Published in final edited form as:

Eur J Radiol. 2014 February ; 83(2): e100–e105. doi:10.1016/j.ejrad.2013.06.033.

Molecular and metabolic pattern classification for detection of brain glioma progression

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Abstract

Objectives: The ability to differentiate between brain tumor progression and radiation therapy induced necrosis is critical for appropriate patient management. In order to improve the differential diagnosis, we combined fluorine-18 2-fluoro-deoxyglucose positron emission tomography (¹⁸F-FDG PET), proton magnetic resonance spectroscopy (¹H MRS) and histological data to develop a multi-parametric machine-learning model.

Methods: We enrolled twelve post-therapy patients with grade 2 and 3 gliomas that were suspicious of tumor progression. All patients underwent ¹⁸F-FDG PET and ¹H MRS. Maximal standardized uptake value (SUVmax) of the tumors and reference regions were obtained. Multiple 2D maps of choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) of the tumors were generated. A support vector machine (SVM) learning model was established to take imaging biomarkers and histological data as input vectors. A combination of clinical follow-up and multiple sequential MRI studies served as the basis for assessing the clinical outcome. All vector combinations were evaluated for diagnostic accuracy and cross validation. The optimal cutoff value of individual parameters was calculated using Receiver operating characteristic (ROC) plots.

Results: The SVM and ROC analyses both demonstrated that SUVmax of the lesion was the most significant single diagnostic parameter (75% accuracy) followed by Cho concentration (67% accuracy). SVM analysis of all paired parameters showed SUVmax and Cho concentration in combination could achieve 83% accuracy. SUVmax of the lesion paired with SUVmax of the white matter as well as the tumor Cho paired with the tumor Cr both showed 83% accuracy. These were the most significant paired diagnostic parameters of either modality. Combining all four parameters did not improve the results. However, addition of two more parameters, Cho and Cr of brain parenchyma contralateral to the tumor, increased the accuracy to 92%.

Conclusion: This study suggests that SVM models may improve detection of glioma progression more accurately than single parametric imaging methods.

Research support: National Cancer Institute, Cancer Center Support Grant Supplement Award, Imaging Response Assessment Teams.

Keywords

Glioma; ¹⁸F-FDG PET; ¹H MRS; Support vector machine

1. Introduction

Most gliomas are characterized by diffuse infiltration of white matter tracts [1]. Eradication of tumors, particularly higher grade neoplasm, is not usually possible. Thus, post-therapy imaging to detect the presence of residual glioma or tumor progression is essential to optimize patient management. Assessments of tumor response to therapy are typically performed by visual interpretation of serial contrast enhanced magnetic resonance imaging (MRI) and computed tomography (CT) scans. Although such examinations provide useful morphologic information, they are not able to reliably distinguish active tumor from radiation necrosis. Anatomic distortion, scarring, altered vascular permeability and edema after therapy often impair interpretation of anatomical imaging studies. In addition, stereotactic biopsy studies have shown tumor infiltration in regions that appear normal on conventional contrast enhanced CT and MRI examinations [2].

Metabolite and molecular imaging methods have been successful in overcoming these issues to some extent. Glucose metabolism quantified by ^{18}F -FDG PET imaging as well as specific biologic information obtained from ^1H MRS such as cell membrane turnover, cellular density and proliferation provide information that can help to distinguish tumor progression from post-radiation necrosis.

Multiple ^1H MRS [3,4] and ^{18}F -FDG PET [5-7] studies have been carried out to describe metabolite and metabolic characteristics of brain tumors. Some of these studies compared ^1H MRS and ^{18}F -FDG PET in the same group of patients [8,9]. However, a literature search shows that a systematic approach aimed at improving diagnostic accuracy by combining information acquired from both modalities has not been conducted.

Herein, we describe the support vector machine (SVM) learning model capable of combining ^1H MRS and ^{18}F -FDG PET data as well as tumor grading and demographic information to distinguish tumor progression from radiation necrosis.

2. Support vector machine

The SVM is a type of machine learning model that uses a training data set to allow classification of a previously unseen entity into a predefined group. This method was developed from statistical learning theory initially introduced by Vapkin and co-workers [10,11]. Typically, data are represented as labeled vectors in high dimensional space. The vectors are chosen to represent features that are responsible for correct classification of the data. The task of the SVM is to construct an optimal separating hyperplane between two classes (e.g., positives/negatives or cases/controls). The optimal separation means that the location of the hyperplane is determined such that the distance to the closest vectors on either side (support vectors) is maximized. The support vectors typically represent a small portion of all data. The majority of the vectors that are farther away from the separating hyperplane do not contribute to the classification rule. This characteristic provides a major computational advantage over other methods. This also demonstrates that the classifier focuses on subtle dissimilarities between two classes and not on obvious differences and is therefore more accurate and efficient.

In many real cases, complete separation of classes is not possible. The SVM tackles this issue in two ways. First, a slack factor can be introduced into the model, which allows a certain number of data points to be on the “wrong side” of the dividing hyperplane. The value of this factor is a trade-off between maximizing the separation margin and minimizing the error. The second method is nonlinear classification of the data using kernels. The kernels are mathematical functions that render explicit mapping of the input space into a

higher dimensional space, called feature space. The data are linearly classified in the feature space, and then transformed back to the input space. The final result is nonlinear classification of data in the input space. Various kernels may be applied for this process. The most commonly applied kernels are polynomial, radial basis and dot functions.

$$K_{Polynomial}(x_j, x_i) = \left((x_j^T x_i) + 1 \right)^d,$$

Polynomial kernel function (d is the degree of the polynomial function)

$$K_{RBF}(x_j, x_i) = \exp \left(\frac{-\|x_j - x_i\|^2}{2\sigma^2} \right),$$

Radial basis kernel function (σ is the scaling factor)

$$K_{dot}(x_j, x_i) = (x_j \cdot x_i)$$

Dot kernel function

The discriminant function of the SVM classifier has the following form:

$$f(x) = \left(\sum_{i=1}^N \alpha_i y_i K(x_j, x_i) + b \right),$$

where x_i represent each of the $i = 1, \dots, N$ input data points, y_i (+1, -1) (+1 represents positive cases and -1 negative cases), α_i are the Lagrange multipliers, b is a weighting coefficient vector, and K is the kernel. This equation is solved using a quadratic programming method. The calculated weighting coefficients represent parameters of the hyperplane dividing the data.

The SVM has shown good performance in many fields, ranging from engineering to biology and medicine. The main application of SVM in medicine has traditionally focused on bioinformatics for gene expression analysis and proteomics. The number of articles taking advantage of SVM in radiology has increased in the recent years. In a recent article, Zöllner et al. proposed an SVM-based glioma grading based on features derived from automatically segmented tumor volumes from 101 DSC-MR examinations and reported a correct prediction of low-grade glioma at 83% and high-grade glioma at 91% [12]. Po, et al. developed an SVM active learning approach to perform automated glioblastoma multiforme segmentation from multi-modal MR Images [13]. In another article, Dukart et al. applied SVM analysis to combined FDG-PET and MRI data for detecting and differentiating dementia and reported substantial gain using this method [14].

3. Materials and methods

3.1. Inclusion and exclusion criteria

We investigated adult male and female patients older than 20 years with clinical symptoms and radiographic findings suspicious for glioma progression. Subjects were drawn from a total of 193 patients who were referred from our neurooncology group for a conventional clinical brain MRI during the period from 3/2007 to 3/2009. From this group 53 patients had a history of grade II or grade III glioma resection, stereotactic radiation and chemotherapy. Patients with no evidence of progression ($N = 24$) and cases demonstrating significant tumor growth were excluded ($N = 3$) from further consideration. The remaining patients ($n = 26$) were referred for an ^{18}F -FDG PET scan.

The seventeen patients who had UPMC health insurance were also evaluated by 3 T ^1H MRS. In most cases the MRS and PET scans were ordered at approximately the same time, and therefore either ^1H MRS or ^{18}F -FDG PET could have been performed first and in all cases no patient was excluded on the basis of ^1H MRS and ^{18}F -FDG PET findings. Of the total of 17 ^1H MRS scans, five cases were excluded from data analysis because the time interval between the two studies was longer than 1 month. Twelve cases (five men, seven women; median age at surgery 39; range, 25–70 years) were selected for the study.

A combination of clinical follow-up and multiple sequential MR studies were used for clinical outcome validation. This retrospective study was approved by our Institutional Review Board which did not require signed informed consent from the patients. The data were analyzed and controlled by one of the academic authors who was not an employee or consultant to medical industry.

3.2. Magnetic resonance spectroscopy imaging

MRI and MRS data were acquired on a Siemens (Erlangen, Germany) 3 T Magnetom TIM Trio whole-body high-performance scanner. The patients were positioned in the standard radiofrequency (RF) 12-channel head coil. A fast 3D gradient echo sequence (MP-RAGE) was performed using a TE of 2.63 ms, TR of 2110 ms, inversion time of 1100 ms, flip angle of 8 degrees, image matrix 256 [2], 128 slices 1.5 mm thick and a 240×192 field of view, resulting in a scan time of 3.8 min. Parallel acquisition techniques (PAT) factor of 2 was used to decrease the imaging time. These parameters resulted in images optimized for the best contrast among gray matter, white matter, and CSF and to provide high-resolution delineation of cortical and sub-cortical structures.

The ^1H MRS data were acquired using a hybrid chemical shift imaging (CSI) sequence with TE of 135 ms, TR of 1700 ms, slice thickness of 10 mm and three averages over a $160 \text{ mm} \times 160 \text{ mm}$ field of view, resulting in a scan time of 6.8 min. Outer volume suppression pulses were used to suppress subcutaneous lipid signals. The positioning of the CSI slice was dependent on the location of the lesion. An automatic 3D shimming was used to maximize spectral resolution and homogeneity over the volume of interest. Water suppression was performed using the vendor-supplied adjustment employing a special pulse train.

Integrals of resonance signals (areas under the peaks) were obtained after baseline correction and phase correction were applied to all the spectra. This allowed for visualization of the voxel-dependent intensities of metabolites within the defined region of interest. Metabolite images were generated on the scanner console using routines provided by the manufacturer. The CSI slice graphic was displayed as an overlay on the MP-RAGE sequence.

3.3. Positron emission tomography method

The patients were instructed to fast for 4–6 h before the injection of 353–532 MBq (9.5–14.4 mCi) of ^{18}F -FDG. Following radiotracer uptake period (range, 48–68 min; mean, 56 min), the PET data were acquired on a Siemens/CTI ECAT HR+ scanner in 3D imaging mode (63 parallel planes); axial field-of-view: 15.2 cm; in-plane resolution: 4.1 mm full-width at half-maximum; slice width: 2.4 mm; 30 min acquisition time. The scanner gantry was equipped with a Neuro-insert (CTI PET Systems, Knoxville, TN) to reduce the contribution of scattered photon events [15]. PET data were reconstructed using filtered back-projection (Fourier rebinning and 2D back projection with Hann filter: kernel FWHM = 3 mm). Data were corrected for photon attenuation, scatter, and radioactive decay. A windowed transmission scan (10–15 min) was obtained for attenuation correction using rotating $^{68}\text{Ge}/^{68}\text{Ga}$ rods and a model-based correction was applied to account for a 3D scatter fraction [16].

3.4. Evaluation of PET and MRS studies

The PET data were fused on the MRI images to better localize the lesions using image analysis and fusion software (MIMvista Corp. Cleveland, OH) (Fig. 1). The maximal and mean standardized uptake values (SUVmax and SUVmean) of the lesion, white matter, and gray matter were obtained. SUVmean was calculated by placing a spherical volume of interest of one-centimeter diameter centered at the voxel with the maximal SUV. Quantitative analysis of ^1H MRS data was performed using single-voxel spectra selected from the lesion and contralateral brain tissue as illustrated in Fig. 2.

3.5. Support vector machines

An SVM was established to take ^1H MRS, ^{18}F -FDG PET, clinical data and tumor grade as input parameters. The ^1H MRS data comprised of estimated concentrations of choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) of the lesion and unaffected contralateral brain tissue. The ^{18}F -FDG PET data consisted of SUVmax and SUVmean of the lesion, cerebellum, contralateral white and gray matters, as well as the dose of administered ^{18}F -FDG and time from radiopharmaceutical administration to scan. In addition, the world health organization (WHO) tumor grading, patients' age, sex, and time from tumor resection surgery to scan were included in the SVM model. A total of 20 features was selected. The kernel used was the dot function (inner product of vectors). The dot function was selected because the final equations would require less mathematical calculations and, therefore, be more suitable for clinical implementation. The parameters of the hyperplane were calculated by quadratic programming function of Optimization Toolbox version 5.0 of MATLAB (Natick, MA, USA). SVM analysis was performed for all vector combinations.

3.6. Receiver operating characteristics curve

All single parameters and multiple parameter combinations that could be reduced to a single variable were evaluated with receiver operator characteristic (ROC) curve methodology. Because of the small number of subjects, the optimal cutoff value was calculated based on a fitted curve to the data.

3.7. Statistical analysis

Sensitivity, specificity, and accuracy with 95% confidence interval (CI) were calculated for variables that provided highest diagnostic accuracy. In addition, the Matthews correlation coefficients (MCC) were computed to better compare the results [17]. The MCC often provides a more balanced assessment than conventional accuracy method because it uses all four parameters of contingency table including the true positive (TP), true negative (TN), false positive (FP) and false negative (FN) cases.

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$$

Normality of parameter distribution was assessed with Shapiro–Wilk test. A 2-sided *p*-value of less than 0.05 was considered significant.

3.8. Composite reference

Histological verification, which would have been the most accurate reference standard, was not feasible in all cases. Therefore, a combination of clinical follow-up and multiple sequential MRI studies served as the basis for assessing the clinical outcome.

4. Results

Twelve cases were selected for the study. Six patients had glioma grade II and six patients had glioma grade III on the basis of initial histological diagnosis (Table 1). Nine patients had complete tumor resection at initial surgery and three patients had partial tumor resection. The mean time from surgery to imaging was 27 months (range, 10–70 months) (Table 2). All cases suspicious of progression demonstrated post-contrast enhancement on MRI studies except one (case 6), who showed progressive increase in fluid-attenuated inversion recovery (FLAIR) signal at the margins of the resection cavity on two consecutive MRI studies. Metabolites and metabolic evaluation of the lesions were performed for all patients within 1 month. MRS preceded PET in five cases. In another five cases, PET preceded MRS and two other cases had both studies on the same day.

Two patients (cases 7 and 10) had subsequent brain biopsies which revealed glioma progression. The remaining ten patients had a minimum of 12 months follow-up. Sequential imaging studies and clinical assessments demonstrated glioma progression in three of these patients (cases 1, 6, and 10). Seven patients did not show any clinical or radiographic evidence of progression during the observation period.

All possible parameter combinations (1,048,576) were evaluated. For each combination the SVM selected supporting vectors and calculated optimal coefficients of a linear equation capable of separating progressive from non-progressive cases as well as accuracy of diagnosis and leave-one-out cross-validation. All combinations were sorted in order of number of contributing parameters, diagnostic accuracy and cross-validation.

The results showed that SUVmax of the lesion was the most significant single diagnostic factor for detection of progression. The SVM provided a cut-off value of 5.7 with 75% accuracy (95% CI, 43–93%) and 75% leave-one out cross-validation. Receiver operating characteristic (ROC) curve analysis also rendered similar accuracy at cut-off value of 4.5. Inclusion of SUVmax of the unaffected white matter increased accuracy to 83% (95% CI, 51–97%) with no changes in cross-validation. Addition of the other PET parameters did not improve the results. These PET parameters were SUVmean of the lesion and contralateral white matter, SUVmax and SUVmean of the cerebellum, contralateral gray matter, as well as the dose of administered ¹⁸F-FDG, and post-injection uptake time.

SUVmax and SUVmean measurements of the lesions can be influenced by a variety of factors, including the post-injection uptake time, patient's weight and blood glucose level at the time of ¹⁸F-FDG administration. In our analysis these factors did not demonstrate statistically significant effect on the outcome.

Analysis of MRS data showed that the estimated choline concentration of the tumor was the most significant single diagnostic MRS factor to detect glioma progression, which had 67% accuracy (95% CI, 35–89%) and 42% cross-validation. The SVM-calculated cut-off value of choline was 13.3 parts per million (ppm). ROC curve analysis also showed similar accuracy at cut-off value of 10.3 ppm. The estimated choline concentration of the tumor along with choline concentration of contralateral brain tissue increased accuracy to 75% (95% CI, 43–93%) and cross-validation to 67%. Addition of other MRS parameters did not improve the results. The patients' age, sex, and time from tumor resection to scan did not add to the diagnostic accuracy.

All analyses hitherto were performed based on linear combinations of parameters. In the next step, the combinations that did not provide significant diagnostic accuracy were eliminated from further analysis and selective parametric ratios were added. nSU-Vmax (SUVmax of the lesion divided by SUVmax of the normal white matter) and Cho/Cr both with 83% accuracy (95% CI, 51–97%) and 75% cross-validation were the most accurate single parametric ratios. The cut-off value of normalized SUVmax was 1.9. ROC curve and analysis also showed a cut-off value at 1.8 had the same accuracy. The cut-off value of Cho/Cr was 2.8 using SVM analysis and 3.0 by ROC curve analysis with identical accuracies. Combination of these two ratios together did not further improve the diagnostic accuracy of detecting tumor progression; however, addition of Choline to Creatine ratio of the contralateral unaffected hemisphere (nCho/Cr) improved the accuracy to 92% (95% CI, 60–100%) and cross-validation to 83% (Table 3). The optimal discriminant equation for detection of progression versus necrosis was $nSU-Vmax + 0.64nCho/Cr > 3.3$.

5. Discussion

We performed a retrospective study to test the hypothesis that combining results of 1H MRS, ^{18}F -FDG PET and clinical data could improve diagnosis of glioma progression. As illustrated in Figs. 1 and 2, ^{18}F -FDG PET and 1H MRS offer different characteristic information about the tumors. ^{18}F -FDG PET can measure the rate at which the glucose is consumed. Most cancer cells, including gliomas, produce energy by a high rate of glycolysis [18], quantifiable by ^{18}F -FDG PET imaging. 1H MRS primarily provides a measure of the tissue concentrations of various metabolites, including choline, creatine, and N-acetylaspartate. Choline is the main metabolite that has been assessed in gliomas. Increased choline levels are associated with higher cell membrane turnover and higher cell density [19], arising from the proliferation of tumor cells [20]. Creatine plays a role in maintaining energy-dependent systems in cells. It is the most stable cerebral metabolite [21] and is used as an internal reference value. An increase in Cho/Cr ratio is suggestive of neoplastic process. NAA is a marker of neuronal viability and density. It is localized in mature neurons and is not found in glial cells [22,23]. A decrease in NAA is considered as evidence of tumor progression.

This study suggests that combining 1H MRS and ^{18}F -FDG PET data may improve detection of progressive gliomas better than either method individually. An explanation for our superior results is that each modality elucidates certain aspects of the tumors. Although findings have some commonalities, they do not completely overlap. Additional complementary information provided by each modality can substantially increase the diagnostic accuracy in combination. The high accuracy obtained in this study could also be partly due to small number of cases. Further investigation involving larger patient cohorts are needed to increase confidence and reproducibility of this method.

This study had several other limitations. Some of these could have been related to the retrospective design of the study. Because of the inherent risks and invasiveness of a

stereotactic biopsy, it was not always reasonable to obtain post-therapy histopathological verification. Only two cases had subsequent tissue biopsy (cases 7 and 10). Sequential morphologic imaging and prolonged clinical follow-up had to be used as surrogate markers for tissue identification in the remainder of patients. We were not able to confirm the possibility of high-grade transformation. All data were analyzed based on the patients' last histopathology report. Genetic analysis was performed for a small subset of patients; therefore we were not able to gain from its complementary information.

^1H MRS analysis was performed based on selection of a single voxel from the lesions on MRI images for spectrum analysis. The ^{18}F -FDG PET images were evaluated visually and a volume of interest was drawn around the entire lesion. The SUVmax and SUVmean were calculated and assigned to the lesion. We did not perform voxel-by-voxel analysis. The histology of most gliomas is heterogeneous. The ^1H MRS spectrum and ^{18}F -FDG PET uptake may therefore vary within the tumor. Future studies are needed to assess brain lesions voxel-by-voxel in a 3D coregistered ^1H MRS and ^{18}F -FDG PET data to take into consideration the heterogeneity of gliomas.

Finally, the current study did not attempt to evaluate other modalities including sodium magnetic resonance spectroscopy and more specific PET biomarkers, such as 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT) and 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA) and O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F -FET) radiotracers. Therefore, it remains unknown whether combining data with these radiotracers and modalities would provide equivalent or superior results. We believe this method would be particularly helpful in analyzing 3-dimensional multivoxel coregistered data acquired by inline MR-PET scanners. In addition to standard images, calculated combined parametric images can be displayed to facilitate diagnosis.

In conclusion, the SVM technique was able to combine ^1H MRS and ^{18}F -FDG PET data. The results suggest this method may improve classification of glioma progression from post radiation necrosis more accurately than either method separately.

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Fig. 1.

(A) MP-RAGE MRI image at the level of the right front lobe glioma (patient 10). (B) ^{18}F -FDG PET study demonstrating abnormally increased tracer uptake corresponding to the right front lobe lesion. (C) Fused ^{18}F -FDG PET on MRI and the selected voxel from MR spectroscopy.

Fig. 2. Magnetic resonance spectroscopy (patient 10). (A) After examining multiple voxels, a single voxel with maximum Cho/Cr was selected as representative of the tumor. (B) Spectra of a mirrored voxel on the normal contralateral hemisphere.

Table 1

Demographic data and histological diagnoses.

Case	Age (y)	Sex	Histology	WHO
1	60	Female	Oligodendroglioma	2
2	29	Female	Anaplastic oligodendroglioma	3
3	60	Female	Anaplastic astrocytoma	3
4	30	Male	Oligodendroglioma	2
5	33	Male	Anaplastic astrocytoma	3
6	54	Female	Astrocytoma	2
7	45	Male	Anaplastic astrocytoma	3
8	49	Male	Anaplastic astrocytoma	3
9	25	Female	Astrocytoma	2
10	29	Male	Anaplastic astrocytoma	3
11	30	Female	Oligodendroglioma	2
12	70	Female	Oligodendroglioma	2

Table 2

Therapies prior to imaging and interval time between PET and MRS studies.

Case	Surgical resection	PET-MRS interval (days) ^a	Surgery to imaging (months)	Radiation to imaging (months)	Chemotherapy to imaging (months)
1	Complete	26	26	–	20
2	Complete	0	10	8	8
3	Complete	–7	19	14	1
4	Complete	–1	20	–	9
5	Partial	11	16	14	3
6	Complete	–20	21	–	15
7	Partial	–12	70	67	62
8	Complete	3	26	24	19
9	Complete	–1	17	14	14
10	Partial	0	69	66	64
11	Complete	19	10	8	2
12	Complete	5	17	11	8

^aPositive numbers demonstrate MRS preceded PET and negative numbers show MRS was performed after PET.

Table 3

SVM and ROC results of selected combinations.

Lesional parameters			Normal brain parameters				WHO	ROC		Support vector machine				Discriminant Equation	
SUV	Cho	Cr	NAA	SUV	Cho	Cr	NAA	Cutoff	Accuracy	Sensitivity	Specificity	Accuracy	MCC	cv	
×								4.5	75%	40% (7%, 83%)	100% (56%, 100%)	75% (43%, 93%)	53% (24%, 80%)	75%	SUVmax > 5.7
	×							10.3	67%	20% (1%, 70%)	100% (56%, 100%)	67% (35%, 89%)	36% (13%, 67%)	42%	Cho > 13.3
×	×									80% (30%, 99%)	86% (42%, 99%)	83% (51%, 97%)	66% (35%, 88%)	75%	SUVmax + 0.15Cho > 6.8
×	×						×			60% (17%, 93%)	100% (56%, 100%)	83% (51%, 97%)	68% (37%, 90%)	83%	SUVmax + 0.17 Cho + 0.91 WHO > 9
	×				×			1.7	75%	40% (7%, 83%)	100% (56%, 100%)	75% (43%, 93%)	53% (24%, 80%)	67%	nCho > 1.9
	×	×						3.0	83%	60% (17%, 93%)	100% (56%, 100%)	83% (51%, 97%)	68% (37%, 90%)	75%	Cho/Cr > 2.8
	×	×			×	×		2.5	83%	60% (17%, 93%)	100% (56%, 100%)	83% (51%, 97%)	68% (37%, 90%)	75%	nCho/Cr > 2.6
×				×				1.8	83%	80% (30%, 99%)	86% (42%, 99%)	83% (51%, 97%)	66% (35%, 88%)	75%	nSUVmax > 1.9
×	×	×		×						60% (17%, 93%)	100% (56%, 100%)	83% (51%, 97%)	68% (37%, 90%)	75%	nSUVmax + 0.55 Cho/Cr > 3.3
×	×	×		×	×	×				80% (30%, 99%)	100% (56%, 100%)	92% (60%, 100%)	84% (51%, 97%)	83%	nSUVmax + 0.64 nCho/Cr > 3.3

SUVmax, maximal SUV of the lesion; nSUVmax, maximal SUV of the lesion divided by maximal SUV of contralateral normal white matter; Cho, choline concentration of the lesion; nCho, choline concentration of the lesion normalized to choline concentration of contralateral normal brain; Cho/Cr, choline concentration of the lesion divided by creatine concentration of the lesion; nCho/Cr, Cho/Cr normalized to contralateral normal brain; Values in the parentheses are 95% confidence intervals; ROC, receiver operator characteristic; CV, cross-validation; MCC, Matthews correlation coefficients.