ORIGINAL ARTICLE

Brain Tumours and Their Metabolic Profiles by Magnetic Resonance Spectroscopy

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ABSTRACT

Introduction: Intracranial brain tumour like meningiomas and glioblastomas are most prevalent tumour. The metastasis to the brain is one of the major issues in the tumours of the central nervous system. The diagnosis of metastatic and primary brain tumour is incomprehensible with standard magnetic resonance imaging (MRI). The magnetic resonance spectroscopy (MRS) is basically performed in standard clinical setting for diagnosing and tracking the brain tumour. **Method:** It is a retrospective study containing 53 patients with MRS. The patients with metastatic tumour (n=10), glioblastomas (n=8) and meningiomas (n=20) are included in the study. Single voxel technique is applied in the tumour core to determine the metabolites. The tumour N-acetyl aspartate (NAA), Choline (Cho), Creatine (Cr), Lactate, Alanine and lipids were analysed. The ratios of NAA/Cr, Cho/NAA and Cho/Cr were recorded and compared between the three tumours. The metabolites were detected between short echo time (TE) to long echo time (TE) during MRS. **Results:** There is a sharp fall of NAA peak in metastatic tumour. The resonance of creatine, lactate and alanine is higher in glioblastomas. A high lipid mean value of 3.13(0.17) is seen in metastatic tumour. The ROC curve shows a low NAA/Cr specificity of 46.7%, high sensitivity of 83.3% in Cho/NAA and Cho/Cr ratio. **Conclusion:** The metabolic profiles of metastatic brain tumour, glioblastomas and meningioma illustrate a divergence in their description that will assist in planning therapeutic and surgical intervention of these tumours.

Keywords: Brain, Metastasis, Glioblastomas, Meningioma, Magnetic resonance spectroscopy

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INTRODUCTION

The primary brain tumour like intracranial meningiomas and glioblastomas are the most prevalent tumours. These tumours are hard to differentiate from metastasis in the brain. Metastasis from the malignant tumours of the breast, lungs and melanoma are the commonest sites (1). They are responsible for high mortality rate. Most of this tumour type and grading are identified with histopathological examination. However, there are possible chances of injury, complications and mortality associated with this procedure. The magnetic resonance imaging is one of the best techniques to recognize these tumours. But still the radiological picture of glioblastomas, metastatic tumour and few of the meningiomas are very similar. There is a need for improvement in magnetic resonance technique that can discover the episodes of abnormal happenings and will help to identify these tumours accurately. In research the use of magnetic resonance spectroscopy (MRS) is highly distinctive. It explores the metabolites to specify and distinguishes the brain tumours (2). A single voxel spectroscopy accession can be executed to estimate and analyze the metabolites noninvasively (3). Most of these metabolites include N-acetyl aspartate (NAA), Choline (Cho), Creatine (Cr), Lactate, Alanine and Lipid. Also the metabolic ratios of NAA/Cr, Cho/NAA and Cho/Cr are estimated (4). There is limited study on magnetic resonance spectroscopy and the metabolic profiles of brain tumour especially in Malaysia. An effort has been made to visualize the concept of metabolites and its relation with different types of intracranial tumour. The main objective of this study is to highlight the clinical application of magnetic resonance spectroscopy. To identify and evaluate the different metabolites in meningiomas, glioblastomas and malignant brain tumour and to analyze the correlation of these metabolites in between these three types of tumour. The out-come of this study will enhance the findings from the previous studies.

MATERIALS AND METHODS

It is a restrospective study. In this study the inclusion criterias include patients with brain tumour above 5 to 70 years of age having magnetic resonance spectroscopy

diagnosed with meningioma, glioblastoma and metastatic brain tumours. These patients are from Malay, Chinese and Indian races and include both genders. The sample brain tumour patients was diagnosed between years 2013 to 2018. The exclusion criterias include postoperative, postradiotherapy patients and patients with head injury. The MR spectrocopy image with artifacts and uninterruptable spectra are also not taken for this study. The data of the patients was collected from their radiological report retrieved from picture archiving and communication system (PACS system). The total patient population with brain tumours selected for this study was 151(n=151). The magnetic resonance spectroscopy (MRS) was performed in 53 patients. Among them 10 patients were identified as having Glioblastoma , 8 patients were detected with metastatic brain tumour and 20 patients with meningiomas. All these patients has undergone magnetic resonance spectroscopy (MRS) in Philips ACHEVA 3 Tesla MRI machine in Hospital University Sains Malaysia, Kelantan, Malaysia. The following sequence of AxT1/T2/FLAIR/DWI/ADC/SagT1/post Gado/MRS/MRA/MRV was used during the procedure. The MRS was conducted mostly in short echo time (TE: 35 ms) with a repeatation time of TR: 2000. The conventional method is short echo time (TE). But to visalize the lactate it is extended to long TE. A pulse of single-voxel point-resolved spectroscopy (PRESS) was applied with changeable sizes in voxel that were normalized for contrast rationale. A trained radiographer with the help of on duty radiologist decided the voxel placement during their analysis. The collected data were analysed by SPSS version 23. The values of NAA/Cr, Cho/NAA and Cho/Cr ratios in tumour core are compared with a box plot between metastatic brain tumours, glioblastomas and meningiomas. Receiver operating characteristic curve (ROC) estimation is conducted between the different metabolite ratios between these three types of tumours. The Youden index (sensitivity +1 specificity -1) was applied at the threshold limit for comparing the ratios of the metabolites in brain tumours.

RESULTS

For standardization and to ensure proper quality the readings of the metabolites NAA, Cho, Cr, Alanine and lipid are taken from contralateral normal appearing side of the brain hemisphere. The value of the metabolic profile was taken from the spectral view during MRI acquisition by radiologist and trained radiographer in neuroimaging. The ratios of NAA/Cr, Cho/NAA and Cho/Cr are also taken in a similar procedure. The mean± SD are calculated for different metabolites from contralateral normal appearing side are described in Table I. The metabolite ratios are outlined also in the table.

The results displayed in Table I also showing the concentration of NAA, Cho, Cr, Lactate, Alanine and lipid concentration in the tumour core of meningioma, glioblastoma and metastatic tumour. The values of these metabolites in the tumour core are lower than the contralateral normal appearing side. The NAA/Cr and Cho/NAA ratios are also seen lower in these three tumours.

Glioblastoma

Glioblastoma shows a low NAA concentration with mean [SE] of 2.44[0.24]. The P value is 0.52 which is more than 0.05. Thus, there is no significant difference in NAA level between glioblastomas, metastatic tumour and meningioma. It also exhibited a high choline (2.84[0.37]) and lactate level (2.29[0.31]). It depicts a high Cho/Cr ratio with mean [SE] of 0.51[0.57] than metastatic tumour (0.46[0.98]) and meningioma (2.47[0.12]) compared to contralateral side. No statistical difference is seen in all the metabolites and their ratios analysed in the normal appearing region. The NAA/Cr ratio is low in glioblastoma 0.05[0.41]) than metastatic tumour (0.22[0.72]) and meningioma

Table I: Different metabolites and their ratios in Meningioma, glioblastoma and metastatic brain tumour in contralateral normal healthy region and tumour core

MRS Parameter	Meningioma		Glioblastoma		Metastatic tumour		P Value		Chi-square	
	Contralateral healthy side	Tumour core	Contralateral healthy side	Tumour core	Contralateral healthy side	Tumour core	Contralateral healthy side	Tumour core	Contralateral healthy side	Tumour core
NAA	2.71(0.99)	2.04(1.03)	3.04(0.23)	2.44(0.24)	2.80(1.12)	1.89(1.43)	0.86	0.52	0.291	1.28
Cho	2.46(1.02)	2.46(1.15)	2.80(0.28)	2.84(0.37)	2.64 (1.25)	2.45 (1.11)	0.68	0.79	0.757	0.461
Cr	2.46(1.01)	2.30(0.99)	2.84(0.34)	2.57(0.32)	2.65(1.12)	1.92(1.54)	0.6	0.9	0.993	0.208
Lactate	1.32(0.54)	1.14(1.21)	1.69(0.17)	2.29(0.31)	1.13(0.32)	1.57(2.69)	0.32	0.43	2.269	1.64
Alanine	1.73(1.17)	1.64(1.27)	2.15(0.38)	1.99(0.24)	0.58(2.37)	1.75(1.49)	0.6	0.97	1.022	0.05
Lipid	1.85(0.53)	2.47(0.12)	2.07(0.31)	2.46(0.67)	2.14(0.11)	3.13(0.17)	0.75	**0.031**	0.567	6.93
NAA/Cr	0.32(0.21)	0.18(0.53)	0.28(0.29)	0.05(0.41)	0.12(0.22)	0.22(0.72)	0.26	0.4	2.626	1.78
Cho/NAA	0.55(0.60)	0.55(0.60)	0.45(0.30)	0.45(0.30)	0.31(0.75)	0.31(0.75)	0.13	0.94	4.012	0.105
Cho/Cr	0.07(0.26)	0.25(0.89)	0.1(0.2)	0.51(0.57)	0.01(0.17)	0.46(0.98)	0.78	**0.01**	0.49	0.756

(0.18[0.53]). However, they have higher Cho/NAA and Cho/Cr ratio. The nonparametric analysis for Cho/Cr ratio shows P=0.01 which is less than significant value of 0.05. It reflects a considerable difference in Cho/Cr ratio between metastatic tumour, glioblastomas and meningioma.

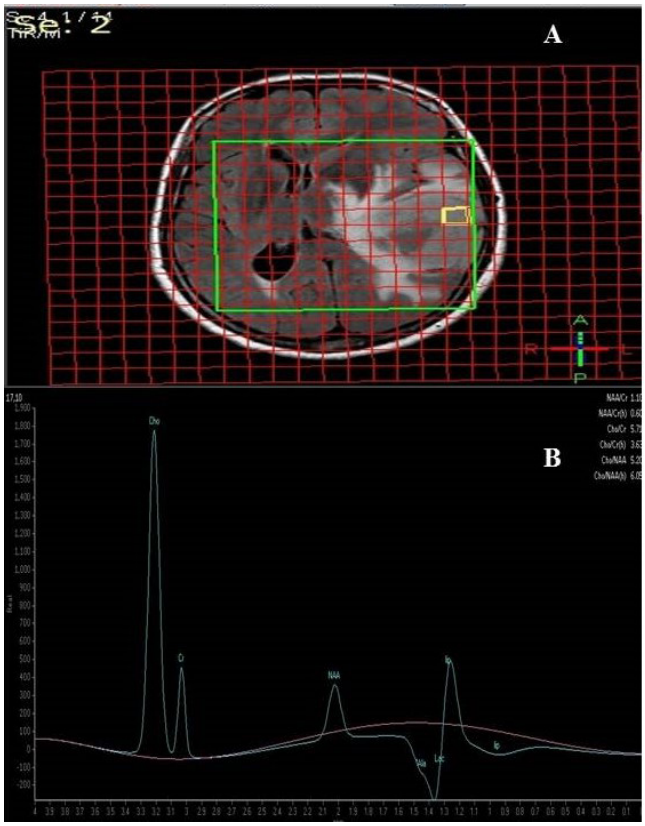

Figure 1: A 48-year-old female patient with features of high grade glioma. The Axial FLAIR image showing: (A) hyperintense mass in left parietal lobe suppressing the lateral ventricle. Magnetic resonance spectroscopy (MRS) from the single voxel in Region of interest (ROI) showing: (B) high peak of choline compared to metastatic tumour and high Cho/NAA of 5.2 and Cho/Cr of 5.71

Metastatic tumour

The metastatic tumours exhibits a higher lipid concentration (3.13[0.17]) compared to glioblastomas (2.46[0.67]) and meningioma (2.47[0.12]). The nonparametric Kruskal Wallis test revealed P value of 0.031 less than 0.05. This shows a significant difference in lipid between glioblastomas, metastatic tumour and meningioma.

Meningioma

The meningiomas expressed a high lipid level in the tumour core (2.47[0.12]) compared to the contralateral healthy side (1.85[0.53]). The Cho/NAA ratio in the tumour core is (0.55[0.60]) which is higher than glioblastoma (0.45[0.30]) and metastatic tumour (0.31[0.75]). But there is no significant difference as P value is 0.94 which is more than 0.05.

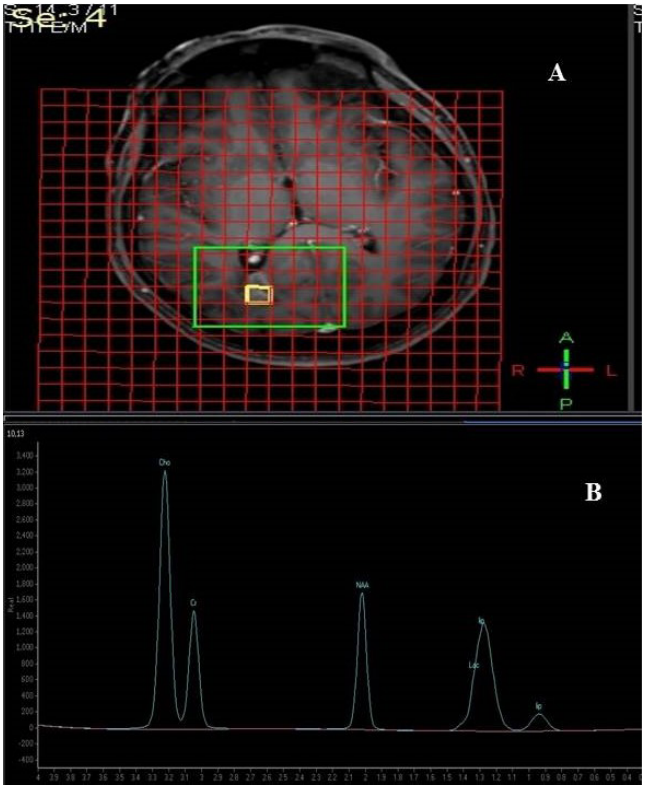

Figure 2: A 50-year-old male with features of metastatic brain lesion: An Axial FLAIR image showing (A) Lobulated hyperintense lesion showing a peripheral rim with perilesional oedema. Magnetic resonance spectroscopy (MRS) from the single voxel in Region of interest (ROI) showing (B) showing elevated peak of Choline in metastatic brain lesion and low Cho/NAA of 0.46 and Cho/Cr of 0.64

DISCUSSION

The identification of brain lesions like meningioma, glioblastomas and metastatic tumour is undetermined with magnetic resonance imaging (MRI). The differences in their findings are important to map out treatment protocols and for further follow up of these two tumours. The magnetic resonance spectroscopy (MRS) provides an appropriate diagnosis from the data of the metabolites taken from tumour core (5). There may be discrepancy in collecting the data which mostly depends on positioning of voxel that may include necrotic areas or edges of the tumour while collecting the data from the tumour core. The majority of the intracranial meningiomas are benign tumour. However, recurrent meningiomas are suspected of having malignant change from WHO grade I type. The transformation leads to an atypical meningioma of WHO grade II type. A few of the meningiomas exhibits as intra-axial malignant tumour like anaplastic astrocytoma, glioblastoma and metastatic tumour especially with well define peritumoural oedema (6). Earlier studies reported that the MRS from the tumour core failed to differentiate between glioblastomas and metastasis (7).

In this study higher Cho/Cr ratio is observed in Glioblastomas than metastatic tumour. This finding

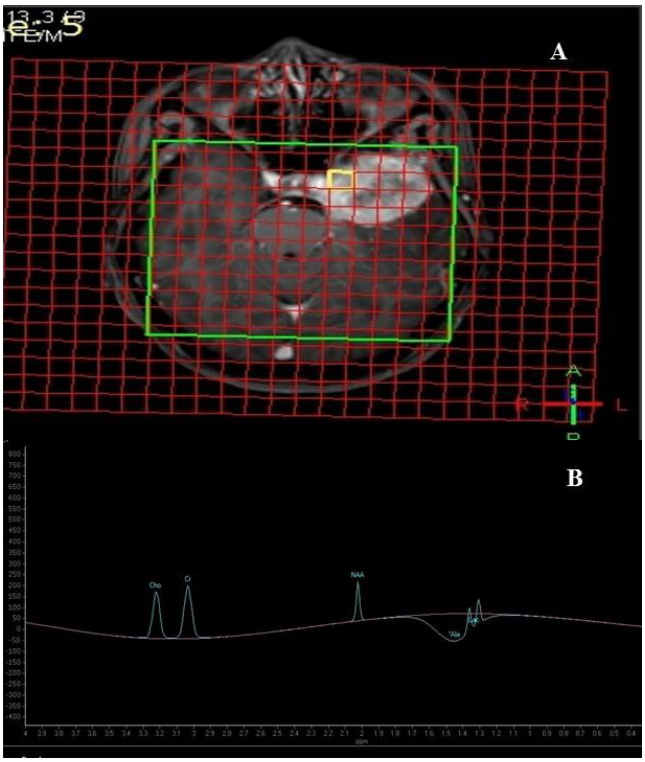

Figure 3: A 43-year-old female with features of meningioma: An Axial FLAIR image showing (A) Lobulated hyperintense extraxial lesion with vasogenic perilesional edema in left temporal lobe. Magnetic resonance spectroscopy (MRS) from the single voxel in Region of interest (ROI) showing (B) reduced peak of NAA in the meningioma and low Cho/NAA of 2.44 and Cho/Cr of 0.81.

goes in line with the results of previous studies (8). In one study there was a wide variation of Cho/Cr of metastatic tumour at medium TE (9). Choline is a part of cell membrane. Its methyl group methylate's the O6-methylguanine-DNA methyltransferase in glioblastomas (10). An elevated peak of choline in high grade glioma signifies an increase cellular density. The creatine (Cr) is an energy metabolism marker that needs amino acid for its production in the kidneys and liver. The creatine level falls in high grade gliomas due to high metabolism in the tumour. This results in a high Cho/Cr ratio seen in glioblastomas (11, 12). A high concentration of choline is also a distinctive feature of atypical meningiomas (13). The results also discovered that there is significance difference in Cho/Cr ratio between glioblastomas, metastatic brain tumour and meningiomas (P=0.01).

The lipid concentration is significantly higher in metastatic tumour than glioblastomas and meningiomas in the present study. There are reports that lipid exists in high amount in meningiomas, glioblastomas and high grade gliomas. This is due presence of necrosis in these type of tumour (14). The collections of lipid are seen in microcystic and also in lipomatous meningiomas. This is due to cells which resemble adipocytes in the tumour (15). In short echo time the peak of lipid concentration is noticed at 1.33ppm and 0.9 ppm in malignant metastasis of brain (16). The previous studies revealed lipid peaks can authorize discrimination between metastasis and glioblastomas. This variation in the concentration of lipids depends on metabolism of lipid and also difference between nature of infiltrative and moving tumour cells (17).

The study also exhibits higher Cho/NAA ratio in tumour core of meningiomas than glioblastomas and brain metastasis which is statistically not significant (18). There are comments that a short peak of NAA can be noticed in metastatic tumour. NAA is an amino acid present abundantly in the brain produced from aspartate and acetyl CoA in the mitochondria of a neuron. Its peak determines the presence of viable neurons in the brain after invasion by the tumour cells (19). The level of NAA/Cr is found to be higher in metastatic brain tumour than glioblastomas and meningiomas with no significant difference of the ratio between the three types of tumour. A similar result on concentration on NAA/Cr was also observed in a previous study (20).

The box plot analysis illustrated in Fig 4 shows NAA/Cr ratio values are more spread out in meningiomas compared to glioblastoma and metastatic brain tumours. There are outliers seen in both the maximum and minimum ends of NAA/Cr ratio of metastatic tumour whereas in glioblastoma outliers are noticed towards maximum end. There are no outliers in NAA/Cr ratios of meningioma. The values of NAA/Cr ratio seems to be more consistent in meningiomas. Similar findings are seen in Cho/NAA ratio of meningiomas in Fig 5 where values are spread out like the NAA/Cr ratio. A whisker is not connected to the lower end in Cho/NAA ratio of metastatic brain tumours. This is because of absence of minimum values this ratio in metastatic tumour. However, an outlier is present in towards minimum end. There are no outliers seen in glioblastomas and meningiomas. The Cho/Cr ratio values (Fig 6) are seen to be widely spread out again in meningioma. The Whiskers are not seen to be connected to both the upper and lower end of metastatic tumour. But outliers are noticed in maximum and minimum end of Cho/Cr ratio of metastatic tumour. For glioblastoma an outlier is seen towards the maximum end. But no outliers are seen in meningioma. So, in conclusion the values of Cho/NAA and Cho/Cr ratios of meningiomas are also noticed to be consistent.

The ROC analysis of NAA/Cr ratio (Fig 7.A) achieves a sensitivity of 85.7% and specificity of 46.7%. The low specificity of NAA/Cr indicates high false positive rates and a low true negative rate. This specifies that metastatic brain tumour will be falsely identified as glioblastomas or meningioma. The finding of Cho/NAA ratio (Fig 7.B) in this study shows a high sensitivity of 83.3% illustrating a high positive rate and a low negative rate. This finding goes in line with results of prior study on sensitivity of

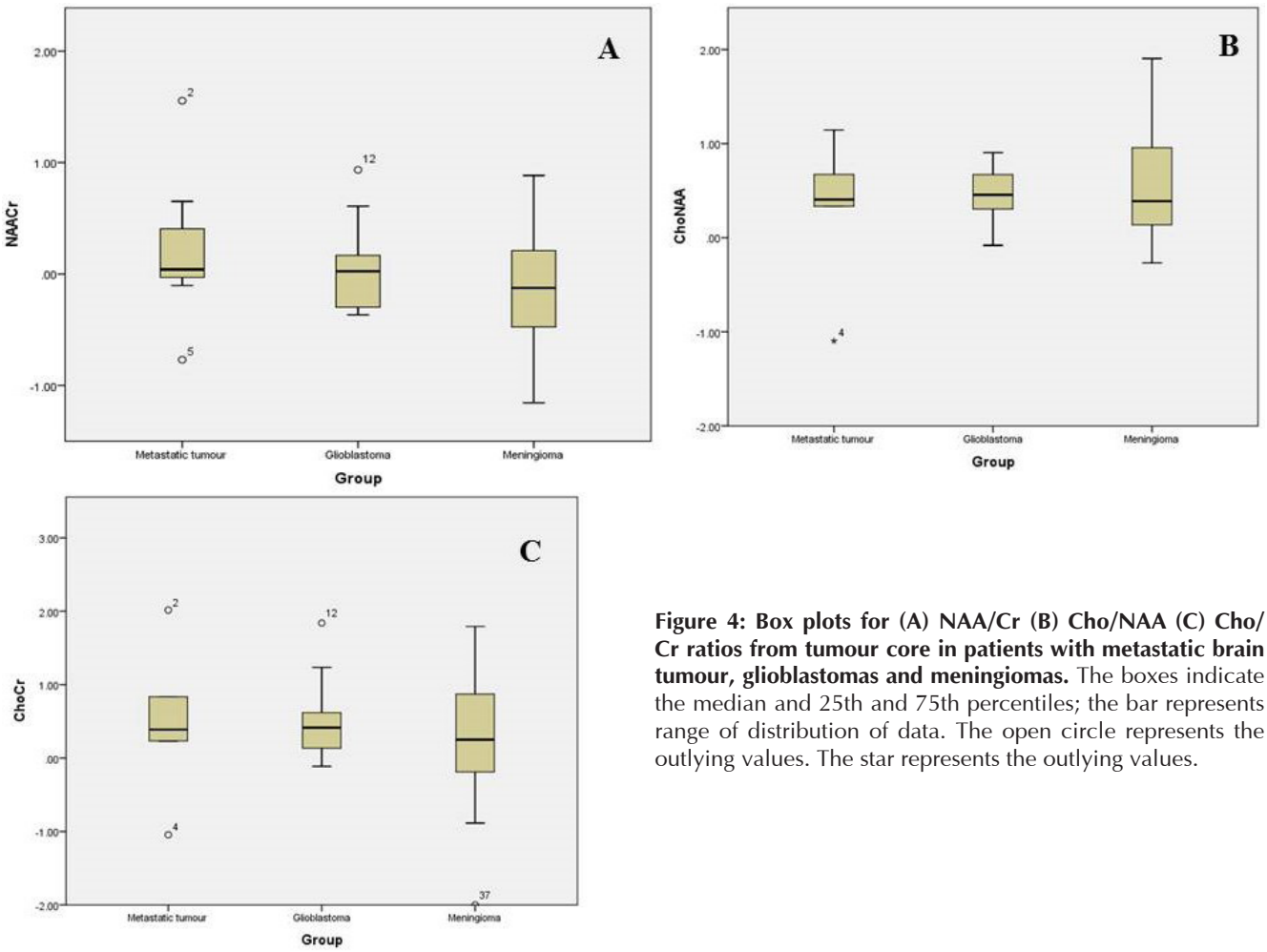

Figure 4: Box plots for (A) NAA/Cr (B) Cho/NAA (C) Cho/Cr ratios from tumour core in patients with metastatic brain tumour, glioblastomas and meningiomas. The boxes indicate the median and 25th and 75th percentiles; the bar represents range of distribution of data. The open circle represents the outlying values. The star represents the outlying values.

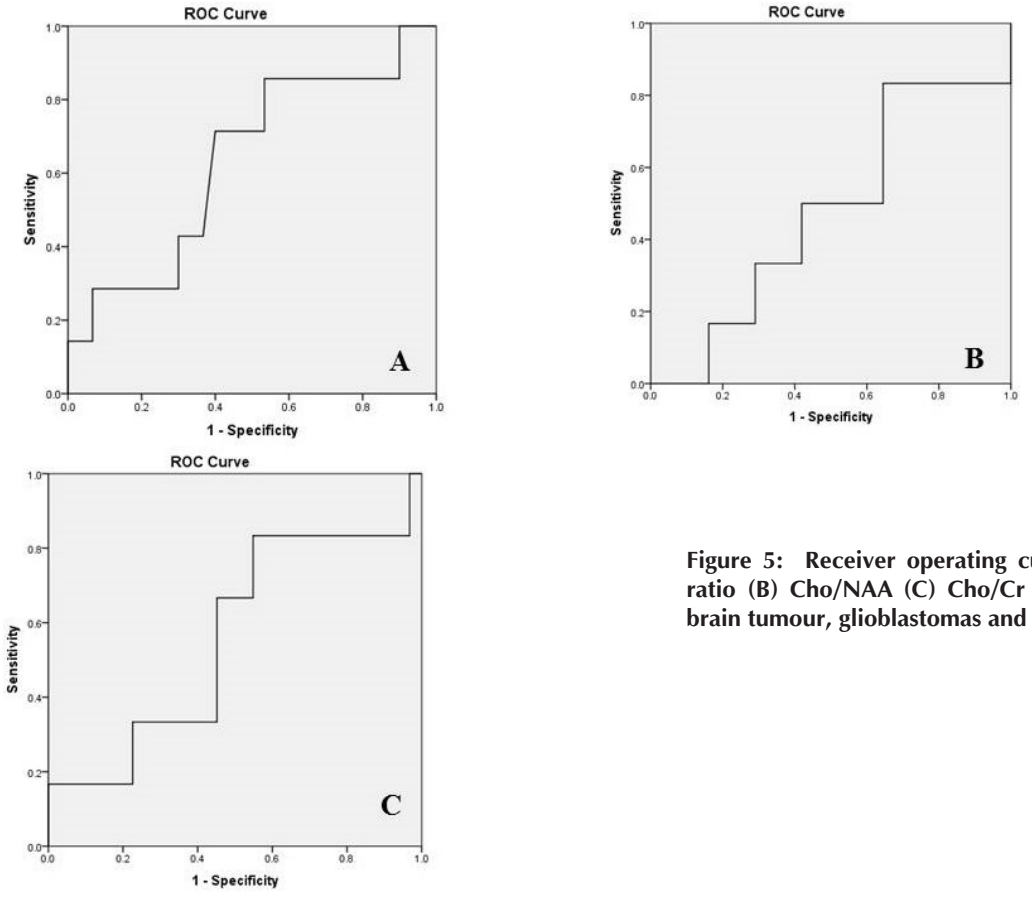

Figure 5: Receiver operating curve (ROC) of (A) NAA/Cr ratio (B) Cho/NAA (C) Cho/Cr tumour core of metastatic brain tumour, glioblastomas and meningiomas

Cho/NAA (22). They have reported 90% of sensitivity in distinguishing glioblastomas from metastatic tumour. However, the curve for Cho/NAA ratio lies below the diagonal of ROC space. It signifies poor accuracy of test for Cho/NAA ratio. The value of Cho/Cr ratio (Fig 7.C) also exhibits a high sensitivity rate of 83.3%. However, a low specificity of 58.1% explains that some metastatic brain tumour may not show a fully developed form of tumour.

The ROC interpretation compares the area under the curve to the value 0.05 for each type of tumour. The small P value shows a significant difference for the three types of tumour. The Cho/NAA ratio in ROC analysis shows the curve falling below the baseline. However, the true positive rate against the false rate is high. This variation may due to diverse in tumour size. Another discrepancy could be due to MRS procedure in retrieving the images. The NAA/Cr ratio in ROC evaluation exhibits the curve having similar pattern and high sensitivity with Cho/Cr curve. But both the ratios display high sensitivity. The main drawback of this research is due its retrospective nature of investigation. The small sample size of the patient population is also one of the factors. Further research is necessary in this topic with a bigger sample size.

CONCLUSION

The magnetic resonance spectroscopy (MRS) is one of the advance approaches that provide strong information on types and grading of brain tumour. It distinguishes a cancerous change in the brain tissue by identifying metabolic activity by detecting different metabolites. It provides a pre-operative tumour grading of brain tumour. In this study an identification of metabolites in meningiomas, glioblastomas and metastatic brain tumour is performed using MRS to differentiate these three tumours. The present research discovered that MRS authorized distinction of metastatic tumour, glioblastomas and meningiomas. This difference is highlighted considerably in the quantification of lipid and Cho/Cr ratio in the tumour core of metastatic brain tumour, glioblastomas and meningiomas. The variations in the metabolites of these neoplasms will guide to decide important therapeutic implications when critical decision about selection of the optimal treatment strategy is to be made.

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