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Accurate classification of childhood brain tumours by *in vivo* ^{1}H MRS – a multi-centre study

Javier Vicente[1,*], Elies Fuster-Garcia[1], Salvador Tortajada[1], Juan M. García-Gómez[1], Nigel Davies[2], Kal Natarajan[2], Martin Wilson[2], Richard G. Grundy[3], Pieter Wesseling[4], Daniel Monleón[5], Bernardo Celda[6], Montserrat Robles[1] and Andrew C. Peet[2]

1 IBIME, Universitat Politècnica de València, Spain

2 University of Birmingham and Birmingham Children's Hospital NHS Foundation Trust, UK

3 The Children's Brain Tumour Research Centre, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK

4 Depts. of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, VU University Medical Center, Amsterdam, The Netherlands

5 Fundación de Investigación Hospital Clínico Universitario Valencia, INCLIVA, Spain

6 Departamento Química Física, Universidad de Valencia, Spain

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[*] Corresponding author: Universitat Politècnica de València. Camino de Vera s/n, Building 8G, 1st floor. 46022, Valencia, SPAIN. Email address: javirob@upv.es (Javier Vicente) URL: http://www.ibime.upv.es. Telephone: +34 963877000 Ext 75278. Fax: +34 963877279

Abstract

Aims: To evaluate the accuracy of single-voxel Magnetic Resonance Spectroscopy (^{1}H-MRS) as a non-invasive diagnostic aid for pediatric brain tumours in a multi-national study. Our hypotheses are (1) that automated classification based on ^{1}H-MRS provides an accurate non-invasive diagnosis in multi-centre datasets and (2) using a protocol which increases the metabolite information improves the diagnostic accuracy.

Methods: 78 patients under 16 years old with histologically proven brain tumours from 10 international centres were investigated. Discrimination of 29 medulloblastomas, 11 ependymomas and 38 pilocytic astrocytomas was evaluated. Single-voxel MRS was undertaken prior to diagnosis (1.5Tesla PRESS, PROBE or STEAM, TE 20-32 ms, and 135-136 ms). MRS data was processed using two strategies, determination of metabolite concentrations using TARQUIN software and automatic feature extraction with Peak Integration. Linear Discriminant Analysis was applied to this data to produce diagnostic classifiers. An evaluation of the diagnostic accuracy was performed based on resampling to measure the Balanced Accuracy Rate (BAR).

Results: The accuracy of the diagnostic classifiers for discriminating the three tumour types was found to be high (BAR 0.98) when a combination of TE was used. The combination of both TE significantly improved the classification performance ($p < 0.01$, Tukey's test) compared with the use of one TE alone.

Other tumour types were classified accurately as glial or primitive neuroectodermal (BAR 1.00).

Conclusions: ^{1}H-MRS has excellent accuracy for the non-invasive diagnosis of common childhood brain tumours particularly if the metabolite information is maximised and should become part of routine clinical assessment for these children.

1 Introduction

Brain tumours are the most prevalent form of solid cancer in children and the most common cause of death from cancer in childhood. Magnetic Resonance Imaging (MRI) is a key investigation in the initial diagnostic work-up of these patients, confirming the presence of a mass, its relationship to surrounding structures and the existence of metastatic disease. Sometimes, a diagnosis is made from clinical information combined with the MRI scan findings such as in children with Neurofibromatosis Type I and an optic pathway glioma. However, the conventional MR images are inaccurate in discriminating between most childhood brain tumours and a diagnosis is usually made from biopsy samples taken at operation with the histology of the tumour being used to formulate the treatment plan. Whilst histopathology provides a definitive diagnosis there would be several advantages to obtaining an accurate non-invasive diagnosis.

For tumours where surgical resection is not the initial therapeutic option, an accurate non-invasive diagnosis would avoid an invasive procedure. For tumours where surgery is undertaken at diagnosis, accurate diagnostic information on the tumour type prior to initial surgery would help surgical decision-making, allow timely adjuvant therapy planning and aid discussions with the family. A common site for childhood tumours is the cerebellum and surgical resection is usually the initial therapeutic intervention. However, the importance of a complete resection varies between the tumour types. A complete macroscopic resection is highly prognostic for ependymomas [1, 2], whereas small amounts of residual medulloblastoma (up to 1.5cm^2) are not of

prognostic significance if treated with radiotherapy and chemotherapy [3] and small residual masses of pilocytic astrocytoma may be observed without further treatment [4]. Histopathology is usually not available for several days after the operation and intraoperative histopathology is commonly used to inform the surgeons of the likely tumour type but the techniques available are not accurate [5] and this strategy does not allow patient-specific clinical management planning prior to surgery. With improved adjuvant treatment, therapeutic strategies may evolve to ones in which surgery is undertaken at a later point, which is already common for childhood tumours outside the brain.

Histopathology remains the 'gold standard' for classifying childhood brain tumours and is the basis for treatment planning in the majority of cases. However, patients with identical histopathological diagnosis can respond in different ways to treatment and there is increasing evidence that additional information from tumour biology can improve the classification [6]. Advances in imaging have allowed tissue properties to be probed non-invasively giving important insights into *in vivo* tumour biology [7]. The aims of modern imaging are therefore not just to give a non-invasive histological diagnosis but rather to improve the classification of tumours.

Multivariate analysis of automated MRS processing is a powerful technique that can yield rapid and robust results and promises to translate into routine clinical practice. However, a multi-centre evaluation of these techniques is required. Although a large number of multi-centre studies on automatic classification of brain tumours has been reported in adults [8-15], these results cannot be extrapolated to children since the overall distribution of the

tumour types, locations and etiology differs markedly from that of adults [16-19]. Establishing the optimal MRS acquisition protocol is important and MRS can potentially give accurate quantification of more metabolites by using a longer acquisition, which combines Short echo time (Short-TE) and Long echo time (Long-TE) MRS [20], but this has currently not been reported in pediatric brain tumours. The present study investigates the accuracy of tumour metabolite profiles measured by ^{1}H-MRS as a diagnostic aid for common childhood brain tumours. The main aim of this work is, to evaluate the automatic classification of pediatric brain tumours in a large multi-centre ^{1}H-MRS study. In addition we test whether increasing the metabolite information available improves the automatic classification of pediatric brain tumours by comparing the combination of Short-TE and Long-TE MRS with the use of one echo time (TE) alone.

2 Methods

2.1 Data acquisition

The study includes 97 patients under 16 years old (mean age 7.3±4.7) with histologically proven brain tumour collected from 10 international centres in the framework of the eTUMOUR project (2004-2009) [21]. Histopathological diagnoses were validated in the context of clinical setting and radiological images and reviewed by the multidisciplinary Clinical Validation Committee. MRS data was reviewed for quality control by expert spectroscopists of eTUMOUR [8, 22].

The classes considered in this study were defined according to the WHO histological classification of the CNS tumours [23]. The cases were distributed as follows: 38 Pilocytic Astrocytoma (PILOA), 20 of them in the Posterior Fossa (PF); 11 Ependymoma grade II (EPEN), 7 in the PF; 29 Medulloblastoma (MED), all in the PF; Additionally we included 10 Diffuse Astrocytoma (DASTRO), 3 in the PF; 3 Subependymal giant cell astrocytoma (SASTRO), 2 in the ventricular atrium and 1 in the frontal lobe; one Supratentorial PNET located in the frontal lobe; 3 Atypical Teratoid Rhabdoid Tumour (ATRT), 2 in the PF; and 2 Pineoblastoma (PINEOB) in the pineal region. Table 1 documents the available cases.

Acquisition protocols for clinical, radiological and histopathological data were defined to ensure the compatibility of the data acquired [22, 24].

Single voxel ^{1}H-MRS at 1.5T from 90 patients were acquired at Short-TE and 61 spectra at Long-TE from Philips, Siemens and General Electric scanners. All patients had just one voxel placed and none were scanned on another occasion or scanner. Both TE were acquired in 54 patients with no change in voxel position or other parameters. Conventional MRI required for the clinical assessment of the child, including contrast enhanced imaging, was performed prior to the MRS acquisition. For each patient, the voxel was placed within the tumour to maximise the contrast enhancing region covered or, if non-enhancing, the high T2 region, whilst avoiding necrosis and CSF identified on the structural images. Voxels were cubic, with a side length of 1.5cm or 2.0cm, with 248 or 128 acquisitions respectively. Review of the voxel position was undertaken by the clinical validation committee. The acquisition protocols

for Short-TE included PRESS, PROBE or STEAM sequences, with Recycling Time (TR) of 1500-2000ms, TE of 20 or 30ms, spectral width of 500-2500Hz, and 512, 1024 or 2048 data-points. Long-TE spectra were acquired with PRESS sequence with TR of 1500-2020ms, TE of 135 or 136ms, spectral width of 1000-2500Hz and 512 or 2048 data-points.

2.2 MRS processing

Two MRS processing methods were compared: MRS quantitation of metabolite concentrations using the TARQUIN software (version 4.1.1) [25]; and the automatic feature extraction technique of Peak Integration (PI) [15, 26].

MRS processing with TARQUIN was performed with the standard metabolite library provided [25]. 21 metabolite, lipid and macromolecule variables were quantified. Details are given in the Supplementary Material.

The PI technique was also applied to estimate the relative concentration of metabolites. PI automatically estimates with proportionality to the concentration of 11 main metabolites for Short-TE and 8 metabolites for Long-TE MRS [15, 26]. Details of these estimations are given in the Supplementary Material. PI was applied after a semiautomatic processing pipeline defined in [20].

12 cases failed the inclusion criteria for QC mainly due to poor SNR.

2.3 Classification and evaluation

The diagnostic classification problem of discriminating between EPEN, PILOA and MED, the three most common pediatric tumour types, is addressed in this study. Since EPEN and PILOA tumours can be found in brain locations other than the PF whereas MED are found only in the PF, training was undertaken twice, once using the tumour cases located in the PF and then with those in any brain location. Classifiers were designed and evaluated using features from Short-TE and Long-TE alone and a combination of both TEs, Short-TE+Long-TE. Our results were compared with those in previous studies [27-30].

Based on the results of previous studies [15, 20, 26, 29, 30], we chose Linear Discriminant Analysis (LDA) as the classification technique. Classifiers were evaluated with a k-Random Sampling Train-Test strategy and the performance measured with Balanced Accuracy Rate (BAR), which is the average of the success rate obtained for each tumour class [31]. Details about the evaluation methodology are described in the Supplementary Material.

3 Results

3.1 Spectral features

Several key features allow visual discrimination of PILOA, EPEN and MED. Figures 1 and 2 show the Short-TE and Long-TE mean spectra of the tumour types. Minimum differences are found between the mean spectra of the tumours in the PF and those in any location. All tumour spectra display an increase in Cho peak (3.2ppm) with respect to Cr peak (3.0ppm). NAA (2.0ppm) presents a less prominent peak in MED and EPEN compared with

PILOA. Elevation of macromolecules and lipids (0.9ppm and 1.3ppm) is observed in Short-TE. Regarding Long-TE, the inverted peak of Lac at 1.3ppm is distinguished in PILOA and EPEN but not in MED.

3.2 Univariate metabolite comparison

Tables 2 and 3 show the metabolite concentrations estimated with TARQUIN in Short-TE and Long-TE for the three tumour types found in any brain location. The Kruskal-Wallis test for the analysis of the variance (α=0.05) was applied to determine the significant differences in metabolite concentrations of PILOA, EPEN and MED. Both Cho components, Glycerophosphocholine (GPC) and Phosphocholine (PCh) ($p \leq 0.01$) showed significant differences. Cr and Tau concentrations were significantly different in both TEs ($p \leq 0.01$). Differences in the mI concentrations ($p \leq 0.01$) were significant in Short-TE. Macromolecules and lipids at 0.9, 1.3 and 2.0ppm ($p \leq 0.05$, $p \leq 0.01$ and $p \leq 0.01$, respectively) exhibited statistical differences in Short-TE MRS.

3.3 Classification

Table 4 summarizes the classification results in the discrimination of PILOA, EPEN and MED found in the PF and those in any brain location. The table shows the performance when using Short-TE, Long-TE and Short-TE+Long-TE. Each discrimination was undertaken with the quantitation estimated with TARQUIN and PI**.**

The discrimination of the three classes obtained a BAR of 0.79 for Short-TE, 0.83 for Long-TE and 0.98 for Short-TE+Long-TE. The best performance was

obtained with Short-TE+Long-TE, showing a significant improvement ($p<0.01$, Tukey's test, $\alpha=0.01$) compared to the best performance obtained with either TE alone. The BAR of the classifiers trained with tumours from any location was slightly higher than that of the models trained only with the PF tumours. Comparable performances were obtained with TARQUIN and PI.

Figure 3 shows the clustering of cases in LDA latent spaces from Short-TE, Long-TE and Short-TE+Long-TE obtained for the discrimination of PILOA, EPEN and MED located in the PF. In addition, Figure 3-d shows the corresponding result from Short-TE for the three tumour types in any brain location.

Other tumour types were classified as glial or primitive neuroectodermal according to the result with the classifier developed for PILOA, EPEN and MED. A BAR of 0.91 was obtained with Short-TE, 0.67 for Long-TE and 1.00 was achieved with Short-TE+Long-TE. Figure 4 shows how these other tumour types cluster when projected onto Figure 3-d and illustrates the potential for generalization of our classifiers to other tumour types: The ATRT and PNET cases fall close to the boundaries of the MED area, the only exception being the ATRT case located in the frontal lobe. The DASTRO and SASTRO cases are spread all over the PILOA and EPEN area, never within the MED area.

4 Discussion

This is the first study of MRS as a non-invasive diagnostic aid in childhood brain tumours to be performed across a large number of centres. Limited

single-centre studies have been reported including the non-invasive diagnosis and characterization of EPEN, MED and PILOA: Wang *et al.* [27] collected data from 26 patients using a Long-TE MRS technique. They obtained an accuracy of 0.85 discriminating the three tumour types using the metabolites ratios NAA:Cho and Cr:Cho. Arle *et al.* [28] obtained an accuracy of 0.88 with a neural network using metabolites ratios of NAA, Cho and Cr from MRS data of 33 patients. Schneider *et al.* [29] combined Short-TE MRS and diffusion-weighted imaging data from 17 patients, obtaining an accuracy of 1.00 when applying an LDA with seven variables from the diffusion-weighted image and six metabolites. Davies *et al.* [30] used an automated method for fitting MRS data of 35 patients to quantify 25 metabolite, lipid and macromolecule concentrations and used this as an input to an LDA. They reported an accuracy of 0.93 when discriminating the three tumour types. In our study, the performances of classifiers using one TE were similar to those reported in these studies [27-30].

Significant differences in metabolite concentrations of PILOA, EPEN and MED were found. Cho was higher ($p \leq 0.01$) in MED (grade IV) and EPEN (grade II) compared to PILOA (grade I) in agreement with Cho as an indicator of cell proliferation and tumour malignancy [17, 18]. EPEN and MED have higher concentrations of lipids and macromolecules, associated with hypoxia, apoptosis and necrosis and linked to high malignancy and poor survival [33, 34]. As previously reported [35, 36, 37], Tau concentration is significantly higher in MED than glial tumours ($p \leq 0.01$) and further investigation of the role

of this metabolite in these tumours is warranted. Low concentrations of Cr were seen in PILOA as in previous studies but remain unexplained [30].

A significant improvement ($p<0.01$, Tukey's test, $\alpha=0.01$) in the diagnosis rates was obtained when the metabolite information was increased with the combination of both TEs compared to the performance when using either TE alone. This finding has been reported for adult cases in [20] but not for pediatric brain tumours.

Estimation of metabolite concentrations was performed with the TARQUIN software (Tables 2 and 3) which is a highly automated and stable method for determining metabolite concentrations from MRS data and allows a non-expert user to process MRS spectra at various echo times without difficulty. The use of TARQUIN quantitation in automatic Decision Support Systems (DSSs) provides a powerful clinical tool. The CURIAM DSS [37, 38] incorporates the classifiers developed in this work, offering the possibility of giving decision support both to the non-invasive diagnosis of brain tumours in adults and children.

Future work should focus on optimising MRS in providing non-invasive biomarkers of prognosis and whether it adds prognostic information to that from histology and structural imaging.

5 Conclusion

^{1}H-MRS data was collected at diagnosis from children with brain tumours in 10 international centres in Europe and South America and was used to test

the ability of MRS to discriminate between different tumour types. Our results show that particularly high diagnostic accuracies are achieved when MRS is collected at two TEs and that this accuracy can be achieved with data collected from multiple centres. MRS with automated processing and pattern recognition provides a useful technique for accurate, non-invasive diagnosis and classification of childhood brain tumours and thereby a powerful diagnostic tool for clinical practice.

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Conflict of interest statement

None declared.

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Acronyms

Ala	Alanine
Asp	Aspartate
ATRT	Atypical Teratoid Rhabdoid Tumour
BAR	Balanced Accuracy Rate
Cho	Choline
CNS	Central Nervous System
Cr	Creatine
DASTRO	Diffuse Astrocytoma
DSS	Decision Support System
EPEN	Ependymoma grade II
GABA	γ Aminobutyric acid
Glc	Glucose
Gln	Glutamine
Glu	Glutamate
Glx	Glutamate + Glutamine
Gly	Glycine
GPC	Glycerophosphocholine

Gua	Guanidinoacetate
Lac	Lactate
LDA	Linear Discriminant Analysis
Long-TE	Long echo time
MED	Medulloblastoma
mI	myo-Inositol
MMLip09	Macromolecules and lipids components at 0.9 ppm
MMLip13	Macromolecules and lipids components at 1.3 ppm
MMLip20	Macromolecules and lipids components at 2.0 ppm
MR	(Nuclear) Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-Acetyl Aspartate
PCh	Phosphocholine
PI	Peak Integration
PILOA	Pilocytic Astrocytoma
PINEOB	Pineoblastoma
PF	Posterior Fossa

PNET	Supratentorial PNET
PRESS	Point-Resolved Spectroscopy
PROBE	Proton Brain Exam
ppm	parts per million
SASTRO	Subependymal giant cell astrocytoma
Scyllo	scyllo-inositol
Short-TE	Short echo time
STEAM	Stimulated Echo Acquisition Mode
Tau	Taurine
TE	Echo Time
TR	Recycling Time
WHO	World Health Organization

Figure 1 Short-TE mean spectra of tumours located in the PF (left) and in any other location than PF (right) with standard deviation by the shaded region. Number of patients is indicated beneath each graph.

Figure 2 Long-TE mean spectra of tumours located in the PF (left) and in any other location than PF (right) with standard deviation by the shaded region. Number of patients is indicated beneath each graph.

Figure 3 LDA latent space for the discrimination of PILOA, EPEN and MED located in the PF using PI applied to: a) Short-TE; b) Long-TE; and c) both echo times. Each triangle represents the centroid of each cloud of samples. Figure d) represents the LDA latent space for discrimination of PILOA, EPEN and MED using PI applied to Short-TE for tumours located in the PF (represented with `x') and other locations (represented with `o').

Figure 4 LDA latent space for the discrimination of Medulloblastoma (MED), Pilocytic Astrocytoma (PILOA) and Ependymoma grade II (EPEN) using PI applied to Short-TE. The proyection of Subependymal giant cell astrocytoma (SASTRO), Diffuse Astrocytoma (DASTRO), Atypical Teratoid Rhabdoid Tumour (ATRT), Supratentorial PNET (PNET) and Pineoblastoma (PINEOB) is shown.

Table 1 Number of cases.

Label	Short-TE	Long-TE	Short-TE+Long-TE	Total different cases
PILOA	37	27	26	38
EPEN	9	7	5	11
MED	28	15	13	29
SASTRO	2	3	2	3
DASTRO	8	8	6	10
ATRT	3	0	0	3
PNET	1	1	1	1
PINEOB	2	0	0	2
TOTAL	90	61	54	97

Table 2 Estimated metabolite concentrations (mM) at several ppm calculated with TARQUIN relative to total water from Short-TE spectra. The standard error of the concentrations is given in brackets. The *p*-value of the analysis of the variance (Kruskal-Wallis test, α=0.05) is shown for discrimination of PILOA, EPEN and MED when significant differences are observed.

	Short-TE			
		Tumour type		*p*-value
Metabolite	PILOA (mM)	EPEN (mM)	MED (mM)	PILOA vs EPEN vs MED
Ala	0.9 (0.9)	2.5 (2.3)	0.6 (0.5)	-
Cr	1.3 (1.1)	3.4 (1.5)	3.6 (1.9)	<0.01
Glc	2.7 (1.7)	2.3 (1.8)	1.9 (1.2)	<0.01
Gln	3.7 (1.9)	6.7 (3.0)	4.1 (3.1)	-
Glu	2.0 (1.6)	3.1 (3.2)	2.5 (1.5)	-
mI[a]	2.1 (1.9)	9.0 (5.3)	5.3 (3.2)	<0.01
Lac	2.4 (1.9)	3.2 (4.3)	2.9 (3.0)	-
NAA	1.6 (1.4)	1.1 (0.3)	1.5 (1.0)	-
Scyllo	0.7 (0.8)	0.6 (0.4)	0.9 (0.5)	<0.05
Tau	1.8 (1.3)	1.8 (1.6)	4.5 (3.6)	<0.01
GPC	0.9 (0.4)	1.6 (0.5)	2.2 (1.2)	<0.01
PCh	1.6 (2.4)	1.3 (1.0)	2.2 (1.6)	<0.01
-$CrCH_2$	1.7 (1.8)	3.2 (1.9)	1.3 (1.1)	-
Gua	1.8 (1.7)	1.2 (1.2)	2.1 (2.0)	-
GABA	3.8 (7.9)	2.2 (1.7)	2.9 (3.5)	-
Asp	9.1 (24.2)	4.5 (3.6)	3.6 (2.7)	-
Cho: GPC+PCh	1.4 (1.6)	2.4 (1.1)	4.1 (1.4)	<0.01
Glx: Glu+Gln	4.9 (2.2)	8.9 (4.2)	5.5 (3.1)	<0.05
MMLip09	4.9 (2.9)	8.1 (5.5)	8.3 (5.9)	<0.05
MMLip13	7.7 (7.0)	27.3 (17.6)	20.5 (18.9)	<0.01
MMLip20	6.2 (2.9)	10.8 (3.3)	11.3 (5.2)	<0.01

[a] Concentration of mI may contain Gly contribution. Gly was not included in the TARQUIN basis-set.

Table 3 Estimated metabolite concentrations (mM) at several ppm calculated with TARQUIN relative to total water from Long-TE spectra. The standard error of the concentrations is given in brackets. The *p*-value of the analysis of the variance (Kruskal-Wallis test, α=0.05) is shown for discrimination of PILOA, EPEN and MED when significant differences are observed.

	Long-TE			
		Tumour type		*p*-value
Metabolite	PILOA (mM)	EPEN (mM)	MED (mM)	PILOA vs EPEN vs MED
Ala	0.5 (0.5)	0.9 (1.1)	1.4 (0.8)	<0.05
Cr	1.8 (1.9)	5.8 (2.2)	5.6 (2.1)	<0.01
Glc	2.1 (1.9)	7.2 (5.4)	3.0 (1.8)	-
Gln	3.3 (2.1)	7.2 (3.5)	3.4 (2.1)	-
Glu	2.8 (2.8)	5.3 (1.9)	5.8 (2.3)	-
mI[b]	7.5 (10.4)	24.1 (14.8)	31.1 (14.5)	<0.01
Lac	2.0 (1.5)	2.2 (1.0)	1.9 (1.7)	-
NAA	1.9 (1.2)	2.4 (1.3)	2.3 (1.6)	-
Scyllo	0.3 (0.3)	0.9 (0.6)	0.8 (0.6)	-
Tau	1.6 (2.6)	4.3 (4.5)	6.9 (6.4)	<0.01
GPC	0.8 (1.1)	2.1 (1.3)	4.1 (4.2)	<0.01
PCh	1.9 (2.0)	3.0 (0.9)	5.7 (5.6)	<0.01
-$CrCH_2$	0.7 (0.8)	3.9 (3.2)	3.4 (3.1)	-
Gua	0.7 (0.5)	1.5 (0.1)	0.7 (0.4)	-
GABA	1.5 (1.1)	-	1.3 (0.8)	-
Asp	1.5 (0.6)	2.4 (1.3)	3.4 (3.1)	-
Cho: GPC+PCh	2.4 (2.7)	4.3 (1.9)	9.5 (5.9)	<0.01
Glx: Glu+Gln	5.7 (3.1)	10.5 (4.9)	7.4 (3.5)	-
MMLip09	0.4 (0.3)	1.8 (1.1)	0.5 (0.2)	<0.05
MMLip13	1.3 (1.3)	9.2 (8.8)	3.6 (2.0)	<0.05
MMLip20	2.0 (2.5)	1.6 (1.3)	1.2 (0.9)	-

[b] Concentration of mI may contain Gly contribution. Gly was not included in the TARQUIN basis-set.

Table 4 Balanced Accuracy Rate (BAR) of the classifiers trained with Short-TE, Long-TE and combination of both echo times (Short-TE+Long-TE) for discrimination of PILOA, EPEN and MED.

PILOA vs EPEN vs MED						
	Cases from tumours located in the PF			Cases from any brain tumour location		
	Short-TE	Long-TE	Short-TE+Long-TE	Short-TE	Long-TE	Short-TE+Long-TE
TARQUIN	0.67	0.94	0.96	0.79	0.83	0.98
PI	0.65	0.62	0.90	0.76	0.69	0.92