

The Detection Of Elevated Choline Metabolite In Magnetic Resonance Spectroscopy To Differentiate Between Benign And Malignant Bone Tumor

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Abstract

Objective: This study was aimed to determine the accuracy of elevated choline metabolite in Magnetic Resonance Spectroscopy (MRS) at bone tumor to differentiate between benign and malignant according to their pathology result.

Materials and Methods: A retrospective study of 40 samples consisted of benign and malignant bone tumor patients who met the inclusion criteria, who had MRS examination from January 2019 to January 2020. Elevated choline metabolite was used to differentiate between benign and malignant lesions based on their pathological result. From this study, we got sensitivity value, specificity value, PPV(positive predictive value), NPV(negative predictive value) and accuracy value.

Results: The total number of patients were 40 who had bone tumor. The 11 benign tumors, consisted of 8 giant cell tumors (GCT), 1 aneurysmal bone cyst (ABC) and 2 abscesses on MRS the 7 of 8 GCTs and 1 ABC did not show elevated choline metabolite in MRS. One GCT and 2 abscesses showed elevated choline metabolite in their respective MRS. The 29 malignant cases consisted of 19 osteosarcomas, 2 chondrosarcomas, 2 plasmacytomas, 1 malignant GCT and 5 metastatic bone diseases. All but one case did not show elevated choline metabolite in their MRS and that was osteosarcoma.

Conclusion: Elevated choline metabolite of proton MRS have higher sensitivity, specificity, PPV, NPV and accuracy to differentiate between benign and malignant bone tumor according to pathological result.

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Keywords: Choline metabolite; Magnetic Resonance Spectroscopy (MRS); sensitivity; specificity; PPV(positive predictive value); NPV(negative predictive value); accuracy; benign and malignant bone tumor.

1. Background

Bone tumor is a neoplastic growth of tissue in bone. Abnormal growths found in the bone can be either benign (noncancerous) or malignant (cancerous). Malignant tumors can spread by invasion and metastasis, whereas benign tumors cannot and remain localized. One of the hallmarks of cancer cells is their ability to grow and divide without undergoing senescence (Abeloff MD, 2007).

In malignant bone tumors, tumor cell invasion into normal tissue occurs where tumor cells secrete specific tumor growth factors that damage the normal tissue cell membrane causing a turn over of the cell membrane. The cell membrane consists of phospholipids so that the metabolism of phospholipids occurs. Phosphatidylcholine which is a phospholipid component of the cell membrane undergoes catabolism to produce choline (Cho) and choline (Cho) undergoes anabolism to produce phosphocholine (PC). Malignant bone tumors there is an increase in choline (Cho) and phosphocholine (PC) at the cellular level (Ty K.

Subhawong X. W., 2011).

Elevated choline concentration in tumors is believed to be primarily due to the accumulation of phosphocholine resulting from increases in the activity of choline kinase which change choline to phosphocholine and phospholipase which change phosphatidylcholine to choline level (Ty K. Subhawong X. W., 2011).

MRS is a modality of MRI examination to assess biochemical processes in the musculoskeletal system. MRS is a non-invasive imaging technique that does not require intravenous contrast administration and can be combined with the anatomical imaging of conventional MRI sequences (Laura M. Fayad M. A., 2012).

MRS protons can be translated into pixel intensity maps based on relative signals from metabolites (water, choline, and lipids), using multi-voxel or single voxel techniques. The advantages of the single-voxel technique are simple, fast acquisition time, and easy placement of the region of interest (ROI) (Ty K. Subhawong X. W., 2011).

The MRS proton detects signals from metabolites in the ROI and provides metabolic information that can be used for evaluation of suspected tumors. Since certain metabolites are elevated in a malignant lesion, MRS has the potential to non-invasively differentiate between malignant and benign lesions. (Fayad LM B. P., 2007).

However, bone tumors with a high degree of malignancy tend to have a complex composition of viable cells, bleeding components, and large necrotic areas. With such a complex and heterogeneous composition, biopsy often does not find representative or adequate specimens (Drapé, 2013).

Regardless of its benefit in bone lesion evaluation, whether accuracy elevated choline metabolite in MRS can differentiate between benign or malignant bone lesions is still controversial. Therefore, this study was aimed to determine the accuracy of elevated choline metabolite in Magnetic Resonance Spectroscopy (MRS) at bone tumor to differentiate between benign and malignant according to their pathology result.

2. Methods

2.1 Patients

This was a cross-sectional study, with retrospective design. The sample size was 40 [20 males, 20 females; age range 11-74 years old (mean $30,11 \pm 17,52$ y.o)]. Obtain within study period, which was January 2019 until January 2020. The population was all bone lesion that had been examined with magnetic resonance spectroscopy. The inclusion criteria was the bone lesion which has pathology examination result. The exclusion criteria was no bone tumor signal was detected on MRI examination, tumors smaller than $2 \times 2 \times 2$ cm³ (voxel size) and no spectroscopy were made on examination.

2.2 MRI Protocols

The examination uses the Siemens Magnetom Skyra 3 Tesla MRI machine. The protocol used was sequence: single voxel spectroscopy; TR: 2000 ms; TE: 135 ms; Acquisition time: 4 minutes 26 seconds; Voxel size: $2 \times 2 \times 2$ cm³ was placed in the solid lesion area that was most suspected of being correlated with the hyperintensity signal at T1WI sequence with contrast and T2WI.

2.3 Choline Elevation

There was an accumulation of phosphocholine (PC) and choline which on spectroscopy of choline metabolite was detected as a total choline value at 3.2 ppm compared to pathological results on structural changes so that bone tumors can be differentiated into benign or malignant (Ty K. Subhawong X. W., 2011).

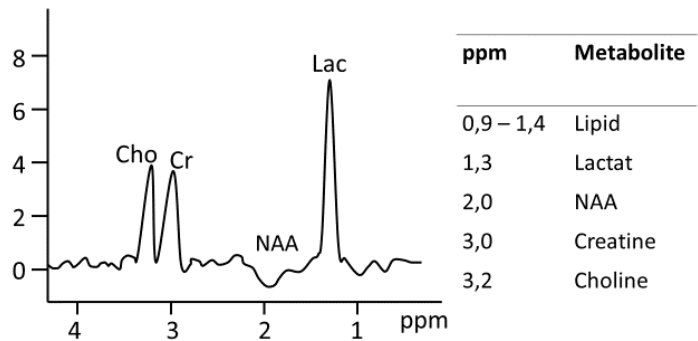


Fig.1. Graph showed protons in different molecules resonate at different frequencies, which are mapped to specific location in parts per million (ppm). Choline (metabolite marker for malignancy) had peak at approximately 3.2 ppm

2.4 Data Analysis

This analysis is used to explain the calculation of sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value) and diagnostic accuracy values of elevated choline metabolite in MRS at bone tumors to differentiate between benign and malignant according to their pathology result.

3. Results

In this study there were 11 samples with benign bone tumors (27.5%) consisted of 8 samples (20%) with giant cell tumor (GCT), 1 sample (2.5%) with aneurysmal bone cyst, and 2 samples (5%) with abscess. 7 samples with GCT and 1 sample with ABC did not show elevated choline metabolite. 3 samples consisted of 1 sample with GCT and 2 samples with abscess showed elevated choline metabolite. There were 29 samples with malignant bone tumors (72.5%) consisted of 19 samples (47.5%) with osteosarcoma, 2 samples (5%) with chondrosarcoma, 2 samples (5%) with plasmacytoma, 1 sample (2.5%) with malignant giant cell tumor and 5 samples (12.5%) with metastatic bone disease. 28 samples consisted of 18 samples with osteosarcoma, 2 samples with chondrosarcoma, 2 samples with plasmacytoma, 1 sample with malignant giant cell tumor and 5 samples with metastatic bone diseases showed elevated choline metabolite. One sample with osteosarcoma did not show elevated choline metabolite.

Table 1. Distribution of bone Tumors Analyzed With Proton MR Spectroscopy

Pathological Examination Result	Number of cases	
	Total (Percentage)	Elevated choline Present
Osteosarcoma	19 (47,50%)	18
Chondrosarcoma	2 (5,00%)	2
Plasmacytoma	2 (5,00%)	2
Malignant giant cell tumor	1 (2,50%)	1
Metastatic bone disease	5 (12,50%)	5
Giant cell tumor	8 (20,00%)	1
Aneurysmal bone cyst	1 (2,50%)	0
Abscess	2 (5,00%)	2
Total	40 (100%)	31

Table 2. Spectroscopy diagnostic performance

MR Spectroscopy		Pathological Examination Result		
		Malignant	Benign	Total
Choline Metabolite	Elevated	28	3	31
	Non elevated	1	8	9
Total		29	11	40

Analysis of qualitative elevated choline metabolite MRS assessment at bone tumor demonstrated 96 sensitivity, 73% specificity, 90% PPV (positive predictive value), 89% NPV (negative predictive value), and 90% accuracy for the presence of elevated choline metabolite as a predictor of malignancy.

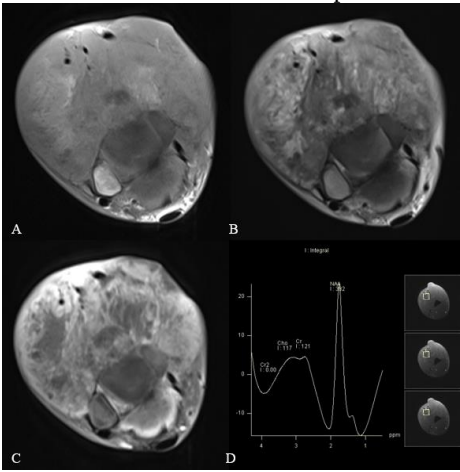


Fig. 2. A 14-years-old male. Right femoral MRI (A) Axial T1WI; (B) Axial T2WI; (C) Axial T1WI with contrast; (D) Spectroscopy showing elevated choline metabolite at 3,2 ppm confirmed pathological examination result with osteosarcoma.

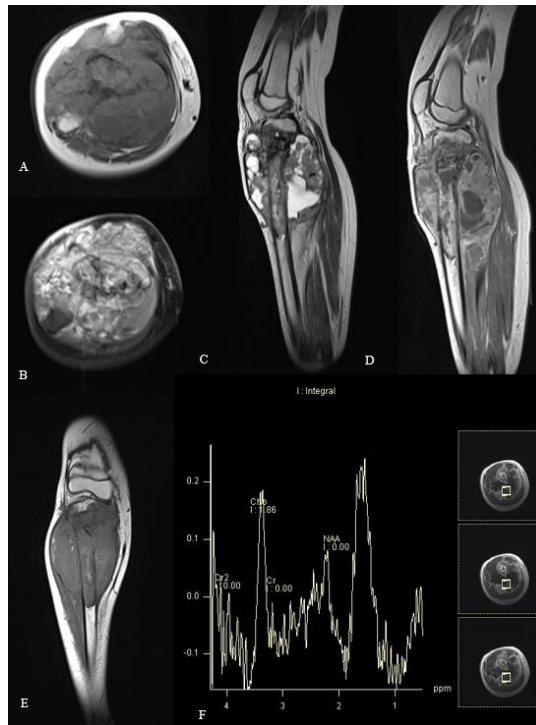


Fig. 3. A 14-years-old female. Left tibial MRI (A) Axial T1WI; (B) Axial T1 fatsat with contrast; (C) Sagittal T2WI; (D) Sagittal T1WI with contrast; (E) Coronal T1WI; (F) Spectroscopy showing elevated choline metabolite at 3,2 ppm confirmed pathological examination result with osteosarcoma.

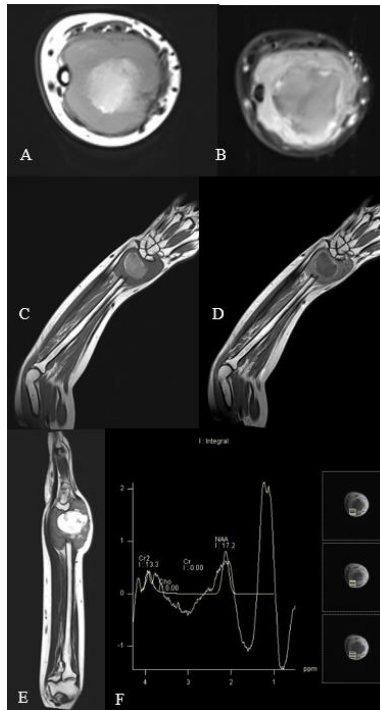


Fig. 4. A 22-years-old female. Right forearm MRI (A) Axial T1WI; (B) Axial T1WI with contrast; (C) Sagittal T1WI; (D) Coronal T1WI with contrast; (E) Sagittal T1WI; (F) Spectroscopy no elevated choline metabolite at 3,2 ppm confirmed pathological examination result with giant cell tumor.

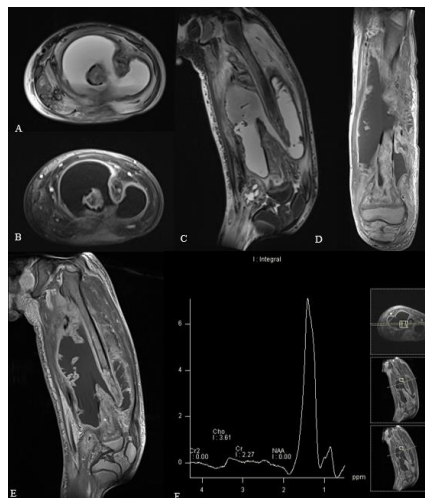


Fig. 5. A 13-years-old male. Left femoral MRI (A) Axial T2WI; (B) Axial T1WI with contrast; (C) Sagittal T2WI; (D) Sagittal T1WI with contrast; (E) Sagittal T1WI with contrast; (F) Spectroscopy showing elevated choline metabolite at 3,2 ppm confirmed pathological examination result with abscess

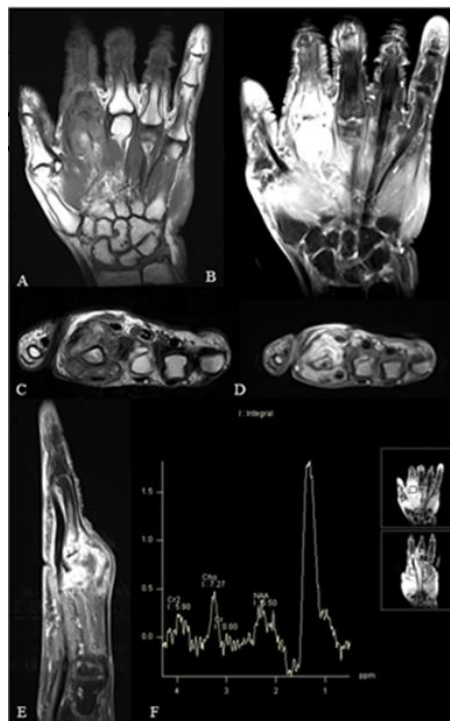


Fig 6. A 74-years-old female. Right hand MRI (A) Coronal T1WI; (B) Coronal T1WI with contrast; (C) Axial T2WI; (D) Axial T1WI with contrast; (E) Sagittal T1WI with contrast; (F) Spectroscopy showing elevated choline metabolite at 3,2 ppm confirmed pathological examination result with abscess.

4. Discussion

Proton MRS provides noninvasive biochemical evaluation of tumors. Various metabolites present in human tissues have specific precession frequencies, and the amplitude of these frequencies in MRS is proportional to the metabolite concentration. In MSK oncology, choline metabolite compounds have been studied as markers of tumor aggressiveness. Choline metabolite compounds participate in the formation of the phospholipid structure of cellular membranes and are elevated in tumors with a high mitotic rate (Pedro A. Gondim Teixeira, 2015).

In this study, we found elevated choline metabolite had 96 % sensitivity, 73% specificity, 90% PPV (positive predictive value), 89% NPV (negative predictive value), and 90% accuracy for the presence of elevated choline metabolite to differentiate between benign and malignant bone tumor.

Benign tumors were 2 of 2 abscesses showed elevated choline metabolite, this similar to study by Chien-Kuo Wang, et al (2004) 1 of 1 abscess and Ty K. Subhawong X.W, et al (2012) 1 of 1 abscess due to abundance of inflammatory cells in the wall of abscess. However elevation of choline metabolite at abscess not as high as malignant bone tumor. 1 of 8 GCT showed elevated choline metabolite, this similar to study by Chien-Kuo Wang, et al (2004) 1 of 3 GCT, QI Zi-hua, et al (2009) 1 of 5 GCT, Ty K. Subhawong X.W, et al (2012) 6 of 16 GCTs and Jing Zhang, et al (2013) 4 of 20 GCTs showed elevated choline metabolite due to locally aggressive. Abscess and GCT were showed elevated choline metabolite and also showed lower specificity value at study by Chien-Kuo Wang, et al (2004), QI Zi-hua, et al (2009), Ty K. Subhawong X.W, et al (2012) and Jing Zhang, et al (2013) were 82%, 83%, 68% and 88% respectively.

Malignant tumors were 1 of 19 osteosarcoma did not show elevated choline metabolite, this similar to study by Ty K. Subhawong X.W, et al (2012) 2 of 14 osteosarcomas, Jing Zhang, et al (2013) 7 of 17 osteosarcomas did not show elevated choline metabolite due to tumor contained extensive necrotic tissue, and hemorrhage, where even though the voxel had been placed on a solid area there was no elevated choline

metabolite. Osteosarcoma was showed non-elevated choline metabolite and also showed lower sensitivity value, NPV and accuracy value at study by Ty K. Subhawong X.W, et al (2012) had 88% sensitivity, 86% NPV (negative predictive value), 76% accuracy and study by Jing Zhang, et al (2013) had 76% sensitivity, 73% NPV (negative predictive value), 82% accuracy.

The pitfall were one GCT and two abscesses that showed choline elevation and one osteosarcoma did not show choline elevation.

So, further research is still needed to determine the reproducibility of MRS in the bone tumor and definitively elucidate its clinical applications.

The future implication of this study are to monitor treatment response and evaluate postoperative assessment of resected tumors for determination of the presence of residual or recurrent disease (Ty K. Subhawong X. W., 2012).

Using an acquisition approach to determine the presence or absence of elevated choline metabolite in bone and soft-tissue tumors in vivo, we found a strong relationship between proton MR spectroscopic and histopathologic findings.

There is limitation of the study, regarding to this retrospective study, so there were some voxel placement in the area of necrotic or bleeding in tumors, it is resulting there is non-elevated choline metabolite, so its important to control for confounding factor.

5. Conclusion

Elevated choline metabolite could be detected in bone tumors or tumor-like lesions in vivo by using a MRS. We could differentiated between benign and malignant in 40 samples bone tumors based on the elevated choline metabolite with the higher sensitivity, specificity, PPV, NPV and accuracy of proton MR spectroscopy.

The information provided with proton MR spectroscopy may complement other findings, such as adjacent bone invasion and may improve accuracy detection of elevated choline metabolite to differentiate between benign and malignant bone tumor.

6. Acknowledgment

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