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Quantitative combination of volumetric MR imaging and MR spectroscopy data for the discrimination of meningiomas from metastatic brain tumors by means of pattern recognition

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Abstract

The analysis of information derived from magnetic resonance imaging (MRI) and spectroscopy (MRS) has been identified as an important indicator for discriminating among different brain pathologies. The purpose of this study was to investigate the efficiency of the combination of textural MRI features and MRS metabolite ratios by means of a pattern recognition system in the task of discriminating between meningiomas and metastatic brain tumors. The data set consisted of 40 brain MR image series and their corresponding spectral data obtained from patients with verified tumors. The pattern recognition system was designed employing the support vector machines classifier with radial basis function kernel; the system was evaluated using an external cross validation process to render results indicative of the generalization performance to “unknown” cases. The combination of MR textural and spectroscopic features resulted in 92.15% overall accuracy in discriminating meningiomas from metastatic brain tumors. The fusion of the information derived from MRI and MRS data might be helpful in providing clinicians a useful second opinion tool for accurate characterization of brain tumors.

Keywords: Brain Tumors; MRI; MRS; Volumetric textural features; Spectroscopic features; Pattern classification

1. Introduction

Cerebral metastases are the most frequent brain tumors in adults. They grow mainly in the brain or cerebellum and less frequently in the meninges [1]. However, solitary dural metastases are the second most frequent meningeal lesions, which from an imaging point of view are difficult to differentiate from meningiomas [2]. Both these tumoral forms can uptake magnetic resonance imaging (MRI) contrast agent in a similar manner. Occasionally, isolated forms of these metastatic tumors have radiological features that strongly suggest a primary tumor, and furthermore, their macroscopic appearance during surgery may even be taken for a meningioma [1]. There are several case studies reported in the literature pointing out the problem of differential diagnosis between these two types of brain tumors [1,3–7]. Most of these studies have indicated that there is a radiographic similarity between these types of tumors while many of them have reported that the radiological images of metastases even display a “dural tail,” a sign usually associated with meningiomas. In particular, Tagle et al. [1] have reported four cases of isolated meningeal metastases, where in all of them a meningioma had been considered as the main preoperative diagnosis. Lath et al. [6] have documented a case of extra-axial metastatic adenocarcinoma of the prostate

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that closely simulated a frontal, parasagittal meningioma, which, however, was revealed at histopathology to be a metastasis from adenocarcinoma of the prostate. In another study [5], Laidlaw et al. reported a case of dural metastases which, on both preoperative computed tomography and MRI and at surgery, had the typical appearance of a falcine meningioma. Histopathology and immunohistochemistry revealed adenocarcinoma of renal cell origin, and the renal primary was identified on subsequent abdominal investigation.

Until now, several studies have proposed and developed pattern recognition systems to provide clinicians' second opinion tools that will assist them in the characterization of brain tumors. However, some of them have utilized features derived only from the tumor's texture [8–12] and a few only from the tumor's MR spectroscopy (MRS) data [13–15].

Regarding MR texture analysis, two-dimensional (2D) and three-dimensional (3D) textural features have been previously employed in pattern recognition systems for the characterization of brain lesions. In particular, in a recent study by Herlidou-Meme et al. [10], discrimination accuracies between different tumor types ranged between 49% (tumors vs. oedemas) and 63% (benign vs. malignant tumors) by utilizing 2D textural features and hierarchical ascending classification with correspondence factorial analysis [16]. In another study, Lerski et al. [11] attained maximum overall accuracy of 95% between brain tumors and oedematous tissues by employing 2D textural features, discriminant analysis and the *k*-nearest neighbor classifier. In a previous study by our group [9], discrimination accuracies of 71%, 72% and 81% were achieved between metastatic brain tumors, gliomas and meningiomas, respectively, using 2D textural features and a modified probabilistic neural network classifier. In a more recent study by our group [17], those discrimination accuracies were elevated to 77% (metastatic tumors), 89% (gliomas) and 93% (meningiomas) employing 3D textural features, bootstrap aggregation and a modified support vector machines (SVM) classifier.

Regarding MR spectroscopy analysis, in a previous study by Devos et al. [14], classification accuracies of 97%, 59% and 96% have been found between metastatic brain tumors and meningiomas, glioblastomas, and astrocytomas, respectively, employing only short-time echo MRS data and the least squares SVM (LS-SVM) classification algorithm. In another study by Lukas et al. [13] on the same tumor types, employing the same data set, lower but comparable discrimination results have been found, employing only long time echo MRS data and the LS-SVM classification algorithm. Finally, Tate et al. [15], by combining spectroscopic data from multiple clinical centers have achieved classification accuracy of 90% between meningiomas, low-grade astrocytomas and aggressive tumors (glioblastomas and metastases), employing linear discriminant analysis.

The combination of textural and spectroscopic features may offer additional information that will improve the accuracy of such pattern recognition systems. However, to the best of our knowledge, there are only two studies in literature that have attempted to combine in pattern recognition systems textural and spectroscopic features [18,19]. More specifically, Luts et al. [19] have attained discrimination accuracies of 97% for astrocytomas, 94% for oligoastrocytomas, 92% for oligodendrogliomas, 96% for meningiomas and 98% for gliomas by employing a combination of four textural features (the averaged values of pixel intensities within the tumor boundaries from four sequences — T1, T2, Proton Density [PD] and gadolinium [GD] enhanced T1) and 10 spectroscopic features (one from each quantified metabolite from the MR spectra) and the LS-SVM classification algorithm. In another study, Devos et al. [18], by combining the same textural and spectroscopic features, have achieved mean classification accuracy of 99% for discriminating low- from high-grade tumors, low- from high-grade gliomas, meningiomas from gliomas and Grade II from Grade III gliomas. However, both these studies, which have relied on the same data set [20], have utilized the same methodology; they have (a) employed only one textural feature (average value), thus depriving their system from higher-order, information-rich, textural features, and (b) have used features from MRS data, concerning 10 metabolites that are cumbersome to quantify on MRI in everyday clinical routine.

The aim of the present study was to extend our previous work on brain tumor characterization by designing, implementing and evaluating an SVM-based pattern recognition system to investigate whether the combination of routinely acquired postcontrast MR image and spectroscopic features might improve discrimination between meningiomas and solitary dural metastasis.

2. Material and methods

2.1. Clinical material

The clinical material utilized in the present study consisted of brain MR-image series and MR spectra of 40 patients with verified and untreated intracranial tumors. Patients were examined on a Siemens Sonata 1.5-T MRI Unit (Siemens, Erlangen, Germany) at the Hellenic Airforce Hospital, Katehaki, Athens, Greece. Although meningiomas are more common than dural metastasis, the available data set comprised 21 patients with solitary dural metastasis and 19 patients with meningiomas. Nearly equal number of patients per tumor type was utilized in order for the proposed system to produce less biased results [21,22]. The mean age of the patients was 67 years old (S.D. 11, range 40–86, 25 male, 15 female). From each case, only the T1-weighted post-contrast (gadolinium) series, with spin echo sequence, echo time (TE=15 ms), repetition time (TR=500 ms) and slice thickness (1.5 mm) were used for further processing. Regarding the acquisition of MR spectra, a single-volume spectroscopy, short time echo (TE=35 ms), stimulated echo acquisition mode Proton Magnetic Resonance Spectroscopic Imaging (^{1}H-MRSI) sequence was used. Spectroscopic Volumes of Interest (VOIs) were determined from the T1-weighted postcontrast axial images positioned entirely within the boundaries of the tumor.

2.2. MRI and MRS feature extraction

A previous study by our group [17] has shown that volumetric (3D) textural features may significantly improve classification accuracy in discriminating primary from metastatic tumors as compared to 2D features. In the present study, volumetric textural features were also used, extracted from the MR series employing a program that was designed using the C + programming language and the Visualization Tool Kit [23]. The developed software utilized the *marching cubes algorithm* [24] to build 3D models from Digital Imaging and Communications in Medicine (DICOM) MRI-series and, thus, to provide the radiologist with a visual aid for segmenting VOIs within brain tumors. Both textural and spectroscopic features were derived from the same tumor volume.

From each VOI, a series of 36 textural features were extracted: four features from the VOI's histogram, 22 from the volumetric co-occurrence matrices [12,25] and 10 from the volumetric run-length matrices [26,27]. The histograms' features describe the occurrence frequency of all the gray tones in the VOI. The co-occurrence matrix measures describe the overall spatial relationships that the gray tones have to one another in the VOI, while the run-length features describe the heterogeneity and tonal distribution of the gray tones in the VOI [25,27]. From the spectroscopic data of each tumor, three metabolites were evaluated [choline (Cho), N-acetyl aspartate (NAA), creatine (Cr)], and the following metabolite integral ratios were formed: Cho/NAA, Cho/Cr and NAA/Cr, to be used as features in the proposed pattern recognition system. These ratios are used in everyday clinical practice by radiologists for assessing various chemical properties of brain neoplasms, thus providing an added value in tumor characterization and management [28,29]. All features were normalized to zero mean and unit standard deviation [30], according to Eq. (1)

$$x_i{}' = \frac{x_i - m}{std}, \tag{1}$$

where x_i and $x_i{}'$ are the ith feature values before and after the normalization, respectively, and m and std are the mean value and standard deviation, respectively, of feature x_i overall patterns and all classes.

2.3. System design and evaluation

An SVM-radial basis function (RBF)-based classification scheme (Fig. 1) was designed to discriminate between meningiomas and metastatic brain tumors employing both textural and spectroscopic features. The SVM classifier [31,32] functions by (a) transforming the training feature vectors to a higher-dimensional space, where the two classes become linearly separable, and (b) finding two parallel hyperplanes with maximum distance between them and at the same time with minimum number of training points in the area between them (also called the *margin*). The general discriminant function of the SVM classifier is given by:

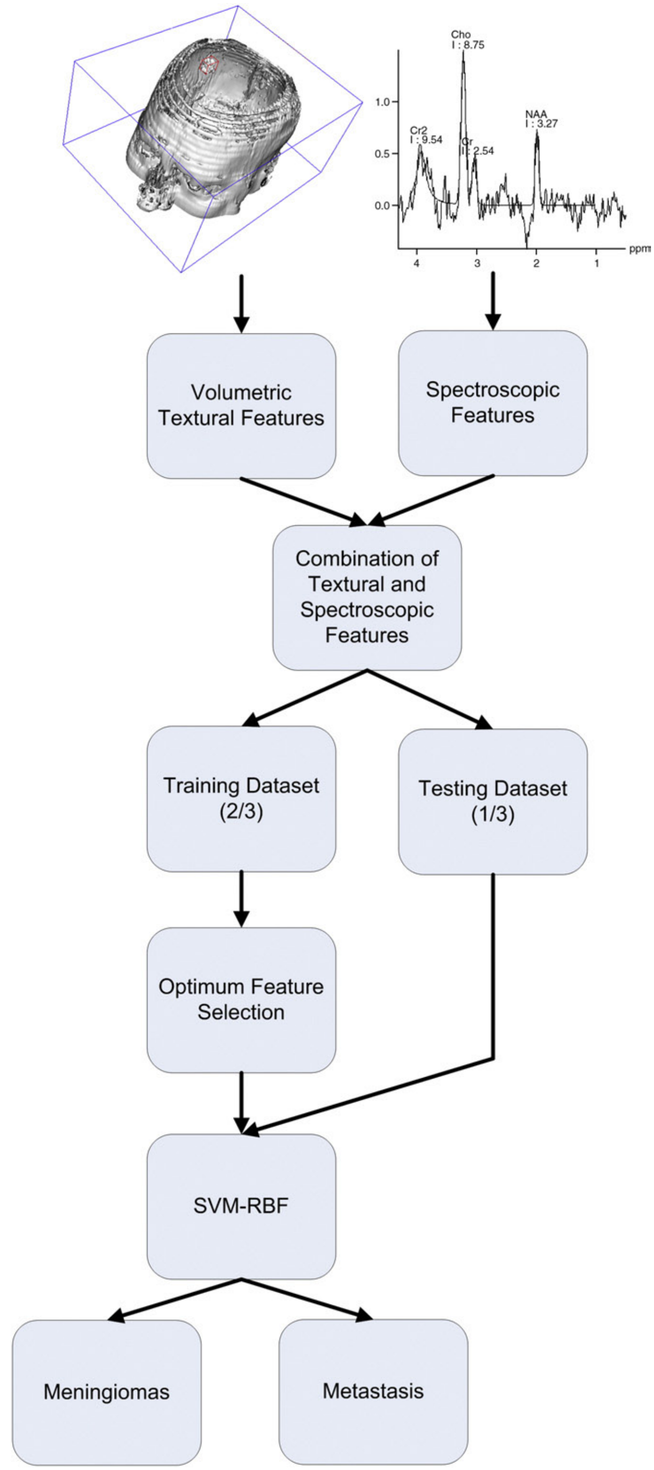

Fig. 1. Classification scheme design.

$$g(\mathbf{x}) = \mathrm{sign}(\mathrm{w} \cdot \Phi(\mathbf{x}) + \mathrm{b}), \tag{2}$$

where, positive sign is referred to the meningiomas data class, negative sign is referred to the metastatic tumor data

Table 1
Comparative classification results for discriminating meningiomas from metastatic tumors employing solely textural features

Number of features	Meningiomas correctly classified (%)	Metastasis correctly classified (%)	Overall accuracy (%)
1	63.16	85.71	75
2	78.95	95.24	87.5
3	84.21	95.24	90
4	89.47	95.24	92.5
5	94.74	95.24	95

class, x is the feature vector to be classified, $\Phi(\mathbf{x})$ is the transformed feature vector in the higher-dimensional space, while $\mathbf{w}$ and b are geometrical parameters of the two hyperplanes. Solving the optimization problem of maximizing the margin by minimizing the number of training patterns inside it, and by employing the widely used Gaussian RBF as kernel (Eq. 3),

$$\Phi(\mathbf{x}) = exp\left(-\frac{(\mathrm{x}_i-\mathrm{x})^T(\mathrm{x}_i-\mathrm{x})}{2\sigma^2}\right), \quad (3)$$

the discriminant function of the SVM-RBF classifier can be written as:

$$\mathrm{g}(\mathbf{x}) = \mathrm{sign}\left(\sum_{\mathrm{i}=1}^{\mathrm{N_S}} \alpha_{\mathrm{i}} y_{\mathrm{i}} exp\left(-\frac{(\mathbf{x}_i-x)^T(\mathbf{x}_i-x)}{2\sigma^2}\right)+b\right), \quad (4)$$

where $\mathbf{x}_i \in \mathbf{R}^d$, i=1...N (where d is the number of features) are N training feature vectors belonging to the two classes (meningiomas, metastases) identified by the label $y_i \in [+1,-1]$, α_i are coefficients that are obtained by solving the optimization problem, N_s is the number of feature vectors (also called the *support vectors*) with non-zero α_i's and σ is the standard deviation.

The system design comprised two stages: (a) features reduction and (b) information-rich features selection for optimum classification system design.

In the features reduction stage, all possible combinations of features (employing the exhaustive search method [30]) were tested for designing the SVM-RBF classifier, and the precision of each design was tested by the leave-one-out (LOO) method [30], whereby all data but one were used (each case being represented by the same features' combination) to design the classifier and the left-out case was classified to one of two classes (meningiomas-metastases). This action was repeated for all available data, and the precision of the classifier, for each particular features' combination, was evaluated as the number of successfully classified cases. Finally, the features' combination that provided the highest classification with the least number of features comprised the best features set that was used in the next stage of the system design. In this stage, an additional step was taken in order to investigate the discriminatory ability of each particular type of features as well as their combination. In particular, the proposed SVM-RBF classification system was designed and evaluated by using solely (a) textural features or (b) spectroscopic features and (c) the combination of textural and spectroscopic features.

Regarding the second stage, optimum system design was accomplished by means of the external cross validation (ECV) method [33] and employing the *best feature*

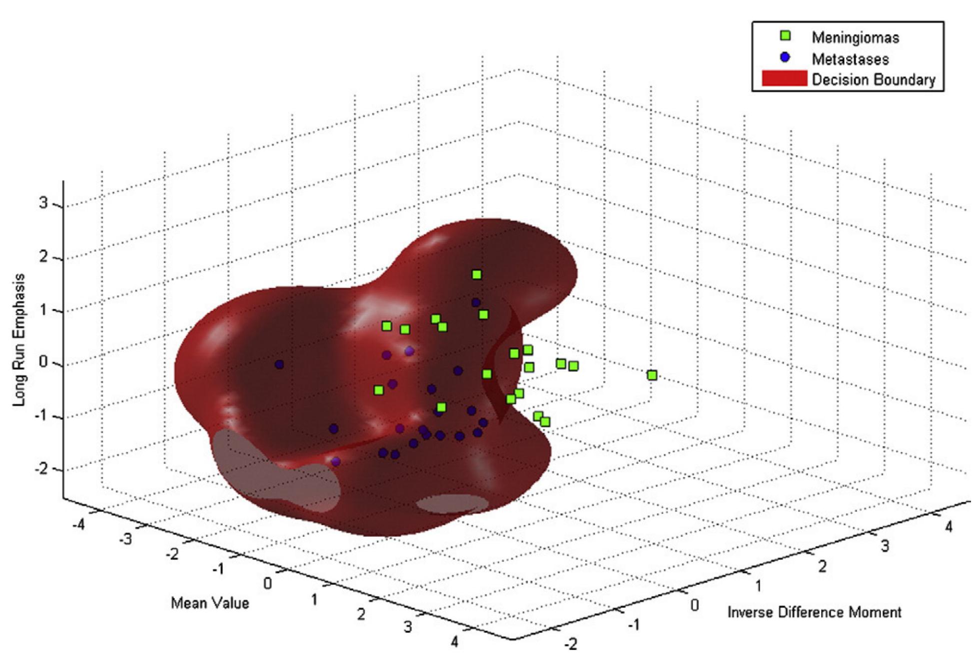

Fig. 2. Scatter diagram of the optimum three features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors employing only textural features.

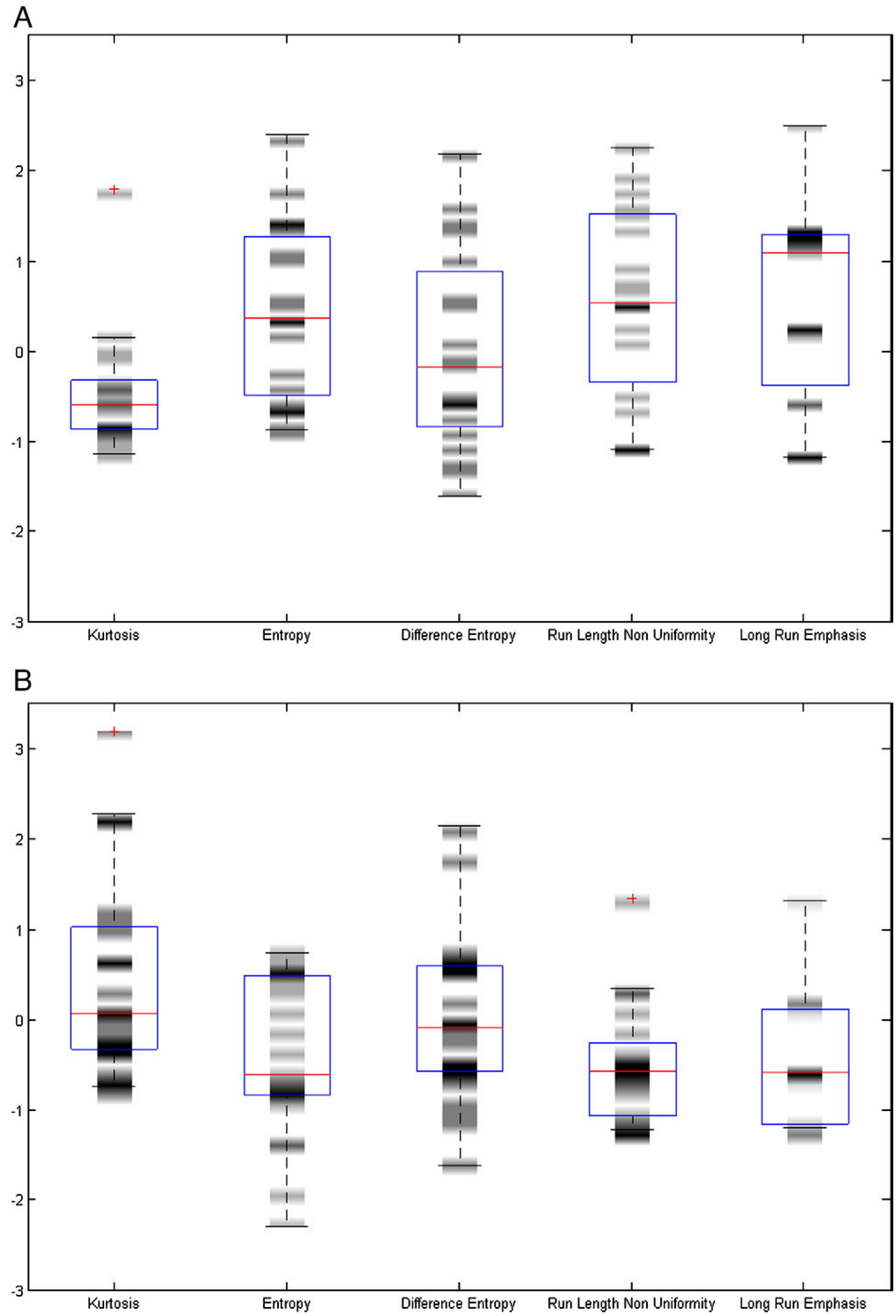

Fig. 3. (A) Boxplot of the best textural features for meningiomas cases. (B) Boxplot of the best textural features for metastatic cases.

combination attained at the first stage of the design. The ECV is essential because the system's performance may be assessed on "unseen data." Accordingly, all possible combinations of features, chosen from within the *best feature combination*, were formed (e.g., Combinations of 2, 3, 4, etc.). For each feature combination, the data set was randomly split in two subsets: one was used to design the SVM-RBF classifier (2/3 of the data set, containing both classes in equal percentages) and the other to evaluate its performance (1/3 of the data set) [33]. This procedure (design-evaluation) was repeated 10 times, each time splitting the data set into two subsets (design set: 2/3 and test set: 1/3), however, choosing randomly subsets' members from the original data set and recording the precision accuracies achieved. Finally, mean classification accuracies and variances were evaluated at each number of combined features.

Table 2
Comparative classification results for discriminating meningiomas from metastatic tumors, employing solely spectroscopic features

Number of features	Meningiomas correctly classified (%)	Metastasis correctly classified (%)	Overall accuracy (%)
1	84.21	85.71	85
2	89.47	85.71	87.5
3	89.47	90.48	90

3. Results

Highest classification accuracy in discriminating meningiomas from metastases was 95%, employing only textural features (kurtosis, entropy, difference entropy, run length nonuniformity and long run emphasis). Individual accuracies in classifying correctly meningiomas was 94.74% and metastatic brain tumors 95.24%. Comparative classification results for various numbers of features are presented in (Table 1). Fig. 2 shows the scatter diagram of the three best features combination along with the corresponding decision boundary. Fig. 3 depicts the boxplot of the best textural features for both meningiomas (Fig. 3A) and metastases (Fig. 3B), normalized according to Eq. 1. The distribution of the normalized feature values was overlaid on the boxplots, employing a gradient bar were darker parts indicate higher value occurrences. Values marked with the plus sign are outliers and the horizontal lines within the boxes indicate median values.

Employing solely spectroscopic features, the overall classification accuracy was 90%. The feature combination that gave the highest discrimination accuracy between meningiomas and metastases comprised all three metabolite ratios utilized in the present study (Cho/NAA, Cho/Cr and NAA/Cr). The individual accuracies obtained were 89.47% for meningiomas and 90.48% for metastatic tumors (Table 2). Fig. 4 illustrates the scatter diagram of the spectroscopic metabolite ratios along with the corresponding decision boundary while Fig. 5 depicts the boxplots for meningiomas (Fig. 5A) and metastases (Fig. 5B).

When the textural features were combined with the spectroscopic, the overall classification accuracy was 100%. Best feature vector, used for the optimal design of the SVM-RBF classifier, comprised correlation, sum average, difference entropy, long run emphasis and the Cho/NAA ratio. Comparative classification results for various numbers of features are presented in (Table 3). Fig. 6 shows the scatter diagram of the three best features combination along with the corresponding decision boundary while Fig. 7 depicts the boxplot of the best features for meningiomas (Fig. 7A) and metastases (Fig. 7B).

Employing the ECV method, for assessing the generalized performance of the system to "unseen data," the mean overall classification accuracy was 92.15% employing 5 features. The mean individual accuracies were 96.66% for meningiomas and 88.57% for metastatic tumors.

4. Discussion

One significant finding of the present study is that the combination of textural and spectroscopic features improved discrimination accuracy between meningiomas and metastases as compared to the classification results obtained by employing solely textural or spectroscopic

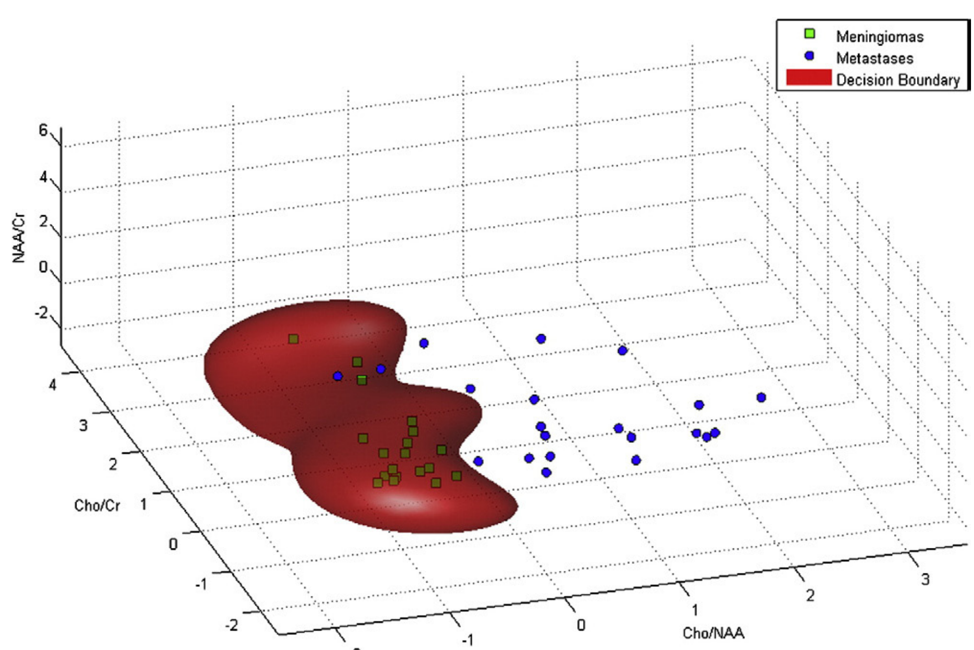

Fig. 4. Scatter diagram of the optimum spectroscopic features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors.

features. Discrimination accuracies attained using textural, spectroscopic or a combination of both were 95%, 90% and 100%, respectively. These results, however, are biased, obtained using the exhaustive search and the LOO evaluation method to design the SVM classifier. To assess the precision of the proposed classification system to “unseen data,” the ECV method was implemented that resulted in overall mean discrimination accuracy of 92.15% for distinguishing between meningiomas and metastases, with 96.66% for predicting correctly meningiomas and 88.57% metastatic tumors. The results obtained employing the ECV technique indicate that the proposed method might be used for accurate discrimination of meningiomas and solitary dural metastasis, which is of crucial importance since there are studies in literature pointing out the need for accurate tumor characterization in order to provide patients the proper clinical management, prolonging survival and quality of life [3,34]. More specifically, in a recent study,

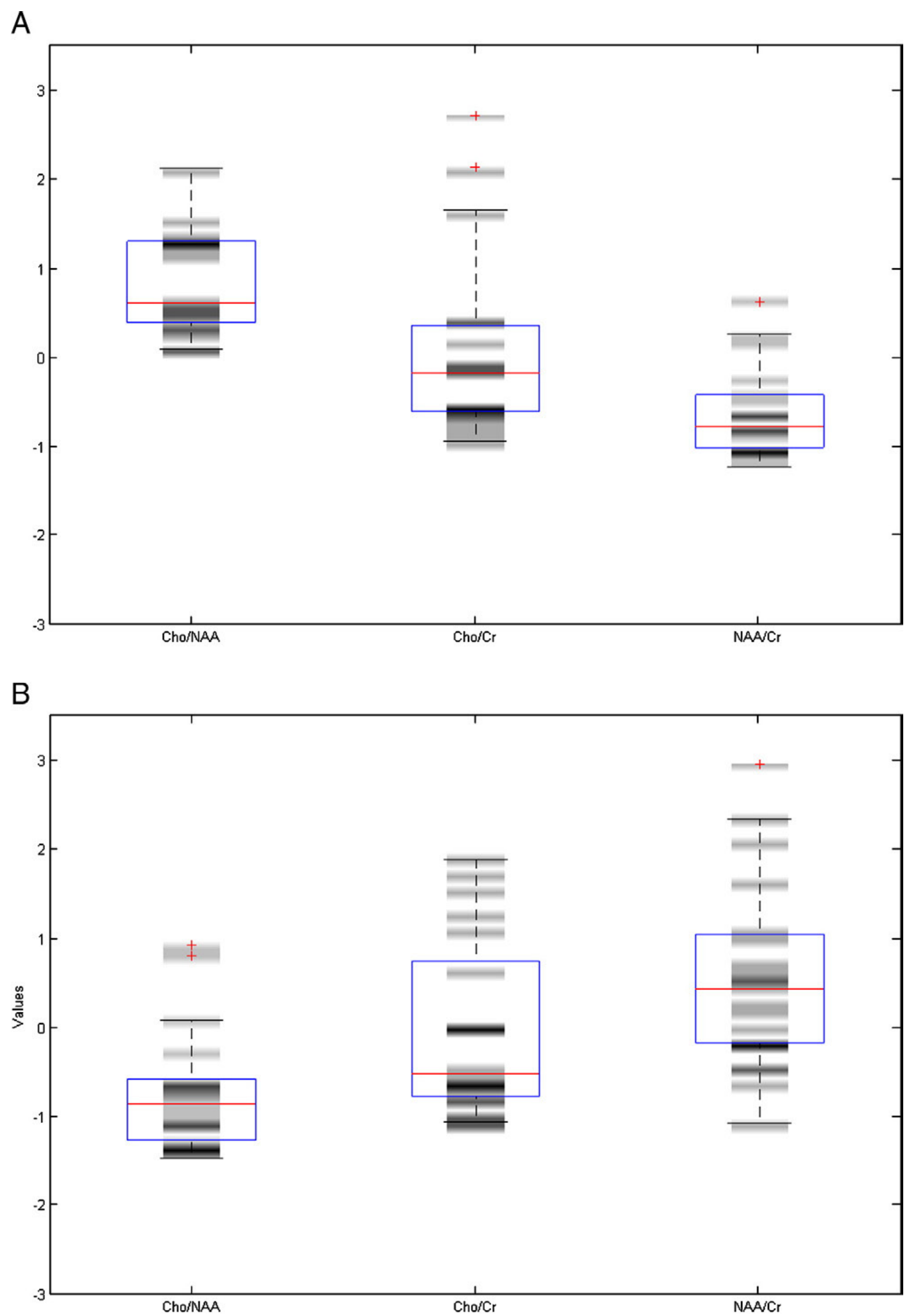

Fig. 5. (A) Boxplot of the spectroscopic features for meningiomas cases. (B) Boxplot of the spectroscopic features for metastatic cases.

Table 3
Comparative classification results for discriminating meningiomas from metastatic tumors employing both textural and spectroscopic features

Number of features	Meningiomas correctly classified (%)	Metastasis correctly classified (%)	Overall accuracy (%)
1	84.21	85.71	85
2	89.47	85.71	87.5
3	94.74	95.24	95
4	94.74	100	97.5
5	100	100	100

Chao et al. [34] provided the evidence for the long-term survival of patients with single metastasis when early and acute tumor characterization along with good prognostic factors (young age, good recursive partitioning analysis) was followed by surgery or stereotactic radiosurgery. In another study, Marosi et al. [3] illustrated that patients with asymptomatic small benign meningiomas can be followed up without therapy, while in symptomatic patients, complete surgical resection should be attempted, which is often curative. For incompletely resected benign tumors, radiotherapy is recommended while for recurrent previously completely resected tumor reresection is recommended followed by radiotherapy.

The textural features that optimized classification results describe the gray-tone linear dependencies (correlation), the dispersion of the gray-tone intensity values (sum average) and the degree of the in-homogeneity of the gray-tones (difference entropy and long run emphasis) within the VOI [25,27]. These features reflect radiological properties, such as texture homogeneity and signal intensity, that the expert physicians use in order to characterize the type of the tumor [35]. The spectroscopic feature that participated in the optimum feature vector was the Cho/NAA metabolite integral ratio. Cho represents various choline-containing compounds, such as acetylcholine, phosphocholine (lecithin), glycerophosphocholine and various other intermediates of phospholipid metabolism. It is an indicator of cell density and cell wall turnover. Elevated Cho levels are found in tumors, especially malignant ones, and in certain demyelinating diseases. NAA is an amino acid found exclusively in neurons and is a marker of neuronal viability. NAA concentrations are decreased in conditions leading to axonal injury or neuronal loss. Decreased concentrations are also seen in tumors, infarction and inflammatory conditions such as multiple sclerosis. Normally, since the NAA is a marker of neuronal viability, it should not be found in meningiomas or metastatic tumors. However, in the present study, the low NAA concentrations that were observed may be attributed to possible contamination by non-tumoral neuronal tissue surrounding the tumor or to possible existence of normal neurons within the tumor [36–38]. When Cho/NAA ratio in a suspicious-for-lesion area is greater than one, the lesion is considered to be positive for neoplasm [28,29]. Both meningiomas and metastases are characterized from low concentrations of NAA, while meningiomas exhibit higher concentrations of Cho than metastases [39], which could be attributed to increased synthesis or increased degradation of tumor cell membranes [40]. Thus the Cho/NAA ratio provided a distinguishable pattern for our system in order to discriminate meningiomas from metastasis.

The enhanced boxplots (enriched with the information derived from the distribution of the normalized feature

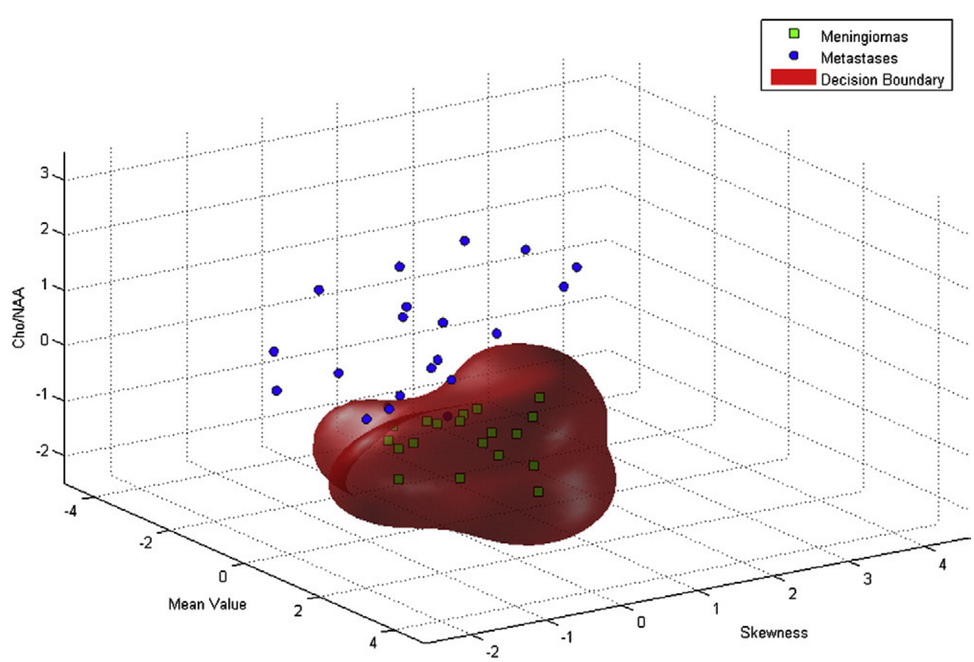

Fig. 6. Scatter diagram of the optimum three features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors employing both textural and spectroscopic features.

values) can furthermore provide an evidence of the discrimination capability of the best feature set attained at the first stage of the system's design. Evaluating the median values of the best normalized feature values of meningiomas and metastases, as presented in the boxplots, it can be observed that meningiomas had positive values while metastatic cases had negative values providing a clear discriminating margin for the classification system designed in the present study.

Judging from the results of the present study, the SVM-RBF classification system, constructed with 3D textural and spectroscopic features, achieved higher accuracies than those obtained in our previous studies that have used solely 2D or 3D textural features [8,9,17]. In particular, in a previous

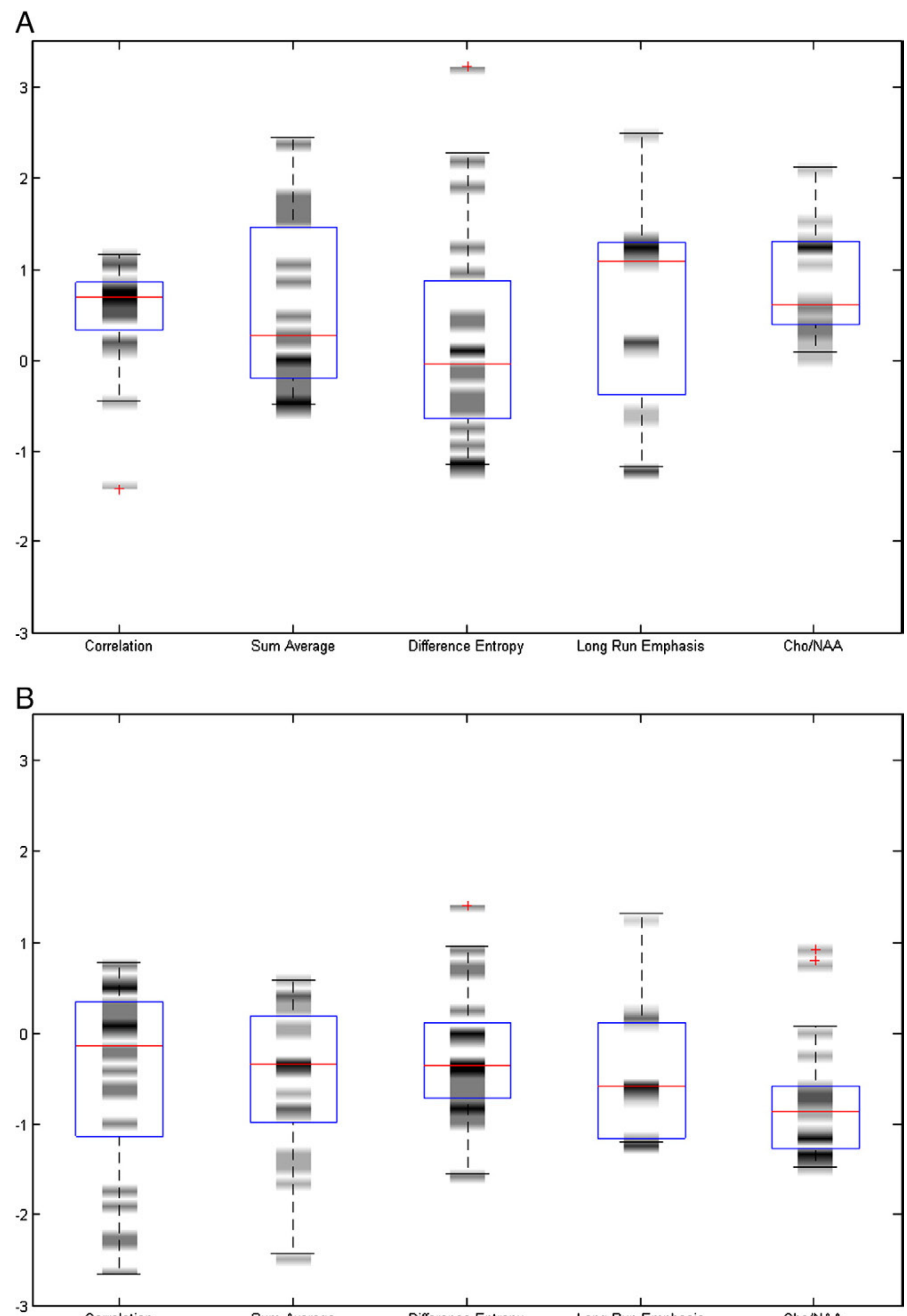

Fig. 7. (A) Boxplot of the best combination of textural and spectroscopic features for meningiomas cases. (B) Boxplot of the best combination of textural and spectroscopic features for metastatic cases.

study by our group [9], by employing an Least Squares Features Transformation (LSFT) modified probabilistic neural network, 2D textural features and the ECV technique, discrimination accuracies of 71.43% for metastases and 81.25% for meningiomas has been achieved. In a more recent study [17], by employing 3D textural features, the ECV method, bootstrap aggregation and an LSFT modified SVM classifier, classification accuracies of 77.14% for metastases and 93.33% for meningiomas have been obtained. The present study improved these accuracies to 88.57% for metastases and 96.66% for meningiomas employing the ECV method. Regarding studies from other groups, Devos et al. [14] attained classification accuracies of 97%, between metastatic brain tumors and meningiomas, employing only short time echo MRS data and the LS-SVM classifier. In another study, Luts et al. [19] attained individual discrimination accuracy of 96% for meningiomas by employing a combination of four textural, 10 spectroscopic features and the LS-SVM classification algorithm. Our findings are comparable. However, since the aim of the present study was to provide evidence that the fusion of routinely taken MR images and spectra can provide better discrimination results from solely textural or spectroscopic features, no modification was applied in the classification scheme (e.g., LSFT, bagging, classifier ensemble) in order to enhance discrimination results.

5. Conclusion

The combination of the information derived from textural and spectroscopic analysis of meningiomas and metastasis on MRI can increase the discrimination accuracy of pattern recognition systems designed to provide to clinicians a useful second opinion tool.

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