The role of multimodal-MRI in the differential diagnosis of single cystic intracranial lesions

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Purpose

Intracranial cystic lesions include primary and secondary brain tumors and non-neoplastic cysts such as brain abscesses.

Differentiation between these entities is essential for adequate treatment planning as well as outcome and prognosis estimation.

Glioblastoma (GBM) is the most common primary malignant brain neoplasm in adults and it is associated with a poor prognosis; the current standard of care is surgical resection followed by radiation therapy and concomitant and adjuvant temozolomide chemotherapy [1]. Metastases are the most common intracranial tumors in adults. Metastases treatment requires multidisciplinary approach tailored for each individual patient; therapeutic options include surgery, whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) [2]. Brain abscess is a neurosurgical emergency and its optimal management involves surgical drainage and administration of high doses of intravenous antibiotics [3].

The radiologist faces a diagnostic dilemma mostly when a single ring-enhancing lesion with perifocal edema has been identified on CT or conventional MR imaging [4] and when clinical presentation and laboratory data are unspecific.

Indeed, brain abscesses and brain tumors may have similar clinical presentation (fever occurs only in < 50% of brain abscess patients [5]). Besides, there are no laboratory data pathognomic of brain abscess.

Patients frequently have normal leukocyte counts and the erythrocyte sedimentation rate-usually elevated- is sometimes normal [6].

Conventional MR imaging is an established and useful tool in the characterization of single intracranial cystic lesions. It provides important information regarding contrast material enhancement, peri-lesional edema, hemorrhage, necrosis, mass effect and so on. Abscesses usually show smooth inner margin of the enhancing rim on contrast-enhanced images, the presence of satellite lesions and a dark rim on T2-weighted images [7-8].

However, differentiation between brain abscesses and brain tumors with conventional MR imaging is sometimes unreliable. Conventional MR imaging does not provide reliable information on tumor physiology such as microvascularty, angiogenesis, metabolism, micronecrosis or cellularity.

Advanced MRI techniques such as Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS) and Dynamic Susceptibility
Contrast (DSC) add metabolic and structural information to anatomical images provided by conventional MRI.

DWI shows changes in water diffusivity. DTI represents a further development of DWI and measures directional variation of water diffusivity for a given voxel by using metrics that quantify diffusion anisotropy and tensor orientation reflecting the directional organization of tissue microstructure [9]. MRS is a non invasive technique that provides metabolic information about normal and pathologic tissue components. DSC provides non invasive measurement of vascularity and Cerebral Blood Volume (CBV) maps, which can be used to identify and quantify areas of neo-vascularization [10].

Several studies show that parameters derived from each of these techniques are useful in discrimination between glioblastomas, metastases and abscesses but little is known about adequate Regions Of Interest (ROIs) placement and cut-offs selection that guarantee the highest sum of sensitivity and specificity in differential diagnosis.

Moreover, some evidences suggest that the ability to distinguish between glioblastomas, solitary cerebral metastases and abscesses is improved when a multi-parametric imaging approach is adopted.

Law et al. [11] reported significant differences in both rCBV and Cho/Cr values in GBMs and metastases peri-tumoral region and they advocated that these imaging parameters could be used together to try and distinguish between the two tumor types.

Similarly, Bulakbasi et al. [12] found both ADC values and MRS values were separately useful in differentiating cerebral tumours, but, when combined, there was added value in predicting tumour type.

Again, the multiparametric approach was used for the discrimination of infectious from cystic neoplastic lesions [13].

The aim of the present study was twofold.

The primary aim was to determine potentially useful threshold values for DWI, DTI, MRS and DSC parameters in differentiating between brain abscesses, glioblastomas and metastases.

The secondary aim was to characterize single intracranial cystic lesions using a data-driven analysis of multiparametric MRI and to compare this method with a qualitative approach based on conventional MRI and a semi-quantitative approach based on a non-systematic criterion-based assessment of PWI, MRS and DTI.
Methods and Materials

**Population**

The study population consisted of twenty-five patients (sixteen males and nine females), with a mean age of sixty years.

Criteria for entry into the study included the presence of a single non-haemorrhagic ring-enhancing cerebral mass in a patient not previously operated.

All lesions were surgically proven: eight were abscesses, nine glioblastomas (World Health Organization, WHO grade IV) and eight metastases (three secondary to lung cancer, two to breast cancer, two to bowel cancer and one to melanoma).

In all patients imaging was performed on a 3-T scanner using a sense dedicated eight-channel head coil.

All patients underwent conventional MRI and advanced technique MRI.

**Conventional Imaging**

Before imaging, an 18- or 20-gauge intravenous catheter was inserted in the ante-cubital area for contrast agent administration.

Conventional MRI included a 3D TFE T1-weighted sequence [7.6 ms TR, 3.7 ms TE, 256x256 matrix, scan time of 1 min and 52 sec] in the sagittal plane obtained before and after gadolinium-based contrast agent administration; T2-weighted turbo spin-echo sequence, in the three orthogonal planes [3000 ms TR, 80 ms TE, 300x256 matrix, 3 mm section thickness with 1 mm intersection gap, scan time of 2 min and 6 sec]; a fluid-attenuated inversion recovery (FLAIR) sequence in the axial plane [11000 ms TR, 125 ms TE, 2800 ms inversion time, 320x200 matrix, 3 mm section thickness with 1 mm intersection gap, scan time of 5 min and 8 sec] and a T2* weighted fast field echo (FFE) sequence [1039 ms TR, 16 ms TE, 35 slices with 3 mm slice thickness, gap 1 mm, 256x197 matrix, scan time of 3 min and 30 sec]. Gadobutrol (Gadovist®; Bayer Schering Pharma, Berlin, Germany) with a dose of 0.1 ml/Kg was used in all patients.

**Advanced Imaging**

Advanced technique MRI included DWI, DTI, MRS and DSC.

**Diffusion Weighted Imaging (DWI)**
DWI was acquired using a single-shot echo-planar imaging (EPI) sequence at multiple levels. 28 slices of 4 mm thickness with 1 mm intersection gap were obtained [3700 ms TR, 67 ms TE, 128x128 matrix, b values of 0 and 1000 s/mm², scan time of 44 sec].

**Diffusion Tensor Imaging (DTI)**

Axial DTI was obtained using a single-shot spin-echo echo-planar imaging (SE-EPI) sequence [6245 ms TR, 60 ms TE, 128×128 matrix, b = 0 s/mm² as reference imaging and b = 800 s/mm², 15 diffusion sensitive dimensions, scan time of 3 min and 58 sec].

**Magnetic Resonance Spectroscopy (MRS)**

2D spectra were obtained using a multivoxel point-resolved spectroscopic sequence (PRESS) [1700 ms TR, 144 ms TE, scan time of 11 min and 57 sec]. Automated optimization of gradient shimming, transmitter pulse power and water suppression were used. For each patient, the volumes of interest (VOIs) of all samples were identical [10 mm × 10 mm × 15 mm].

**Dynamic Susceptibility Contrast (DSC)**

Before acquiring DSC an intravenous saturation bolus injection of 3 ml gadobutrolo (Gadovist®; Bayer Schering 1mMol/L) at a flow rate of 2 ml s⁻¹ was followed by a 20 ml saline flush. After a three minutes wait, for susceptibility-based PWI, the transitory signal loss during the bolus passage was detected with a T2* weighted FFE-EPI sequence [1576 ms TR, 40 ms TE, 25 slices with 4 mm slice thickness, 96x96 matrix, scan time of 1 min and 25 sec]. 50 dynamic scans with a time resolution of 1.6 sec per volume were performed after an intravenous bolus injection of 5 ml contrast media at a flow rate of 4 ml s⁻¹ and a 20 ml saline flush.

**Image Analysis**

All images were transferred to a workstation for data analysis. Evaluation was performed by two radiologists in consensus.

**Qualitative evaluation**

Qualitative evaluation was based on T1W, T2W, FLAIR and DWI images. From this evaluation readers were asked to provide an opinion concerning diagnosis (abscess, metastasis or glioblastoma).
Semi-quantitative evaluation

Semi-quantitative evaluation was based on the radiological report initially written when the patient presented. In this situation, at least two neuro-radiologists (with over ten years' experience) used the map images derived from DTI, PWI and MRS and cut-offs reported in literature.

Quantitative evaluation

For each patient, Regions Of Interest (ROIs) were placed in 4 areas (Fig. 1 on page 9):

1) Ring Enhancement (RE)
2) Lesion Cavity (LC)
3) Perilesional Edema (PE)
4) Controlateral Normal Appearing White Matter (NAWM)
Fig. 1: 3D TFE T1-weighted sequence in the axial plane after contrast agent administration. Frontal single cystic ring-enhancing lesion with surrounding edema and mass effect. Regions of interest (ROIs) were placed in lesion cavity (green), ring enhancement (red), peri-lesional edema (blue) and contralateral normal appearing white matter (yellow).

References: Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT

From DSC data blood volume maps, blood flow maps and mean transit time maps were generated and relative Cerebral Blood Volume (rCBV: $\text{CBV}/\text{CBV}_{\text{NAWM}}$), Cerebral Blood Flow (CBF) and relative Mean Transit Time (rMTT: $\text{MTT}/\text{MTT}_{\text{NAWM}}$) were assessed in each area.
For analysis of MRS data the metabolite ratios [Choline/Creatine (Cho/Cr), Cho/N-acetylaspartate (Cho/NAA), Lactate/Creatine (Lac/Cr) and Lipids/Creatine (Lip/Cr)] were estimated in voxels corresponding to LC and PE. We didn't consider for analysis RE spectroscopic parameters because the voxel size was not small enough to allow separation between RE and LC-PE.

From DWI data Apparent Diffusion Coefficient (ADC) maps were generated and relative ADC values (rADC: ADC/ADC\textsubscript{NAWM}) were assessed in each area.

For analysis of DTI data Fractional Anisotropy (FA) was calculated in each area from respective map.

**Statistical Analysis**

Independent samples Kruskal-Wallis test was used to evaluate differences among groups. The level of significance was defined by a P value # 0.05.

To determine significant variables cut-off that optimize sensitivity and specificity, Receiver Operator Characteristic (ROC) curve analysis was performed, alpha was set to 0.05 and beta to 0.20 with an acceptable area under ROC curve (AUC) of 0.75 compared to the Null Hypothesis value of 0.50.

For data-driven multifactorial approach (quantitative evaluation) a discriminant analysis was applied to determine whether integration of these variables in a predictive model for group membership could further improve the discrimination between abscesses, glioblastomas and metastases. Finally, ROC-analysis was performed to test diagnostic accuracy of the discriminant analysis model.
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Results

Conventional MRI accurately predicted the diagnosis in 16 of 25 of the cases (qualitative evaluation accuracy = 64%).

Conventional MRI, when combined with map images derived from DTI, PWI and MRS and cut-offs reported in literature, accurately predicted the diagnosis in 20 of 25 of the cases (semi-quantitative evaluation accuracy = 80%).

Kruskal-Wallis test demonstrated significant differences among the three patients group for rADC in LC (Fig. 2 on page 16), rADC in RE (Fig. 3 on page 17) and rCBV in RE (Fig. 4 on page 18).

Fig. 2: Box and whisker plots depicting abscesses, metastases and glioblastomas LC-rADC. The mean LC-rADC was significantly reduced (P < 0.007) for abscesses relative to metastases and glioblastomas using independent samples Kruskal-Wallis test.

References: Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT
Fig. 3: Box and whisker plots depicting abscesses, metastases and glioblastomas RE-rADC. The mean RE-rADC was significantly reduced (P < 0.0001) for glioblastomas and metastases relative to abscesses using independent samples Kruskal-Wallis test

**References:** Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT
**Fig. 4:** Box and whisker plots depicting abscesses, metastases and glioblastomas RE-rCBV. The mean RE-rCBV was significantly increased (P < 0.001) for glioblastomas relative to abscesses and metastases using independent samples Kruskal Wallis test. **References:** Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT
**Fig. 5:** Box and whisker plots depicting abscesses, metastases and glioblastomas LC-FA. The mean LC-FA was increased for abscesses relative to glioblastomas and metastases but this result was not significant (p=0.6).

**References:** Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT

For differentiation between abscesses and glioblastomas-metastases a threshold value of <1.20 for RE-rADC provided sensitivity and specificity of 92.86% and 87.50%, respectively; a threshold value of >1.06 for LC-rADC provided sensitivity and specificity of 87.50% and 62.50%, respectively; a threshold value of >1.50 for RE-rCBV provided sensitivity and specificity of 100% and 80%, respectively. Results are summarized in Table 1 on page 20 and Fig. 6 on page 20.
Table 1: Threshold values for RE-rADC, LC-rADC and RE-rCBV for differentiation between abscesses and glioblastomas-metastases.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ring enhancement rADC</td>
<td>&lt;1.20</td>
<td>92.86%</td>
<td>87.50%</td>
</tr>
<tr>
<td>lesion cavity rADC</td>
<td>&gt;1.06</td>
<td>87.50 %</td>
<td>62.50%</td>
</tr>
<tr>
<td>ring enhancement rCBV</td>
<td>&gt;1.50</td>
<td>100%</td>
<td>80%</td>
</tr>
</tbody>
</table>

References: Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT

Fig. 6: ROC curve showing the diagnostic value of LC-rADC, RE-rADC and RE rCBV. Areas Under the Curve (AUC) were 0.800, 0.857 and 0.943, respectively.

References: Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT

Parameters included in the discriminant analysis function were RE-rADC, LC-rADC and RE-rCBV. The sensitivity and specificity of the discriminant analysis model to distinguish
between abscesses and glioblatomas-metastases was tested using a ROC analysis which demonstrated sensitivity 100%, specificity 87.50% and AUC= 0.95 (Fig. 7 on page 21).

**Fig. 7**: ROC curve showing the diagnostic value of the discriminant analysis model. Area Under the Curve (AUC) was 0.95.

**References**: Magnetic resonance, Institute of Advanced Biomedical Technology - Chieti/IT
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Fig. 3: Box and whisker plots depicting abscesses, metastases and glioblastomas RE-rADC. The mean RE-rADC was significantly reduced (P < 0.0001) for glioblastomas and metastases relative to abscesses using independent samples Kruskal-Wallis test

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**Fig. 4:** Box and whisker plots depicting abscesses, metastases and glioblastomas RE-rCBV. The mean RE-rCBV was significantly increased (P < 0.001) for glioblastomas relative to abscesses and metastases using independent samples Kruskal Wallis test.

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Conclusion

**DWI**

DWI is a widely used tool to distinguish between brain abscesses and cystic or necrotic brain tumors [14].

In 1996 Ebisu et al. first reported the finding of restricted diffusion within the cavity of a brain abscess. The likely reason for this finding is the high viscosity of pus since it is made up of inflammatory cells, bacteria, necrotic tissue and exudate that collectively impede the microscopic motion of water molecules [15].

Further studies confirmed the restricted diffusion in abscesses central cavity, with high DWI signal intensity and corresponding low ADC values [16-17].

Similarly, we found lower LC-rADC values in abscesses than in primitive and secondary brain tumors (Fig. 8 on page 29). The sensitivity and specificity with the use of LC-rADC of 1.06 as a threshold value were 100% and 69%, respectively.
**Fig. 8:** A 67-year-old man with surgically proven pyogenic brain abscess in the left temporal lobe. (A) Diffusion-weighted image ($b = 1000 \text{ s/mm}^2$) shows marked hyperintensity in the abscess cavity and isointensity in the surrounding edema. (B) Apparent diffusion coefficient map reveals hypointensity in the abscess cavity, indicating restricted diffusion and hyperintense areas in the surrounding edema. (C) Post-contrast 3D TFE T1-weighted sequence in the axial plane shows a ring-shape cystic lesion and surrounding edema. (D) CBV map reveals low CBV values in the ring enhancement area.

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In one case (a 50-year-old man with an antibiotic-treated purulent medial otitis) we observed elevated abscess LC-rADC values (3.13) (Fig. 2 on page 29).

Elevated abscess LC-rADC values were already reported in literature.

In 1997 Krabbe et al. [18] first reported the case of an abscess with high ADC values in the central cavity. Mishra et al. [19] studied 29 patients with brain abscess and reported high ADC values in 8 cases: all of them underwent MRI after antibiotic treatment. Lai et al. [20] also reported a case of antibiotic-treated abscess showing high ADC values in the central cavity.

These studies suggest that high LC-rADC values correlate with reduction of purulent content and successful treatment of brain abscess.

In our study abscess cavity rADC values ranged from 0.5 to 3.13. This variability might be related to precedent treatments as well as abscess size, abscess age, different pathogenic organisms and host immune response [21-23].

In contrast, we observed high LC-rADC values in all tumor patients. This finding is consistent with those of previous studies [24-25].

Glioblastomas and metastases central cavity contains cellular debris, serum, haemorrhagic fluid and fewer inflammatory cells than abscess central cavity: as a result water molecules diffusivity is higher and consequently ADC values are 4 to 10 times greater than those of pus [26].

In our study RE-rADC values were lower in tumors than in abscesses and a threshold value of 1.20 provided a sensitivity of 92.86% and a specificity of 87.50% (Fig. 9 on page 30).

A reason for low RE-rADC values in primary and secondary brain tumors could be the high cellularity in the peripheral portion of the tumor consequent to the presence of highly-replicating malignant cells.

On the other hand, higher RE-rADC values in abscesses could be consequent to the extra-cellular fluid increase as a result of inflammation [27].
Fig. 9: A 80-year-old man with surgically proven glioblastoma in the right frontal lobe. (A) Diffusion-weighted image shows hypointensity in the abscess cavity and in the surrounding edema and hyperintensity in the ring-enhancement area. (B) Apparent diffusion coefficient map reveals hyperintensity in the abscess cavity and in the surrounding edema indicating increased diffusion and hypointensity in the ring-enhancement area indicating restricted diffusion. (C) Post-contrast 3D TFE T1-weighted sequence in the axial plane shows a ring-shape cystic lesion and surrounding edema. (D) CBV map reveals CBV values in the ring enhancement area higher than in contralateral normal appearing white matter.

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**PWI**

PWI permits to identify and quantify areas of neovascularization.

Neo-angiogenesis is crucial for survival and growth of tumors.

A number of studies reported that cystic or necrotic brain tumors peripheral portion shows high rCBV values [28].

Accordingly, we observed that RE-rCBV is significantly higher in tumors than in abscesses Fig. 8 on page 29 D and Fig. 9 on page 30 D) and a threshold value of 1.5 provides a sensitivity of 100% and a specificity of 80%.

The probable reason is that high grade tumors are associated with a high degree of tumoral infiltration, neo-angiogenesis and consequent elevated peripheral perfusion.

In contrast, abscesses show high amount of mature collagen and decreased peripheral vascularity.

For other parameters, differences among the three groups were not significant.

**MRS**

Findings from several studies suggest that in vivo Proton MR Spectroscopy might contribute to differential diagnosis between brain tumors and brain abscesses [29].

The main characteristic of pyogenic abscesses is resonance of amino-acids (end products of proteolysis by enzymes released by neutrophils in pus), acetate, succinate, lactate and lipids.

In contrast, cystic or necrotic tumor spectra show only lactate and lipids peaks [29].

Therefore, lactate and lipids are unspecific metabolites and they can be observed in the central cavity of both brain abscesses and primitive and secondary brain tumors [30-31].

In this study we didn't observe significant spectral pattern differences between brain abscesses and brain tumors.

PE-Cho/Cr values were greater in glioblastomas as regards metastases and abscesses.

This is an interesting data: many glioma-grading studies focused on the role of PE-Cho/Cr values [32].

According to these studies, elevated PE-Cho/Cr values could be correlated with tumor infiltration and tumoral high histological grade.
We hypothesized that lower PE-Cho/Cr values we observed in metastasis and abscesses could be due to the absence of infiltrating cells. Anyway, in our study, this difference was not significant; probably it was a consequence of the small sample size.

**DTI**

As far as DTI is concerned, studies have not brought univocal results.

Some Authors reported lower LC-FA values in glioblastomas than in abscesses [33].

They supposed that tumor cavity diffusion is more isotropic, probably because its content is more serous than pus and, for this reason, there are less barriers to water diffusion [34].

Other Authors reported higher LC-FA values in brain abscesses than in normal brain.

In this case, it was hypothesized that diffusion is more anisotropic in abscess because its cavity is rich of "orientated" inflammatory cells, as a consequence of expression of various cell-surface-adhesion-molecules known to be up-regulated in presence of bacteria [8].

We observed higher LC-FA values in abscesses than in glioblastomas, but this difference was not significant (p=0.5) (Fig. 5 on page 31).

**DISCRIMINANT ANALYSIS**

The use of isolated cut-offs didn't provide adequate characterization of abscesses, metastases and GBMs, given the heterogeneity of these lesions.

For this reason, we performed a data-driven discriminant analysis.

This is a quantitative multi-factorial approach that integrate metabolic, perfusional and microstructural characteristics of different lesion ROIs.

We found that diagnostic accuracy of this quantitative multi-factorial approach was higher than accuracy of qualitative and semi-quantitative approaches.

Finally, this study suggests that LC-rADC, RE-rADC, and RE-rCBV are the best predictors in detecting glioblastomas, metastases and abscesses.

We propose that a quantitative multi-parametric approach to advanced MRI techniques can improve diagnostic accuracy in differential diagnosis of single cystic intra-cranial lesions.
Fig. 8: A 67-year-old man with surgically proven pyogenic brain abscess in the left temporal lobe. (A) Diffusion-weighted image (b = 1000 s/mm²) shows marked hyperintensity in the abscess cavity and isointensity in the surrounding edema. (B) Apparent diffusion coefficient map reveals hypointensity in the abscess cavity, indicating restricted diffusion and hyperintense areas in the surrounding edema. (C) Post-contrast 3D TFE T1-weighted sequence in the axial plane shows a ring-shape cystic lesion and surrounding edema. (D) CBV map reveals low CBV values in the ring enhancement area.
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