

Single voxel ¹H magnetic resonance spectroscopy in the diagnosis of musculoskeletal mass lesions

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ABSTRACT

Introduction: *In vivo* magnetic resonance spectroscopy (MRS) is an established technique for evaluation of malignant tumors in brain, breast, prostate, etc.,. However, its efficacy in the diagnosis of musculoskeletal (MSK) mass lesions is yet to be established. We present our experience with MRS of these lesions. **Materials and Methods:** Magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI and single-voxel ¹H MRS was performed in 30 consecutive patients with histologically proven benign and malignant MSK tumors/mass lesions each, on a 1.5-T magnetic resonance scanner. MRS was performed with echo times (TE) of 40, 135 and 270 ms. A clearly identifiable peak at 3.2 ppm in at least two of the three spectra acquired at the three TE was taken as positive for choline. MRS imaging and enhancement patterns were compared in these two groups and were analyzed by a Radiologist blinded to the histopathological findings. **Results:** Ages of patients in the malignant age group ranged from 2 to 65 years (M: F - 19:11) while that of patients in the benign group ranged from 7 months to 56 years (M: F - 17:13). There were two patients with Type I curve, 18 with Type II curve and 10 with Type III curve on dynamic contrast enhanced images in the malignant group while there were no patients with Type I curve, 5 with Type II curve and 25 with Type III curve in the benign group. The sensitivity of MRS for predicting malignancy was 60%, specificity was 93.33%, positive predictive value was 90%, negative predictive value was 70% and accuracy was 76.66%. **Conclusion:** MRS is a promising technique for evaluation of MSK mass lesions. The accuracy at present remains low. We recommend that it be used as an adjunct to routine MRI.

Key words: Dynamic contrast enhanced imaging, magnetic resonance imaging, soft-tissue tumors, spectroscopy

INTRODUCTION

Magnetic resonance imaging (MRI) is the modality of choice for evaluation of musculoskeletal (MSK) mass lesions the world over. The differentiation between benign and malignant masses on MRI is based mainly on the evaluation of morphological parameters such as size, demarcation of margins, involvement of adjacent vital structures, signal homogeneity, measurements of relaxation times and contrast enhancement.^[1-3] It did not however, live up to

the expectations as a diagnostic tool which could be used for histologic classification of these lesions because of high contrast resolution. Various studies have consistently demonstrated low sensitivity of MRI for grading tumors.^[3]

Magnetic resonance spectroscopy (MRS) is being used as an adjunct to MRI in the evaluation of various tumors particularly that of brain, breast and prostate cancers and has been shown to improve diagnostic accuracy and specificity. The level of choline containing metabolites (in particular phosphocholine) is elevated in the malignant tumors related to these organs. The degree of choline rise has been found to be related to the histologic aggressiveness of the tumor as it is thought to play an important role in cancer progression, invasion and metastasis. Its reappearance after radiation therapy is useful in detecting tumor recurrence.^[4] However, the elevated levels of choline on MRS is not a tumor-specific marker as it has also been shown in non-neoplastic lesions and benign tumors.

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Very few authors have studied the role of ¹H MRS in the evaluation of MSK mass lesions.^[5,6] MRS detection of elevated choline peak was reported to be 95% sensitive in differentiating benign from malignant musculoskeletal tumors by Wang *et al.*^[5] We undertook this prospective study to evaluate the role of dynamic contrast enhanced MRI features and ¹H MRS in the diagnosis of these lesions.

MATERIALS AND METHODS

MRI, dynamic contrast-enhanced MRI and Single-voxel ¹H MRS was performed in 30 consecutive patients with histologically proven benign and malignant MSK mass lesions each, on a 1.5-T whole-body MRI system (Gyrosan Intera; Philips, Best, the Netherlands). Approval of the ethical committee and institutional board of studies was taken to perform this study and informed consent was taken from all the patients.

MRI was performed in all patients in axial, sagittal and coronal plane using T1-weighted turbo spin echo sequence (repetition time/echo time [TR/TE]; 500/15, matrix 400 × 400, reconstruction 512 × 512, three signals were acquired), T2-weighted turbo spin echo sequence (TR/TE; 3780/100, matrix 400 × 400, reconstruction 512 × 512, three signals were acquired) and fat suppressed images (spectral presaturation with inversion recovery) short T1 inversion recovery (TR/TE; 6240/100; matrix 352 × 352, reconstruction 512 × 512). Slice thickness, field of view, section thickness and intersection gap varied depending on the size of the lesion.

Dynamic contrast enhanced images were obtained using 3D T1-weighted gradient-echo sequence (TR/TE; 3.2/1.13, flip angle 35, one signal acquired, total sequence time 3 min) after the injection of 0.1 mmol/kg of body weight of gadopentetate di-meglumine (Magnevist; Schering [now Bayer health-care] Berlin, Germany) injected at 2 mL/s (using MR-compatible power injector [Spectris; Medrad, Pittsburgh, Pa]) followed by 20-mL normal saline. Each dynamic scan lasted no longer than 8 s and the entire lesion was covered during the scan. Signal intensity was obtained by placing the region of interest in the early enhancing portion of the tumor and it was plotted against time with a resulting time-signal intensity curve described below. The delayed contrast-enhanced images were then obtained.

Type I curve: Maximum signal intensity was achieved rapidly after contrast agent administration followed by a gradual decrease (washout).

Type II curve: Rapid initial enhancement was followed by a plateau phase or sustained late enhancement.

Type III curve: Gradual increase or no increase in signal intensity was seen until the end of dynamic imaging.

MRS was performed using the point-resolved spectroscopic sequence with TE of 40, 135 and 270 ms and time of repetition as 2000. Volume of interest (VOI) was carefully placed to include early enhancing areas of the tumors. In case of no enhancement the VOI was placed to fit the lesion. The data was acquired at a spectral width of 1000 Hz and 128 signals were acquired. Choline was said to be present when there was a clearly identifiable peak at 3.2 ppm in at least two spectra acquired at different TEs. The signal-to-noise (SNR) ratio of the apparent choline peak at 3.2 ppm (defined as the ratio of amplitude of choline peak to the amplitude of the baseline noise measured at a signal-free region of the spectrum) was measured whenever there was a doubt as to the presence of choline. Choline was said to be present if the SNR was greater than two.

MRS imaging and enhancement patterns were compared in these two groups and were analyzed by a radiologist blinded to the histopathological findings.

Statistical analysis

The true positive, true negative, false positive and false negative values were counted to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of MRS. Chi-square test and Fisher test were used to analyze the curves obtained after dynamic contrast enhanced imaging. *P* < 0.001 was considered to be significant.

RESULTS

Ages of patients in the malignant age group ranged from 2 to 65 years (M: F-19:11), while that of patients in the benign group ranged from 7 months to 56 years (M: F-17:13). There were two patients with Type I curve, 18 with Type II curve and 10 with Type III curve on dynamic contrast enhanced images in the malignant group while there were no patients with Type I curve, 5 with Type II curve and 25 with Type III curve in the benign group. The sensitivity of MRS for predicting malignancy was 18/30 (60%), specificity was 28/30 (93.33%), PPV was 18/20 (90%), NPV was 28/40 (70%) and accuracy was 46/60 (76.66%).

In the malignant group, there were spindle cell ca; 03, lymphoma; 03, fibrosarcoma; 04 (01 was a recurrent tumor and 01 was a case of inflammatory fibrosarcoma), myxoid liposarcoma; 01, osteosarcoma; 04, ewings sarcoma; 03 (02 were recurrent tumors and 01 was a case of soft-tissue tumor), malignant nerve sheath tumors; 02, squamous cell ca; 01, synovial cell ca; 01, rhabdomyosarcoma; 01, Papillary cell cystadenosarcoma of the ovary infiltrating into

soft-tissue; 01, high grade anaplastic undifferentiated sarcoma; 02 [Figure 1], well differentiated mesenchymal malignant tumor revealing myxoid and chondroid differentiation; 01, reticulum cell ca; 02, metastasis; 01 [Figure 2].

Choline peak was negative in: Well-differentiated mesenchymal malignant tumor revealing myxoid and chondroid differentiation; 01, Reticulum cell ca; 02, ewings sarcoma (Out of these one cases was of recurrent tumor); 02, Spindle cell ca; 01, Osteosarcoma; 04, squamous cell carcinoma; 01, myxoid liposarcoma; 01 [Figure 3]. The first case revealed a Type III curve. Patient with recurrent ewings revealed a Type III, while the other revealed a Type II curve. Both patients with reticulum cell carcinoma and patient with squamous cell carcinoma revealed Type II curve and patient with myxoid liposarcoma revealed a Type III curve.

In the benign group, there were patients with abscess; 04 (one patient had a fungal abscess), osteomyelitis; 01, bursitis; 01, cystic hygroma; 01, aneurysmal bone cyst; 01, giant cell tumor (GCT); 04 (one patient had recurrent soft-tissue GCT), neurogenic tumor; 06, juvenile aponeurotic fibroma; 01, fibroma; 01, desmoids tumor; 02, hamartoma; 01, humeral lipoma; 01, fibrolipoma; 02 [Figure 4], hypertrophid scar; 01, leiomyoma; 01, fibromatosis; 01, lipoma; 01. Choline peak was seen in two patients of GCT. These revealed a Type I curve [Figure 5] and Type III curve each.

The distribution of the various curves is shown in Table 1. Findings were significant for Type III curve for benign lesions and Type II curve for malignant lesions.

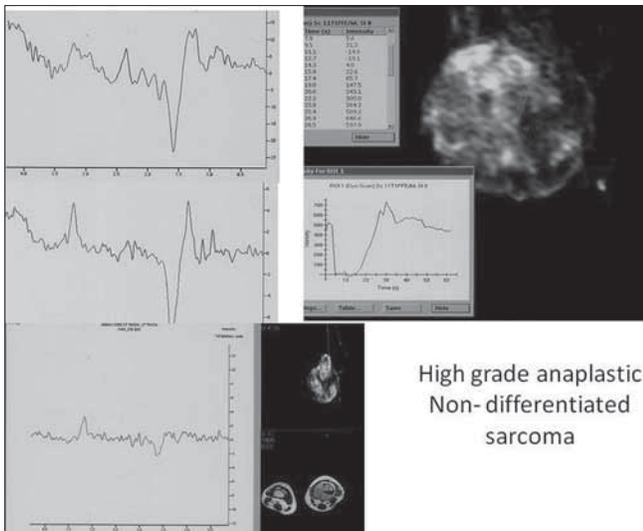


Figure 1: High grade anaplastic undifferentiated sarcoma in a 18-year-old female involving lower metaphysis of left femur. Choline peak was seen on all three spectra i.e. 40 echo time (TE) (top right) both 135 TE (middle right) and 270 TE (bottom right). Dynamic contrast enhanced magnetic resonance imaging revealed a Type I curve (top left)

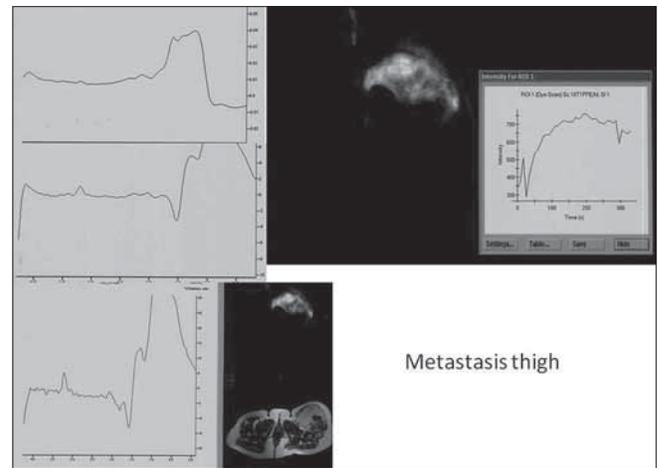


Figure 2: Metastasis left thigh in a 40-year-old female with carcinoma breast. Choline peak is seen on both spectra at 135 echo time (TE) (middle right) and 270 TE (bottom right). Dynamic contrast enhanced magnetic resonance imaging revealed a Type II curve

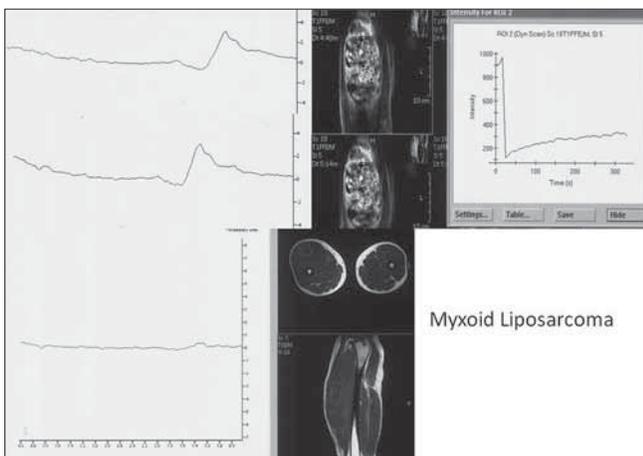


Figure 3: Myxoid liposarcoma in a 45-year-old male. No choline peak was visualized in any of the spectra. Dynamic contrast enhanced magnetic resonance imaging revealed a Type III curve

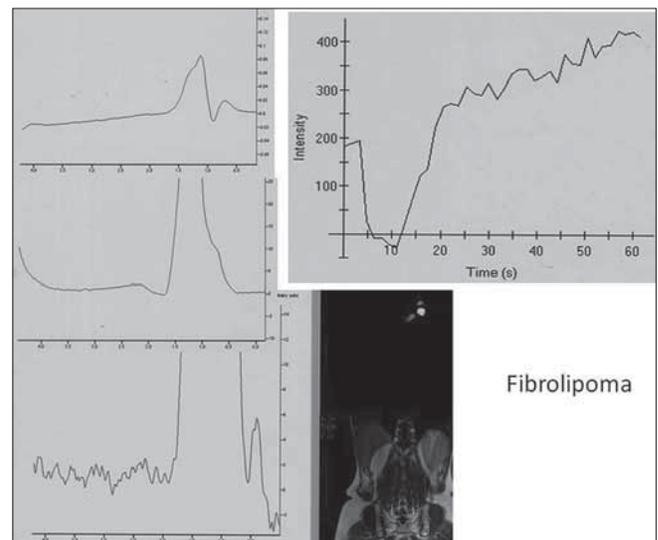


Figure 4: Fibrolipoma of the back in a 52-year-old female. No choline peak was visualized in any of the spectra. Dynamic contrast enhanced magnetic resonance imaging revealed a Type III curve

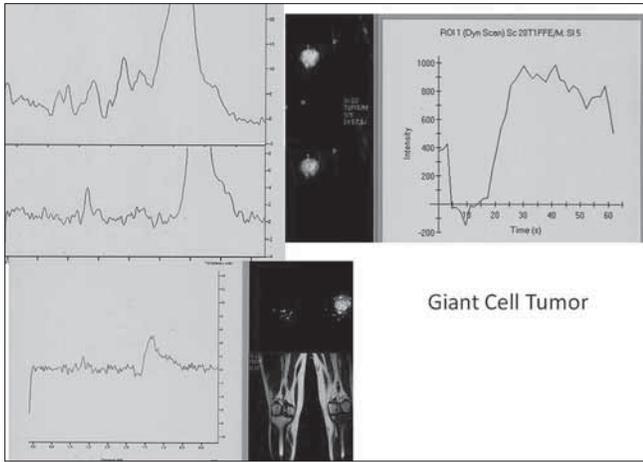


Figure 5: Giant cell tumor of the upper epiphysis of the left tibia in a 23-year-old female. Choline peak was seen in spectra at 135 echo time (TE) and 270 TE. Dynamic contrast enhanced magnetic resonance imaging revealed a Type I curve

Table 1: Distribution of the types of curves in relation to the types of lesions

Type of mass lesion/tumor	Types		
	I curve	II curve	III curve
Benign	0	5	25
Malignant	2	18	10

DISCUSSION

The diagnostic accuracy of MRI for detecting soft-tissue tumors reveals a wide range of 34-90%; even though, efforts are being made consistently to improve it.^[7-9] A variety of grading parameters including origin, size, shape, margins, signal homogeneity, changing pattern of homogeneity, contrast enhancement, low signal intensity septations, hemorrhage, peritumoral edema, distribution and growth rate, have been described in the literature.^[10] However, all these signs reveal low sensitivity and specificity.

Proton MRS provides a unique insight into the biochemical profile of tissues *in vivo*. A choline peak at 3.2 ppm seen in various malignancies consists of phosphocholine, phosphatidyl choline, glycerophosphocholine and free choline, which are markers of cellular proliferation and membrane turnover. These are not associated with malignancy *per se*.^[15,11] However, choline peak on MRS continues to be considered a useful marker of malignancy.

A wide range of benign breast lesions, including chronic inflammatory lesions with atypia, atypical ductal hyperplasia, fibroadenoma, fibrocystic disease, etc., may occasionally show a choline peak on MRS.^[12,13] Physiologic increase has also been described in breasts of lactating mothers and in brains of neonates. Similarly, benign tumors of the brain may also show raised choline levels. MRS of the brain in tuberculomas, fungal granulomas,

adrenoleukodystrophy, post-traumatic cognitive disorders, the subacute phase of global hypoxic-ischemic injury, progressive multifocal leukoencephalopathy, demyelinating lesions, etc., can show a choline peak. Hence, the accuracy of MRS remains low.^[5,14]

Wang *et al.*^[5] found that 18 of 19 malignant soft-tissue tumors and 3 of 17 benign tumors displayed the choline (Cho) peak. Choline was found in three benign lesions, including one perineurinoma, one GCT and one abscess. Choline was not detected in one parosteal osteosarcoma. They concluded that differentiation of benign from malignant musculoskeletal tumors is possible with high accuracy based on the presence or absence of choline metabolites. Russo *et al.*^[15] performed a similar kind of study and found sensitivity and specificity of 95% and 83% respectively. They studied the lesions at a TE of 150 ms and found no choline peak in a patient of dermatofibrosarcoma. It was however, present in 03 benign lesions, which were desmoids tumor, myositis ossificans and an eccrine spiradenoma.

Zhou *et al.*^[6] found a lactate peak in musculoskeletal tumors, which was at 1.33 ppm and double peaks. It reflects quick growth of malignant tumors, more anabolic metabolism and the accumulation of lactic acid because of damaged transport system. However, they did not agree that the lactate was related to the malignant grade, which was the same as the research about brain tumors. We did not find lactate peak in any of our tumors probably because VOI was placed on the early enhancing portion of the tumor.

Angiogenesis plays a central role in the growth and spread of tumors and this is adequately demonstrated by dynamic contrast-enhanced MRI. Rapid wash-in and washout of contrast material (Type I curve) is the hallmark of most malignancies including breast and soft-tissue tumors.^[16,17] It has been demonstrated that overall there is a correlation between choline metabolism and dynamic MRI findings because cell replication (reflected in choline levels) requires angiogenesis to support tumor growth.^[18] Although most of the malignant bone tumors reveal a Type I curve, exceptions have been described with a number of benign tumors such as aneurismal bone cyst, osteoblastoma, GCT, etc., which are also associated with this type of curve. Due to this lack of specificity dynamic contrast-enhanced MRI is no longer considered useful in differentiating benign from malignant tumors.^[17] There were however, no patients with benign tumors showing this Type I curve in our study. In our study, two of patients with GCTs revealed choline peak possibly due to rapid cell growth and angiogenesis. These revealed Type I and Type III curve each. 12 patients with benign GCTs studied by Sah *et al.*^[14] revealed elevated choline levels in four and out of these three revealed aggressive appearance on radiographs. In their study, 11 out of 12 patients revealed

a Type I curve and hence they concluded that raised choline level in a tumor was a relatively more specific marker of malignancy than a Type I curve.

There were three patients, which revealed a false positive result in the study by Wang *et al.*^[5] and these included one perineurioma, one GCT and one abscess. There was one false negative result in their study and this was a patient with parosteal osteosarcoma. Patients with perineurioma and GCT revealed hypervascularity and hypercellularity on histopathology. While the patient with abscess revealed abundance of inflammatory cells in the wall of the abscess. The two patients of GCT in our study with raised choline peak also revealed a more aggressive appearance with hypervascularity and hypercellularity. Furthermore, one patient each with neurogenic tumor, bursitis and an abscess revealed a choline peak in only one spectra i.e. at 270 TE, 135 TE and 40 TE respectively.

The malignant tumors in our study which revealed no choline peak were better differentiated compared with the other tumors in this group. All four osteosarcomas were of osteoblastic variety and predominantly consisted of neoplastic bone. In two of the other tumors from the malignant group it could have been due to myxoid and chondroid elements.

The position of VOI is determined with dynamic contrast-enhanced images and it is placed on early enhanced regions inside the lesions. According to van der Woude *et al.*^[17] this early enhanced region represents areas of high biologic activities with increased cellularity, cell turn over time and neovascularity. In malignant tumors, these areas are likely to contain more choline-containing compounds. The VOI in our patients was also placed on early enhancing portions of the tumor as determined by dynamic contrast enhanced MRI.

A small voxel size i.e., <1 cm³ cannot be used for *in vivo* ¹H MRS with 1.5-T MR imager, as the decreased SNR makes interpretation of spectra difficult. The 3.0-T MR imager increases SNR and hence can be used to acquire reliable spectra from smaller lesions. All the tumors included in this study were larger than 1 cm³ and attempts were made to avoid the necrotic portions in the lesions as diagnosed by MRI images.

The spectral baseline was more stable at 40 TE with noise being the maximum at 270 TE. The height of the choline peak was also maximum at 270 TE. A ratio of two used by us to differentiate choline peak from noise was also used by Sah *et al.*^[14]

Limitation of this study is that a heterogenous group of lesions has been studied i.e. metastasis and osteosarcoma on

one hand and abscess and bursitis on the other. Hence, no definite conclusion can be drawn regarding a single disease entity. Wang *et al.*^[19] studied 210 consecutive MSK lesions larger than 1.5 cm in diameter and evaluated the various factors that might affect the diagnostic accuracy of *in vivo* ¹H MRS at 1.5-T MR scanner using a TE of 135 ms. They found overall diagnostic accuracy of 73.3% for all lesions. It was 54.4% for mixed lesions and 80.4% for solid non-sclerotic lesions. Furthermore, it was lower for larger lesions. No difference was found for bone versus soft-tissue lesions or as a function of MR scanner or voxel size. Most of the lesions studied by us were also larger than 4 cm.

CONCLUSION

This study reveals that the presence of choline peak in MRS can be used as an adjunct to routine MR imaging in the evaluation of MSK mass lesions. The accuracy of MRS presently has revealed variable results in various studies and hence more research is required to evaluate this technique as a diagnostic tool.

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