Role of the apparent diffusion coefficient as a predictive factor for tumor recurrence in patients with intracranial epidermoid tumor

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Research Article

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Abstract

Purpose.

Intracranial epidermoid tumors are slowly growing benign tumors, but due to adjacent critical neurovascular structures, surgical resection is challenging, with the risk of recurrence. The apparent diffusion coefficient (ADC) has been used to evaluate the characteristics of brain tumors, but its utility for intracranial epidermoid tumors has not been specifically explored. This study analyzed the utility of preoperative ADC values in predicting tumor recurrence for patients with intracranial epidermoid tumors.

Methods.

Between 2008 and 2019, 23 patients underwent surgery for intracranial epidermoid tumor, and their preoperative ADC data were analyzed. The patients were divided into two groups: the recurrence group, defined by regrowth of the remnant tumor or newly developed mass after gross total resection on magnetic resonance imaging (MRI); and the stable group, defined by the absence of growth or evidence of tumor on MRI. Receiver operating characteristic (ROC) analysis was used to obtain the ADC cutoff values for predicting tumor recurrence. The prognostic value of the ADC was assessed using Kaplan-Meier curves.

Results.

The minimum ADC values were significantly lower in the recurrence group than in the stable tumor group ($P = 0.046$). ROC analysis showed that a minimum ADC value lower than 804.5×10^{-6} mm^2/s could be used to predict higher recurrence risk of intracranial epidermoid tumors. Subtotal resection, younger age, and mean and minimum ADC values lower than the respective cutoffs were negative predictors of recurrence-free survival.

Conclusions.

Minimum ADC values could be useful in predicting the recurrence of intracranial epidermoid tumors.

Declarations

Funding none

Conflicts of interest none

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

H.C.O. and H.H.P. were responsible for the study concept and design, data acquisition, analysis, and interpretation, and manuscript drafting. C.K.H., J.H.Y. and K.S.L. reviewed the manuscript. Y.J.C., S.J.A. and S.H.S. assisted in data interpretation.

Ethics approval

The current study design and the use of clinical data were approved by the Gangnam Severance Hospital institutional review board. All experiments were carried out in accordance with approved guidelines and with the 1964 Helsinki Declaration and its later amendments. The requirement to obtain informed consent was waived, and all data were fully anonymized.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Introduction

Intracranial epidermoid tumors account for approximately 1% of all brain tumors [1,2]. They are thought to develop from the trapped ectodermal squamous epithelium during neural tube closure, and most of them are generally located off the midline, such as at the cerebellopontine angle (CPA) [1,3,4]. These tumors are composed of keratinized stratified squamous epithelium filled with keratin debris, lipid, protein, and cholesterol crystals that can spread throughout the cerebrospinal fluid space (i.e., cisterns, sulci, and ventricle) [5-7]. Although they have a benign nature with slow growth rates, surgical resection is generally conducted if they cause neurologic deficits due to compression of neural structures. However, there are risks of surgical morbidity and recurrence because the tumor capsule adherent to the adjacent critical neurovascular structures makes it difficult to surgically eradicate the tumor [1,2,4,8].

In cases of recurrent symptomatic epidermoid tumors, reoperation is still the mainstay of treatment, and some studies advocate adjuvant radiotherapy due to increased surgical morbidities [8-10]. Several studies have investigated factors related to recurrence in intracranial epidermoid tumors [8,11,12], but the understanding of the disease behavior is still limited due to its rarity and pathologic simplicity. The extent of resection (EOR) is the only known prognostic factor predicting tumor recurrence, and there are no reliable factors able to predict tumor behavior before surgery.

The apparent diffusion coefficient (ADC) has been utilized to predict tumor behavior in central nervous system tumors such as glioma [13], meningioma [14], and chordoma [15] because it could reflect tumor cell characteristics. In the management of intracranial epidermoid tumors, preoperative, postoperative, and follow-up magnetic resonance imaging (MRI), including diffusion weighted image (DWI) sequences, are always conducted. These data allow not only detection of the presence of an epidermoid tumor, but also acquisition of ADC values. In this study, we evaluated the behavior of intracranial epidermoid tumors using preoperative ADC values, and determined the ADC cutoff values to predict tumor recurrence.

Methods

Study population

We conducted a retrospective single-institution analysis of 27 patients who underwent surgery for newly diagnosed intracranial epidermoid tumors between January 2008 and December 2019. Among them, three patients had extradural epidermoid tumors and one had a frontal convexity epidermoid tumor. Tumors located in the extradural and the frontal convexity area have limited space to spread compared with those located in cisterns or ventricles. As a result, they manifest as a mass with well-circumscribed margins, have low ADC values due to the dense environment, and can be totally removed without recurrence at the surveillance. It is consistent with a previous report that scalp epidermoid tumor has low ADC values than those of intracranial epidermoid tumors [16]. Thus, we classified intracranial epidermoid tumors into two categories: the extensive type (i.e., cisterns and ventricles) and the limited type (i.e., extradural and convexity) according to the occupied space, and excluded the latter group from the analysis. The 23 extensive type epidermoid tumors were divided into a stable group and a recurrence group. The stable group was defined by the absence of growth or evidence of tumor on consecutive MRI follow-ups. The recurrence group was defined as regrowth of the remnant tumor or newly developed mass after gross total resection based on consecutive MRI follow-ups (Fig. 1). The mean follow-up period was 33.8 months (range 3.6-73 months), and all recurrences except for one case occurred within 2 years. The current study design and the use of clinical data were approved by the Gangnam Severance Hospital institutional review board. All experiments were carried out in accordance with approved guidelines and with the 1964 Helsinki Declaration and its later amendments. The requirement to obtain informed consent was waived, and all data were fully anonymized.

The EOR was based on operative notes and confirmed by the first postoperative MRI within 3 months of surgery. Gross total resection (GTR) was defined as complete removal of both capsule and contents; near-total resection (NTR) was defined as complete content removal and incomplete capsule removal; subtotal resection (STR) was defined as incomplete resection of both capsule and contents [17]. Postoperative diffusion-weighted MRI sequences were utilized to confirm the degree of resection. If MRI indicated no recurrence of disease after surgery, imaging studies were typically performed annually.

Analysis of radiologic data

Two patients were imaged with a 1.5T MRI device (Optima MR450w GEM, GE Healthcare, Milwaukee, WI, USA) and 21 patients were imaged with a 3T clinical MRI device (Discovery MR750, GE Healthcare, Milwaukee, WI, USA). Our MRI protocol for intracranial epidermoid tumor included routine diffusion-weighted echo-planar sequences (repetition time/echo time [TR/TE], 8000/65.6 ms; slice thickness/intersection gap, 4/1 mm; matrix size, 160 × 160; field of view [FOV], 240 × 240 mm; three directions; b-value = 0 and 1000 s/mm^2), and T2-weighted fast-spin-echo sequences (TR/TE, 5414/96 ms). After intravenous gadolinium-based contrast agent was administered at a dose of 0.1 mmol/kg body weight, axial fluid-attenuated inversion recovery sequences (TR/TE/inversion time, 4000/80/2000 ms) and 3D T1 fast-spoiled gradient-recalled sequences (TR/TE, 8.2/3.2 ms; flip angle 12°; slice thickness, 1 mm; matrix size, 256 × 256; FOV, 220 × 220 mm) were taken sequentially. ADC values were automatically calculated by the operating console of the MRI device and were displayed as ADC maps.

Two neurosurgeons and two neuroradiologists independently outlined four round or oval regions of interest (ROIs) within the tumor for the evaluation of ADC values (Fig. 1c and 1i). All continuous sections of the ADC maps that included tumor were evaluated. Each region of interest was positioned carefully to avoid contamination from adjacent tissues. ADC values < 10×10^{-6} mm^2/s were considered as artifacts. A ROI containing lowest ADC value among the four ROIs was chosen for analysis. The mean, minimum, and maximum ADC values were obtained within this same ROI. ADC cutoff values for predicting intracranial epidermoid tumor recurrence were obtained by comparing the preoperative ADC values between the two groups. These cutoff values were then used for recurrence-free survival (RFS) analysis. The ADC measurements were assessed for interobserver reliability using the interclass correlation coefficient. T1 and T2 weighted image signal intensity and computed tomography (CT) density were evaluated based on comparison with adjacent brain tissue.

Statistical analysis

Mean, maximum and minimum ADC values, patient age at the time of first surgery, sex, body mass index, EOR, CT density, signal intensity on T1 and T2 weighted images, T1-weighted contrast enhancement, diffusion restriction, and postoperative complications were compared between the two groups using the Student's t-test for continuous variables and Fisher's exact test for nominal variables. The cutoff ADC values were assessed using receiver operating characteristic (ROC) analysis to predict tumor recurrence. Logistic regression analysis was performed to determine independent risk factors for recurrence. Multiple logistic regression analyses were performed on variables with significant unadjusted effect on simple logistic regression analysis. RFS was analyzed using Kaplan-Meier curves and compared between the groups using log-rank tests with the following variables: mean and minimum ADC cutoff values, age, and EOR. All statistical analyses were performed using IBM SPSS statistics version 25.0 (IBM Corp, Armonk, NY, USA). Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

There were 5 male (21.7%) and 18 female (78.3%) patients, with a mean age of 39.4 years (range 21-60 years). GTR was achieved in nine cases (39.1%), NTR in five cases (21.8%), and STR in 9 cases (39.1%). Twenty cases involved the CPA area, and three cases were in the 4th ventricle or confined to the ambient cistern. Most operations were via lateral suboccipital craniotomy (34.8%) or posterior petrosal approach (34.8%).

There were 12 cases in the stable group (52%) and 11 cases (48%) in the recurrence group. Most STR cases recurred, and all recurrence events occurred within 2 years except for one patient (mean 12.1 months, range 5-24.5 months). Patient characteristics are summarized in Table 1. The mean age was lower in the recurrence group than in the stable group (P = 0.024). The extent of resection was analyzed into two different ways. When considering GTR, NTR, and STR separately, the rate of STR was higher in the recurrence group than in the stable group (P = 0.021). Likewise, when NTR and STR were considered together as cases of “non-total resection”, the rate of non-total resections was higher in the recurrence group than in the stable group *(*P = 0.036). The minimum ADC values were significantly lower in the recurrence group than in the stable group (P = 0.046). The interclass correlation coefficient for interobserver reliability of the minimum ADC values was 0.881 (95% CI, 0.720-0.950). There were no significant differences in sex, BMI, postoperative complication, CT density, T1, T2 signal intensity, T1 weighted contrast enhancement, diffusion restriction, or mean and maximum ADC values between the two groups. Most intracranial epidermoid tumors showed as hypodense on CT, hypointense on T1, hyperintense on T2 MRI sequence, non-enhancing, and restricted on DWI.

Risk factors for predicting the recurrence of intracranial epidermoid tumors

According to the ROC analysis, the ADC cutoff values that distinguished the recurrence from the stable group were as follows: mean ADC 1043×10^{-6} mm^2/s, sensitivity of 0.73, specificity of 0.75, and area under the curve (AUC) of 0.689 (P = 0.124; 95% CI, 0.458-0.921); maximum ADC 1189×10^{-6} mm^2/s, sensitivity of 0.91, specificity of 0.33, and AUC of 0.424 (P = 0.538; 95% CI, 0.184-0.665); and minimum ADC 804.5×10^{-6} mm^2/s, sensitivity of 0.82, specificity of 0.75, and AUC of 0.750 (P = 0.042; 95% CI, 0.534-0.966) (Fig. 2).

These cutoff ADC values and the parameters found to be significantly different in the previous analysis (age and EOR) were used in logistic regression analysis. Logistic regression analysis with adjustment showed that a minimum ADC value $\leq804.5\times10^{-6}$ mm^2/s was independently associated with recurrence of intracranial epidermoid tumors (P = 0.039; Table 2). Age less than 40 years, EOR, and mean ADC value $\leq1043\times10^{-6}$ mm^2/s were associated to P-values of 0.027, 0.027, and 0.029, respectively, in simple logistic regression, but did not reach statistical significance after adjustment.

Prediction of recurrence-free survival in intracranial epidermoid tumors

The predictive factors associated with recurrence of intracranial epidermoid tumors in Table 2 were used in a Kaplan-Meier survival analysis of recurrence. The log-rank test showed that mean ADC value

≤1043×10^{-6} mm^2/s (P = 0.029), minimum ADC value ≤804.5×10^{-6} mm^2/s (P = 0.018), EOR (STR) (P = 0.046), and age less than 40 years were significantly associated with poor RFS (Fig. 3).

Discussion

To the best of our knowledge, this is the first study to show the utility of ADC values for predicting intracranial epidermoid tumor recurrence. Epidermoid tumors are slow-growing tumors often involving the posterior fossa, such as the CPA, and cause neurologic deficits when leading to mass effects or stretching onto adjacent neurovascular structures [5,8,12]. Although there are no established treatment guidelines, maximal safe surgical resection is generally conducted, and reoperation is often considered for recurrent cases. Due to its benign nature and pathologic simplicity, many studies related to intracranial epidermoid tumors focus on surgical techniques, cranial nerve function preservation, and recurrence after surgery [2,5,8,12,18-21]. The EOR was shown to be a significant prognostic factor for recurrence in these studies, but there are no known preoperative factors that can predict tumor behavior. ADC values have been used to represent tumor characteristics in several central nervous system tumors [15,22,23], and DWI sequence is always taken for detection of epidermoid tumor recurrence [24]. Thus, in the present study, we analyzed 23 patients using ADC values, hypothesizing that they could be useful in predicting the recurrence of intracranial epidermoid tumors.

There have been many debates about the optimum extent of resection in intracranial epidermoid tumors [2,5,8,25]. The proliferation of stratified squamous epithelium is considered to be the cause of tumor recurrence, leading to accumulation of acellular debris such as keratin, protein, and lipid [1,8,9]. Considering the pathogenesis of this tumor, many studies have revealed that complete excision, including of the tumor capsule, reduces the risk of recurrence compared with STR [2,5,8]. Our case series confirms that patients treated with total resection showed lower recurrence rates than those treated with non-total resection (P = 0.036). While many neurosurgeons attempt GTR to minimize the recurrence rate, surgical morbidity must also be considered. The capsule can be highly adherent to adjacent critical neurovascular structures, and excessive surgical resection can lead to serious complications such as cranial nerve palsy and infarction [2,8,18]. Thus, some authors support intentional STR if an attempt at GTR seems too risky, especially in older patients with significant medical comorbidities [8,20].

A recent meta-analysis reported that the recurrence rate of intracranial epidermoid tumors is roughly one in ten patients, and some studies showed no recurrence even after subtotal resection [8]. However, several studies included in that meta-analysis obtained follow-up imaging only when symptoms occurred and did not perform MRI annually, which might make their interpretation problematic [2,19,26]. In the current study, we annually repeated MRI studies to radiologically screen for tumor recurrence, and we found that most STR cases do recur, most recurrences occurring within 2 years of surgery. Our results also show that younger age is significantly correlated with higher probability of tumor recurrence. Although epidermoid tumors generally show benign behavior when GTR is achieved, it should be emphasized that they can often recur after STR, as our study shows. Therefore, the optimum EOR should be tailored for each patient considering recurrence risk, age, comorbidities, and surgical morbidities. For instance, most

patients, in particular younger ones, should receive GTR to reduce the recurrence rate, but STR might be chosen to avoid perceived morbidities while being aware of the recurrence risk.

Some remnant epidermoid tumors have a benign course without recurrence, but some do recur even after GTR [8]. The understanding of the natural course of this tumor is still limited and a grading system to distinguish its characteristics is not even available, due to its pathological simplicity. It is generally thought to grow slowly and to be benign, but some cases recur rapidly and rarely undergo malignant transformation [27]. Several studies have also reported that 'white epidermoid tumors' have more protein components within the capsules than others [6,28]. That is, there are differences in the characteristics of epidermoid tumors, such as in the production and accumulation of their components, although they are all classified as "intracranial epidermoid tumors". To reflect these differences, we measured the ADC values using preoperative DWI because the ADC has been shown to represent the nature of the tumor in several brain tumors [13-15]. Diffusion measurements reflect intra- and extra-cellular water motion and could indicate tumor characteristics [29]. We found that the mean ADC values ranged roughly from 750 to 1500 (10^{-6} mm^2/s), and the minimum ADC values ranged from 600 to 1200 (10^{-6} mm^2/s), which is consistent with previous epidermoid ADC studies [16,30,31]. We focused on the minimum ADC values because the tumor ROIs often contain cerebrospinal fluid, which could increase the maximum and mean ADC values. We also distinguished intracranial extradural epidermoid tumors and convexity tumors from cisternal and ventricular tumors, which tend to spread into the subarachnoid space, and classified them into the "limited" and "extensive" types, respectively. Limited type epidermoid tumors have low ADC values with well circumscribed margins in a limited space, and were totally removed without difficulty in our cases, again consistently with previous reports [16,17]. However, extensive type epidermoid tumors, such as those located in the CPA area, have variable ADC values and prognosis.

Using these ADC values, we analyzed whether they reflected tumor behavior and could be predictive factors in intracranial epidermoid tumors of the extensive type. Our results show that the minimum ADC values in the recurrence group were significantly lower than in the stable group. Moreover, cases with minimum ADC values lower than the cutoff showed significantly shorter RFS (mean 19.1 months) than those with higher values (mean 50.6 months). That is, we could predict the prognosis of intracranial epidermoid tumors using their preoperative ADC maps. These findings are similar to those of previous reports showing that aggressive clival chordoma and high-grade meningioma and glioma have lower ADC values than those of less aggressive or low-grade tumors [13-15]. Therefore, close MRI follow-up is recommended for cases with minimum ADC values lower than the cutoff to screen for recurrence after surgery.

There are several limitations to this study. First, its design was retrospective, with a small sample size. Intracranial epidermoid tumor is a rare disease, making large-scale prospective studies difficult. Second, the follow-up period was not long enough, considering the benign behavior of intracranial epidermoid tumors. Although all cases of recurrence, except for one, occurred within 2 years, a further long-term follow-up investigation is required in the future. Third, most tumors were located in the CPA area rather than in the parasellar region. Fourth, there were no cases of malignant transformation, and we could not

analyze their ADC values. Despite these limitations, our results suggest that preoperative ADC values could be useful in predicting the recurrence of intracranial epidermoid tumors. In this respect, our study is the first to analyze the significance of ADC values as recurrence predictors in intracranial epidermoid tumors.

In conclusion, we found that minimum ADC values and age were significantly lower in the recurrence group than in the stable group. Minimum ADC values lower than the cutoff value of 804.5×10^{-6} mm^2/s and patients younger than 40 years showed significantly poorer RFS than those with higher ADC values and older than 40 years. Thus, preoperative ADC values can be useful in predicting the recurrence of intracranial epidermoid tumor as well as in diagnosis.

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Tables

TABLE 1. Patient demographics and clinical characteristics

Variable	Stable group (n = 12)	Recurrence group (n = 11)	P-value
Age at first operation (year, mean ± SD)	44.83 ± 12.20	33.45 ± 9.92	**0.024**
Sex (Female, %)	11 (91.7%)	7 (63.6%)	0.155
BMI (Kg/m2)	22.51 ± 3.09	24.57 ± 2.71	0.105
Location			0.590
CPA	11 (91.7%)	9 (81.8%)	
No CPA	1 (8.3%)	2 (18.2%)	
Surgical approach			
Lateral SOC	6	2	
Midline SOC	1	1	
Posterior petrosal	3	5	
Anterior petrosal	1	0	
Combined petrosal	0	1	
Other	1	2	
Extent of resection I*			**0.021**
GTR	7 (58.3%)	2 (18.2%)	
NTR	3 (25.0%)	2 (18.2%)	
STR	2 (16.7%)	7 (63.6%)	
Extent of resection II*			**0.036**
Total	8 (66.7%)	2 (18.2%)	
Non-total	4 (33.3%)	9 (81.8%)	
Postop complication (Meningitis)	0 (0%)	1 (9.1%)	0.478
CT Hypodensity	11 (91.7%)	11 (100%)	1
T1 weighted (Low, %)	11 (91.7%)	11 (100%)	1
T2 weighted (High, %)	12 (100%)	11 (100%)	1
T1 enhancement (No enhancement, %)	12 (100%)	11 (100%)	1
Diffusion restriction (Restriction, %)	11 (91.7%)	11 (100%)	1
Mean ADC ($10^{-6}mm^2/s$, mean ± SD)	1095.00 ± 172.69	1011.45 ± 83.91	0.161
Maximum ADC ($10^{-6}mm^2/s$, mean ± SD)	1349.33 ± 224.80	1396.45 ± 227.30	0.623
Minimum ADC ($10^{-6}mm^2/s$, mean ± SD)	889.50 ± 175.91	768.73 ± 70.15	**0.046**

ADC = afferent diffusion coefficient, BMI = Body mass index, CPA = Cerebellopontine angle, GTR = Grossly total resection, NTR = Near total resection, SD = standard deviation, SOC = Suboccipital craniotomy, STR = Subtotal resection. Boldface type indicates statistical significance. *Extent of resection was analyzed two different ways: I, total versus near total versus subtotal, separately; II, total versus non-total, which includes all near-total and subtotal cases combined.

TABLE 2. Multivariable logistic regression analysis of factors associated with recurrence

	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Age at first operation (year)				
> 40	1		1	
≤ 40	9.000 (1.285-63.025)	**0.027**	10.826 (0.626-187.187)	0.101
Extent of resection I*				
GTR	1		1	
NTR	2.333 (0.216-25.245)	0.486	2.579 (0.103-64.489)	0.564
STR	12.250 (1.327-113.060)	**0.027**	11.633 (0.506-267.684)	0.125
Extent of resection II*				
Total	1			
Non-total	9.000 (1.285-63.025)	**0.027**		
Mean ADC				
> 1043 ($10^{-6}mm^2/s$)	1			
≤ 1043 ($10^{-6}mm^2/s$)	8.000 (1.243-51.506)	**0.029**		
Maximum ADC				
> 1189 ($10^{-6}mm^2/s$)	1			
≤ 1189 ($10^{-6}mm^2/s$)	0.200 (0.019-2.162)	0.185		
Minimum ADC				
> 804.5 ($10^{-6}mm^2/s$)	1		1	
≤ 804.5 ($10^{-6}mm^2/s$)	13.500 (1.802-101.125)	**0.011**	19.892 (1.164-340.023)	**0.039**

ADC = afferent diffusion coefficient, GTR = Grossly total resection, NTR = Near total resection, STR = Subtotal resection. Boldface type indicates statistical significance. *Extent of resection was analyzed two different ways: I, total versus near total versus subtotal, separately; II, total versus non-total, which includes all near-total and subtotal cases combined

Figures

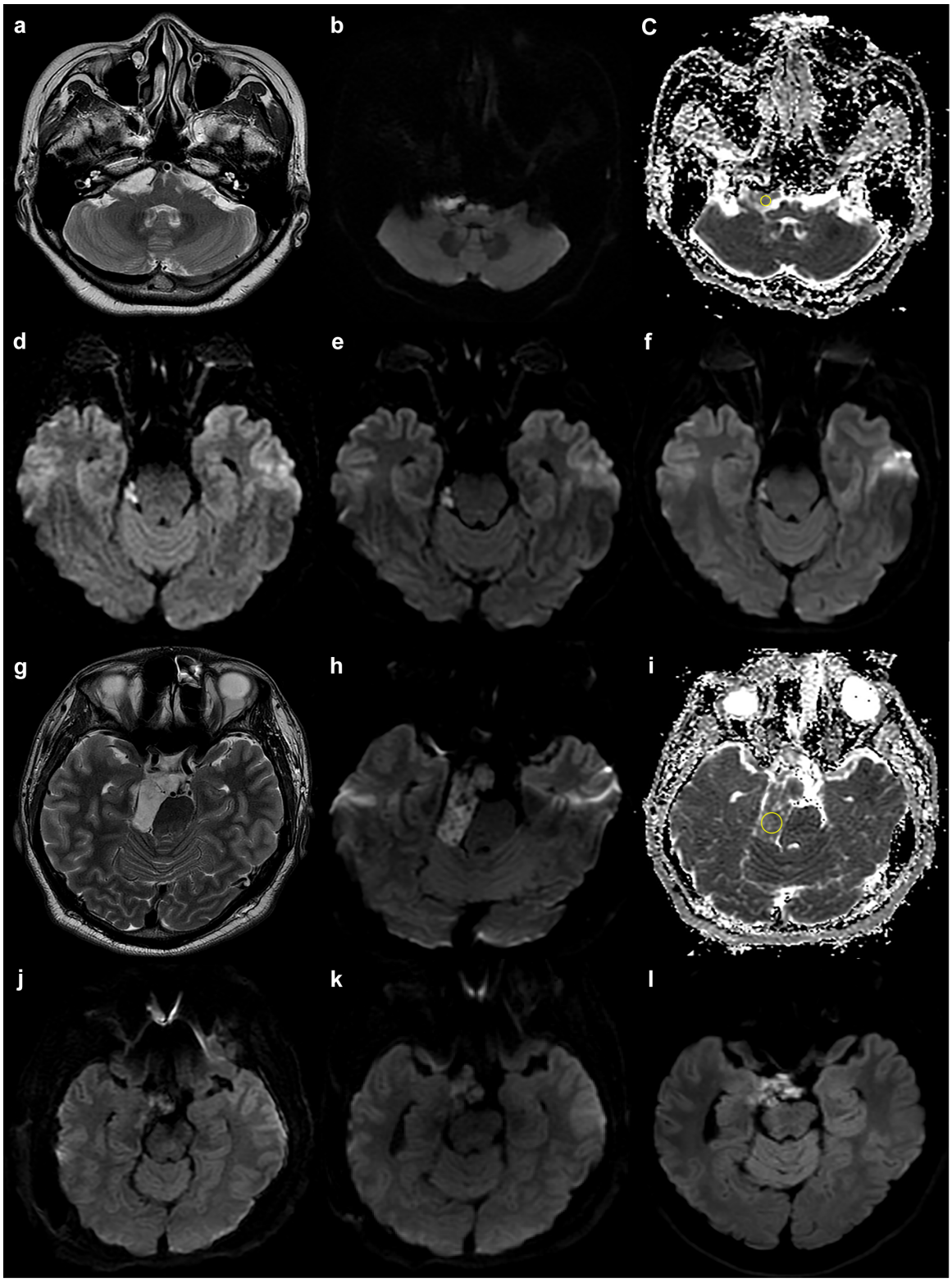

Figure 1

a A 54-year-old woman was diagnosed with an intracranial epidermoid tumor and classified in the stable group. Preoperative T2-weighted imaging showed a tumor located in the right CPA area and spread into the ambient cistern. b Preoperative diffusion weighted imaging showed diffusion restriction in the same area. c The ROI outlined in yellow on the ADC map represents decreased water diffusivity (mean ADC 1067 × 10−6 mm2/s, minimum ADC 997 × 10−6 mm2/s). d Postoperative diffusion weighted imaging

shows remnant tumor at the right ambient cistern. Surgery was performed via lateral suboccipital craniotomy, and subtotal resection was achieved. e Diffusion weighted imaging obtained a year after surgery showed stable disease. f Diffusion weighted imaging 5 years after surgery still indicates stable status. g A 35-year-old man diagnosed with an intracranial epidermoid tumor and classified in the recurrence group. Preoperative T2-weighted imaging showed a tumor located from the suprasellar cistern to the right CPA area. h Preoperative diffusion weighted imaging showed diffusion restriction in the same area. i The ROI outlined in yellow on the ADC map represents decreased water diffusivity (mean ADC 977 × 10−6 mm2/s, minimum ADC 776 × 10−6 mm2/s). j Postoperative diffusion weighted imaging shows remnant tumor at the suprasellar cistern. Surgery was performed via the posterior petrosal approach and subtotal resection was achieved. k Diffusion weighted imaging obtained a year after surgery showed an increase in size of the remnant tumor. l Diffusion weighted imaging 4 years after surgery reveals progressive recurrence. CPA, cerebellopontine angle; ADC, apparent diffusion coefficient; ROI, region of interest

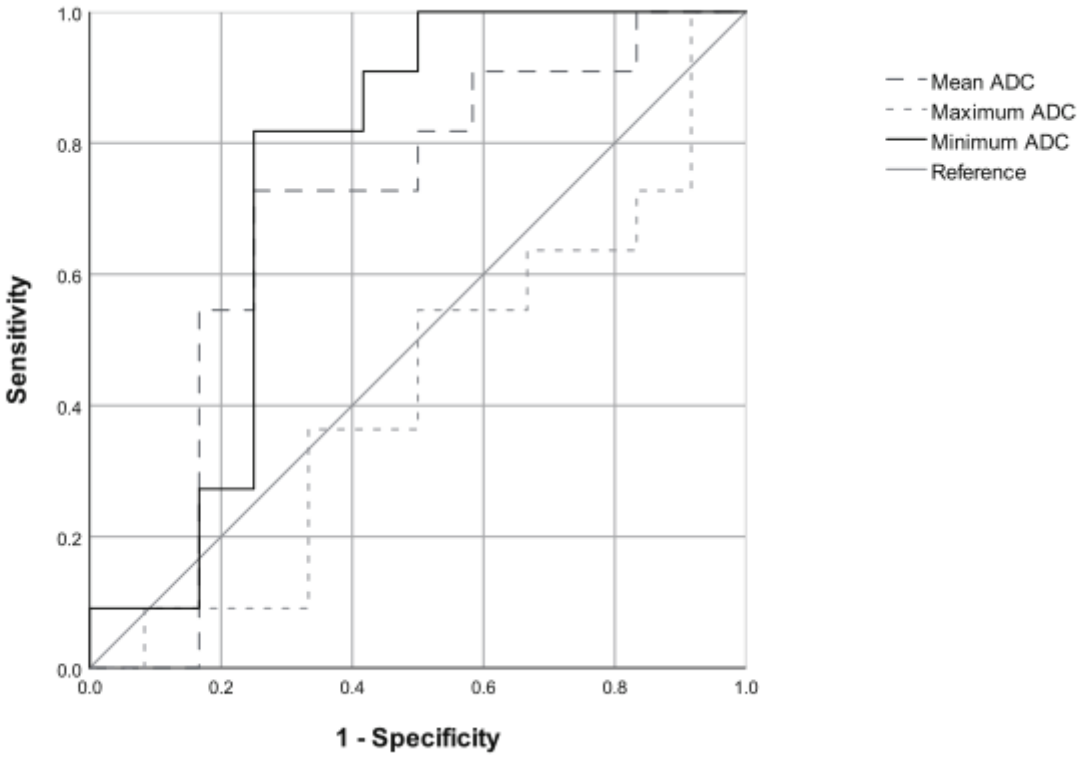

Figure 2

ROC curves for the ADC values differentiating the recurrence group from the stable group. ROC, receiver operating characteristic; ADC, apparent diffusion coefficient

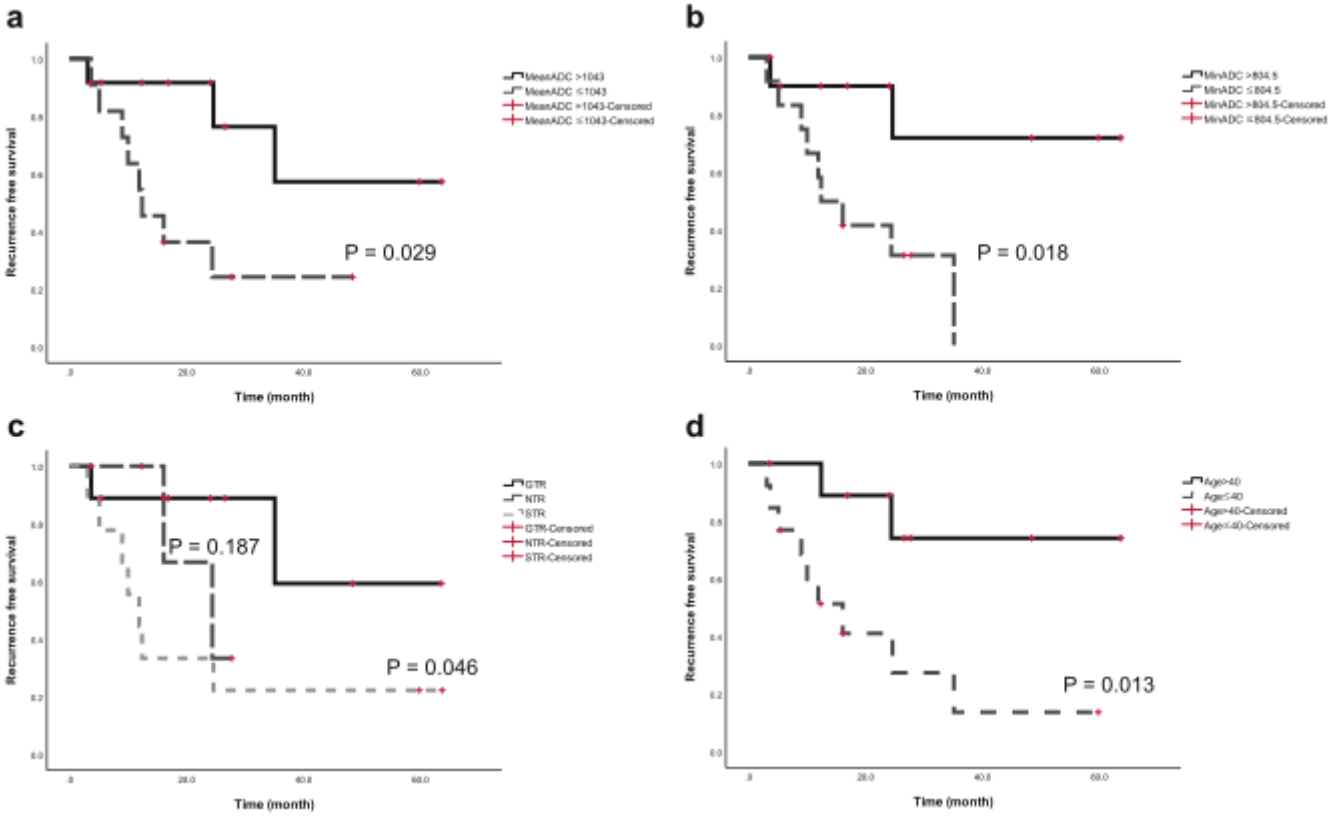

Figure 3

Kaplan-Meier curves using log-rank tests for recurrence-free survival. a RFS according to mean ADC values; b RFS according to minimum ADC values; c RFS according to extent of tumor resection; d RFS according to age. RFS, recurrence-free survival; ADC, apparent diffusion coefficient