ORIGINAL ARTICLE

Accuracy of magnetic resonance imaging in differentiating between benign and malignant vertebral lesions: Role of Diffusion-weighted imaging, in-phase/opposed-phase imaging and apparent diffusion coefficient

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Magnetic resonance imaging; Diffusion; Apparent diffusion coefficient; In-phase/ out-of-phase; Fractures; Vertebra; Osteoporosis; Metastasis

Abstract
Objective: To determine the ability of MRI to distinguish between benign and malignant vertebral lesions.

Materials and methods: We included 85 patients and studied a total of 213 vertebrae (both pathologic and normal). For each vertebra, we determined whether the lesion was hypointense in T1-weighted sequences and whether it was hyperintense in STIR and in diffusion-weighted sequences. We calculated the in-phase/out-of-phase quotient and the apparent diffusion coefficient for each vertebra. We combined parameters from T1-weighted, diffusion-weighted, and STIR sequences to devise a formula to distinguish benign from malignant lesions.

Results: The group comprised 60 (70.6%) women and 25 (29.4%) men with a mean age of 67 ± 13.5 years (range, 33–90 y). Of the 85 patients, 26 (30.6%) had a known primary tumor. When the lesion was hypointense on T1-weighted sequences, hyperintense on STIR and diffusion-weighted sequences, and had a signal intensity quotient greater than 0.8, the sensitivity was 97.2%, the specificity was 90%, and the diagnostic accuracy was 91.2%. If the patient had a known primary tumor, these values increased to 97.2%, 99.4%, and 99%, respectively.

Conclusion: Benign lesions can be distinguished from malignant lesions if we combine the information from T1-weighted, STIR, and diffusion-weighted sequences together with the in-phase/out-of-phase quotient of the lesion detected in the vertebral body on MRI.

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Introduction

Computed tomography (CT) and magnetic resonance (MR) are the most useful modalities to perform differential diagnoses of one vertebral lesion and are available in most hospitals. Determining the benign or malignant nature of one vertebral lesion is not always possible. It is especially hard to know if the oncologic patient’s pathologic tears are osteoporotic or metastatic. Some purely morphologic characteristics show some sensitivity, specificity and diagnostic accuracy >90% both in the CT and the MR.1,2,3 This is no obstacle for the diagnosis of a far from negligible percentage of lesions to require more sophisticated tests – even biopsies. During the last years several articles have been published on the use of MR sequences like phase/out-of-phase4-9 studies, diffusion-weighted sequences10-18 or the apparent diffuse coefficient (ADC)19-22 in an effort to try to better distinguish one benign vertebral lesion from a malignant one. The outcomes of these studies are not completely clear and show some discrepancies. On the other hand most have focused on establishing the difference between osteoporotic and metastatic tear.

The goal of our study was to determine the diagnostic capability of MR to distinguish between benign and malignant vertebral lesions by assessing the combination of signal characteristics in T1, STIR, diffusion-weighted sequences; out-of-phase/in-phase signal correlation coefficient, and the ADC.

Materials and methods

Patients

Between March 2011 and September 2012 we prospectively included 85 patients with a clinical presentation of acute back pain who underwent one dorsal or lumbar spine MRI to discard vertebral fracture. The decision to include a patient was made after acquiring and reviewing immediately the sagittal T1-weighted sequence. If one vertebra was seen showing one hypointense (signal, focal or diffuse alteration exactly the same or lesser than that of the muscle) or hyperintense lesion (signal, focal or diffuse alteration similar to that of subcutaneous fat) the full protocol of sequences and measurements was activated. Such protocol was also implemented when in the presence of morphologic alteration of the vertebral body (wedging >25%). In the T1-weighted sequences not only lesions suspicious of malignancy were included but also any hypo or hyperintense lesions as well. In each and every patient one normal vertebra (without morphologic alterations or hypo or hyperintense lesions) and one, two or three pathologic vertebrae, including one variable number of pathologic vertebrae depended on the number of vertebrae showing lesions in one single patient. The total number of vertebrae studied (both pathologic and normal) was 213 that is an average 2.5 vertebrae per patient. The ultimate diagnosis of each lesion was established through the different image modalities (X-ray, ultrasound, CT, MR, PET–CT), analyses and clinical evolution. For example in patients with metastasis the presence of similar lesions in other vertebrae, high tumor markers and the patient’s oncologic history allowed us to reach the diagnosis very precisely. Besides these criteria 6-month-follow up was added in all patients to guarantee the stability both in the number and characteristics of the lesion. In 6 cases it was necessary to perform biopsies.

All patients signed the informed consent that is usually handed out and one spinal cord MRI is performed. It was not necessary to include special consent or the approval from the ethical committee since the protocol implemented.
did not require aggressive measures, no IV contrast was administered or ionizing radiations used and it is the routine protocol used in our department when trying to establish a differential diagnosis of benign/malignant lesions.

**Study technique**

All explorations were performed with a 1.5 T-MR equipment (Signa Excite; General Electric). The image protocol included T1-weighted SE sequences (TR/TE 500/16 ms) and T2-weighted FSE in the axial (TE/TE 3700/110 ms) and sagittal planes (TR/TE 4225/110 ms); STIR (TR/TE/TI 3975/50/150 ms) in the sagittal plane; phase-in/phase-out sequences (TR/TE 175/4.2 ms; 30° inclination angle) and out-of-phase (TR/TE 175/2 ms; 30° inclination angle) in the sagittal plane; and single shot SE EPI-weighted sequence (TR/TE 3200/78.5 ms with b = 0 and b = 400 values) in the sagittal plane too.

**Data mining**

Two radiologists with over 15 years of experience in musculoskeletal radiology (first and second author) reviewed the images and determined for each and every one of the 213 vertebral bodies if there was signal or morphologic alteration in the T1-weighted sequences and if the lesion was or not hyperintense with respect to the normal bone marrow and STIR sequences and diffusion-weighted image. In the working station we estimated the value of the out-of-phase/in-phase coefficient after placing one ROI in every vertebral body and locating it at the center of the vertebra (if normal) or in the focal lesion. The value of the ADC of each vertebra was obtained too.

**Statistical analysis**

Qualitative variables present as absolute and relative frequencies and quantitative variables as standard and median deviations.

To study the validity of parameters in the diagnosis of metastasis we calculated the sensitivity, specificity and diagnostic accuracy. To assess the discriminating capacity of quantitative markers, the out-of-phase/in-phase coefficient and the ADC, the ROC area under the curve was estimated and we calculated the cutting point maximizing the values of sensitivity and specificity with its confidence intervals at 95%. We combined the evaluated parameters looking for one diagnostic algorithm with maximum sensitivity and specificity. The statistical analyses were performed through the SPSS Statistics 17 program (IBM, Armonk. New York. U.S.A.).

**Results**

The average age was 67 ± 13.5 years (range 33–90 years). The group included 60 (70.6%) women and 25 (29.4%) men. Among the 85 patients, 26 (30.6%) had a personal history of primary neoplasm – 11 patients with breast neoplasm, 6 of lung origin, 5 prostate neoplasms and 4 other locations. Of a total of 213 vertebras, 85 (39.9%) were normal and 128 (60.1%) pathologic. The distribution of lesions was: metastasis (35 cases; 27%), acute osteoporotic tears (28 cases; 22%), hemangiomas (19 cases; 15%), osteoporotic chronic tears (16 cases; 12.3%), spondylitis (14 cases; 11%) and miscellaneous (16 cases; 12.5%). These last cases included cases of spondylolitis, Schmor’s nodes and other benign tumors.

Of the 35 metastatic cases studied most of them were focal or diffuse lesions without alteration of the height of the vertebral body. There were only 4 metastatic tears. The number of patients showing metastasis was 17/85 that is a prevalence of 20% in our series.

All hemangiomas were typical (hyperintense in the T1 and T2-weighted images) except for one hypointense hemangioma in the T1-weighted images and another one that was painful (both cases confirmed through biopsy).

The cases of spondylitis consisted of vertebral bodies showing Modic-type lesions of any kind.

Among the 6 biopsies performed, the histopathologic study confirmed 2 metastases (breast carcinoma and single metastatic tear) and 4 benign lesions (2 hemangiomas, 1 spondylolitis and one case with inflammatory changes).

In Table 1 the outcomes of several evaluated parameters can be seen: normal vertebral, spondylitis, hemangioma, chronic tear, acute tear (Fig. 1) or metastasis (Fig. 2). Both the characteristics of acute tears and metastases were similar because in both cases the vertebra was hyperintense in the T1-weighted sequences and hypointense in STIR and in the diffuse-weighted sequences. The ADC values were variable. In general the highest values correspond to acute tears yet all entities studied showed great variability. On

<table>
<thead>
<tr>
<th></th>
<th>T1. Hypointense</th>
<th>Diffusion. Hyperintense</th>
<th>STIR. Hyperintense</th>
<th>Out-of-phase/in-phase, cutting point 0.835</th>
<th>ADC, cutting point 0.845</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Normal</td>
<td>5</td>
<td>5.7</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>Acute tear</td>
<td>27</td>
<td>96.4</td>
<td>24</td>
<td>85.71</td>
<td>27</td>
</tr>
<tr>
<td>Chronic tear</td>
<td>4</td>
<td>25.0</td>
<td>5</td>
<td>6.25</td>
<td>3</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>1</td>
<td>5.3</td>
<td>5</td>
<td>26.32</td>
<td>8</td>
</tr>
<tr>
<td>Metastases</td>
<td>35</td>
<td>100.0</td>
<td>35</td>
<td>100.0</td>
<td>35</td>
</tr>
<tr>
<td>Spondylitis</td>
<td>4</td>
<td>28.6</td>
<td>9</td>
<td>64.29</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>13</td>
<td>92.9</td>
<td>9</td>
<td>64.29</td>
<td>9</td>
</tr>
</tbody>
</table>

ADC: apparent diffuse coefficient; STIR: short-tau inversion-recovery.
the contrary the out-of-phase/in-phase coefficient >0.8 was very suggestive of malignant lesion. Out of the 19 vertebral hemangiomas in 10 the signal intensity coefficient was >0.8. Some acute tears were also beyond his value. Lastly there are several of the non-malignant entities like spondyloiscities, Schmörl's nodes (Fig. 3) and other benign tumors that can have a similar behavior to that of metastatic lesions but we cannot get to any statistically significant conclusions due to the size of the sample.

In Table 2 the outcomes of the validation of different parameters considered for the diagnosis of metastasis can be seen. The sensitivity values of signal intensity changes in the T1, STIR and diffusion-weighted images are extremely high—close to 100%. Specificity is also acceptable—between 70% and 80%.

When it comes to the signal intensity coefficient and the ACD the areas under the curve were 0.926 and 0.773, respectively (Fig. 4). The cutting poing maximizing specificity and sensitivity is 0.83 for the coefficient and 0.85 for the ACD. If we take 1.95 was the coefficient cutting point the specificity improves until 95%—especially when it is necessary to reduce the likelihood of a false positive.

From parameters showing high sensitivity in T1, diffusion and STIR and looking for cutting points of high specificity in the coefficient we were able to establish a combined diagnostic test of the malignant lesion in such a way that a study showing one hypointense lesion in the T1-weighted images, hyperintense in both STIR and the diffuse-weighted images and with one out-of-phase/in-phase signal intensity coefficient >0.8 will have a 97.2% sensitivity, a 90% specificity and a 91.2% diagnostic accuracy.

If these variables are found in one patient with a known primary tumor the values are 97.2, 99.4, and 99%, respectively, that is, specificity and diagnostic accuracy increase.

**Discussion**

The purpose of our study has been to evaluate signal changes in vertebral bodies both in benign and malignant lesions in T1, STIR-weighted images as well as the discrimination value of the out-of-phase/in-phase coefficient and that of ACD values. Based on our studies one hypointense
lesion in the T1-weighted images, hyperintense in STIR and in the diffusion-weighted images and one out-of-phase/in-phase coefficient >0.8 has a 97.2% sensitivity, a 99.4% specificity and a 99% diagnostic accuracy for the diagnosis of a malignant lesion as long as the patient has a known primary tumor.

The differential diagnosis of a vertebral body is especially important in the oncologic patient since it is very important to distinguish metastatic origin from the osteoporotic cause. The early studies suggested that the combination of morphologic parameters that individually are non-specific allows us to reach very high values of sensitivity and specificity (beyond 90%) both through CT and MRI, which seems rather reasonable to establish the differential diagnosis in most cases of clinical practice. The use of new sequences like diffusion-weighted images and the estimation of quantitative parameters like the out-of-phase/in-phase coefficient or the ACD have proven useful in the diagnosis of these patients.

In the medical literature it is widely been reported that metastases look hypointense in T1-weighted images except for the hyperintense metastases of melanomas that are rare. In our study 100% of metastases were hypointense in T1-weighted images. However the acute tears are shown the same way (96.4% of cases in our series). Something similar happens in the STIR sequence where both kinds of lesions are not hyperintense—data that match those of other studies—or even in the diffusion-weighted sequence where variability in bibliography is high. The diffusion-weighted sequence is one functional image modality that provides information complementary to conventional sequences. Baur et al. were the first ones to claim that this sequence is very useful to distinguish metastatic tears from acute osteoporotic tear. They studied 22 patients with acute tears and 17 with metastatic tears. All vertebrae with benign lesions looked iso- or hypointense lesions in the diffusion-weighted sequence while metastatic vertebrae were hyperintense. These promising results were not confirmed by other authors, who did not benefit from using diffusion for differential diagnoses yet it is remarkable that our sample included 15 patients only. The first meta-analysis published by Karchevsky et al. confirmed the variab-

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Values of sensitivity, specificity and diagnostic accuracy.</th>
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<tr>
<td>No. = 213 vertebral bodies</td>
<td>Sensitivity (CI)</td>
</tr>
<tr>
<td>T1. Hypointense</td>
<td>100% (90.6-100%)</td>
</tr>
<tr>
<td>Diffusion. Hyperintense</td>
<td>100% (90.6-100%)</td>
</tr>
<tr>
<td>STIR. Hyperintense</td>
<td>100% (90.6-100%)</td>
</tr>
<tr>
<td>Phase/out-of-phase, cutting point 0.835</td>
<td>97% (85.8-99.5%)</td>
</tr>
<tr>
<td>ADC, cutting point 0.845</td>
<td>81% (65.85-90.5%)</td>
</tr>
</tbody>
</table>

ADC: apparent diffuse coefficient; CI: confidence interval; ROC: receiver operating characteristic; STIR: short time inversion recovery.
ity of results and that in 8 of the studies analyzed both metastatic and acute osteoporotic tears showed signal boost in diffusion-weighted images due to the T2 effect that masked the real value of diffusion and that could be solved just by estimating the ACD. Other authors have shown similar data. In one series of 64 lesions with 27 benign tears and 27 tumor tears studied through T1, T2, STIR and diffusion-weighted images the hyperintensity of diffusion-weighted sequences showed sensitivity and specificity values of 93 and 90%, respectively. In our series all metastases restricted diffusion so they were hyperintense.

However many acute tears showed subtle signal boosts in the diffusion-weighted images maybe due to the T2 effect and only 4 cases (16%) showed overt hyperintensity. Nonetheless this sequence is not enough when it comes to differential diagnosis because it is highly sensitive but not that specific. The finding in the diffused-weighted images and ACD values need to be interpreted with other signs. Also sclerotic metastases give rise to false negatives because they do no boost the signal in the diffusion-weighted images.

In some former studies the ACD value has been useful to distinguish between benign and malignant lesions. Pozzi et al. studied 33 cases (23 malignant tears and 10 osteoporotic tears) and both the diffusion-weighted images and the ACD value were useful. Balliu et al. studied 45 patients (16 osteoporotic tears, 15 metastatic tears and 14 infectious processes) in which the ACD value was useful to distinguish osteoporotic from metastatic tears but not to distinguish osteoporosis from infection. Conversely, Maeda et al. studied 36 cases of malignant and benign vertebral tears and came to the conclusion that ACD values overlap. In the same line of these authors the ACD—even though it is higher in the acute osteoporotic tears of our series—overlaps with that of metastases but mainly there is overlapping between metastases and chronic tears.

Another parameter studied in several articles is the coefficient between the signal in the out-of-phase and in-phase sequences. All of them found significant outcomes when they took as the cutting point to discriminate benign from malignant the value 0.8. For example for Erly et al. the sensitivity was 95% and specificity 89%. These findings coincide with ours and they are a differential parameter way more relevant than ACD.

Our results show that there is no one single parameter to separate benign from malignant lesions. One recent meta-analysis reviewed systematically 31 published articles that tried to distinguish malignant from benign vertebral tears. The conclusion was that there are 6 morphologic criteria that say if the structure is malignant, 4 morphologic criteria suggesting that the tear is benign, another 2 morphologic criteria oriented towards malignancy (other metastases) or benignity (osteoporotic tears) and 2 quantitative parameters (out-of-phase/in-phase coefficient and ACD) of excellent sensitivity (beyond 95) and specificity >80%.

What is so special about our study is that it integrates the characteristics of signal of vertebral bodies with the calculation of quantitative variables so we could diagnose metastases with a 97.2% sensitivity, a 90% specificity and a 91.2% diagnostic accuracy. Yet if these variables (hypointense lesion of T1-weighted images, hyperintense in STIR and diffusion-weighted images, and coefficient >0.8) are found in patients with a known primary tumor the values go up to 97.2, 99.4, and 99%, respectively.

In our opinion distinguishing between osteoporotic vertebral and tumor tears is not usually an issue in most cases. From our experience when a patient with a known primary tumor has a suspicious vertebral lesion it usually turns out to be metastasis in 99% of cases. Conversely in patients without a prior known oncologic history but with symptoms leading us to perform one vertebral MR there are benign lesions with characteristics of malignancy that eventually make us perform biopsies yet in either one of them the lesion was malignant.

Our study has some limitations. In the first place there is patient selection bias because way more MRIs are requested from oncologic patients than from patients with osteoporotic tears that even though they are more common they are not represented with respect to such frequency. The same thing happens with multiple myeloma—one relatively common entity that in our field is not usually studied through MRIs. Other entities we grouped under the epigraph miscellanea, of which we can do an adequate statistical analysis, are not well represented either. Secondly the value b = 400 that our MRI equipment allows us is a little too low and it can promote the T2 effect in diffusion-weighted images yet it was a parameter we could not modify. Thirdly the de facto of the non-evaluation of pure morphologic parameters by thinking they were properly studied in the reference can also be regarded as another limitation. Lastly the anatopmopathologic diagnosis was possible in 6 patients only yet the image findings, the clinical history and the evolution—all patients were followed for at least 6 months—allow us to say that the diagnosis of benign or malignant disease was correct.
In sum the differential diagnosis between benign and malignant lesion can be performed through MRIs if we assess both the characteristics of signal in the T1, STI, and diffused-weighted images and the out-of-phase/in-phase coefficient detected by the vertebral body and only in a small number of patients we need to resort to performing biopsies. It is very interesting to perform prospective studies by avoiding the aforementioned biases while including morphological, signal intensity, and qualitative variables.

Ethical responsibilities

Protection of people and animals. Authors confirm that no experiments have been performed on human beings or animals.

Data confidentiality. Authors confirm that in this report there are no personal data from patients.

Right to privacy and informed consent. Authors confirm that in this report there are no personal data from patients.

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Conflict of interests

Authors reported no conflicts of interests.

References

