World Journal of Radiology

TOPIC HIGHLIGHT

Clinical decision support systems for brain tumor characterization using advanced magnetic resonance imaging techniques

Evangelia Tsolaki, Evanthia Kousi, Patricia Svolos, Efthychia Kapsalaki, Kyriaki Theodorou, Constastine Kappas, Ioannis Tsougos

Evangelia Tsolaki, Evanthia Kousi, Patricia Svolos, Kyriaki Theodorou, Constastine Kappas, Ioannis Tsougos, Medical Physics Department, University of Thessaly, Biopolis, 41110 Larissa, Greece

Efthychia Kapsalaki, Department of Radiology, University Hospital of Larissa, Biopolis, 41110 Larissa, Greece

Author contributions: Tsolaki E and Tsougos I designed the research; Tsolaki E, Kousi E and Svolos P performed the research; Tsolaki E, Kousi E and Tsougos I wrote the paper; Kapsalaki E, Theodorou K and Kappas C performed a critical review and data analysis.

Correspondence to: Ioannis Tsougos, MSc, PhD, Assistant Professor in Medical Physics Department, University of Thessaly, Panepistimiou 2, Biopolis, 41110 Larissa, Greece. tsougos@med.uth.gr

Telephone: +30-241-3501863   Fax: +30-241-3501863

Received: November 12, 2013   Revised: January 23, 2014

Accepted: March 17, 2014

Published online: April 28, 2014

Abstract

In recent years, advanced magnetic resonance imaging (MRI) techniques, such as magnetic resonance spectroscopy, diffusion weighted imaging, diffusion tensor imaging and perfusion weighted imaging have been used in order to resolve demanding diagnostic problems such as brain tumor characterization and grading, as these techniques offer a more detailed and non-invasive evaluation of the area under study. In the last decade a great effort has been made to import and utilize intelligent systems in the so-called clinical decision support systems (CDSS) for automatic processing, classification, evaluation and representation of MRI data in order for advanced MRI techniques to become a part of the clinical routine, since the amount of data from the aforementioned techniques has gradually in-creased. Hence, the purpose of the current review article is two-fold. The first is to review and evaluate the progress that has been made towards the utilization of CDSS based on data from advanced MRI techniques. The second is to analyze and propose the future work that has to be done, based on the existing problems and challenges, especially taking into account the new imaging techniques and parameters that can be introduced into intelligent systems to significantly improve their diagnostic specificity and clinical application.

Core tip: The quantification of the imaging profile of brain neoplasms by combining conventional magnetic resonance imaging and advanced imaging techniques introduces critical underlying pathophysiological infor-mation which seems to be the key to success. Thus, it is evident that the pursuit of this goal should be oriented towards the development of decision support software that will utilize large amounts of clinical data with extremely significant diagnostic value which often remain unexploited, hence resulting in a more valid and precise method of differential diagnosis and the selec-tion of the most successful treatment scheme.

Tsolaki E, Kousi E, Svolos P, Kapsalaki E, Theodorou K, Kappas C, Tsougos I. Clinical decision support systems for brain tumor characterization using advanced magnetic resonance imaging techniques. *World J Radiol* 2014; 6(4): 72-81 Available from:

INTRODUCTION

The introduction of magnetic resonance imaging (MRI) systems has induced revolutionary changes in the medical imaging field and has contributed much on a diagnostic and therapeutic level. In recent years, there has been a shift towards advanced MRI techniques, such as magnetic resonance spectroscopy (^{1}H-MRS), diffusion weighted imaging (DWI), diffusion tensor imaging (DTI) and perfusion weighted imaging (PWI), in order to resolve demanding diagnostic problems. These techniques offer a more detailed and non-invasive evaluation of brain tumors[1-3] and have added incremental diagnostic information regarding brain tumor characterization over conventional MRI alone[4,5].

^{1}H-MRS has been studied for more than a decade as a promising diagnostic tool for a variety of pathologies. If coupled with the morphological features provided by MRI techniques, it can provide accurate identification and quantification of biologically important chemical compounds in soft tissue, thus increasing the understanding of the underlying pathologies. There have been numerous studies that indicate the significant contribution of ^{1}H-MRS for the characterization of brain tumors[6-8], and fewer studies have concentrated on pediatric tumors[9,10]. Even if ^{1}H-MRS does not change the final diagnosis, it may significantly rule out a differential diagnosis and thereby reduce the need for biopsy. However, challenges still remain in brain lesion classification regarding the use of ^{1}H-MRS. The most important one is the limited number of available spectra per lesion type which may induce difficulties in reaching specific conclusions. Moreover, the simultaneous analysis and evaluation of multiple spectroscopic parameters is a time-consuming process, required specific expertise and may not be practical in a clinical environment.

In addition to ^{1}H-MRS, the other advanced MRI techniques, DWI[11], DTI[12] and PWI have already found increasing use in the evaluation of cerebral tumors and still remain a subject of intense research[1,13,14]. DWI probes local tissue microstructure reflected by the freedom of microscopic motion of water molecules and provides a sensitive means to detect alterations in the integrity of white matter structures, while PWI facilitates the prediction of brain lesion progression in conjunction with histopathology[15].

It is evident that the continuously developing magnetic resonance systems have transformed from pure imaging systems to extremely precise metric systems that produce a considerable amount of numerical data that originate from the application of the aforementioned advanced MRI techniques. Taking into account the complex structure of the clinical data and the difficulty of brain tumor discrimination due to their intrinsic heterogeneity, the research community has shifted towards the application of machine learning algorithms, in order to assign different tissue types to specific patterns. Several studies have previously investigated the differentiation of brain tumors in adults based on machine learning techniques[16-20], as well as the discrimination of pediatric brain tumors[21,22].

By importing and utilizing these intelligent techniques in a clinical decision support system (CDSS), several advanced MRI techniques may become a part of the clinical routine in order to resolve demanding diagnostic problems. CDSSs based on pattern recognition have been widely accepted in medical applications, due to their capability for optimization, flexibility, accuracy for predictive inference and interpretability[23].

A CDSS according to van Bemmel *et al*[24] is defined as any piece of software that takes, as input data, the information about a clinical situation and produces, as output, the inferences regarding the clinical situation that can assist practitioners with their decision-making, and that would be judged as "intelligent" by the program's users.

Regarding brain tumor diagnosis, great efforts have been made in the implementation of intelligent systems for brain tumor differentiation, automatic processing, classification, evaluation and representation of clinical data. This effort is facilitated further by the evolvement of computer power that is available for the processing needs of these systems.

The purpose of the present study is to provide a literature review that focuses in the development of the CDSS, based on advanced MRI techniques for brain tumor characterization: (1) the first part provides an overview and an extensive description of the already developed CDSSs; and (2) in the second part, the study concludes to future objectives concerning the development of CDSSs for brain lesion characterization.

LITERATURE REVIEW

A thorough literature review was executed during the period 2000-2013. Initially, the research was limited to CDSS for brain tumor discrimination and the inclusion criterion was the kind of biomedical data that was utilized for their development. Specifically, the literature review was focused on the use of ^{1}H-MRS, DWI, DTI and PWI data in CDSS development. To the best of our knowledge, up to this point none of the CDSS was developed using features extracted from DWI, DTI or PWI techniques. However, the interest of the scientific community focused on the use of spectroscopic data in order to develop these systems. Thus, the research identified articles that corresponded to clinical systems that were implemented using chemical shift imaging (CSI) or single voxel MRS[25,26]. Furthermore, a number of articles and congress proceedings regarding the usability and effectiveness of these CDSS were collected.

Table 1 Validation results of the clinical decision support systems based on chemical shift imaging data

Ref.	Voxel assignment	Accuracy
De Edelenyi *et al*[27]	Low-grade gliomas	92.9%
	High-grade gliomas	79.16%
	Metastasis	60%
	Meningiomas	100%
	Necrosis	100%
	Healthy tissue	100%
	Cerebrospinal fluid	100%
Simonetti *et al*[29]	Healthy tissue	100%
	Cerospinal fluid	97%
	Glioma grade Ⅱ	83%
	Glioma grade Ⅲ	88%
	Glioma grade Ⅳ	100%
Luts *et al*[32]	Glioma Ⅱ	66.6%
	Glioma Ⅱ / Ⅲ	100%
	Glioma Ⅳ	100%
	Meningioma	100%
McKnight *et al*[28]	Low grade gliomas *vs* grade Ⅲ	89%
Li *et al*[34]	Glioblastoma multiforme	100%
	Glioma Ⅱ	100%

BRAIN TUMOR CDSS

CSI MRS data

The research revealed eight studies focused on the development of DSS based on proton MRSI, in order to gain information about the size, shape and the heterogeneity of the tumor. All of these studies used statistical or classification techniques in order to assign each voxel of the spectra to a specific tumor type and grade.

De Edelenyi *et al*[27] presented the first CDSS for brain tumor diagnosis focusing on CSI data. The authors proposed a method to create a "nosologic image" in order to extract information about the brain tumor type and the grade based on long TE ¹H-MRSI data, since biopsy does not always reveal the real grade of the tumor, due to tumor heterogeneity. Regarding this heterogeneity, each voxel of the spectroscopic image was colored according to the assigned histopathologic class (low or high grade glioma, metastasis and meningioma). However, McKnight *et al*[28] followed a different approach to extract image maps of long TE MV spectral data. Regarding the N-acetylaspartate and Cho levels of the spectrum, they investigated a score that was used to differentiate areas that present normal metabolite levels from regions that correspond to gliomas. Then, they utilized this score as a degree of abnormality throughout the lesion area. Afterwards, Simonetti *et al*[29] extracted nosologic images based not only to metabolic information but also exploiting the image variables of each voxel. They investigated the overlap between different classes (healthy, cerebrospinal fluid, grade Ⅱ, grade Ⅲ, grade Ⅳ) in the featured space, and constructed a probability map that corresponded to the probabilities of classification based on MRI and MRS data. Similarly to De Edelenyi *et al*[27], Simonetti *et al*[29] focused only on the metabolite and image characteristics of each voxel, ignoring the spatial information of the area under study. De Vos *et al*[30] used Short TE spectra to cre-

ate nosologic images. They applied canonical correlation analysis in order to investigate the tumor type and the heterogeneity of the region of interest. Similarly, Laudadio *et al*[31] applied canonical correlation analysis to 2-dimensional turbo MRSI data in order to combine spectra and spatial MRS information. The resulting correlation maps were used to construct nosologic images where all the detected tissue types were visualized. From the same research group, Luts *et al*[32] proposed a new method to generate nosologic images of the brain comparing to previous approaches. They used digital brain atlases presented by Prastawa *et al*[33] in order to investigate the incremental value of MRI over MRSI data. They added subject-specific abnormal tissue for image segmentation purposes, and the resulting framework was more flexible and able to exploit spatial information more efficiently, leading to improved nosologic images. Contrary to previous studies, Li *et al*[34] used unsupervised classification methods to construct nosologic images, in order to overcome the need of large datasets to train classifiers. Another difference was that they provided an error map along with the nosologic image in order to underline spectra variations due to tumor inhomogeneity.

The validation results of the majority of the clinical systems described previously are presented in Table 1.

Single voxel MRS data

Regarding the use of single voxel MRS data for CDSS development, during the last 10 years, four projects, the International Network for Pattern Recognition of Tumors Using Magnetic Resonance (INTERPRET) (2000-2002), eTUMOUR (2004-2009), HealthAgents (2005-2008) and CURIAM BT (2004-2010), were developed.

INTERPRET

INTERPRET was the outcome of a multicenter European collaboration[35,36] that was funded under the 5th EU Framework Programme IST-1999-10310. A computer-based CDSS was developed in order to enable clinicians who have minimum knowledge of the MR spectrum to evaluate MR spectra and to discriminate between different brain tumors. During the INTERPRET development, one significant achievement was the creation of an important repository of brain tumors that contained 304 histopathological validated Short TE cases low grade gliomas [astrocytomas, oligodendrogliomas, oligoastrocytomas World Health Organization (WHO) grade Ⅱ], meningiomas (WHO grade I and Ⅱ) and high grade malignant tumors (glioblastomas, metastases). Another important achievement was the definition of a data acquisition protocol to ensure the compatibility between the MRS data coming from different clinical collaborative centers as well as the quality control protocol development, in order to define the quality requirements that MR spectra should fulfill.

Furthermore, a single voxel INTERPRET graphical user interface (GUI) was developed, providing easy access to the spectra database, to images and clinical informa-

Table 2 Validation results of the clinical decision support systems based on single voxel data

Ref.	CDSS	Differentiation problem	Accuracy			Supportive raw files
			Short TE	Long TE	Short + Long TE	
Pérez-Ruiz et al[38]	INTERRET	Low grade meningiomas vs low grade glial tumors	94[a] 89[b] 89[c]	83[b]	84[c] 89[c]	
		Pseudotumoural disease[d] vs tumors[e] vs normal brain	86[c]	81[c]	92[c]	
García-Gómez et al[41]	eTUMOUR	Low grade glioma vs high grade tumor	92	84	92	1.5 Tesla MRS data of Philips (sdat/spar) GE up to 9X (SAGE Pxxxx with an shf or sdf/shf) siemens scanners (numaris 4) jMRUI[58] text file
		Meningioma vs glioma/Met	92	78	94	
		Low men vs glioma/Met vs low grade glioma	87	75	90	
Sáez et al[44]	HealthAgents	Aggressive tumor vs meningioma vs low grade glial	94	-		
		Meningioma vs metastasis	91	-		
		High grade tumor vs low grade tumor	87	68 (ch)		
		Affected tissue vs non affected tissue	99	-		
		Tumor vs non tumor	97	-		
		Aggressive tumor vs non aggressive tumor	81	72 (ch)		
		Glioma vs embryonal tumor	-	72 (ch)		
		Glioblastoma vs low grade glioma	84	-		
		Glioblastoma vs meningioma	91	-		
		Meningioma vs low grade glioma	92	-		
		Metastasis vs low grade glioma	85	-		
Vicente et al[46]	CURIAM BT	Aggressive tumor vs non aggressive tumor	85	87 (ch)		1.5 or 3 Tesla MRS data of different manufactures (Siemens, GE, Philips) by means of jMRUI[58] and jDMS[36]
		Pilocytic astrocytoma/ependymoma grade Ⅱ vs medulloblastoma	88 (ch)	85 (ch)	89 (ch)	
		Pilocytic astrocytoma vs medulloblastoma	92 (ch)	94 (ch)	95 (ch)	
		Pilocytic astrocytoma vs ependymoma grade Ⅱ vs medulloblastoma	76 (ch)	69 (ch)	92 (ch)	

It is indicated where the classification accuracy corresponds to classifier trained on pediatric tumor data (ch). [a]International Network for Pattern Recognition of Tumors Using Magnetic Resonance (INTERPRET) version 1.1; [b]INTERPRET version 2.0; [c]INTERPRET version 3.0; [d]Pseudotumoural disease: Acute infarct, multiple sclerosis, acute disseminated encephalomyelitis, and no specific pseudotumoral disease; eTumors: Astrocytoma World Health Organization (WHO) grade Ⅱ, oligodendroglioma WHO grade Ⅱ, oligoastrocytoma WHO grade Ⅱ, astrocytoma WHO grade Ⅲ, oligoastrocytoma WHO grade Ⅲ. CDSS: Clinical decision support systems; MRS: Magnetic resonance spectroscopy; MRUI: Magnetic Resonance User Interface.

tion from all the validated cases of human brain tumors. It was designed to provide the display of classification plots, which is useful for the automatic classification of tumor spectra[37]. The differentiation between different tumor groups was achieved by plotting the boundaries that were defined by the bisectors between the centroids of each class[38]. The users could enter their own spectrum, position it automatically among the tumor groups of the system and compare it with other spectra.

Until 2010 many improvements have been gradually released in successive versions and can be categorized in three different aspects: GUI enhancements, increased analysis capabilities, and data quality and assessment checks[38]. Specifically in the last version, an embedded database was developed for the permanent storage of the data into the system, more MRS data were supported compared to the previous versions (Short TE, Long TE and concatenated Short TE and Long TE Spectra) and six more classifiers were embedded to the system. Hence, the final version of INTERPRET not only offers the ability to differentiate common tumor types as in its first release, but also to differentiate among tumoral and pseudotumoral diseases (acute infarct, multiple sclerosis, acute disseminated encephalomyelitis). To address the latter classification problem, the metabolite ratios of the spectra were also used. The evaluation results of the different versions of INTERPRET CDSS are shown to Table 2.

eTUMOUR

Another European project eTUMOUR took up the research on the development of CDSS[39]. A more complex CDSS was developed that combined single voxel and CSI MRS data. The eTUMOUR CDSS upgraded and facilitated the clinical application of MRS in adult and pediatric brain tumor diagnosis, prognosis and treatment selection by using a combination of histology results, high resolution metabolic profiles (HR-MAS) and transcriptomic (DNA micro-arrays) *ex vivo* data to define the classification outcome[40]. Regarding the acquisition and quality control procedure, the experience obtained from the INTERPRET project was used, whereas suitable protocols for the techniques of tissue analysis (HR-MAS, DNA microarrays and micro-RNA) were defined.

A web-based database (eTDB) was created, which was able to manage a wide range of data types such as clinical information, histological images, MRI, single voxel, MRSI, HR-MAS and DNA microarray data. This database comprised a complete and detailed GUI and also a structure for online uploading and downloading data *via* the web.

A user friendly computer aided decision system (CADS) DSS was developed and tested in eTUMOUR project.

The embedded classifiers were trained to solve three different discrimination problems (meningioma *vs* non-meningioma, aggressive tumor *vs* low grade glial and meningioma *vs* aggressive tumor *vs* low grade glial) using short time echo spectrum, long time echo spectrum and combination of both spectra (Table 2). Furthermore, the design of the DSS provided a comparative analysis with the average spectra of 12 standard brain tumor types of an unknown brain tumor. During the classification procedure the assigned class as well as the posterior probabilities of each class were displayed to the system[39,41].

HealthAgents
HealthAgents[42] was a distributed DSS (d-DSS) built upon INTERPRET and eTUMOUR projects. The great difference of this project was its architectural structure since it was based on agent-based architecture in order to decentralize the process of brain tumor differentiation in a distributed decision support framework that supports data partitioning and sharing[43]. Since the accumulation of a sufficient number of cases for each tumor type or less common adult or childhood tumors was a very difficult and time consuming procedure, a collaborative network of different medical centers was constructed that contributed to the development of a repository of brain tumors, used for the training of robust classifiers for brain tumor differentiation.

The user, utilizes a local web-based GUI to enter the clinical data of a patient into the system and to request the appropriate classifiers from the network. These classifiers could be located anywhere on the collaborative HealthAgents network that consisted of different medical centers with their local existing databases of cases and their classifiers. Finally, the system would suggest the appropriate classifiers and indicate their specific location. Furthermore, a ranking tool was provided to the user, since many different classifiers coexisted in the system, in order to identify the classifiers that are more suitable for the diagnosis of particular case, to rank the obtained results from a set of classifiers and to solve possible conflicts between classifiers, by giving contradictory answers, which could occur when a test case was close to a decision boundary in one or more classifiers[44].

Regarding the classification framework of the HealthAgents DSS its primary functionality was based on the INTERPRET DSS system. Until 2011, 25 classifiers were embedded and shared the system for the differentiation of aggressive tumors, like glioblastomas and metastases, benign meningiomas and low-glial mixture, such as astrocytomas grade II, oligodendrogliomas and oligoastrocytomas. The classification procedure was based on short time echo MRS data, long time echo MRS data and on the combination of them. The optimum classification results are presented to Table 2.

Curiam BT
Curiam BT[45,46] was developed in parallel to eTUMOUR and HealthAgents projects. CURIAM BT supported any kind of metabolic data either on short or long TE or both of different manufactures. Regarding the classification framework of this clinical system, it was able to determine the aggressiveness of a brain tumor in adults (non aggressive: grades I and II *vs* aggressive: grade III and IV) and to discriminate among the three most common pediatric brain tumors such as ependymoma grade II, pilocytic astrocytoma and medulloblastoma. Furthermore, compared with previous systems an additional opportunity was included, according to which the user could embed new classifiers to the system. Similar to the ranking tool in HealthAgents DSS, the audit and similarity methods were incorporated to the system to address the generalization ability of the coexisting classifiers. These methods proved to be significant as they provided the clinicians with the appropriate classifiers set regarding each differentiation problem and a specificity score of each classifier that determines its discrimination accuracy over time.

USABILITY AND EVALUATION OF CDSS
Regarding the evaluation of the single voxel CDSSs, there are several studies that reported their effectiveness and usability in the classification of different brain tumors during the clinical routine. These studies demonstrate the accuracy values that CDSSs present in various diagnostic problems, evaluate their contribution in combination with other diagnostic outcomes and survey CDSS usability regarding their user friendly module and acceptance by the clinical community. Considering the CDSSs that were based on CSI data, more research is needed since there is not a sufficient number of articles to demonstrate the overall contribution of these clinical systems to the clinical routine.

Fellows *et al*[47] investigated the discrimination ability of INTERPRET version 2.0 in order to differentiate high and low grade tumors. The classification outcome of the system was compared with the neuroradiological tissue diagnosis and the conclusion of the spectroscopists. The results did not reveal significant differentiations between the accuracy levels of each participating modality.

INTERPRET version 3.0 proved to be superior for the characterization of grade III astrocytomas when compared to the spectroscopic and the radiologists' evaluation[48].

Regarding the clinical evaluation of eTUMOUR, an agreement of 79.1% was obtained between the DSS outcome and the radiologic diagnosis. This rate increased up to 88.4% when the averaged spectra from DSS were used for brain tumor classification. When the CDSS, averaged spectra and radiologic findings were compared with the histopathological diagnosis, agreement scores of 76.7%, 79.1% and 81.4% were respectively achieved[49].

When the CDSS results were compared with MRI, the overall percentage of correct predictions were 82.2% and 78.48%, respectively. Furthermore, the CDSS classification outcome was also compared with the corresponding outcome of MRI for the differentiation of

low grade gliomas, high grade gliomas and meningiomas. Specifically, the sensitivity and specificity values in low *vs* high grade gliomas classification problem, CDSS proved superior to the MRI corresponding values. Finally, the usefulness and applicability of the CADS was rated 86% and 71%, respectively[50].

Regarding the HealthAgents CDSS, an evaluation about its incremental diagnostic value was executed, and consequently 26 expert physicians were interviewed. As an overall response, they believed that the use of the CDSS would be beneficial for improving the quality of their brain tumor diagnoses. In addition, they considered the system easy to use, which is an important point in a DSS, especially in a clinical environment[44].

When the evaluation of CURIAM BT was carried out, it reached 71% and 85% regarding the user's perspective on its usefulness and convenience, respectively[51]. A comparing test was also executed in order to evaluate the contribution of CURIAM BT in the clinical routine. In that case, no significant differences were observed between the established diagnosis when conventional MRI, DWI and PWI were used, and the diagnosis derived from the above techniques combined with CDSS. Only in the case of high grade and low grade gliomas, did the observed differences reach 70%. Hence, a further evaluation should be implemented in order to investigate the CURIAM BT contribution in different diagnostic problems.

FUTURE PERSPECTIVES

One should consider CDSS as a supportive tool by providing additional information about the patient's state of health from which the clinician may establish a more educated and informed decision. As described in the "Usability and evaluation of CDSS" section, most of the studies proved the efficacy of the additional information that CDSS provide regarding improvements in clinical outcome. However, it is also evident that further evaluation should be implemented in order to investigate the CDSS contribution in different diagnostic problems. In addition, CDSS development involves much more than just the implementation of a software application. It requires adaptation by clinicians to use and engage in the refinement of CDSS both as a process and as a tool, as we move toward the goal of healthcare delivery that is consistent, effective, and of high quality[52]. In order to accomplish the above objectives and to reinforce the application of CDSS in clinical routine, there are a number of future perspectives that should be implemented.

Regarding the classification framework of the clinical systems, there are two significant issues which arise. First, the improvement of the classification performance and second, the inclusion of more difficult differential diagnostic problems such as glioblastomas *vs* solitary metastasis. Hence, the retraining of the existing classifiers and the development of new ones, are necessary in order to optimize the classification performance and to extend the discrimination ability of the CDSS.

Until now all the CDSSs developed for brain tumor differentiation are based on static classification methods. The use of static classifiers results in an implicit assumption that the learning procedure stops when the training set has been processed. The performance of a classifier strongly depends on the size of the training set for each class. Nevertheless, the accumulation of biomedical data is often a time-consuming and expensive procedure, and hence it may be not practical, especially in cases of uncommon cerebral pathologies like abscesses and lymphomas or pediatric brain tumors. In such cases, the implementation of incremental learning algorithms is a promising solution for clinical environments. Tortajada *et al*[53] evaluated the performance of an incremental classifier based on single voxel Short TE spectra in comparison to static classifiers. The results revealed that the classification performance was improved when the incremental classifiers were used comparing to performance of the static classifies.

Another future objective is to incorporate metabolic data from both ^{1}H-MRS techniques (single voxel-CSI) into the classification framework of a DSS. The two techniques can be utilized simultaneously in order to investigate tumor heterogeneity whereas; the advantages of each spectroscopic technique can be exploited. Therefore, the metabolic characteristics of different tumor regions could be summarized into one image and the corresponding biochemical compounds can be studied. Hence, the spatial and the quantitative data of the spectrum will be used for an overall evaluation of the tumor. The complementary use of the spectroscopic techniques may contribute to the optimization and the accuracy of the preoperative diagnosis, and it may increase the understanding of the underlying pathologies.

An important future aspect is to enrich the DSS datasets with metabolic data from the peritumoral and contralateral regions regarding the brain tumor under study. With this perspective, the pattern recognition methods will be extended towards a more accurate differentiation scheme of brain tumors.

Growing intracranial neoplasms exhibit various effects in their peritumoral area. According to Chernov *et al*[54] lactate-producing neoplasms are associated with more prominent reduction of the relative NAA content in the surrounding cerebral tissue, independently on the presence or absence of any other factor. According to Fan *et al*[55] both a high Cho peak and elevated Cho/Cr ratio were found in the peritumoral regions of high-grade gliomas, but not in metastases. This suggests that the infiltration of adjacent brain tissue by tumor is a unique feature of high-grade glioma.

Another plan is to incorporate quantitative data from other MR-based methodologies. Di-Costanzo *et al*[56] showed that in the case of brain tumor classification, when ^{1}H-MRS parameters were considered as features, 83.3% of brain tumors were correctly classified. Whereas, when ^{1}H-MRS variables were combined with relative cerebral blood volume (rCBV) values from perfusion MRI, a 100% classification accuracy between high- and low-grade gliomas was achieved. They also showed that in a

peri-enhancing tumor region 73.7% of the cases were correctly classified when considering only ^{1}H-MRSI variables, 84.2% when considering ^{1}H-MRSI variables and apparent diffusion coefficient (ADC), and 89.5% when considering ^{1}H-MRSI variables, ADC and rCBV. Zonari *et al*[57] achieved 80% sensitivity and 78.6% specificity when using rCBV parameter alone in grading cerebral neoplasms, and when combined with ^{1}H-MRS the sensitivity increased to 87.7% and specificity dropped to 76.2%.

Hence, it is evident that the continuous progress of imaging systems has induced revolutionary changes in the medical imaging field and has contributed utmost on a diagnostic and therapeutic level. The most important aspect however is that the continuous development of imaging techniques have transformed these modalities from conventional imaging to high-level metric systems, which may provide a quite large amount of quantitative information.

These large amounts of numeric data with an extremely significant diagnostic value may often remain unexploited during the clinical routine. The main reason for this is that the simultaneous analysis and evaluation of multiple parameters, is a time consuming process, requires specific expertise and may not be feasible during the clinical routine. It is prudent to mention that the available clinical time per patient may be estimated at about 30 min, while the process and evaluation of data from MRS and DTI usually takes more than 1 h. Especially when a specialized medical physicist for data manipulation is unavailable, these techniques are often handled by radiologists under a qualitative perspective rather than quantitative, which may lead to a biased differential diagnosis.

Therefore, an automatic evaluation of these data and a rapid display of the results are the minimum requirement during the clinical interpretation of an examination that will lead to a better clinical management of the patients, since the evaluation of the data will be done in an easier, and more effective way, which would ultimately lead to cost effectiveness by avoiding misdiagnosed cases. Towards this direction, the objective and future perspective would be to design and develop a CDSS, using incremental machine learning methods, based on all numeric data from the aforementioned advanced imaging techniques. The system should integrate and combine all the available metabolic, diffusion and perfusion data. The hypothesis is that the combination of multiple data from the aforementioned imaging modalities is expected to optimize the differential diagnosis of brain pathologies, which will be eventually beneficiary for tailored patient treatment.

Hence, these kind of systems should be specifically designed in such a way that the user (that is: radiologist, medical physicist and in general neuroscientists), with minimum knowledge of pattern recognition analysis, will be able to: (1) categorize and illustrate the clinical data on a single template in order to ensure that the data will not be dispersed; (2) perform a fully automated pattern recognition analysis towards the optimum differential diagnosis; (3) quantify the degree of uncertainty in the prediction of ambiguous diagnostic problems by offering a diagnostic orientation; and (4) use the system as a supportive tool for the selection of the most appropriate treatment strategy and the most successful treatment scheme.

From our personal experience, it should be stressed that a CDSS by no means substitutes for the expert's diagnostic decision, but rather supports the clinician by evaluating simultaneously a large amount of complicated MR data. Thorough analysis and evaluation of these data requires additional time, which exceeds by far the available clinical time per patient, hence this information may remain unexploited.

Furthermore, despite the good discrimination ability of the embedded classification schemes, it should be emphasized that the decision-making process with the use of a clinical decision system should be a procedure of two individual parts. The first part should include the classification result or a good orientation towards a clinical outcome, based on the evaluation of quantitative MRI data and the second part should involve the co-evaluation of the aforementioned result with all the available diagnostic and imaging information. Under these perspectives, a well designed CDSS may be used as an assistant diagnostic tool which can be implemented into the clinical routine and substantially aid the interpretation of an exam and optimize decision making.

CONCLUSION

Diagnosis and consequently treatment of brain neoplasms may greatly benefit from the introduction and utilization of intelligent systems in the form of CDSS for automatic processing, classification, evaluation and representation of the spectroscopic data as part of the clinical routine. Major progress has been made in the last few years towards this direction, as several systems exist and are continuously developing. Nevertheless, the quantification of the imaging profile of neoplasms by combining conventional MRI and advance imaging techniques (MRS, DWI, DTI and PWI) introduces critical underlying pathophysiological information which seems to be the key to success.

Thus, it is evident that the future directions should be oriented towards the development of software that will be implemented in the clinical routine, by utilizing large amounts of clinical data with extremely significant diagnostic value which often remain unexploited, resulting in a more valid and precise method for differential diagnosis of brain pathologies and the selection of the most successful treatment scheme.

REFERENCES

1   **Chiang IC**, Kuo YT, Lu CY, Yeung KW, Lin WC, Sheu FO,

Liu GC. Distinction between high-grade gliomas and solitary metastases using peritumoral 3-T magnetic resonance spectroscopy, diffusion, and perfusion imagings. *Neuroradiology* 2004; **46**: 619-627 [PMID: 15243726 DOI: 10.1007/s00234-004-1246-7]

2   **Liu X**, Tian W, Kolar B, Yeaney GA, Qiu X, Johnson MD, Ekholm S. MR diffusion tensor and perfusion-weighted imaging in preoperative grading of supratentorial nonenhancing gliomas. *Neuro Oncol* 2011; **13**: 447-455 [PMID: 21297125 DOI: 10.1093/neuonc/noq197]

3   **Tsougos I**, Svolos P, Kousi E, Fountas K, Theodorou K, Fezoulidis I, Kapsalaki E. Differentiation of glioblastoma multiforme from metastatic brain tumor using proton magnetic resonance spectroscopy, diffusion and perfusion metrics at 3 T. *Cancer Imaging* 2012; **12**: 423-436 [PMID: 23108208 DOI: 10.1102/1470-7330.2012.0038]

4   **Chang SC**, Lai PH, Chen WL, Weng HH, Ho JT, Wang JS, Chang CY, Pan HB, Yang CF. Diffusion-weighted MRI features of brain abscess and cystic or necrotic brain tumors: comparison with conventional MRI. *Clin Imaging* 2002; **26**: 227-236 [PMID: 12140151]

5   **Reiche W**, Schuchardt V, Hagen T, Il'yasov KA, Billmann P, Weber J. Differential diagnosis of intracranial ring enhancing cystic mass lesions--role of diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI). *Clin Neurol Neurosurg* 2010; **112**: 218-225 [PMID: 20053496 DOI: 10.1016/j.clineuro.2009.11.016]

6   **Möller-Hartmann W**, Herminghaus S, Krings T, Marquardt G, Lanfermann H, Pilatus U, Zanella FE. Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions. *Neuroradiology* 2002; **44**: 371-381 [PMID: 12012120 DOI: 10.1007/s00234-001-0760-0]

7   **Hollingworth W**, Medina LS, Lenkinski RE, Shibata DK, Bernal B, Zurakowski D, Comstock B, Jarvik JG. A systematic literature review of magnetic resonance spectroscopy for the characterization of brain tumors. *AJNR Am J Neuroradiol* 2006; **27**: 1404-1411 [PMID: 16908548]

8   **Kousi E**, Tsougos I, Tsolaki E, Fountas KN, Theodorou K, Fezoulidis I, Kapsalaki E, Kappas C. Spectroscopic evaluation of glioma grading at 3T: the combined role of short and long TE. *ScientificWorldJournal* 2012; **2012**: 546171 [PMID: 22919334 DOI: 10.1100/2012/546171]

9   **Astrakas LG**, Zurakowski D, Tzika AA, Zarifi MK, Anthony DC, De Girolami U, Tarbell NJ, Black PM. Noninvasive magnetic resonance spectroscopic imaging biomarkers to predict the clinical grade of pediatric brain tumors. *Clin Cancer Res* 2004; **10**: 8220-8228 [PMID: 15623597 DOI: 10.1158/1078-0432.CCR-04-0603]

10   **Panigrahy A**, Krieger MD, Gonzalez-Gomez I, Liu X, McComb JG, Finlay JL, Nelson MD, Gilles FH, Blüml S. Quantitative short echo time 1H-MR spectroscopy of untreated pediatric brain tumors: preoperative diagnosis and characterization. *AJNR Am J Neuroradiol* 2006; **27**: 560-572 [PMID: 16551993]

11   **Schaefer PW**, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. *Radiology* 2000; **217**: 331-345 [PMID: 11058626]

12   **Tang CY**, Friedman J, Shungu D, Chang L, Ernst T, Stewart D, Hajianpour A, Carpenter D, Ng J, Mao X, Hof PR, Buchsbaum MS, Davis K, Gorman JM. Correlations between Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (1H MRS) in schizophrenic patients and normal controls. *BMC Psychiatry* 2007; **7**: 25 [PMID: 17578565 DOI: 10.1186/1471-244X-7-25]

13   **Zhang H**, Rödiger LA, Shen T, Miao J, Oudkerk M. Perfusion MR imaging for differentiation of benign and malignant meningiomas. *Neuroradiology* 2008; **50**: 525-530 [PMID: 18379768 DOI: 10.1007/s00234-008-0373-y]

14   **Sentürk S**, Oğuz KK, Cila A. Dynamic contrast-enhanced susceptibility-weighted perfusion imaging of intracranial tumors: a study using a 3T MR scanner. *Diagn Interv Radiol* 2009; **15**: 3-12 [PMID: 19263367]

15   **Järnum H**, Steffensen EG, Knutsson L, Fründ ET, Simonsen CW, Lundbye-Christensen S, Shankaranarayanan A, Alsop DC, Jensen FT, Larsson EM. Perfusion MRI of brain tumours: a comparative study of pseudo-continuous arterial spin labelling and dynamic susceptibility contrast imaging. *Neuroradiology* 2010; **52**: 307-317 [PMID: 19841916 DOI: 10.1007/s00234-009-0616-6]

16   **Lukas L**, Devos A, Suykens JA, Vanhamme L, Howe FA, Majós C, Moreno-Torres A, Van der Graaf M, Tate AR, Arús C, Van Huffel S. Brain tumor classification based on long echo proton MRS signals. *Artif Intell Med* 2004; **31**: 73-89 [PMID: 15182848 DOI: 10.1016/j.artmed.2004.01.001]

17   **Devos A**, Lukas L, Suykens JA, Vanhamme L, Tate AR, Howe FA, Majós C, Moreno-Torres A, van der Graaf M, Arús C, Van Huffel S. Classification of brain tumours using short echo time 1H MR spectra. *J Magn Reson* 2004; **170**: 164-175 [PMID: 15324770 DOI: 10.1016/j.jmr.2004.06.010]

18   **Dimou I**, Tsougos I, Tsolaki E, Kousi E, Kapsalaki E, Theodorou K, Kounelakis M, Zervakis M. Brain lesion classification using 3T MRS spectra and paired SVM kernels. *Biomed Signal Process Control* 2011; **6**: 314-320 [DOI: 10.1016/j.bspc.2011.01.001]

19   **Tsolaki E**, Svolos P, Kousi E, Kapsalaki E, Fountas K, Theodorou K, Tsougos I. Automated differentiation of glioblastomas from intracranial metastases using 3T MR spectroscopic and perfusion data. *Int J Comput Assist Radiol Surg* 2013; **8**: 751-761 [PMID: 23334798 DOI: 10.1007/s11548-012-0808-0]

20   **Svolos P**, Tsolaki E, Kapsalaki E, Theodorou K, Fountas K, Fezoulidis I, Tsougos I. Investigating brain tumor differentiation with diffusion and perfusion metrics at 3T MRI using pattern recognition techniques. *Magn Reson Imaging* 2013; **31**: 1567-1577 [PMID: 23906533 DOI: 10.1016/j.mri.2013.06.010]

21   **Davies NP**, Wilson M, Harris LM, Natarajan K, Lateef S, Macpherson L, Sgouros S, Grundy RG, Arvanitis TN, Peet AC. Identification and characterisation of childhood cerebellar tumours by in vivo proton MRS. *NMR Biomed* 2008; **21**: 908-918 [PMID: 18613254 DOI: 10.1002/nbm.1283]

22   **Raschke F**, Davies NP, Wilson M, Peet AC, Howe FA. Classification of single-voxel 1H spectra of childhood cerebellar tumors using LCModel and whole tissue representations. *Magn Reson Med* 2013; **70**: 1-6 [PMID: 22886824 DOI: 10.1002/mrm.24461]

23   **Lisboa PJ**, Wong H, Harris P, Swindell R. A Bayesian neural network approach for modelling censored data with an application to prognosis after surgery for breast cancer. *Artif Intell Med* 2003; **28**: 1-25 [PMID: 12850311 DOI: 10.1016/S0933-3657(03)00033-2)]

24   **van Bemmel JH**, Musen MA. Modeling for Decision Support. In: Handbook of Medical Informatics. Springer-Verlag, 1997

25   **Law M**, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW. High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. *Radiology* 2002; **222**: 715-721 [PMID: 11867790 DOI: 10.1148/radiol.2223010558]

26   **Kousi E**, Tsougos I, Kapsalaki E. Proton Magnetic Resonance Spectroscopy of the Central Nervous System. In: Novel Frontiers of Advanced Neuroimaging. InTech, 2013: 19-50 [DOI: 10.5772/53892]

27   **De Edelenyi FS**, Rubin C, Estève F, Grand S, Décorps M, Lefournier V, Le Bas JF, Rémy C. A new approach for analyzing proton magnetic resonance spectroscopic images of brain tumors: nosologic images. *Nat Med* 2000; **6**: 1287-1289 [PMID: 11062544 DOI: 10.1038/81401]

28   **McKnight TR**, Noworolski SM, Vigneron DB, Nelson SJ. An automated technique for the quantitative assessment of 3D-MRSI data from patients with glioma. *J Magn Reson Imaging*

2001; **13**: 167-177 [PMID: 11169821 DOI: 10.1002/1522-2586(2 00102)13:2<167::AID-JMRI1026>3.0.CO;2-K]

29 **Simonetti AW**, Melssen WJ, van der Graaf M, Postma GJ, Heerschap A, Buydens LM. A chemometric approach for brain tumor classification using magnetic resonance imaging and spectroscopy. *Anal Chem* 2003; **75**: 5352-5361 [PMID: 14710812]

30 **De Vos M**, Laudadio T, Simonetti AW, Heerschap A, Van Huffel S. Fast nosologic imaging of the brain. *J Magn Reson* 2007; **184**: 292-301 [PMID: 17118683 DOI: 10.1016/j. jmr.2006.10.017]

31 **Laudadio T**, Martínez-Bisbal MC, Celda B, Van Huffel S. Fast nosological imaging using canonical correlation analysis of brain data obtained by two-dimensional turbo spectroscopic imaging. *NMR Biomed* 2008; **21**: 311-321 [PMID: 17907275 DOI: 10.1002/nbm.1190]

32 **Luts J**, Laudadio T, Idema AJ, Simonetti AW, Heerschap A, Vandermeulen D, Suykens JA, Van Huffel S. Nosologic imaging of the brain: segmentation and classification using MRI and MRSI. *NMR Biomed* 2009; **22**: 374-390 [PMID: 19105242 DOI: 10.1002/nbm.1347]

33 **Prastawa M**, Bullitt E, Ho S, Gerig G. A brain tumor segmentation framework based on outlier detection. *Med Image Anal* 2004; **8**: 275-283 [PMID: 15450222 DOI: 10.1016/j.media.2004.06.007]

34 **Li Y**, Sima DM, Van Cauter S, Himmelreich U, Croitor Sava AR, Pi Y, Liu Y, Van Huffel S. Unsupervised nosologic imaging for glioma diagnosis. *IEEE Trans Biomed Eng* 2013; **60**: 1760-1763 [PMID: 23192480 DOI: 10.1109/TBME.2012.2228651]

35 INTERPRET Consortium. Available from: URL: http: //azi-zu.uab.es/INTERPRET/

36 **Tate AR**, Underwood J, Acosta DM, Julià-Sapé M, Majós C, Moreno-Torres A, Howe FA, van der Graaf M, Lefournier V, Murphy MM, Loosemore A, Ladroue C, Wesseling P, Luc Bosson J, Cabañas ME, Simonetti AW, Gajewicz W, Calvar J, Capdevila A, Wilkins PR, Bell BA, Rémy C, Heerschap A, Watson D, Griffiths JR, Arús C. Development of a decision support system for diagnosis and grading of brain tumours using in vivo magnetic resonance single voxel spectra. *NMR Biomed* 2006; **19**: 411-434 [PMID: 16763971 DOI: 10.1002/nbm.1016]

37 Single voxel DSS tutorial. Available from: URL: http: //azi-zu.uab.es/INTERPRET/sv_tutorial/index.php#description

38 **Pérez-Ruiz A**, Julià-Sapé M, Mercadal G, Olier I, Majós C, Arús C. The INTERPRET Decision-Support System version 3.0 for evaluation of Magnetic Resonance Spectroscopy data from human brain tumours and other abnormal brain masses. *BMC Bioinformatics* 2010; **11**: 581 [PMID: 21114820 DOI: 10.1186/1471-2105-11-581]

39 Web accessible MR Decision Support System for Brain Tumour Diagnosis and Prognosis, Incorporating in vivo and ex vivo genomic and metabolic data. Available from: URL: http: //cordis.europa.eu/documents/documentlibrary/127824941EN19.doc

40 **Arus C**, Celda B, Dasmahaptra S, Dupplaw D, Gonzalez-Velez H, Van Huffel S, Lewis P, Lluch i Ariet M , Mier M, Peet A, Robles M. On the Design of a Web-Based Decision Support System for Brain Tumour Diagnosis Using Distributed Agents. Hong Kong, 2006: 208-211 [DOI: 10.1109/WI-IATW.2006.97]

41 **García-Gómez JM**. Pattern Recognition Approaches for Biomedical Data in Computer-Assisted Cancer Research, PhD thesis, Universidad Politécnica de Valencia, Departamento de Sistemas Informáticosy Computación Inteligencia Artificial, Reconocimiento de Formas e Imagen Digital. 2009

42 **Gonzalez-Velez H**, Mier M, Julià-Sapé M, Garcia-Gomez TN, Robles JM, Peet A, Arus C, Celda B, Van Huffel S, Lewis P, Dupplaw D, Dasmahapatra S. HealthAgents: Distributed Multi-Agent Brain Tumor Diagnosis and Prognosis. *J Appl Intel* 2009; **30**: 191-202 [DOI: 10.1007/s10489-007-0085-8]

43 **Hu B**, Croitoru M, Roset R, Dupplaw D, Lurgi M, Dasmahapatra S, Lewis P, Martínez-Miranda J, Sáez C. The HealthAgents ontology: how to represent the knowledge behind a brain tumour distributed decision system. *Knowl Eng Rev* 2011; **26**: 303-328

44 **Sáez C**, García-Gómez JM, Vicente J, Tortajada S, Luts J, Dupplaw D, Van Huffel S, Robles M. A generic and extensible automatic classification framework applied to brain tumour diagnosis in HealthAgents. *Knowl Eng Rev* 2011; **26**: 283-301 [DOI: 10.1017/S0269888911000129]

45 **Sáez C**, García-Gómez JM, Vicente J, Tortajada S, Fuster E, Esparza M, Navarro A, Robles M. Curiam BT 1.0, Decision Support System for Brain Tumour Diagnosis. In ESMRMB Congress. Antalya, Turkey: EPOS Posters/Paper Posters/Info-RESO, 2009: 538

46 **Vicente J**. Clinical Decision Support Systems for Brain Tumour Diagnosis: Classification and Evaluation Approaches. Departamento de Física Aplicada - Departament de Física Aplicada, 2012

47 **Fellows GA**, Wright AJ, Sibtain NA, Rich P, Opstad KS, McIntyre DJ, Bell BA, Griffiths JR, Howe FA. Combined use of neuroradiology and 1H-MR spectroscopy may provide an intervention limiting diagnosis of glioblastoma multiforme. *J Magn Reson Imaging* 2010; **32**: 1038-1044 [PMID: 21031506 DOI: 10.1002/jmri.22350]

48 **Julià-Sapé M**, Coronel I, Majós C, Candiota AP, Serrallonga M, Cos M, Aguilera C, Acebes JJ, Griffiths JR, Arús C. Prospective diagnostic performance evaluation of single-voxel 1H MRS for typing and grading of brain tumours. *NMR Biomed* 2012; **25**: 661-673 [PMID: 21954036 DOI: 10.1002/nbm.1782]

49 **Celda B**, Cano JG, Martinez-Bisbal MC, Martinez-Granados B. Clinical evaluation of a fully automated Computer Aid Decision System (CADS) for brain tumour supported diagnosis. eTUMOUR project FP6-2002-LSH-503094. In Joint Annual Meeting ISMRM-ESMRMB; May 1-7, Stockholm, Sweden, 2010

50 **Celda B**, Monleon D, Pla P, Gil-Cano J, Martinez-Granados B, Molla E, Revert A, Mart-Bonmati L, Leon J. Computer Aid Decision System (CADS) of eTUMOUR. Initial results of clinical evaluation for brain tumour classification In ESMRMB Congress, October 1-3, Antalya, Turkey, 2009

51 **Sáez C**, García-Gómez JM, Alberich-Bayarri Á, Edo MÁ., Vanyó M, Català-Gregori A, Barber C, Poyatos C, Mollà E, Martí-Bonmatí L, Robles M. Clinical Validation of the Added Value of a Clinical Decision Support System for Brain Tumour Diagnosis-Based on SV 1H MRS: Randomized Controlled Trial of Effectiveness and Qualitative Evaluation. Proceedings of 24th European Medical Informatics (MIE) Conference; 2012, August 26-29; Pisa-Italy: Quality of Life through Quality of Information

52 **Bryan C**, Boren SA. The use and effectiveness of electronic clinical decision support tools in the ambulatory/primary care setting: a systematic review of the literature. *Inform Prim Care* 2008; **16**: 79-91 [PMID: 18713524]

53 **Tortajada S**, Fuster-Garcia E, Vicente J, Wesseling P, Howe FA, Julià-Sapé M, Candiota AP, Monleón D, Moreno-Torres A, Pujol J, Griffiths JR, Wright A, Peet AC, Martínez-Bisbal MC, Celda B, Arús C, Robles M, García-Gómez JM. Incremental Gaussian Discriminant Analysis based on Graybill and Deal weighted combination of estimators for brain tumour diagnosis. *J Biomed Inform* 2011; **44**: 677-687 [PMID: 21377545 DOI: 10.1016/j.jbi.2011.02.009]

54 **Chernov MF**, Kubo O, Hayashi M, Izawa M, Maruyama T, Usukura M, Ono Y, Hori T, Takakura K. Proton MRS of the peritumoral brain. *J Neurol Sci* 2005; **228**: 137-142 [PMID: 15694194 DOI: 10.1016/j.jns.2004.11.039]

55 **Fan G**, Sun B, Wu Z, Guo Q, Guo Y. In vivo single-voxel proton MR spectroscopy in the differentiation of high-grade gliomas and solitary metastases. *Clin Radiol* 2004; **59**: 77-85

[PMID: 14697379 DOI: 10.1016/j.crad.2003.08.006]

56   **Di Costanzo A**, Scarabino T, Trojsi F, Popolizio T, Catapano D, Giannatempo GM, Bonavita S, Portaluri M, Tosetti M, d'Angelo VA, Salvolini U, Tedeschi G. Proton MR spectroscopy of cerebral gliomas at 3 T: spatial heterogeneity, and tumour grade and extent. *Eur Radiol* 2008; **18**: 1727-1735 [PMID: 18389246 DOI: 10.1007/s00330-008-0938-5]

57   **Zonari P**, Baraldi P, Crisi G. Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging and echo-planar perfusion imaging. *Neuroradiology* 2007; **49**: 795-803 [PMID: 17619871 DOI: 10.1007/s00234-007-0253-x]

58   Magnetic Resonance User Interface (MRUI). Available from: URL: http: //sermn02.uab.es/mrui/