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ORIGINAL ARTICLE **CME**

Peri-tumoural Magnetic Resonance Spectroscopy to Differentiate Solitary Primary Intra-axial High-grade Glioma and Brain Metastasis: a Pilot Study

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ABSTRACT

Objective: *To determine whether the peri-tumoural choline/N-acetyl-aspartate ratio can be used to differentiate solitary primary intra-axial brain tumour and metatasis.*

Methods: *In this retrospective study, 18 treatment-naïve adults presenting with a solitary intra-axial mass underwent conventional contrast-enhanced and proton spectroscopic magnetic resonance imaging. The images were interpreted retrospectively by an experienced neuroradiologist and a radiology fellow with 6 years' experience. The radiologists were blinded to the clinicopathological and demographic data. The choline/N-acetyl-aspartate ratio was measured over the area of peri-tumoural oedema, which was defined by T2 hyperintensity and non-enhancing areas immediately adjacent to the enhancing portion of the tumour. A peri-tumoural choline/N-acetyl-aspartate ratio of >1 was classified as positive, meaning primary brain tumour. Statistical analysis was performed using a 2 x 2 contingency table. The interclass correlation coefficient (alpha) was calculated as the index of concordance exceeding chance for inter-rater reliability.*

Results: *Of 18 patients, four were excluded from the study owing to absence of peri-tumoural cerebral oedema. Of the remaining 14 patients, nine had a solitary intra-axial high-grade gliomas confirmed pathologically, of whom eight had a peri-tumoural choline/N-acetyl-aspartate ratio of >1. The remaining five patients were classified as having a solitary brain metastasis with no known primary. A choline/N-acetyl-aspartate ratio of >1 in peri-tumoural region can be used as a parameter predicting a primary brain tumour; respective values for sensitivity, specificity, positive and negative predictive values were 90%, 100%, 100% and 83%, respectively.*

Conclusion: *The peri-tumoural choline/N-acetyl-aspartate ratio of >1 can be used as a parameter to differentiate the intra-axial primary brain tumour from metastasis.*

Key Words: *Brain neoplasms; Choline; Glioma; Image enhancement; Protons*

中文摘要

瘤周區磁共振波譜對孤立原發性顱內高級別膠質瘤及腦轉移瘤的鑒別診斷：初步研究結果

黃鎮昇、朱曉青、馬嘉輝

目的：探討胆碱化合物/N-乙酰冬氨酸峰的比值（Cho/NAA比值）是否可以分辨出孤立原發性顱內腫瘤及腦轉移瘤。

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方法：本回顧研究對象為18位孤立顱內腫瘤但未接受治療的患者。他們接受常規的造影增強及質子磁共振波譜檢查，得出的影像由一位經驗豐富的腦神經放射科醫生和另一位有六年經驗的放射治療師審閱，他們審閱前並未知道病人的病理及其他臨床資料。按著在腫瘤信號增強部分的附近位置，利用T2高信號及無強化區域來介定瘤周區，從而量度此區的cho/NAA比值。如果瘤周區的cho/NAA比值大於1，表示病人有原發性腦腫瘤（陽性反應）。用2行2列表作統計學上的分析。一致性指數超越評分者信度，即得組內相關系數（alpha）。

結果：18位病人中，4位因瘤周區沒有腦水腫的情況而未被納入研究。餘下的14人中，9人經病理學資料證實為孤立性顱內高級別膠質瘤，其中8人瘤周區的cho/NAA比值大於1。另外5人有腦轉移瘤但未發現其原發性腫瘤。瘤周區的cho/NAA比值大於1可作為原發性腦腫瘤的一個預測指標；其敏感性為90%、特異性100%、陽性預測值100%和陰性預測值83%。

結論：瘤周區的cho/NAA比值大於1可以區分原發性腦腫瘤及腦轉移瘤。

INTRODUCTION

Primary intra-axial glioma and metastasis are the two most common malignant brain neoplasms in adults.[1] Differentiation of the two is sometimes feasible using a multiplicity of investigations and the clinical history. Nonetheless, in patients with solitary intra-axial brain tumours and no relevant clinical history, the diagnosis poses a challenge to radiologists. An accurate diagnosis is essential to guide further management. In most institutions, total tumour excision followed by adjuvant chemotherapy or radiotherapy is used to treat primary brain tumours, while a more conservative approach is adopted for brain metastasis. Conventional magnetic resonance imaging (MRI) and MR spectroscopy that only focuses on the enhancing portion of the tumour is unreliable as a means of differentiating the two disease entities.[2,3] With the advance of imaging techniques, perfusion-weighted MRI and MR spectroscopy focusing on the peri-tumoural area have been used in previous studies, which showed promising results for the above issue.[2,4-6]

To the best of our knowledge, the peri-tumoural choline/N-acetyl-aspartate (Cho/NAA) ratio is sparsely reported as a parameter to differentiate solitary intra-axial primary brain and brain metastasis. The aim of this study was to share our local experience and validate the use of this parameter. We focused on the high-grade gliomas, which encompass grade III and IV diseases according to the World Health Organization classification of astrocytomas.

METHODS

Participants

The MRI of patients aged more than 16 years presenting with solitary intra-axial cerebral lesions during the period from January 2007 to June 2007 were retrospectively reviewed. The review was done by two experienced radiologists. The reviews were conducted independently by an experienced neuroradiologist, and a fellow radiologist with six years' experience. They were blinded to each other's rating of the peri-tumoural Cho/NAA ratio, as well as to the demographic and clinical data pertaining to the respective patients. The demographic, operative, and pathology data were retrieved from the radiological information system and the electronic patient record system of the Hong Kong Hospital Authority.

Magnetic Resonance Imaging

All MRI was performed on a Siemens 1.5T (Avanto; Siemens, Germany) whole-body unit with a phased-array head coil. The MRI sequences were as follows: axial SE T2 (TR 4390 ms, TE 95 ms), axial SE T1 (TR 579 ms, TE 9.1 ms), post-contrast axial Flair (TI 2500 ms, TR 8500 ms, TE 109 ms), post-contrast MPRAGE (TR 1160 ms, TE 4.24 ms) and two-dimensional single-slice chemical shift imaging using an SE sequence (TR 1690 ms, TE 135 ms, PRESS localisation). The Voxel size was 10 x 10 x 15 mm with 5 mm slice thickness.

Statistical Analysis

The pathological findings served as the gold standard for the diagnosis of primary brain tumour (0 = absence, 1 = presence), whereas the consensus readings of the peri-tumoural Cho/NAA ratio was the tested variable. Peri-tumoural Cho/NAA ratio of ≥1 was regarded as an indicator of primary brain tumour and Cho/NAA ratio of <1 was indicative of its absence. The confidence intervals of sensitivity, specificity, and predictive values

of the peri-tumoural Cho/NAA ratio were derived using the 2 X 2 contingency table and a calculator available at http://faculty.vassar.edu/lowry/VassarStats.html. The interclass correlation coefficient (alpha) was calculated as the index of concordance exceeding chance for inter-rater reliability.

RESULTS

Characteristics of Participants

Because the definition of the peri-tumoural region was based on the cerebral oedema adjacent to the enhancing portion of the tumour, tumours without visible surrounding cerebral oedema were excluded from the study.

Of 18 adult patients who presented with solitary intra-axial cerebral lesions during the period January 2007 to June 2007, four were excluded due to non-detectable peri-tumoural white matter cerebral oedema. None of the participants had received treatment prior to their MRI. The mean age of the remaining 14 patients was 52 years, 10 (71%) were males. Of the 14 patients, 64% had a primary brain tumour, in nine of whom there was a histological diagnosis of glioma (glioblastic multiforme, grade IV, n = 7; anaplastic oligoastrocytoma, grade III, n = 1; mixed astrocystoma, grade III, n = 1) and five had metastases. The metastases were from bronchogenic carcinoma (n = 2), breast cancer (n = 1), colon cancer (n = 1), and oesophageal cancer (n = 1).

Reliability and Validity of Peri-tumoural Choline/N-acetyl-aspartate Ratio

The inter-rater reliability of the Cho/NAA ratio measurement yielded an alpha coefficient of 0.92. As shown in the Table, the peri-tumoural Cho/NAA ratio was ≥1 in eight out of nine patients who had histological confirmation of a primary brain tumour (sensitivity, 0.89; 95% confidence interval [CI], 0.51-0.99). All the patients in whom the Cho/NAA ratio rated <1 had metastatic brain lesions of known origin (specificity, 1; 95% CI, 0.46-1.00). Thus the positive predictive value was 1 (95% CI, 0.60-1.00) and the negative predictive value was 0.83 (95% CI, 0.36-0.99) [Figures 1 and 2].

Table. Validation of the peri-tumoural choline/N-acetyl-aspartate (Cho/NAA) ratio in differentiation of primary brain tumour from metastatic brain lesion.

Peri-tumoural Cho/NAA ratio	Histological diagnosis	
	Primary brain tumour (high-grade glioma)	Metastasis
≥1	8	0
<1	1	5

DISCUSSION

Brain metastasis and primary intra-axial gliomas are the two most common types of malignancy in adult patients.[1] They can usually be differentiated by their multiplicity and the clinical history. However, when solitary lesions are encountered in the absence of a relevant clinical history, they sometimes pose a challenge to both clinicians and radiologists. To the best of our knowledge, there is no technique that can reliably differentiate the two disease entities by conventional cross-sectional imaging. It is well-documented in the literature that even MR spectroscopy, if focusing only on the enhancing portion of the tumour, is not completely reliable in differentiating primary intra-axial glioma from brain metastasis.

Nowadays, people have shifted the area of interest from enhancing tumour portion to the peri-tumoural area. The relative cerebral blood flow, mean diffusivity, spectroscopic metabolite levels, and abnormal fluid-attenuated inversion recovery signal in the peri-tumoural area provide promising results in this respect. This approach was based on the hypothesis that there could be different types of surrounding cerebral oedema with primary intra-axial gliomas and brain metastasis.[2,4]

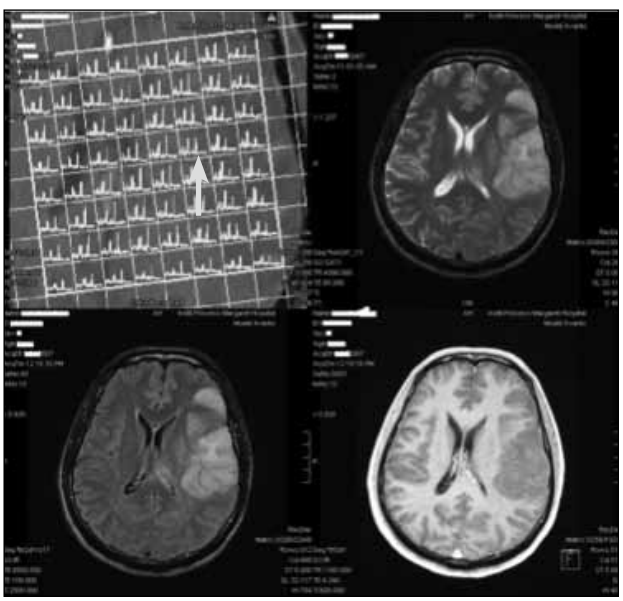

Figure 1. Chemical shift imaging, selected axial T2-weighted, fluid-attenuated inversion recovery with contrast and T1 with contrast images of a young male patient with pathologically proven glioma. The choline/N-acetyl-aspartate ratio in the peri-tumoural cerebral oedema is >1. Arrowed is the voxel used for interpretation.

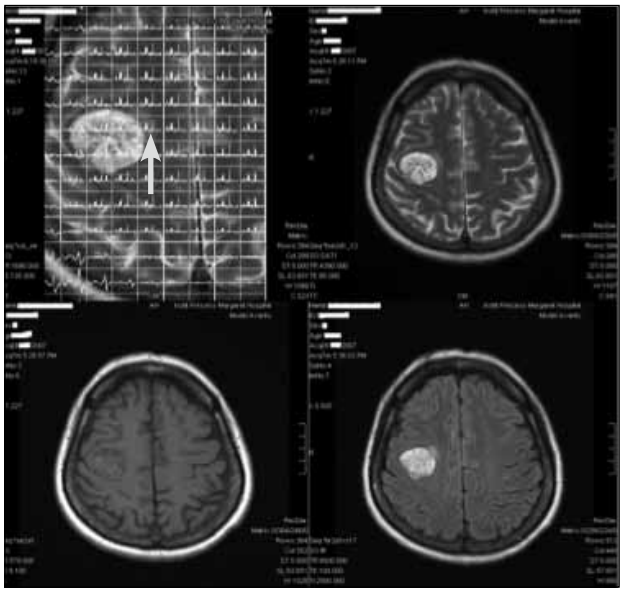

Figure 2. Chemical shift imaging (CSI), selected axial T2-weighted, fluid-attenuated inversion recovery with contrast and T1 with contrast images of a female elderly patient with renal cell carcinoma. The choline/N-acetyl-aspartate ratio in the peri-tumoural cerebral oedema is <1. Arrowed is the immediate peri-tumoural cerebral oedema and its corresponding CSI is used as interpretation.

In this study, we tried to review the characteristics of the metabolite pattern in MR spectroscopy of the peri-tumoural region of these two disease entities. NAA is a metabolite normally found in neurons. When normal neurons are destroyed by a neoplasm, the level of NAA decreases.

Choline is a marker for cell membrane turnover by tumour growth and cell destruction. Therefore, its level is high in malignant neoplasms.[7] In the case of primary intra-axial glioma, the peri-tumoural regions are believed to be infiltrated by tumour cells and thus the phenomenon of high choline with low NAA levels.

While in the case of brain metastasis, the peri-tumoural regions consist of just vasogenic oedema without tumour cells infiltration. Therefore, they do not yield high choline and low NAA levels.[8,9]

In this study, the peri-tumoural Cho/NAA ratio used to differentiate primary or secondary intra-axial brain lesions had a sensitivity of 0.89 (95% CI, 0.51-0.99). Its specificity was 1 (95% CI, 0.46-1.00), the positive predictive value was 1 (95% CI, 0.60-1.00), and the negative predictive value was 0.83 (95% CI, 0.36-0.99). These results imply that this parameter is an appropriate tool for this purpose.

The specificity of this parameter was very remarkable. However, the 95% CI was in a wide range (0.46-1.00), which we believe was due to the small sample size. This study can therefore be a regarded as a pilot project and a further study with a larger sample size should be carried out. Another limitation was that patients diagnosed to have brain metastases were not proven by histology. However, there is general consensus that brain metastasis is the most common intra-axial lesion, especially in patients with known primary tumours.[10,11]

CONCLUSION

A solitary intra-axial brain lesion without relevant clinical history can sometimes pose a diagnostic dilemma for the radiologist relying on the conventional MRI sequences. Peri-tumoural Cho/NAA ratio can be used as a relatively sensitive and specific parameter to differentiate the two disease entities.

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