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The role of MRS in the differentiation of benign and malignant soft tissue and bone tumors

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ABSTRACT

Objective: The aim of our study was to investigate the value of choline in the discrimination of benign and malignant soft tissue and bone tumors.
Materials and methods: The study group consisted of thirty subjects with bone or soft tissue tumors larger than 1.5 cm in diameter. The experiments were performed in a 1.5 T MR scanner. Coils were selected according to specific locations. A single-voxel MRS was performed for three different TE (time to echo) (31, 136, 272 ms). The volume of interest was positioned on the brightest enhancement. The presence of a cholin peak on at least 2 of these spectrums was considered as the marker of malignancy. The sensitivity, specificity and accuracy of the MRS in the detection and diagnosis of malignant lesions were calculated. The reproducibility of MRS and histopathological results were tested with kappa statistics.
Results: Histopathologically, 18 (60%) of the lesions were classed as malignant whereas 12 (40%) were classed as benign. With MRS, 15 (50%) of these lesions were classed as malignant and 15 (50%) as benign. Two patients who were found spectroscopically to have malignant tumors were shown histopathologically to have benign types. Five patients with an MRS showing a benign type were classed with malignant types in histopathological examinations. MRS had a sensitivity rate of 72.2%, specificity of 83.3%, and an accuracy rate of 76.6% in detecting malignant bone and soft tissue tumors. The interrater reliability of both techniques had a kappa value of 0.533.
Conclusions: MRS may help in the differentiation of benign and malignant soft tissue and bone tumors.

1. Introduction

As in other parts of the body, the ability to differentiate between benign and malignant soft tissue and bone tumors is of crucial importance for the planning of treatment and prognosis. With the establishment of a definitive diagnosis following the pathological examination of biopsy or surgical material, imaging methods are often applied to obtain further information with non-invasive methods. Magnetic resonance imaging (MRI) provides detailed information about the morphological characteristics of the masses. However, information to enable benign–malignant differentiation is more often obtained from the investigation of the lesions' features such as contrast agent retention.

Magnetic resonance spectroscopy (MRS) is a diagnostic method that can non-invasively measure and display on a spectrum the biochemical characteristics and metabolites of the tissues [1]. Its clinical use is more common in brain examinations and proton MRS is widely used for this purpose. Recently, proton MRS has been shown to provide helpful information in the evaluation of soft tissues and also of bone masses [2–6]. However, since there is a lack of studies on this topic and its use is only possible with devices that have the required technical equipment to perform the examination, widespread use of this method is not available at present.

The aim of our study was to examine the value of choline in the discrimination of benign and malignant soft tissue and bone tumors.

2. Materials and methods

2.1. Patients

Thirty consecutive patients (16 men, 14 women, mean age: 48 ± 12 SD, range: 18–77 years) with 30 soft tissue or bone tumors who underwent conventional MR and MR spectroscopy imaging were included in our study. Tumors which were smaller than 1.5 cm were excluded from the study. The largest tumor dimension for malignant tumors ranged from 2.4 to 15.2 cm (mean size, 6.8 cm), and for benign tumors it ranged from 3.4 to 18.5 cm (mean

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Table 1
MRS and histopathological outcomes of the cases.

Case no.	TE: 31	TE: 136	TE: 272	MRS	Histopathological diagnosis
1	+	+	+	3+ (M)	Lymphoma (M)
2	+	+	–	2+ (M)	Epidermoid carcinoma (M)
3	–	–	+	1+ (B)	Mucoepidermoid carcinoma (M)
4	–	+	+	2+ (M)	Benign schwannoma (B)
5	+	+	+	3+ (M)	Invasive urothelial tumor metastasis (M) I
6	–	–	–	0+ (B)	Enchondroma (B)
7	–	–	+	1+ (B)	Osteoma (B)
8	–	–	–	0+ (B)	Hemangioma (B)
9	–	+	+	2+ (M)	Adenocarcinoma (M)
10	–	–	+	1+ (B)	Transitional cell carcinoma metastasis (M)
11	–	–	–	0+ (B)	Granulomatous inflammation (B)
12	–	–	–	0+ (B)	Giant cell tumor (B)
13	–	+	+	2+ (M)	Lymphoma (M)
14	–	–	–	0+ (B)	Epidermal cyst (B)
15	–	+	+	2+ (M)	Paraganglioma (B)
16	–	–	–	0+ (B)	Squamous cell carcinoma (M)
17	–	–	–	0+ (B)	Lipoma (B)
18	–	–	–	0+ (B)	Transitional cell carcinoma metastasis (M)
19	–	–	–	0+ (B)	Granulomatous inflammation (B)
20	+	+	+	3+ (M)	Papillery thyroid carsinoma metastasis (M)
21	–	+	+	2+ (M)	Malignant giant cell malignant mesenchymal tumor (M)
22	+	–	–	1+ (B)	Malignant fibrous histiocytoma (M)
23	+	+	–	2+ (M)	Squamous cell carcinoma (M)
24	+	+	+	3+ (M)	Ekstramedullary solitary plasmacytoma (M)
25	+	+	+	3+ (M)	Malignant epithelial tumor metastasis (M)
26	–	+	–	1+ (B)	Nonossifying fibroma (B)
27	+	+	+	3+ (M)	Epidermoid carcinoma (M)
28	+	+	–	2+ (M)	Lymphoma (M)
29	–	–	–	0+ (B)	Osteomyelitis (B)
30	–	+	+	2+ (M)	Lymphoma (M)

M: malignant; B: benign; (+): cholin peak exists; (−): no cholin peak.

size, 7.6 cm). Informed consent was acquired from all patients. Our prospective study received institutional review board approval. In our study group, all bone and soft tissue lesions were previously depicted by ultrasound and/or CT, and all lesions were histologically confirmed after MRI and MR spectroscopy examinations (Table 1).

2.2. MRI examination

All cases were examined with a superconducting magnetic resonance imaging device (Gyroscan Intera Master, Philips, Best, the Netherlands) with a 1.5 T main magnetic field and 32 mT/m maximal gradient strength. The preparation phase of the examination consisted of a standard protocol to determine possible location and morphologic characteristics of the lesions. Appropriate one from the body, cervical or superficial coils were selected regarding the locations of space-occupying lesions. T1-weighted spin echo (TR/TE/NEX = 450–550/10–17/2), T2-weighed turbo spin echo (TR/TE/NEX = 500–1000/90–120/3) and fat suppression (TR/TE/NEX/IR = 1500/60/3/165) sequences were also taken in the axial, coronal and sagittal planes according to the location of the lesion. Section gap and the gap between the sections were chosen according to lesion size.

In the period following the preparation phase, a paramagnetic contrast agent was intravenously injected into the patients. Gadolinium-DTPA (Magnevist, Schering, Germany) was used as the contrast agent. The total administered dose was set at 0.2 mmol/kg. The injection was performed through an MRI-compatible dual head automatic pump (8SBP 2000, Spectris, Medrad, USA) connected to a 21G intravenous cannula that was inserted into the subjects. With the stated system first of all the patients were injected with the contrast agent at a velocity of 5 ml/s and then by a total dose of 30 ml normal saline at a velocity of 5 ml/s.

On dynamic examination, the first sequence was a T1-weighted dynamic fast echo sequence (TR/TE/FA/NEX = shortest/4.6/10/1, matrix: 256 × 256, display area: 305 mm^2, section thickness: 5.0/1.0 and section number 18) performed in the axial plane. A 9 cm lesion area in the axial plane was examined as the mass identified in the preparation phase to be studied. Data acquisition started simultaneously with the contrast agent and included 16 consecutive series, each of which lasted about 20 s. Dynamic examination lasted 320 s. A total of 360 sections were obtained over this period. Conventional contrast-sections were taken in the axial, coronal and/or sagittal planes after dynamic examination.

2.3. Proton MR spectroscopy

The PRESS (point resolved surface coil spectroscopy) technique was used for single-voxel MRS examination of the lesions. The voxel size was chosen as 12 mm × 12 mm × 12 mm–20 mm × 20 mm × 20 mm according to lesion size. The voxels were inserted into the region with the most contrast retention in the dynamic examination. If there was no obvious retention, the voxel was inserted into the solid area so as to be far away from the cystic area, subcutaneous fat tissue and normal bone cortex. Water suppression was performed with the CHESS (chemical-shift selective saturation pulse) method.

Three separate spectrums were obtained using short (TR: 2000, TE: 31 ms) and long (TR: 2000, TE: 136 ms) (TR: 2000, TE: 272 ms) echo times. A spectral bandwidth of 1000 Hz was used. After the spectrums were obtained, “baseline” correction (zero fillings) operations were performed manually and the metabolite peaks were defined before the calculation of metabolite rates.

2.4. Image analysis

Choline peaks were used to differentiate benign and malignant lesions. The presence of a choline peak visually identified at 3.2 ppm

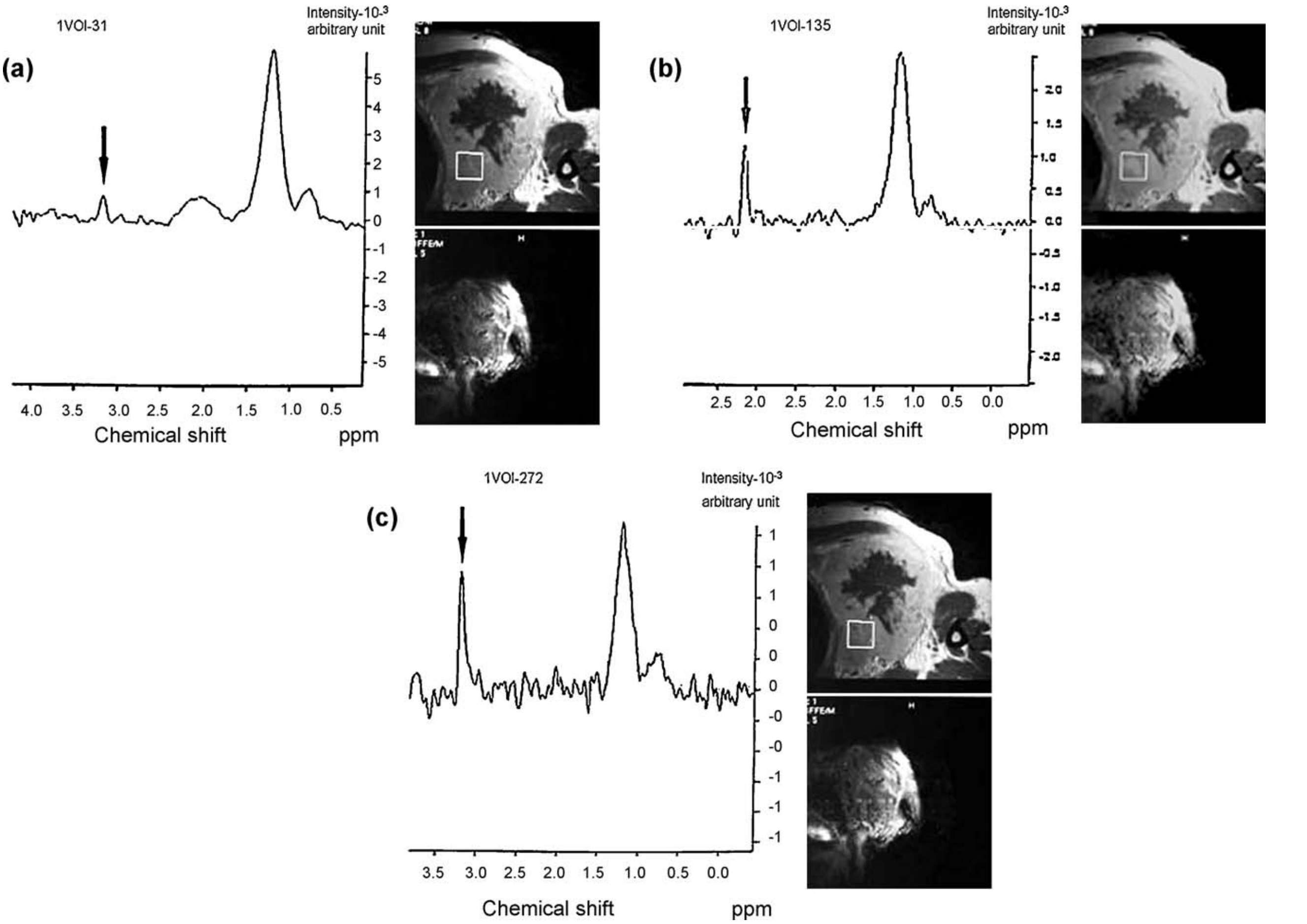

Fig. 1. Choline peak is observed on each of the three spectrums in a case with histopathological diagnosis of uroepithelial tumor metastasis ((a) TE: 31, (b) TE: 136 and (c) TE: 272) (arrows).

in at least 2 of the spectrums obtained using 3 different echo times was accepted as the criterion of malignancy. MR spectroscopy was evaluated by a radiologist who was experienced in this topic. All spectrums were evaluated before the histological examinations, and care was taken that the interpreter should not have information about the lesion enhancement.

2.5. Histopathological evaluation

Biopsy or surgical materials obtained from bone and soft tissue tumors were evaluated by experienced pathologists within a week of the MRI examination. Histopathological results were recorded.

2.6. Statistical analysis

Kappa statistics were used for the comparison between MRS outcomes and histopathological outcomes. Kappa values were calculated separately for the presence of a choline peak in at least 2 of the 3 spectrums and for each three spectrums. SPSS 11.0 statistical software was used for data analysis. Kappa values under 0.40 were accepted as indicative of low compatibility, 0.40–0.75 as good compatibility and 0.75–1.00 as excellent compatibility. $p < 0.05$ values were considered statistically significant. True positive, true negative, false positive and false negative values were defined and MRS values such as sensitivity, specificity, negative predictive value and positive predictive value, which could be used as criteria to define malignancy for soft tissue and bone tumors, were calculated.

3. Results

The histopathological and proton MRS outcomes of the lesions belonging to the subjects included in our study are given in Table 1.

In the analysis of MRS and histopathological findings, the kappa value was calculated as 0.500 ± 0.131 ($p < 0.002$) for the TE: 31 MRS examination, 0.459 ± 0.162 ($p < 0.11$) for the TE: 136 MRS examination, and 0.400 ± 0.164 ($p < 0.025$) for the TE: 272 MRS examination. The existence of a choline peak was seen in at least 2 of the three spectrums, and the kappa value was calculated as 0.533 ± 0.151 ($p < 0.003$). While good compatibility was defined for all criteria, the maximal kappa value was seen to be obtained by the existence of a choline peak in at least 2 of the three spectrums. Using this feature as a diagnostic criterion, 15 (50%) of the 30 cases were classed as malignant on proton MRS (Fig. 1). Lack of a choline peak, or only one cholin peak, was defined for the other 15 cases (50%) and these were classed as benign; whereas in the histopathological examination, 18 (60%) of these cases were defined as malignant and 12 (40%) as benign.

Despite two cases in our study being classed as malignant according to MRS criteria, their histological diagnosis was benign. The histopathological diagnosis was schwannoma (Fig. 2) for one and paraganglioma for the other.

The biopsy outcomes of 5 cases which were evaluated as benign according to proton MRS criteria turned out to be malignant. Of these cases, two were diagnosed as transitional cell carcinoma metastasis, one as mucoepidermoid carcinoma, one as squamous cell carcinoma and the last as malignant fibrous histiocytoma.

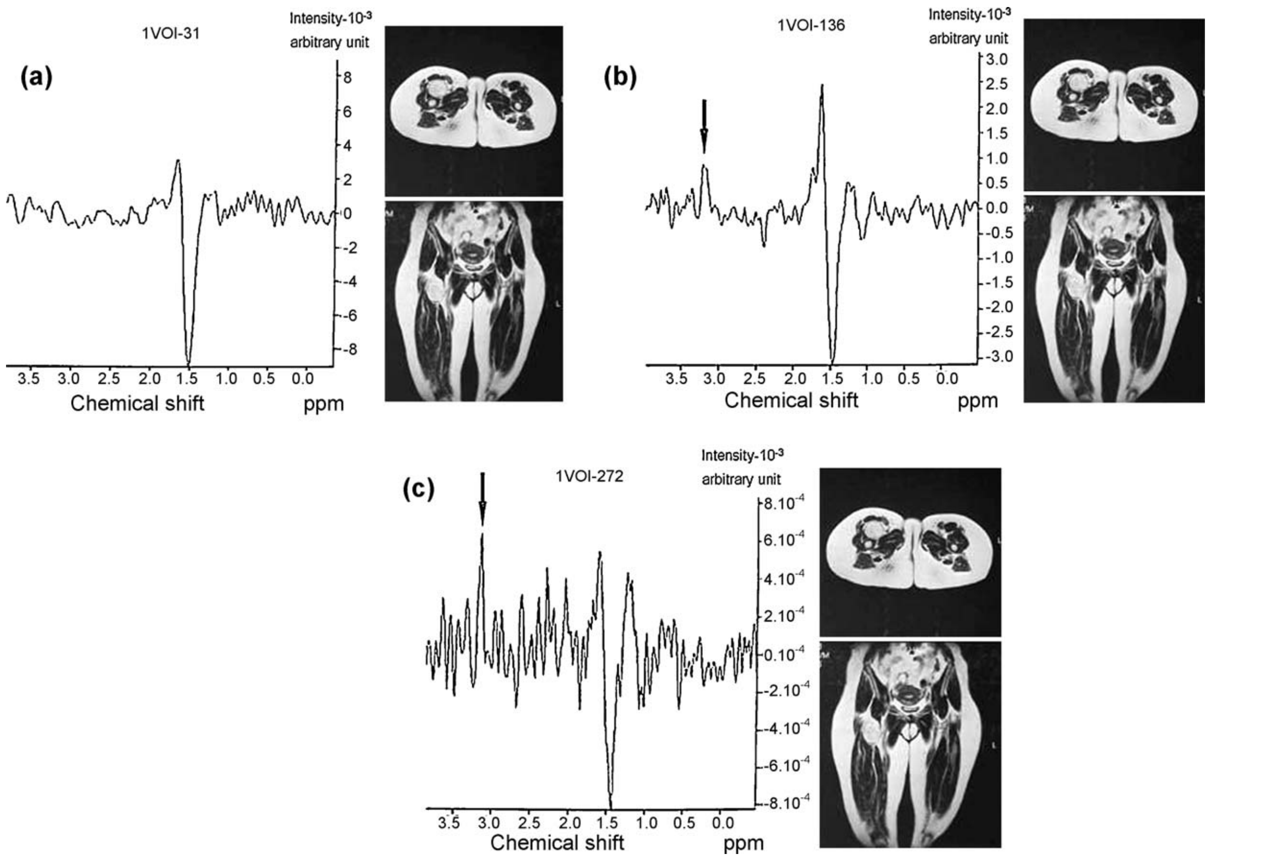

Fig. 2. Although MR spectrums were interpreted as malignant for the case without a choline peak observed in short echo time ((a) TE: 31) but a choline peak was observed in long echo times ((b) TE: 136 and (c) TE: 272) (arrows), histopathological diagnosis was benign (schwannoma).

In 30 cases, the true positive number was found as 13, true negative as 10, false positive as 2 and false negative as 5. Therefore, proton MRS sensitivity for soft tissues and bone lesions was calculated as 72.2%, specificity as 83.3%, positive predictive value as 86%, negative predictive value as 66% and accuracy rate as 76.6%.

4. Discussion

The incidence of bone and soft tissue tumors has gradually increased in industrialized and developing countries. Early diagnosis and differentiation of malignant and benign lesions is important for quality of life and prognosis. A diagnosis of malignity is not always possible with imaging methods such as direct graphy. Therefore, the need for advanced imaging methods has arisen.

The development of tumors, degree of proliferation and response to treatment can be evaluated by an assessment of the metabolites on MRS. A choline peak (3.2 ppm) consists of choline, phospholid choline and glycerophosphocholine. Choline and its derivatives are considered to form an important component in the phospholipid mechanism of cell membranes. An increase in this peak represents membrane phospholipid biosynthesis, and it is an active indicator of cellular proliferation [7]. Choline levels increase mainly in high degree malignant tumors. The choline level increases in accordance with the proliferation and malignity of a tumor [8]. In our study an increase in choline peaks in MR spectroscopy was also investigated based on the increase of cellular and membrane synthesis in malignant tumors.

Early contrast retention areas on MRI have been shown to represent high biological activity areas such as cell turnover/transformation time and neovascularity [9]. Therefore, in our study the voxel was inserted into solid areas with maximum contrast retention.

In our study, two tumors which were defined as malignant according to the outcomes obtained with MRS were histopathologically interpreted as benign (schwannoma and paraganglioma). Both cases showed well contrasted mass lesions according to the MRI findings, and a positive choline peak was identified in 2 of the three MR spectrums. The common features of both lesions were histopathological findings presenting hypercellularity and hypervascularity. In previous studies, hypercellular benign lesions were defined as indicating elevated levels of choline [10]. In a study by Qi et al. high choline peaks were identified in one case of schwannoma and one of neurofibroma, although they were benign [11].

False negative outcomes were obtained in 5 of the 30 cases in our study. These cases included one of mucoepidermoid carcinoma, two cases of transitional cell tumor metastasis, one of malignant fibrous histiocytoma and one of squamous cell carcinoma metastasis. We believe the reasons for false negativity results were the small size of the tumors, difficulty in insertion of the voxel and the proximity of the voxel to the fat tissue and bone cortex. In their study Qi et al. found one liposarcoma and one osteosarcoma did not have a choline peak [11]. In that study, the histological inspection revealed cell nucleus fission was less in liposarcoma, which meant low malignancy; therefore, the spectrum had no choline peak. The osteosarcoma without a choline peak was that of osteoblastic osteosarcoma, the majority of which was neoplastic bone. The ROI was unable to avoid osteoid, so there was no choline peak [11].

In their study of 36 cases with bone and soft tissue lesions, Wang et al. reported sensitivity as 95%, specificity as 82% and the accuracy rate as 89% [2]. When compared with our results, although the sensitivity, specificity and accuracy rates were close to each other, all three values in the study by Wang et al. were higher than those in our study. We suggest that larger patient number, the difference of patient numbers in the definition of benign–malignant rate and difference of tumor sizes contributed to these results. Similarly, in a study by Lee et al. with 27 cases, sensitivity was found as 68.4%, specificity as 87.5%, the positive predictive value as 92.8% and the negative predictive value as 53.8% [6]. Patient number and outcomes were quite similar to our study.

MRS applications can be performed with various metabolites. Phosphorus MRS is used intensively, particularly in musculoskeletal studies. However phosphorus MRS is available in only a few devices due to its high cost. Since only proton MRS was available in our clinic, we conducted our study on the differentiation of benign–malignant soft tissue and bone tumors using this method. In our study, although there were various pathologies such as primary malignant or benign soft tissue and/or bone tumors, metastases and numerous non-neoplastic lesions, the number of cases was limited. To make a significant interpretation considering a specific disease was difficult with these limited numbers. More specific findings could be obtained with further studies focused on a specific disease in larger patient groups.

Differential diagnosis, development, degree of proliferation and the tumor's response to treatment can be evaluated by measuring definite metabolites in a non-invasive and non-destructive way at a cellular level on MRS without the need for contrast agents. However, the use of contrast agents is needed to define the area to be examined. Contrast agent use, makes the process invasive, even if only slightly and, in addition, the automatic pump injector used during contrast agent injection increases the cost of the examination. In our study, after MR examination with dynamic contrast of the mass, we performed a spectroscopic examination, inserting the voxel into the area with maximum contrast retention. It is possible that in the future MRS examination may be conducted without the need for contrast agent owing to studies on the differentiation of benign–malignant according to MR spectrums which are obtained by inserting voxels into the solid areas of the mass without the use of contrast agents. If this happens, MRS will have the great advantage compared to other examination methods of being non-invasive and not requiring high costs.

5. Conclusion

We found a significant relationship between the outcomes obtained using different echo times with MRS to define the existence or lack of the choline in bone and soft tissue tumors and those obtained with histopathology. In particular, identification of choline peak existence in at least two of the spectrums obtained with 3 different echo times was found to be in agreement with the histopathological diagnosis.

Information obtained through MRS can be helpful in providing additional evidence such as neighboring bone invasion and tissue destruction and this can increase the diagnostic specificity of MRI examination in the definition of malignancy. Therefore, MRS use can be of assistance in the early diagnosis of soft tissue and bone tumors, definition of the treatment protocol and monitoring of the lesions.

The limited number of studies on this subject is not sufficient to promote the widespread use of this method. We suggest that further studies should be conducted with a larger patient spectrum to make MRS an important future examination method for the differentiation of benign and malignant lesions in soft tissue and bone tumors.

Conflict of interest

The authors declare that they have no conflict of interest to the publication of this article.

References

[1] Negendank W. Studies of human tumors by MRS: a review. NMR Biomed 1992;5:303–24.
[2] Wang CK, Li CW, Chien SH, Liu GC, Tsai KB. Characterization of bone and soft tissue tumors with in vivo H MR spectroscopy: initial results. Radiology 2004;2:599–605.
[3] Oya N, Aoki J, Shinozaki T. Preliminary study of proton magnetic resonance spectroscopy in bone and soft tissue tumors: an unassigned signal at 2.0–2.1 ppm may be a possible indicator of malignant neuroectodermal tumor. Radiat Med 2000;18:193–8.
[4] Hsieh TJ, Li CW, Chuang HY, Liu GC, Wang CK. Longitudinally monitoring chemotherapy effect of malignant musculoskeletal tumors with in vivo proton magnetic resonance spectroscopy: an initial experience. J Comput Assist Tomogr 2008;32:987–94.
[5] Fayad LM, Barker PB, Bluemke DA. Molecular characterization of musculoskeletal tumors by proton MR spectroscopy. Semin Musculoskelet Radiol 2007;11:240–5.
[6] Lee CW, Lee JH, Kim DH, et al. Proton magnetic resonance spectroscopy of musculoskeletal lesions at 3 T with metabolite quantification. Clin Imaging 2010;34:47–52.
[7] Ruiz-Cabello J, Cohen RS. Phospholipid metabolites as indicators of cancer cell function. NMR Biomed 1992;5:226–33.
[8] Hermingaus S, Pilatus U, Moller-Hartman W. Increased choline levels coincide with enhanced proliferation activity of human neuroepithelial brain tumors. NMR Biomed 2002;15:385–92.
[9] Van Der Woode HJ, Verstraete KL, Hogendoorn PC, et al. Musculoskeletal tumors:dose fast dynamic contrast enhanced subtraction MR imaging contribute to be characterization? Radiology 1998;208:821–8.
[10] Rand SD, Prost R. Accuracy of single voxel proton MR spectroscopy in distinguising neoplastik from nonneoplastic brain lesions. AJNR Am J Neuroradiol 1997;18:1695–704.
[11] Qi ZH, Li CF, Li ZF, Zhang K, Wang Q, Yu DX. Preliminary study of 3 T 1H MR spectroscopy in bone and soft tissue tumors. Chin Med J 2009;122:39–43.