Diagnosis of Peritoneal Metastases with Abdominal Malignancies: Role of ADC Measurement on Diffusion Weighted MRI

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Abstract

Objective: The purpose of our study was to evaluate the utility of the apparent diffusion coefficient (ADC) value measurement in the diagnosis of peritoneal metastases on diffusion weighted magnetic resonance imaging.

Materials and Methods: Diffusion weighted imaging with conventional magnetic resonance imaging sequences was performed on twenty consecutive oncology patients (group I) with peritoneal metastases. The ADC values of the metastases, the peritoneal fat around the metastases (group I) and the peritoneal fat in patients with no malignancy (group II) at b (0-100), b (0-600), and (b 0-1000) s/mm² gradients were measured and compared.

Results: The apparent diffusion coefficient values of three gradients in peritoneal metastases (2.27±0.4; 1.67±0.7 and 1.09±0.4x10⁻³ mm²/s at b 100, 600 and 1000 gradients, respectively) were significantly lower than the ADC values of the peritoneal fat around the metastases (3.07±0.4; 2.07±0.4; 1.33±0.3x10⁻³ mm²/s at b 100, 600 and 1000 gradients, respectively) (p<0.05). There was no significant difference between the ADC values of peritoneal fat in the patients of group I and group II at the 3 diffusion gradients (p>0.05).

Conclusion: The measurement of ADC values may be used as a supplementary diagnostic method in differentiating peritoneal metastases from peritoneal fat on Diffusion Weighted MRI (DWMRI).

Key Words: Apparent diffusion coefficient value, Diffusion weighted imaging, Malignancy, Metastasis, Peritoneum

Introduction

The depiction of peritoneal metastases associated with abdominal malignancies is more emphasized in conjunction with improved diagnostic imaging modalities [1-3]. Various imaging modalities, including ultrasonography (US), multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI), are used for diagnosing peritoneal metastases [1]. Among these modalities, US is a time consuming and operator dependent technique for evaluating peritoneal metastases when careful assessment is required. Computed tomography is the most popular imaging modality for evaluating peritoneal tumors. MRI of the abdomen is a noninvasive and nonionizing imaging modality that provides multiplanar images [3]. However, compared to CT, respiratory movement artifacts, lower spatial resolution and difficulty
with interpretation for clinicians are the main disadvantages for MRI [1]. Diffusion weighted magnetic resonance imaging (DWIMRI) is a functional imaging technique that reflects molecular water movement in biological tissues. The movement of water molecules is restricted secondary to the hypercellularity and increased integrity of cellular membranes [3]. The restricted movement of water molecules results in an increased signal on DWMRI. As a result, malignant lesions appear as hyperintense foci on DWMRI.

With the advent of faster sequences, DWMRI is used more frequently in abdominal imaging. DWMRI was reported to be a highly effective imaging modality for depicting peritoneal metastases, with a sensitivity of 81% and accuracy rate of 71%. These values provide a new imaging paradigm [4]. It also permits the quantitative evaluation of the apparent diffusion coefficient (ADC) values from images with different b-values. ADC values have an inverse relationship with tumor cellularity, which may be useful for distinguishing benign and malignant tissues [3, 5, 6]. The diagnostic utility of ADC has been emphasized for various abdominal pathologies in the literature, including focal and diffuse lesions of the liver, pancreas, kidney, and prostate [3-6]. However, to the best of our knowledge there is no study investigating the role of ADC values in the diagnosis of peritoneal metastases. To date, no studies have compared the ADC values of metastases surrounded by peritoneal fat. Since peritoneal metastases arise from various malignant cell types, the ADC values of these lesions are expected to be lower than the values of the surrounding fat. The purpose of our study was to evaluate the utility of ADC measurement on DWMRI for the diagnosis of peritoneal metastases by distinguishing metastases from the surrounding peritoneal fat in abdominal malignancies.

Materials and Methods

Participants
Twenty-eight consecutive oncology patients with abdominal malignancies were referred to our department for MRI examination between May 2007 and August 2009. MRI examinations with DW sequences were performed on these patients to evaluate the location and extent of the tumor in the abdomen and pelvis. Eight patients with peritoneal metastases were excluded from the study; four patients were excluded because their peritoneal metastases were too small (<1 cm) and, the other 4 patients, because distinguishing between the peritoneal metastasis and the neighboring bowel, which was was observed to be hyperintense on DW imaging secondary to the T2 shine through effect, was too difficult. Twenty patients with appropriate DW imaging were classified as group I (15 women, 5 men; mean±SD age: 61.3±4, range: 30-75 years). Primary tumors included ovarian cancer (n=6), stomach (n=2), GIST (n=2), colon (n=2), carcinoid (n=1), endometrium (n=2), PNET (n=2), pancreas (n=1), gallbladder (n=1), and malignant fibrous histiocytoma (n=1). Peritoneal metastases were diagnosed in 15 of 20 patients through abdominal operations (n=10) and percutaneous biopsies (n=5), which were performed within 15 days of the MRI examination. In 5 patients, peritoneal metastases were diagnosed by repeated MDCT and MRI. The mean follow-up period for the diagnosis of peritoneal metastases on these patients was 12-months (range, 6-24 months). Nodular lesions, which were enhanced on MDCT and during the delayed phase of the gadolinium-enhanced images on MRI, were distinguished from lymphadenopathy and were diagnosed as peritoneal metastasis. The clinical histories and presentations of patients were carefully evaluated for accurate image interpretation because peritonitis may mimic peritoneal carcinomatosis by showing enhancement on delayed CT and MR images.

We also measured the mean ADC values of peritoneal fat in 20 patients (group II, control group, 13 women, 7 men; mean±SD age: 57.2±6, range: 22-80 years) without malignancy and peritoneal metastases to compare the ADC values of peritoneal fat in group II and the peritoneal fat surrounding the metastases in group I.

MRI
The DWMRI sequences were acquired synchronously with conventional MRI sequences. Magnetic resonance imaging examinations were performed with Signa Excite 1.5 T system (GE Healthcare, Milwaukee, WI, USA) with a four-channel TORSOPA body coil. The abdomen and pelvis were imaged in all patients. Before DWI, breathhold T1-weighted, fat-saturated fast spin echo T2 weighted, dual echo fast spoiled gradient-echo (FSPGR) and single shot fast spin echo (SSFSE) T2 weighted images were obtained. Isotropic DWI was generated using three orthogonal-axis images and combining the diffusion signal from all three vectors. Diffusion weighted images were obtained before contrast administration with b-values of 0, 100, 600, and 1000 s/mm². Short TI inversion recovery (STIR) sequence was used for fat suppression to eliminate a background signal. Imaging parameters for DWIs were as follows: TR/TE, 8000/90 ms; FOV, 300x300 mm (changed according to body size); number of excitation, 1; matrix size, 128x128; section thickness, 5 mm; and intersection gap, none. DW sequences required a total of 96 s to scan on MR with free breathing. The array spatial sensitivity encoding technique (ASSET) with a factor of 2 was used as a parallel imaging technique.

A breath-hold, dynamic 3D T1 weighted (FAME) sequence was performed after the DWIs (bolus injection of 20 mL gado-pentetate dimeglumine 1.5 mL/sec).

Image analysis
This retrospective review of MRI studies was approved by our institutional ethics committee. Written informed consent from patients was not required.
Peritoneal metastases were recorded as focal areas of hyperintensity that did not represent T2 shine-through from structures containing fluid. Conventional MRI was used to provide the anatomical location of the hyperintense nodular shaped images on the DW images. DW images were interpreted together with contrast enhanced CT and MRI for the depiction of peritoneal metastases. Nodular hyperintense lesions on DWMRI, which were enhanced on contrast enhanced MDCT and MRI, were diagnosed as peritoneal metastases. After evaluating the imaging findings, we measured the ADC values of lesions detected on conventional MRI sequences and DWMRI. Analysis and measurements of DWI data were performed using an MRI workstation (Advantage Windows, software version 2.0, GE Medical Systems, USA). The ADC measurements were performed on color and gray-scale ADC maps from each lesion and by calculating the difference between $b = 0 - 100$, $b = 0 - 600$, and $b = 0 - 1000 \ \text{mm}^2/\text{sec}$ gradient values by using 3 circumferential region of interests (ROI). Fifteen patients had multiple peritoneal metastases. The ADC measurements were performed on the largest metastasis in patients with multiple metastases. These metastases were correlated with surgical findings and biopsies after the ADC measurement. All round shaped ROIs were placed within the confines of the lesions on DW images and transferred to the ADC maps in the corresponding locations. All of the ROIs from the same patient had the same diameter. ROI diameters changed between patients according to the metastasis size. The mean area of the ROIs drawn in this study was 124±22 mm$^2$ (range between 84-172 mm$^2$). We applied 3 ROI cursors on each lesion, and the peritoneal fat around the metastases and the mean values were recorded. The ADC values of patients with metastases and in the control group were measured by M.R.O., who has with 8 years of experience in abdominal radiology, and M.A., who has 4 years of experience in abdominal radiology. The mean ADC values of the peritoneal metastases and peritoneal fat were compared in order to understand the differences between the ADC values of peritoneal metastases and peritoneal fat at $b = 100$, $b = 600$, and $b = 1000$ gradients. After ADC measurements, the operation reports and repeated CT and MRI examinations were retrospectively reviewed to confirm the location of the metastases and normal peritoneal fat. No mislocalization of ROIs was found.

**Statistical analysis**

The Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) software package was used for data collection. All data are expressed as the mean±standard deviation. ADC values were analyzed using Prism 5.0 software (Graphpad software, Inc., San Diego, CA, USA). Comparisons of the ADC values of the peritoneal metastases and peritoneal fat around the metastases and peritoneal fat in healthy subjects were done with the unpaired t-test with Welch correction. P values less than 0.05 from two-tailed tests were considered statistically significant.

**Results**

The mean diameter of the peritoneal metastases was 30.5 mm (range, 12-85 mm). Metastases, which were selected using the ADC measurements observed on the DWMRI images, were seen as hyperintense nodular lesions due to restricted diffusion.

The locations of the peritoneal metastases were as follows: mesentery (n=6), omentum (n=6), right subdiaphragmatic space (n=2), subhepatic area (n=2), right paracolic space (n=2), falciform ligament (n=1), and left subdiaphragmatic space (n=1). The mean ADC values of the peritoneal metastases, the peritoneal fat around the metastases and the peritoneal fat in the control group at $b = 100$, $b = 600$ and $b = 1000$ gradients for each group are shown in Table 1 and Figure 1. Comparisons of the mean ADC values at all 3 gradients yielded a statistically significant difference between the peritoneal metastases and the peritoneal fat around the metastases (Figure 2).

There was no statistically significant difference between the mean ADC values of the peritoneal fat around the metastases (group I) and the peritoneal fat in group II (p=0.32) (Figure 3).

![Boxplots of ADC values of peritoneal metastases (L) and peritoneal fat around metastases (M) at b 100, 600 and 1000 gradients.](image-url)

**Table 1. Mean ADC values of peritoneal metastases, peritoneal fat around metastases and peritoneal fat in the control group at 3 different (b 100, b 600 and b 1000) gradients (±standard deviation)**

<table>
<thead>
<tr>
<th>ADC VALUES ($\text{x}10^{-3} \ \text{mm}^2/\text{s}$)</th>
<th>Metastases</th>
<th>Peritoneal fat (group I)</th>
<th>Peritoneal fat (group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b 100</td>
<td>2.27±0.4</td>
<td>3.07±0.4</td>
<td>3.12±0.7</td>
</tr>
<tr>
<td>b 600</td>
<td>1.67±0.7</td>
<td>2.07±0.4</td>
<td>2.13±0.2</td>
</tr>
<tr>
<td>b 1000</td>
<td>1.09±0.4</td>
<td>1.33±0.3</td>
<td>1.42±0.1</td>
</tr>
</tbody>
</table>
Discussion

The peritoneum is a double-layered serosal membrane that lines the abdominal and pelvic cavities, envelops the intraperitoneal organs, and connects anatomical compartments [7]. The peritoneum in abdominal radiology is unique because of its involvement in the metastatic spread of cancer via intraperitoneal dissemination, the direct spread of tumors along peritoneal surfaces and through hematogenous metastases [7, 8]. Primary tumors of the peritoneum are rare, whereas metastatic disease is the most commonly encountered neoplastic process involving the peritoneum. Treatment protocols (medical treatment or surgery) are determined by the location and spread of peritoneal tumors [2].

Ultrasound has a limited role in depicting peritoneal metastases because its sensitivity significantly decreases due to bowel gas. However, large lesions neighboring the anterior or lateral abdominal wall are easily identified by ultrasound. Contrast enhanced CT is frequently used to diagnose peritoneal metastases, but major limitations of this technique include the relative insensitivity for lesions smaller than 5 mm and radiation exposure [2]. Dynamic MRI with contrast administration has an important role with advantages of high sensitivity (85-93%) and specificity (78-96%) values. However lengthy examination times and susceptibility to respiration and bowel motion artifacts may prevent optimal diagnoses [9, 10].

The use of DWI of the abdomen and pelvis provides a new opportunity to evaluate patients with abdominal malignancy from either a primary tumor or metastases [11-17]. DWMRI enables tissue characterization at the microscopic level and uses a mechanism differs from T1 and T2 relaxation [18]. Solid tumors show restricted diffusion because of their high cellularity, which results in an increased signal intensity on DW images [19]. DWMRI can reveal foci of peritoneal metastases equal to or larger than 5 mm, irrespective of their anatomical locations in the abdomen and pelvis [7]. Peritoneal metastases show high signal intensity on DW images. These findings are more prominent with high b values, primarily because of the diffusion effect of water molecules on these gradients. Mesenteric tumors, bowel serosa tumors, and tumors involving the peritoneal reflections around the liver and pancreas are usually better seen on DW images because of the higher signal intensity of peritoneal tumors on these images [4]. However, bowels may be seen as hyperintense areas and mimic metastases on DWMRI because of the T2 shine-through effect, which is a particular problem for DW images with smaller b values. ADC maps eliminate the high signal from the T2 prolongation, which depicts changes in signal intensity that are solely due to water diffusion. These findings may help distinguish areas of T2 shine-through from restricted diffusion.

The interpretation of DW images is easier when viewed and correlated with conventional MR images, which provides a better depiction of anatomical landmarks [4]. In this study, we interpreted DW images with axial T1, T2 weighted and contrast enhanced T1 weighted images to make appropriate assessments. This approach enabled us to localize metastases and unaffected peritoneal fat. The STIR sequence was used to suppress fat tissue on DW images in this study. STIR has fewer susceptibility artifacts than the chemical shift selective technique and can obtain DW images with excellent fat suppression [20]. When using STIR, most of the short T1 signals from the bowels were suppressed, and higher contrast between the disseminated tumor and bowel was obtained.

Restriction of diffusion is not a specific feature of malignancy. Infectious, inflammatory, and ischemic processes can also present with areas of high signal intensity on DWMRI [4]. Past medical history and findings from other imaging modalities play an important role in identifying peritoneal metastases. In our study, the presence of peritoneal metastases in 15

Figure 2. A) Axial contrast enhanced fat saturated T2-weighted image reveals a peritoneal metastasis from a gastrointestinal stromal tumor as a hyperintense solid mass (arrows). B) Peritoneal metastasis manifests on DWMRI (at b 600 gradient) with increased signal intensity (arrows). C) On an ADC map, a metastatic lesion is seen with a green color. The mean ADC value of a metastasis (0.78x10^-3 mm²/s) was significantly lower than adjacent peritoneal fat (2.35x10^-3 mm²/s).
patients was confirmed both surgically and histopathologically. However, in another 5 patients, the follow-up imaging examinations with a 64 channel MDCT and MRI were consistent with peritoneal metastases. Clinical history, presentation and patient follow-up excluded the possibility of infectious and inflammatory conditions that affect the peritoneum.

Fujii et al., [20] reported high sensitivity (90%) and specificity (95%) values of DWMRI in the diagnosis of peritoneal metastases and indicated that there was a need for studies regarding ADC values on peritoneal metastases. Only one study reports ADC measurements for peritoneal metastases from ovarian cancer [3]. According to this report, Sala et al. used multiple diffusion gradients (0, 100, 150, 200, 250, 350, 500, 750, 1000) and found that the mean ADC value of peritoneal metastases (0.89x10⁻³ mm²/s) was lower than primary ovarian cancer and omental cake [3]. In our study, we also used 3 different gradients (b 0-100, 0-600, 0-1000) and compared the mean ADC values of peritoneal metastases from various malignancies with the peritoneal fat around the metastasis (Figure 2). We aimed to understand the value of the ADC measurements in the diagnosis of peritoneal metastases from various malignancies other than ovarian carcinoma. Using multiple diffusion gradients was advised to evaluate the diagnostic value of ADC measurements in various pathologies. We thus used a wide range of diffusion gradients (low-b 100, medium-b 600, high-b 1000) and the mean values of these gradients to evaluate the utility of the ADC measurements in the diagnosis of peritoneal metastases [6, 19]. Comparisons between the mean ADC value of the 3 gradients in metastases and peritoneal fat yielded significant differences revealing a high reliability for identifying peritoneal metastases. There were significant differences between the mean ADC values of peritoneal metastases and peritoneal fat at b 100 (p=0.0008), b 600 (p=0.004) and b 1000 gradients (p<0.003).

Although CT and MRI provide discrimination of peritoneal metastases from surrounding tissues, millimetric or sub-millimetric metastases in peritoneal fat are difficult to identify. This difficulty leads us to question whether millimetric peritoneal metastasis influence the ADC values of the peritoneal fat.

Figure 3. A) DW image of a patient with peritoneal metastasis at b 1000 gradient. Peritoneal metastasis is demonstrated with increased signal intensity (arrows) in comparison to surrounding tissues. One ROI (7) is inserted within the metastasis while the other three ROIs (5, 6, 8) are inserted in the surrounding fat to measure the ADC values on the corresponding ADC map. B) On an ADC map, the green colored area represents metastasis and restricted diffusion (ROI 7). The mean ADC value of peritoneal fat around a metastasis is 2.01x10⁻³ mm²/s. C) The peritoneal fat in a patient in group II is seen as being hypointense on a DW image at b 1000 gradient. D) On an ADC map, the mean ADC value of normal peritoneum in a patient without malignancy reveals the ADC value as 1.96x10⁻³ mm²/s.
around metastases. In order to answer this question, we measured the ADC values of peritoneal fat from patients in the control group (group II) with abdominal MRI for reasons other than malignancy and without peritoneal deposits (Figure 3). There was no significant difference (p > 0.05) between the mean ADC values of the peritoneal fat in the control group (group II) and the peritoneal fat around peritoneal metastases in patients with malignancy (group I). According to this finding, ADC measurements from the peritoneal fat around peritoneal metastases are a reliable method for distinguishing peritoneal metastases from peritoneal fat.

The main limitations of this study include the small patient population and the lack of surgical and histopathologic confirmation of the peritoneal metastases in 5 patients. These 5 patients were diagnosed radiographically by repeated CT and MRI. However, we carefully interpreted the images and considered the clinical history of these patients. This interpretation included comparing the findings of follow-up US, CT and MRI examinations of the same lesions on the same patients, evaluating the response of these lesions to chemotherapy and evaluating the imaging findings in the context of the patient’s clinical history and presentation to distinguish these malignant deposits from inflammatory and tuberculosis peritonitis. Another limitation is the relatively large diameter of the metastatic lesions in our patients (the minimum and mean diameter of the lesions were 12 mm and 31 mm, respectively). In our study, we excluded 4 patients with peritoneal metastases that were <1 cm. Difficulty in measuring the ADC values in peritoneal metastases <1 cm may hinder the clinical usage of ADC measurement in the detection of these lesions.

Detection of peritoneal metastases can change the stage of the abdominal malignancies and affect the treatment protocol. Although CT is the most frequently used imaging technique in the diagnosis of peritoneal metastases, DWMRI may also depict peritoneal metastases with the advantage of avoiding radiation exposure.

In conclusion, the measurement of ADC values may be used as a complementary diagnostic method to evaluate peritoneal metastases on DWMRI. The ADC value as a quantitative parameter of DWMRI provides objective assessments of the DW images in addition to visual assessment.

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

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