review board of our hospital approved this retrospective study and waived the requirement for informed patient consent. Patient information was kept confidential by removing all identifiers from our records at the completion of our analyses.

Patients, diagnosis and treatment

Between February 1998 and January 2006, 49 patients (29 males, 20 females) with histologically confirmed supratentorial glioblastoma were treated at our institution. Of these, 16 were excluded from this study for reasons such as incomplete MRI, progression from anaplastic or low-grade glioma, infratentorial tumors, and incomplete- or no postoperative irradiation or chemotherapy. The remaining 33 patients (24 males, 9

females; age range 10 – 76 years) with new, histologically confirmed glioblastoma who underwent pretreatment MRI were included in this study. Maximum tumor resection was performed in all patients; it was followed by postoperative external-beam radiation therapy and chemotherapy. Histopathological diagnoses based on World Health Organization criteria were determined by consensus between two authors (V.J.A., Y.T.) who were blinded to the MRI results. Gadolinium-enhanced MRI performed within 1 week after surgery was used to categorize the surgical results according to the removed tumor proportion, i.e., biopsy = ≤50%; partial removal = 50 - 95%; subtotal removal = 96 - 99%; total removal = >99%. Nitrosourea-based chemotherapy and radiation therapy were administered concurrently. Patients were followed up to evaluate tumor control after postoperative radiation therapy. Follow-up included physical and neurological examinations and MRI study. Salvage surgery, additional radiation therapy, and/or chemotherapy were considered in patients with tumor recurrence or progression.

MRI study and image interpretation

All MRI scans were performed using a 1.5-T superconducting system (Signa

Horizon; GE Medical Systems, Milwaukee, WI, USA) with a circularly polarized head coil. All patients underwent MRI studies that included at least unenhanced and contrast-enhanced transverse T1-weighted-, unenhanced transverse T2-weighted-, unenhanced transverse fluid-attenuated inversion-recovery (FLAIR)-, and unenhanced transverse DW images. The transverse T1-weighted spin-echo MR sequence was performed using the following parameters: repetition time msec/echo time msec, 400/8; field of view (FOV), 22 × 16 cm; matrix size, 256 (frequency), 192 (phase); section thickness, 5 mm; section gap, 2.5 mm; two signals were acquired. The contrast-enhanced T1-weighted sequences were obtained after administering 0.1 mmol of gadodinium compound per kg body weight. The transverse fast spin-echo T2-weighted sequence was performed using the following parameters: 3500/100; FOV, 22 × 16 cm; matrix size, 256 × 192; echo train length, 12; section thickness, 5 mm; section gap, 2.5 mm; two signals. Transverse FLAIR images were acquired using fast and interleaved multi-section sequences with the following parameters: 10,000/150; inversion time, 2,200 msec; FOV, 22 × 22 cm; matrix size, 256 × 192; echo train length, 16; section thickness, 5 mm; section gap, 2.5 mm; one signal. Transverse DW images

were acquired using a single-shot T2-weighted echo planar spin-echo sequence before contrast-enhanced T1-weighted imaging. We calculated ADC values according to the formula ADC = -[ln(*Sb*/*S*0)]/*b*, where *Sb* is the signal intensity (SI) of the region of interest (ROI) obtained through 3 orthogonally-oriented DW images, *S*0 the SI of the ROI acquired through reference T2-weighted images, and *b* is the gradient *b* factor with a value of 1,000 sec/mm^2. ADC maps were calculated on a pixel-by-pixel basis using software integral to the MR unit. The ADC was measured by manually placing ROI in tumor regions on the ADC map at the site of enhanced lesions on contrast-enhanced T1-weighted MRI. Cystic components were differentiated as areas of hyperintensity on T2-weighted- and hypointensity on FLAIR MRI scans. Necrotic components were differentiated on contrast-enhanced T1-weighted images as the interior of enhanced lesions. Hemorrhagic lesions were identified on unenhanced T1-weighted MRI as areas of hyperintensity and on unenhanced T2-weighted MRI as areas of hypointensity. We compared the ADC maps and other MR images, being careful to manually place the ROI only in the solid tumor components. Based on 6 –10 ROI ranging in size from 40 to 60 mm^2 on the ADC maps, we obtained ADC_{mean}, ADC_{MIN}, and ADC_{MAX},

respectively. We performed DWI using the following parameters: before July 2003: 1,600/107; diffusion gradient encoding in 3 (x, y, z) orthogonal directions; *b* values of 250, 500, 750, and 1,000 sec/mm2; FOV, 24 × 24 cm; matrix size, 128 × 128; section thickness, 7.5 mm; section gap, 0 mm; one signal. After July 2003 the parameters were: 5,000/107; diffusion gradient encoding in 3 (x, y, z) orthogonal directions; *b* values of 1,000 sec/mm2; FOV, 24 × 24 cm; matrix size, 128 × 128; section thickness, 7.5 mm; section gap, 0 mm; one signal.

Statistical analyses

Survival was measured from the time of operation to the time of death or last follow-up (range, 3.6 to 54.4 months; median, 16.6 months). Of the 33 patients, 6 were alive at the time of the latest follow-up. We used the median of ADC_{mean}, ADC_{MIN}, and ADC_{MAX} as the cutoff value. We also applied a categorization cutoff of 1.0×10^{-3} mm^2/sec because earlier studies used this value (4, 10). We analyzed the relationship between patient survival and prognostic factors determined from clinical and MRI data. Prognostic factors included the patient age, gender, duration of symptoms, Karnofsky

performance scale (KPS) score, extent of surgery (biopsy, partial, subtotal or total resection) and ADC (>1.0×10^{-3} vs. ≤1.0×10^{-3} mm^2/sec). Survival curves were calculated with the Kaplan-Meier method, the log-rank test was used to analyze overall differences in the survival curves. The influence of prognostic factors was adjusted using multiple regression analysis with the Cox proportional hazards model. We applied the likelihood test to make comparisons among ADC_{mean}, ADC_{MIN}, and ADC_{MAX} as prognostic factors. All statistical analyses were performed using computer software (StatView version 5.0; SAS Institute, Cary, NC). For all statistical tests, P <0.05 was adopted as the significance level.

Results

Patient characteristics and imaging

The patients ranged in age from 10 to 76 years (mean ± standard deviation (SD): 57.3 ± 16.3; median 62). The KPS scores were 30 and 50 in 1 patient each, 60 and 70 in 4 each, 80 in 11, 90 in 9, and 100 in 3 patients. Surgery consisted of biopsy (n = 6), partial- (n = 12), subtotal- (n = 8), and total (n = 7) tumor removal. The ADC_{mean} of all

tumors ranged from 0.716×10^{-3} to 1.389×10^{-3} mm^2/sec (mean ± SD $1.070 \pm 0.141 \times 10^{-3}$ mm^2/sec; median 1.066×10^{-3} mm^2/sec). The ADC_{MIN} ranged from 0.676×10^{-3} to 1.260×10^{-3} mm^2/sec (mean ± SD $0.934 \pm 0.144 \times 10^{-3}$ mm^2/sec; median, 0.933×10^{-3} mm^2/sec). The ADC_{MAX} ranged from 0.935×10^{-3} to 1.585×10^{-3} mm^2/sec (mean ± SD $1.248 \pm 0.151 \times 10^{-3}$ mm^2/sec; median, 1.230×10^{-3} mm^2/sec) (Fig. 1). There was no statistical difference under our 2 imaging conditions.

Comparison among ADC_{mean}, ADC_{MIN}, and ADC_{MAX} values by likelihood analysis

We initially performed comparisons among ADC_{mean}, ADC_{MIN}, and ADC_{MAX} values to identify the most powerful prognostic factor according to likelihood analysis (Fig. 1). We analyzed the ADC with surgical results because "total removal" was the most sensitive prognostic factor according to our analyses. The results of likelihood analysis were ADC_{mean}, $\chi^2 = 16.291$ ($P = 0.003$); ADC_{MIN}, $\chi^2 = 19.739$ ($P < 0.0001$), and ADC_{MAX}, $\chi^2 = 13.633$ ($P = 0.0011$). Based on these findings we used ADC_{MIN} in further analyses.

Univariate analyses of prognostic factors

Univariate analysis (Table 1) revealed that the significant factors in overall survival were the KPS score ($P < 0.05$) (Fig. 2A), total surgical removal ($P < 0.01$; Fig. 2B), and ADC_{MIN} ($P < 0.05$; Figs. 2C, 3, and 4). Other factors were not associated with overall survival. Among our 33 patients, the ADC_{MIN} value was below 1.0×10^{-3} mm^2/sec in 23; it was higher in 10 patients. The group-specific survival rate at 1.5 years was 30.4% and 60.0% for patients in the low- and high ADC_{MIN} value groups, respectively ($P < 0.05$; Fig. 2C).

Multivariate analysis of prognostic factors

We evaluated the prognostic factors for overall survival using multivariate analysis. The results of multiple regression analysis with the Cox proportional hazards model (Table 2) confirmed that incomplete tumor removal was the most important prognostic factor (hazard ratio 19.187; $P < 0.01$). Our results also confirmed that a low ADC_{MIN} value was a statistical prognostic factor (hazard ratio 3.915; $P < 0.05$). No other factors were significantly associated with overall survival.

Survival analysis of patients with incomplete tumor removal

We analyzed the prognostic factors in patients whose tumors could not be totally removed because the biological features of postoperative residual tumors may affect overall survival. Univariate analysis with the log-rank test revealed that the only significant factor for overall survival was the ADC_{MIN} ($P < 0.01$; Fig. 5). Neither the patient age (≥50 y) nor the gender, symptom duration (≤3.0 months), KPS (≥80), subtotal tumor removal, nor surgical achievements were of prognostic value. The results of multivariate analysis with the Cox proportional hazards model also confirmed that low ADC_{MIN} was a powerful prognostic factor (hazard ratio 6.107, $P < 0.01$).

Discussion

Our results suggest that the ADC value of tumors, obtained from preoperative MRI scans, represents a prognostic factor in patients with glioblastoma. Although ADC_{mean}, ADC_{MIN}, and ADC_{MAX} were statistically significant prognostic factors in our patients, we confirmed that ADC_{MIN} was the most sensitive predictive factor for the

overall survival of these patients. Others (9, 10) who assessed the value of the ADC for predicting the prognosis of patients with malignant astrocytic tumors used ADC_{MIN} based on the hypothesis that this value reflects the sites of highest cellularity within heterogeneous tumors and that these sites are of prognostic importance. Studies of ADC that documented an inverse relationship between tumor cellularity and the glioma grade support this hypothesis (6, 11, 12). Tissues with high cellularity manifest a low ADC because the mobility of water protons is impeded; cystic and necrotic regions, on the other hand, exhibit a high ADC due to the rapid diffusion of water protons (13, 15). However, no previous reports have compared the value of the ADC_{MIN} versus the ADC_{mean} and ADC_{MAX}. Our likelihood analysis confirmed that ADC_{MIN} was the most sensitive prognostic factor and that it can be used to evaluate overall survival in patients with glioblastoma.

Our observation that a low ADC_{MIN} value is associated with a poor prognosis is consistent with previous studies. According to Higano et al. (9) who studied 37 patients with malignant astrocytic tumors including 22 glioblastomas, the outcomes were more favorable in groups with $ADC_{MIN} > 0.90 \times 10^{-3}$ mm^2/sec than $\leq 0.90 \times 10^{-3}$ mm^2/sec (9).

We also applied the cutoff values of 0.90×10^{-3} mm^2/sec of ADC_{MIN} and of the median 0.933×10^{-3} mm^2/sec (median of ADC_{MIN}) in our statistical analyses. At both cutoff values, groups with a lower ADC had a statistically poorer prognosis ($P < 0.01$, log-rank test; data not shown) and our results agree with their findings. Higano et al. (9) also found a significant negative correlation between ADC_{MIN} and the Ki-67 labeling index; this may explain why the group with the lower ADC_{MIN} value had a poor prognosis. Murakami et al. (10) studied 79 malignant supratentorial astrocytic tumors, including 50 glioblastomas; patients whose $ADC_{MIN} > 1.00 \times 10^{-3}$ mm^2/sec had better outcomes than patients with $ADC_{MIN} \leq 1.00 \times 10^{-3}$ mm^2/sec, a value they considered the most important factor in predicting a poor prognosis (hazard ratio 10.459). Although they did not provide information regarding the degree of surgical resection, our results coincide with theirs. Our findings and those of others confirm that the ADC_{MIN} statistically correlates with the prognosis of glioblastoma patients.

In our series, total, but not subtotal removal or less affected overall survival; an observation that coincides with that of others (16). Interestingly, we found that the ADC_{MIN} of tumors on pretreatment MR images was a useful predictor of the overall

survival of glioblastoma patients whose tumors could not be totally removed. Oh et al. (8) who evaluated the ADC_{mean} of glioblastomas on MR images obtained after surgery but before the start of radiation therapy found that the survival of patients with a low ADC was substantially shorter. Our findings support their results.

In combination with conventional MRI findings, the ADC can yield additional useful information about physiological changes since the entire tumor can be assessed. Tissue sampling, on the other hand, may not yield information about the entire tumor. Furthermore, if the chosen biopsy site is suboptimal, the glioma grading may be incorrect because these tumors are histologically heterogeneous. Thus, because the ADC helps to identify areas of highest cellularity within a tumor, it is useful for selecting the biopsy target (9).

Our study has some limitations. DWI does not eliminate perfusion effects attributable to tumor vessels or white matter tracts. In addition, ADC changes due to cystic, necrotic, and/or hemorrhagic areas and the influence of artifacts caused by inhomogeneous structures such as the skull base, bone, and sinus air must be considered. To avoid the influence of susceptibility artifacts or ADC changes, we excluded patients

with infratentorial tumors or gross hemorrhage from our study. Another limitation was the variability of the calculated ADC. Significant variability in ADC values reportedly reflects the coil systems and imagers used, the instrument vendors, and the field strengths applied for MR re-imaging (17, 18). We set the cut off value of ADC_{MIN} at 1.00×10^{-3} mm^2/sec and this value would be affected, therefore, we suggest that the optimal absolute ADC be established by larger studies. The semiquantitative use of the ADC such as its ratio to the contralateral side, may help to eliminate these variabilities. However, as the ADC is inhomogenous in various brain lesions and is affected by aging (19-21), these ADC changes must be considered when the ratio to the contralateral normal-appearing side is to be established. Future studies are necessary to standardize ADC measurement methods. Although our retrospective study showed that ADC_{MIN} is one of the most important prognostic factors, due to the heterogeneous nature of glioblastomas, other variables related to the characteristics of the patients, the tumors, and the treatment strategies must be taken into account.

Conclusions

The ADC_{MIN} value of tumors obtained from preoperative MR images is a useful clinical prognostic biomarker for overall survival in patients with glioblastoma. Patients whose tumors have a low minimum ADC ($\leq 1.0 \times 10^{-3}$ mm^2/sec) may have a poor prognosis, especially when the tumor cannot be completely resected. Thus, pretreatment DW-MRI and calculating the ADC values may be helpful for planning therapy in patients with glioblastoma.

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Table 1. Univariate Analysis of Specific Prognostic Factors

Prognostic Factor	No. of Patients (n = 33)	Overall Survival*	P value†
Age(y)			
≤49	8	37.5%	NA
≥50	25	40.0%	
Sex			
male	24	41.7%	NA
female	9	33.3%	
Symptom duration (mo)			
≤3	25	36.0%	NA
>3	8	50.0%	
Karnofsky Perfomance Score			
≥80	23	47.8%	<0.05
≤70	10	20.0%	
Extent of Surgery			
total	7	71.4%	<0.01
not total (subtotal, partial and biopsy)	26	30.8%	
Apparent Diffusion Coefficient			
≤1.00 ($\times 10^{-3}$ mm^2/sec)	23	30.4%	<0.05
>1.00 ($\times 10^{-3}$ mm^2/sec)	10	60.0%	

* Data are 1.5-year overall survival rates, expressed as percentages. The 1.5-year overall survival rate for all 33 patients was 39.4% (13 patients). †P values calculated with the log-rank test. NA, not applicable; hazard ratio not calculated when P ≥ 0.05.

Table 2. Multivariate Analysis of Specific Prognostic Factors

Prognostic Factor	Hazard Ratio	P value
Age (≥ 50)	NA	NA
Gender	NA	NA
Symptom duration (≤ 3.0 months)	NA	NA
KPS score (≤ 70)	NA	NA
Extent of resection (not total)	19.187	< 0.01
Minimum ADC (≤ 1.0×10^{-3} mm^2/sec)	3.915	< 0.05

NA, not applicable; hazard ratio not calculated when P ≥ 0.05.

* Numbers in parentheses are 95% confidence intervals.

Figure legends

Figure 1. Parallel boxplots showing the distribution of mean, minimum and maximum ADC values for all glioblastoma patients.

Figure 2. Kaplan-Meier survival curves for all patients with glioblastoma (including 6 who remain alive) showing the relationship between minimum ADC and survival time measured from the date of surgery. Comparisons were done between KPS ≥80 and KPS ≤70 (A), between total and not total removal (B), and between ADC > 1.0×10^3 and ≤ 1.0×10^3 mm^2/sec (C).

Figure 3. MR images and pathological results obtained in 60-year-old man with glioblastoma. *A,* T1-weighted-, *B,* T2-weighted-, *C,* FLAIR-, *D,* contrast-enhanced T1-weighted images show an enhancing tumor and peritumoral edema. *E,* On the DW image, the enhancing area exhibits moderately high signal intensity. *F,* On the ADC map, the enhancing area manifests a minimum ADC of 1.05×10^{-3} mm2/sec. The tumor was

partially removed and this patient survived for 31 months after the initial MRI study. *G,* Histologic specimen (× 160) shows the mildly hypercellular nature of the tumor.

Figure 4. Transverse MR images obtained in 67-year-old man with glioblastoma. *A,* T1-weighted-, *B,* T2-weighted-, and *C,* FLAIR image. *D,* Contrast-enhanced T1-weighted images show an enhancing tumor. *E,* On the DW image, the enhancing area exhibits high signal intensity. *F,* On the ADC map, the enhancing area has a minimum ADC of 0.902×10^{-3} mm2/sec. The tumor was subtotally removed and this patient died 13 months after the initial MRI study. *G,* Histologic specimen (× 160) shows marked hypercellularity of the tumor.

Figure 5. Kaplan-Meier survival curves based on minimum ADC ($> 1.0 \times 10^3$ vs. $\leq 1.0 \times 10^3$ mm^2/sec) in the subgroup of patients with incomplete tumor removal.

Figure 1

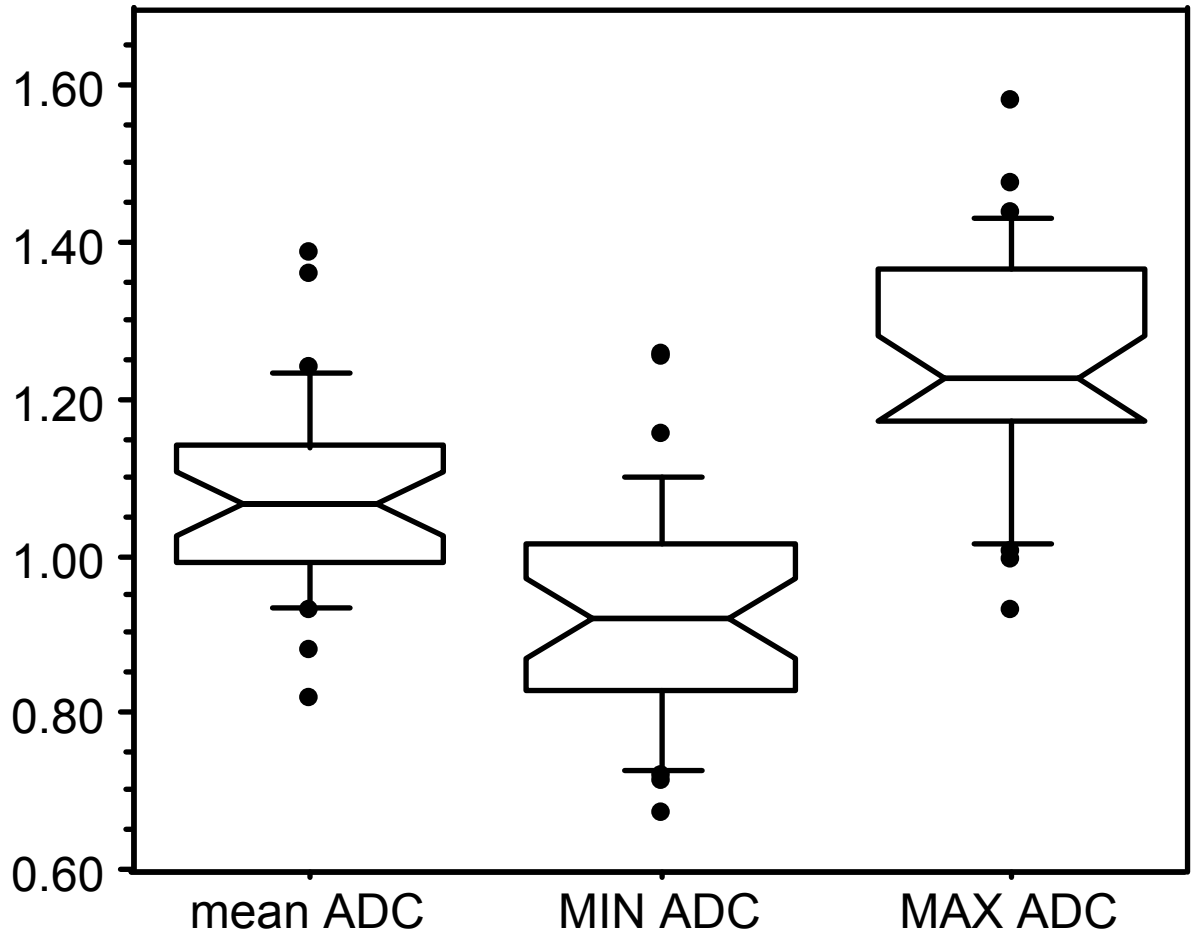


Figure 2A

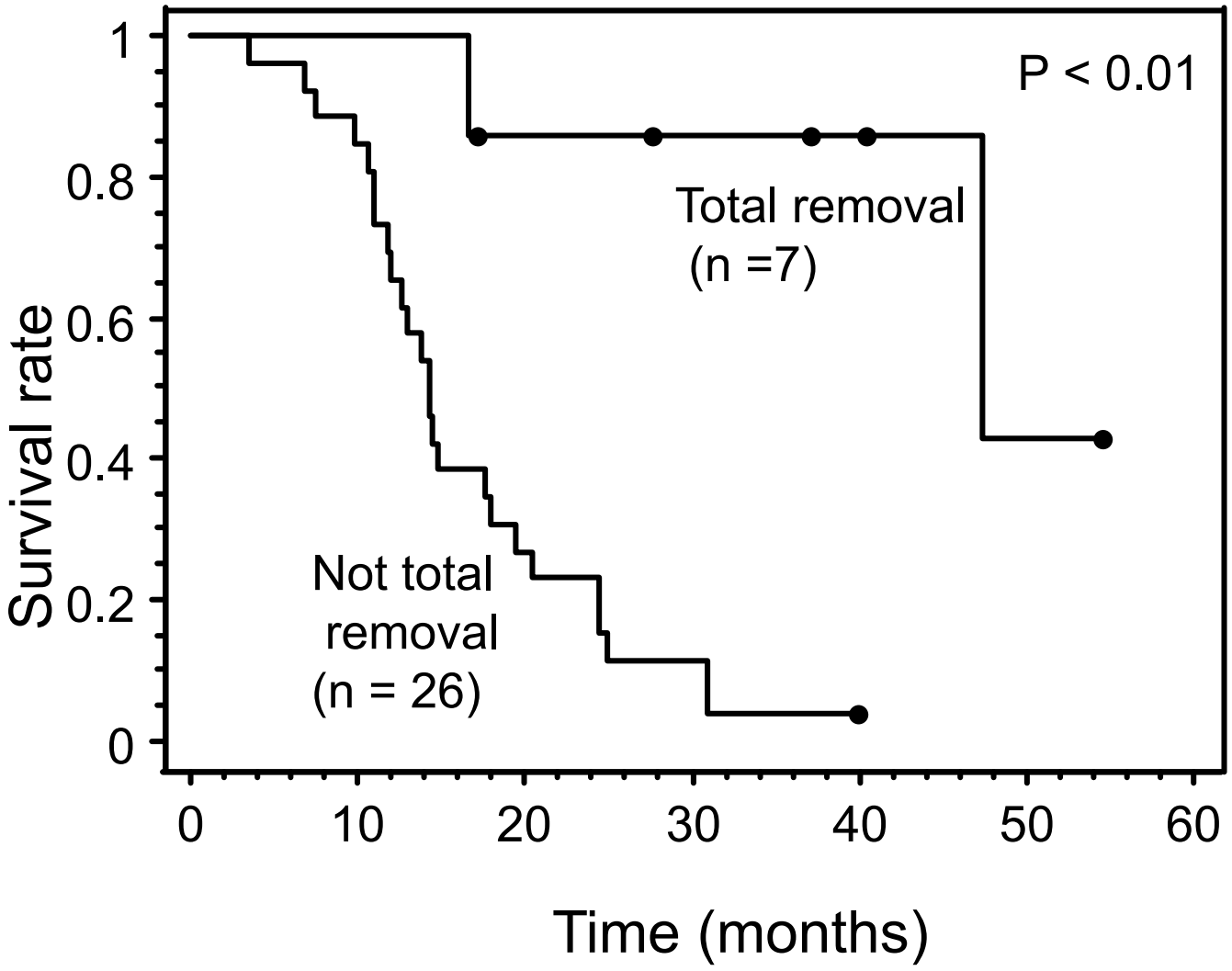

P < 0.01
Total removal
(n =7)
Not total
removal
(n = 26)
Survival rate
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Time (months)

Figure 2B

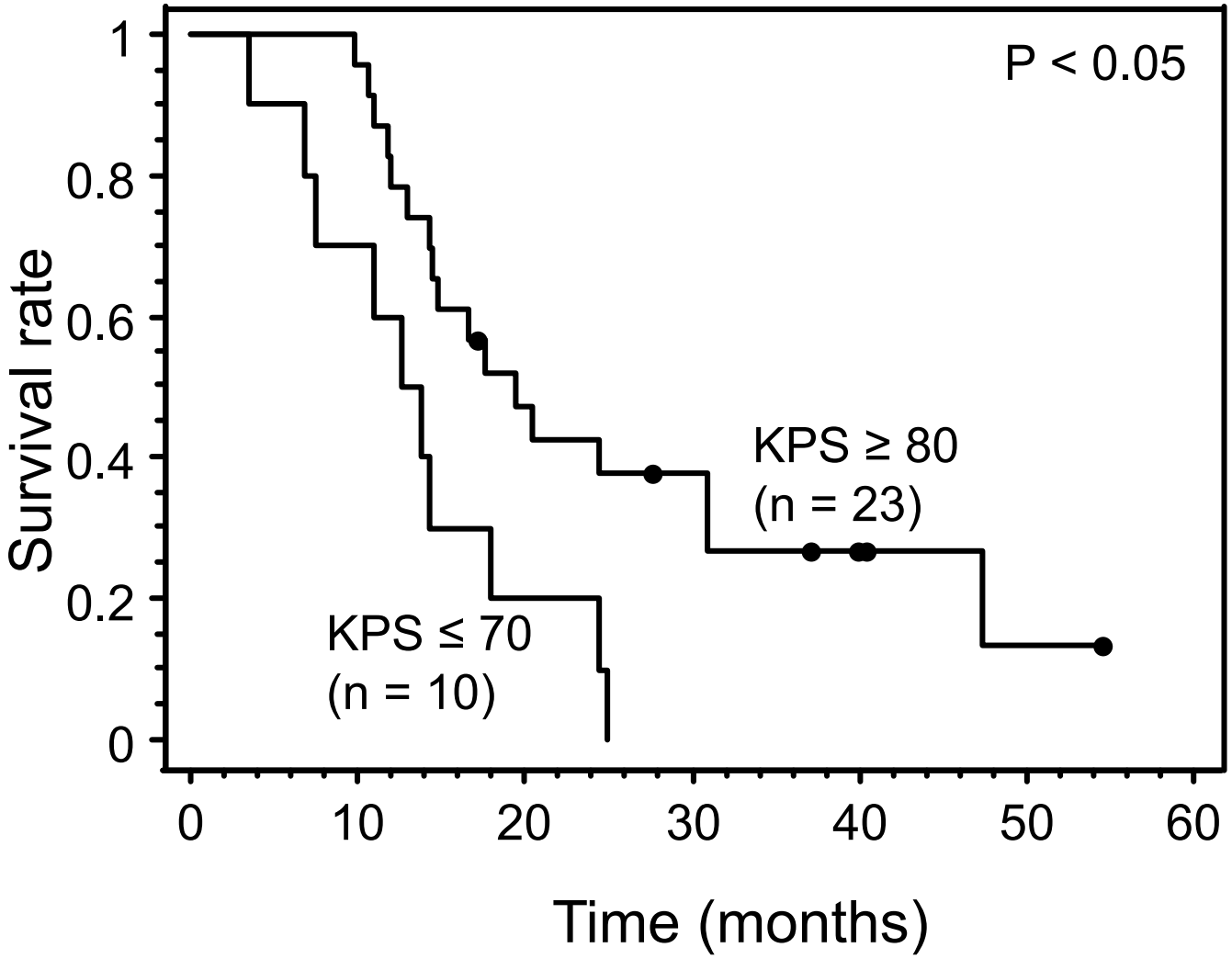
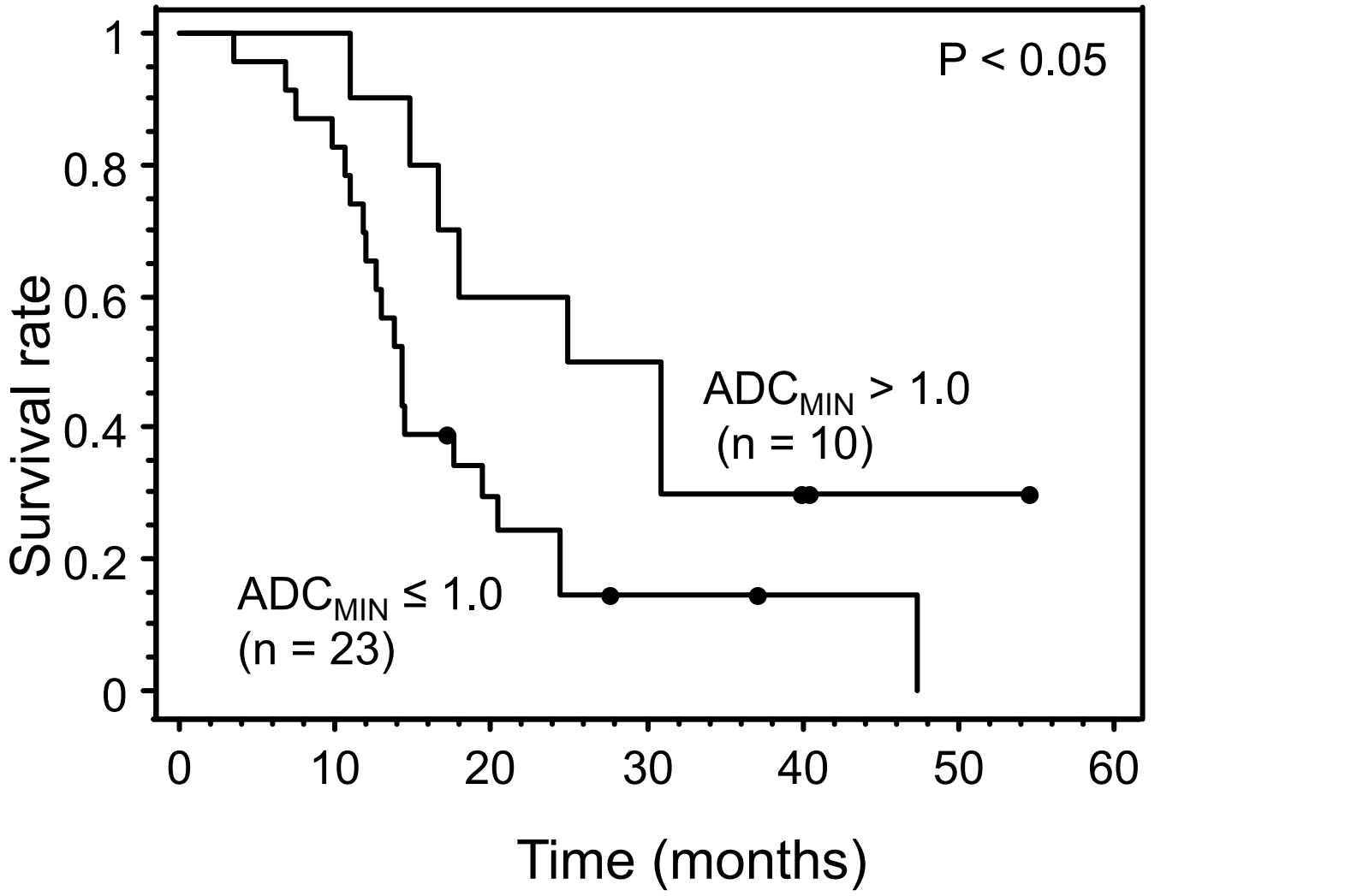
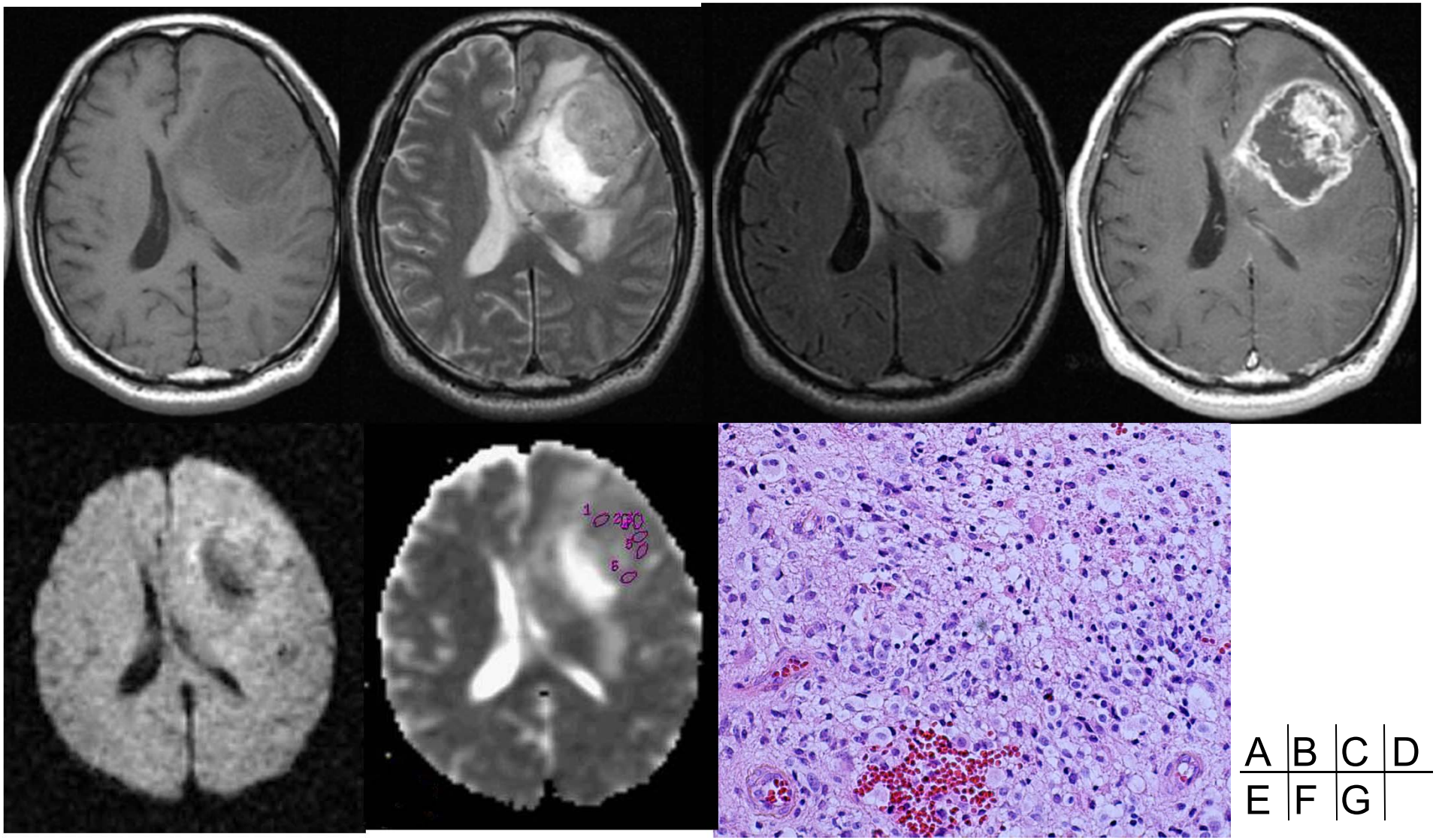

P < 0.05
KPS ≥ 80
(n = 23)
KPS ≤ 70
(n = 10)
Survival rate
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Time (months)

Figure 2C



(ADC$_{MIN}$ × 10^{-3} mm^2/sec)

Figure 3



A	B	C	D
E	F	G	

Figure 4

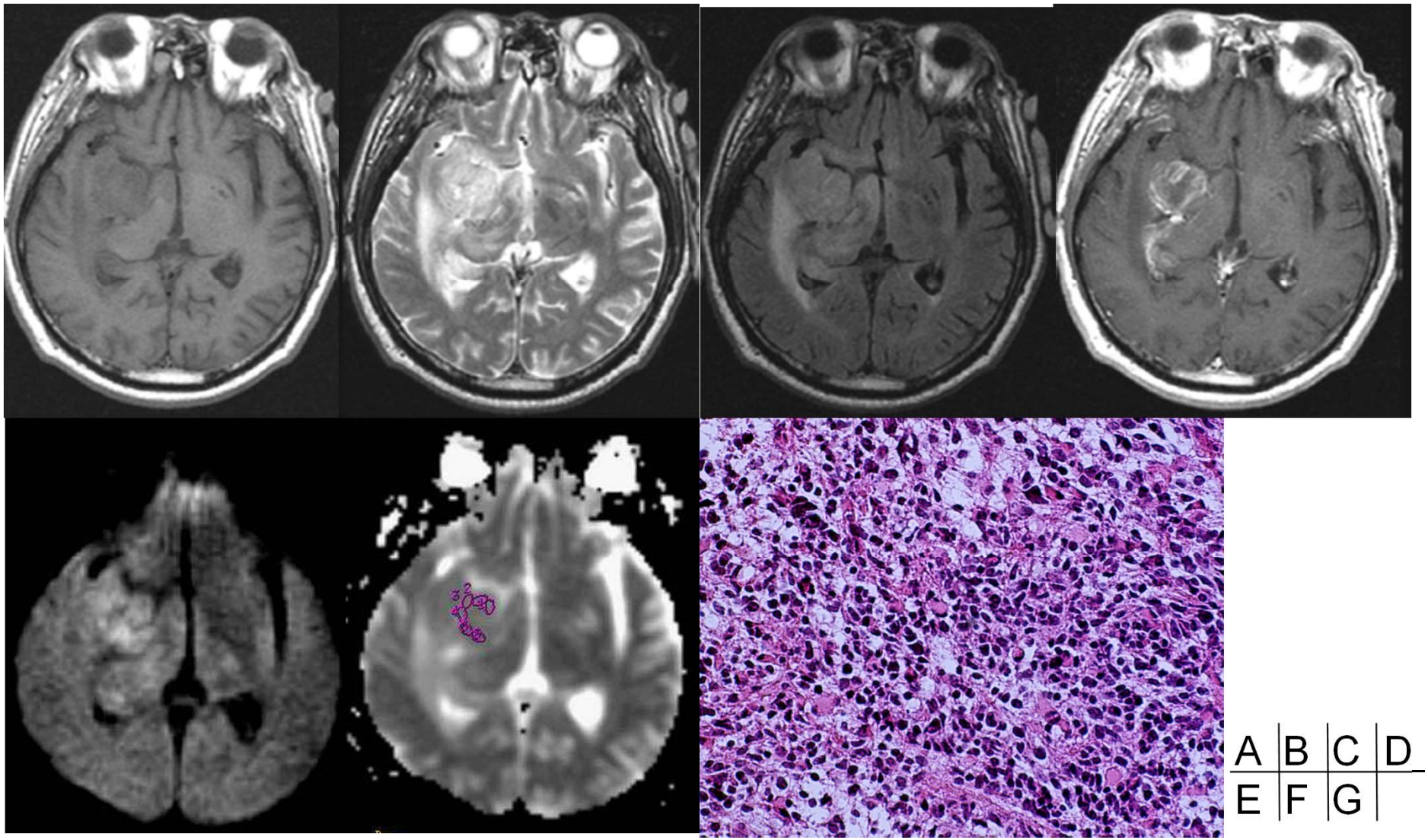
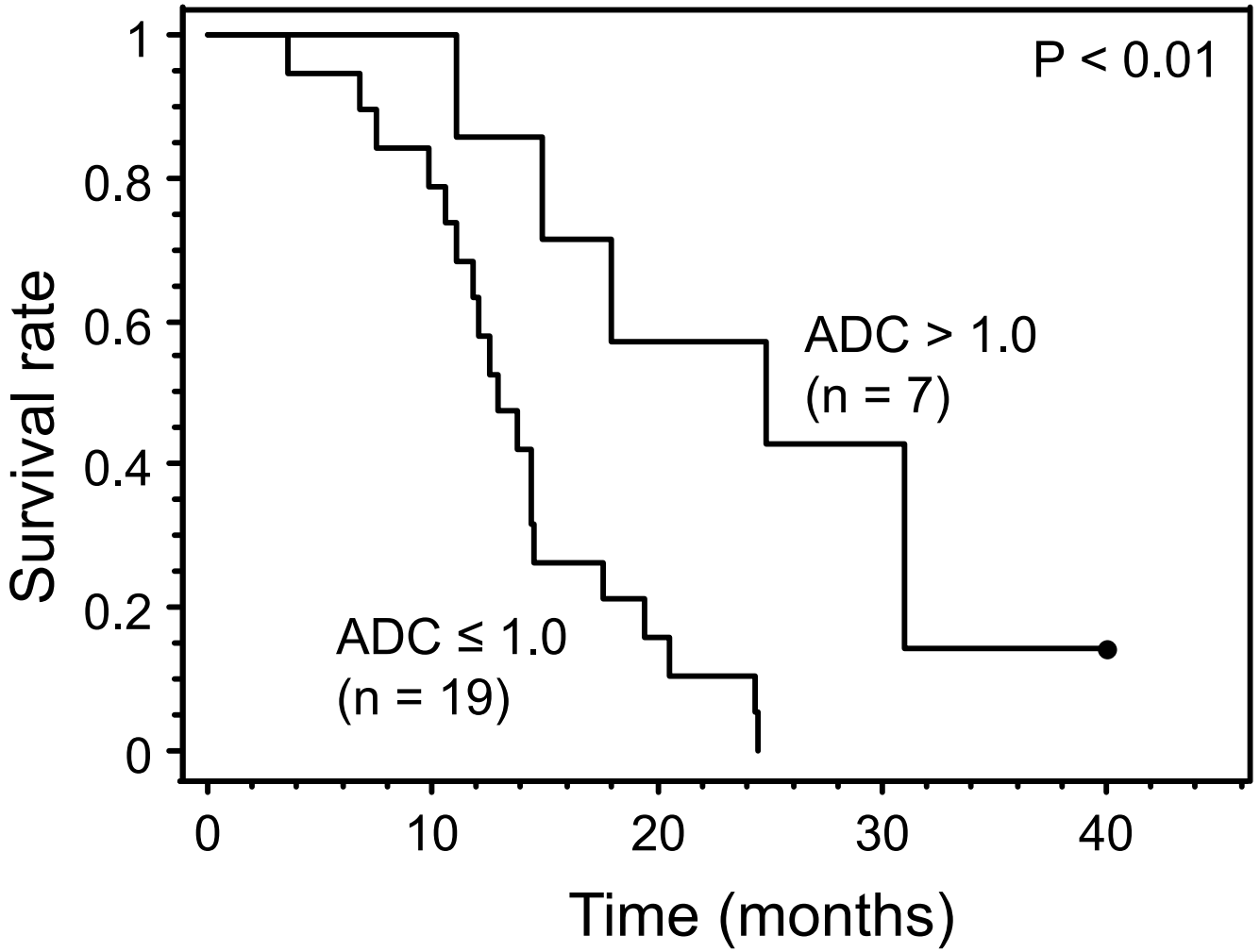


Figure 5



(ADC × 10^{-3} mm^2/sec)