

THE EFFECTIVENESS OF WHOLE BODY MAGNETIC RESONANCE IMAGING (DIFFUSION-WEIGHTED IMAGING AND FAT SATURATED T2-WEIGHTED IMAGING) IN THE EVALUATION OF PATIENTS WITH NEWLY DIAGNOSED MALIGNANCIES IN COMPARISON WITH POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY

G. Oncel¹, D. Oncel², I. Karapolat³, F. Sever⁴

Purpose: To evaluate the effectiveness of WB-MRI for the detection of primary and metastatic lesions in comparison to PET-CT in patients with newly diagnosed malignancies

Material and Methods: In this prospective study, 36 patients were evaluated between August 2008 and October 2012. The findings of WB-MRI (DWI and fat saturated T2 weighted images) were compared to the findings of PET-CT regarding the primary lesions and metastasis. Sensitivity, specificity, positive and negative predictive values were calculated. To assess the agreement between PET-CT and WB-MRI, kappa analysis was performed.

Results: The sensitivity, specificity, positive and negative predictive values for WB-DWI for the detection of primary and metastatic lesions in comparison to PET-CT were 96%, 89%, 97% and 84%, respectively. These are calculated as 96%, 56%, 90% and 77%, for fat-saturated T2W images. According to kappa analysis, the agreement between PET-CT and WB-DWI was excellent ($\kappa = 0.83$), but between PET-CT and fat-saturated T2 weighted images, it was moderate ($\kappa = 0.58$).

Conclusion: Providing both morphological and functional data, WB-MRI with DWI is emerging as a promising alternative imaging tool in the evaluation of cancer patients and may become complementary to PET-CT in several clinical applications.

Key-words: Neoplasms, MR – Neoplasms, emission CT.

Thorough evaluation and accurate staging of neoplasms are crucial in determination of the appropriate therapy and assessment of the prognosis. Recently, positron emission tomography (PET) with 2-deoxy-2 [F] fluoro-d-glucose (FDG) in combination with computed tomography (PET-CT) has become an important imaging modality for the staging of various tumors as well as and monitoring of the therapy and follow up in some instances (1, 2). PET/CT combines the anatomic details depicted with CT and metabolic information obtained with PET, yielding more precise anatomic information. PET/CT has disadvantages, however, such as radiation exposure, higher cost, and limited depiction of small volumes of metabolically active tumor (1, 2).

Whole-body magnetic resonance imaging (WB-MRI), with its lack of ionizing radiation, but high contrast and spatial resolution, is a promising whole body imaging tool for detection and staging of various neoplastic diseases (2-4). WB-MRI provides mainly morphological information on tumor spread. The lack of func-

tional information has been overcome by the introduction in diffusion whole body imaging (3-5). Diffusion-weighted imaging (DWI) allows measurement of water diffusion on a molecular level and provides functional data about tumor cellularity. Therefore, tumor sites may be detected throughout the entire body with high contrast resolution as areas of impeded diffusion (3-7).

The aim of our study is to compare the effectiveness of WB-MRI (i.e. DWI and T2-weighted sequences) with PET-CT as a standard of reference in the evaluation of patients with newly diagnosed malignancies.

Materials and methods

Patients

This prospective study was approved by the local institutional review board, and written informed consent was obtained from all participants.

A total of 36 consecutive patients (20 males and 16 females; mean age of 60.11 years; range 41-75) with diagnosis of malignant disease were

included in the study between August 2008 and October 2012. Patient characteristics are shown in Table I.

Inclusion criteria were age 18 years and older and the presence of newly diagnosed histopathologically proven malignancy. Exclusion criteria were general contraindications to MRI (such as implanted pacemaker and claustrophobia) and previous diagnosis of malignancy, previous chemotherapy and radiotherapy.

The primary malignancies, which were confirmed by histopathology, included non-Hodgkin lymphoma (n = 6), gastric cancer (n = 3), lung cancer (n = 9), colorectal cancer (n = 7) and breast cancer (n = 11). Metastatic lesions were confirmed by follow-up over 6 months or biopsy

All patients underwent WB-MRI, and PET/CT. Both examinations were performed on the same day or otherwise within a period of one week. PET/CT examinations were performed for staging purpose according to our institutional guidelines. PET-CT images were used as standard of reference.

MR imaging

WB-MRI was performed with a 1.5 Tesla scanner (Avanto, Siemens AG Medical Solutions, Erlangen, Germany) with high-performance gradients (maximum amplitude, 40 mT/m,

From: 1. Department of Radiology, Sifa University, Izmir, 2. Department of Radiology, Tepecik Training and Research Hospital, Izmir, 3. Department of Nuclear Medicine, Sifa University, Izmir, 4. Department of Chest Disease, Sifa University, Izmir, Turkey.
Address for correspondence: Dr Dilek Oncel, Department of Radiology, Tepecik Training and Research Hospital, Izmir, Turkey. E-mail: dilekoncel@hotmail.com

Table I. – Patient characteristics.

Male	n = 20
Female	n = 16
Age (mean,range)	60.11 years (41-75)
<i>Tumor histopathology</i>	
Non-Hodgkin lymphoma	n = 6
Gastric cancer	n = 3
Lung cancer	n = 9
Colorectal cancer	n = 7
Breast cancer	n = 11
<i>Metastatic lesions</i>	
Lymph node	n = 22
Liver	n = 8
Lung	n = 4
Bone	n = 8
Adrenal gland	n = 1

slew rate , 200 mT/m/sec) with the patient in supine, feet-first position on an automatic moving table. Whole body images were obtained in five steps covering the body from head to mid thigh. For signal detection two elements of the spine coil, which are integrated into the patient table, and two elements of a multi-channel phased-array surface radio-frequency coil were used.

The whole-body MR imaging protocol consisted of unenhanced T1-weighted turbo field-echo (TFE), fat saturated (STIR) T2-weighted TFE and DW sequences. DW images were acquired using single-shot echo-planar imaging (EPI) sequences with a short inversion time inversion recovery (STIR) pre-pulse for fat suppression, using free-breathing technique on coronal plane. Motion probing gradients (MPGs) in three orthogonal axes were applied for b values 0 and 800 s/mm², with 6 signal sampling average.

The total acquisition time for WB-MRI was approximately 40-45 minutes.

PET-CT imaging

Data acquisition was performed on a dual-modality PET/CT system (Biograph 6, Siemens AG Medical Solutions, Erlangen, Germany) which provides an in-plane spatial resolution of 4.8 mm, an axial field view of 16.2 cm, and three-dimensional image acquisition. All patients fasted for at least 6 hours before scanning and were tested for normal

glucose levels before intravenous injection of 370-500 MBq (adapted to body weight). of the tracer 18F-FDG Scanning started approximately 60 minutes after injection of the tracer with the patients in a supine position with the arms overhead. First, the CT was acquired from the head to the mid-thigh in cranio-caudal direction during a limited breath-hold to avoid motion-induced artifacts in the area of the diaphragm. Immediately after, PET data were collected in cranio-caudal direction with the arms down and normal shallow breathing. FDG PET images were reconstructed using CT data for attenuation correction.

Image interpretation and analysis

All WB-MR images were analyzed on an external workstation (Leonardo, Siemens AG Medical Solutions, Erlangen, Germany) with by two experienced radiologists (G.O. and D.O., over 10 years of MR experience). Both evaluators were unaware of the results of PET-CT scans. Disagreements were resolved by consensus. Image interpretation regarded the detection of primary disease and assessment of local/distant metastasis.

DW signal was evaluated visually. Any distinct focus with increased signal intensity on WB-DWI at a b-value of 800 s/mm² compared to the signal intensity of the surrounding normal tissue (eg, surrounding liver parenchyma in case of malignant liver lesions) or compared to the sig-

nal intensity of the background were considered as malignant lesion. ADC values were compared to healthy surrounding tissue. Lymph node involvement was based on morphologic criteria (eg. short axis diameter > 10mm; long axis-to short axis ratio > 1) together with the evidence of increase in signal intensity on DW images. Lymph nodes with increased signal intensity and low ADC values compared to certainly benign regional lymph nodes were considered malignant, even if they were smaller than the region-specific cutoff diameter.

Fat saturated T2W images were evaluated separately. The interval between the two analyses was at least five days with different orders of evaluation.

PET/CT images were interpreted by an experienced nuclear medicine physician (I.K, with 8 years of experience) blindly and independently. A lesion or lymph node with increased FDG uptake in comparison with the surrounding normal tissue was considered positive for malignancy.

Statistical analysis

Statistical analysis was performed with SPSS 15.0 (SPSS Inc., Chicago, IL) for Microsoft Windows. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for WB-MRI (fat saturated T2W images and DWI, separately). PET-CT was the reference standard.

In addition, to assess the agreement between PET-CT and WB-MRI datasets (DWI and fat-saturated T2) in the detection primary tumors and metastasis, kappa analysis was performed. According to Landis and Koch (8), a kappa value of 0 indicates poor agreement; 0.01-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81-1.00, excellent agreement. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

We evaluated 36 patients with newly diagnosed malignancy (6 non-Hodgkin lymphoma, 3 gastric cancer, 9 bronchial cancer, 7 colorectal cancer and 11 breast cancer). In PET-CT examination, in 18 patients, apart from the primary lesions, no metastasis was detected (4 non-Hodgkin lymphoma, 1 gastric cancer, 4 bronchial cancer, 3 colorectal cancer and 6 breast cancer) In the remaining

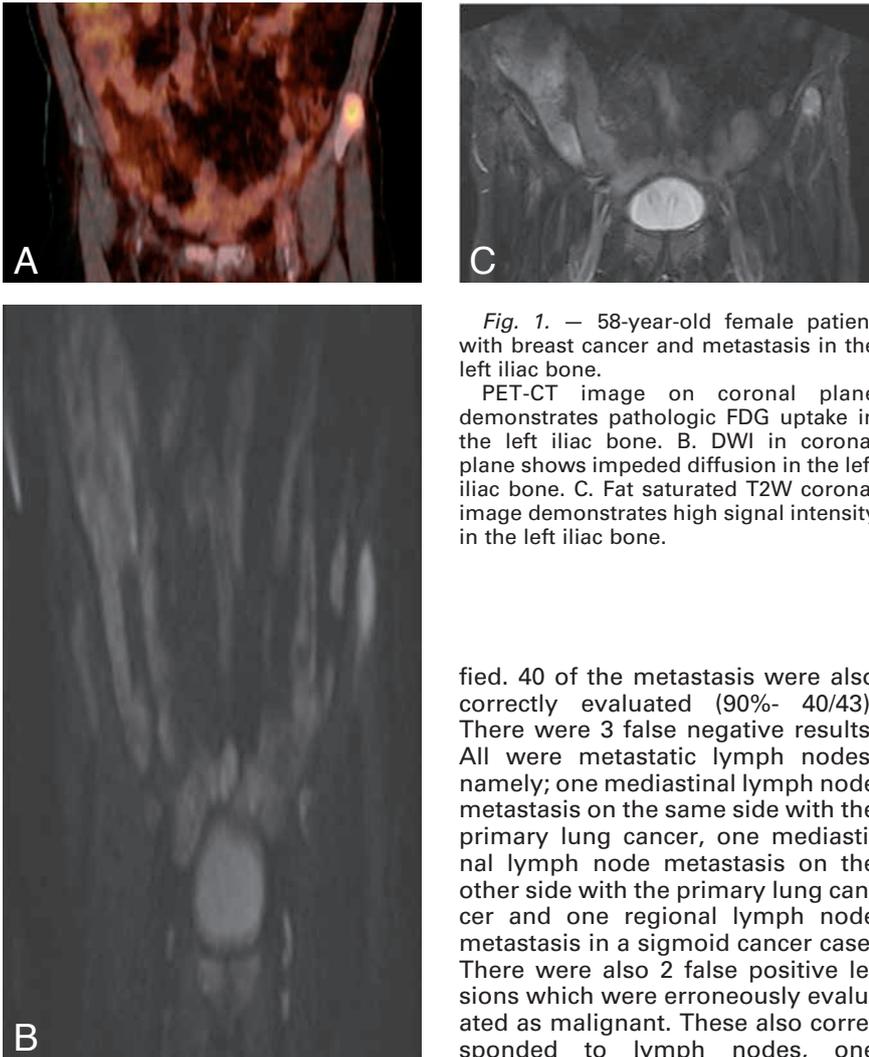


Fig. 1. — 58-year-old female patient with breast cancer and metastasis in the left iliac bone.

PET-CT image on coronal plane demonstrates pathologic FDG uptake in the left iliac bone. B. DWI in coronal plane shows impeded diffusion in the left iliac bone. C. Fat saturated T2W coronal image demonstrates high signal intensity in the left iliac bone.

fied. 40 of the metastasis were also correctly evaluated (90%- 40/43). There were 3 false negative results. All were metastatic lymph nodes, namely; one mediastinal lymph node metastasis on the same side with the primary lung cancer, one mediastinal lymph node metastasis on the other side with the primary lung cancer and one regional lymph node metastasis in a sigmoid cancer case. There were also 2 false positive lesions which were erroneously evaluated as malignant. These also corresponded to lymph nodes, one regional lymph node in a gastric cancer case and one mediastinal lymph node on the other side with the primary lung cancer.

In fat saturated T2W images, all of the primary lesions (n = 36) were correctly identified, as well. There were again 3 false negative results and all corresponded to metastatic lymph nodes (one mediastinal lymph node metastasis on the same side with the primary lung cancer, one regional lymph node metastasis in a colon cancer patient and one region-

al lymph node metastasis in a gastric cancer case. But T2W images demonstrated 8 false positive lesions as malignant. Five of these were lymph nodes (2 axillary lymph nodes in 2 breast cancer cases, one mediastinal lymph node on the same side in a lung cancer case, one mediastinal and one neck lymph nodes (region 3a) in 2 lymphoma patients), 2 were bone lesions and one was a liver lesion in patients with breast cancer.

According to these results, the sensitivity, specificity, positive and negative predictive values for WB-DWI for the detection of primary and metastatic lesions in patients with newly diagnosed malignancy in comparison to PET-CT were 96%, 89% , 97% and 84%, respectively. These are calculated as 96%, 56%, 90% and 77%, respectively for fat-saturated T2W images (Table II).

According to kappa analysis, the agreement between PET-CT and WB-DWI in the detection primary tumors and metastasis was excellent ($\kappa = 0.83$). However, it was found to be moderate ($\kappa = 0.58$) between PET-CT and fat-saturated T2 weighted images (Table II).

Discussion

For the detection and staging of malignant lesions as well as for monitoring the response to therapy, along with the morphologic evaluation, functional imaging methods play an important role (9-12). 18F-FDG PET and DWI are both functional imaging modalities and provide a high lesion-to-background contrast, although they are based on completely different biophysical and biochemical mechanisms (9-13).

FDG PET/CT is often regarded as one of the most accurate noninvasive diagnostic tools for whole-body oncologic imaging. Currently available data indicate that combined PET/CT is more sensitive and specific than PET alone. PET/CT combines the anatomic details depicted with

18 patients, a total of 43 metastatic lesions were detected. There was 22 lymph node metastasis, 8 liver metastasis, 4 lung metastasis, 8 bone metastasis and 1 adrenal gland metastasis. Together with the primary lesions, a total of 79 malignant lesions were detected (Table I).

In WB-DWI, all of the primary lesions (n = 36) were correctly identi-

Table II. — Diagnostic performance of WB-MRI in comparison to PET-CT findings.

	Sensitivity	Specificity	PPV	NPV	kappa analysis
DWI	96%	89%	97%	84%	$\kappa = 0.83^*$
Fat-sat T2W	96%	56%	90%	77%	$\kappa = 0.58^{**}$

DWI: Diffusion weighted imaging
 Fat-sat T2W: Fat saturated T2 weighted
 PPV: positive predictive value
 NPV: negative predictive value

* $\kappa = 0.83$ indicates excellent agreement between PET-CT and WB- DWI datasets.

** $\kappa = 0.58$ indicates moderate agreement between PET-CT and fat saturated T2W datasets.

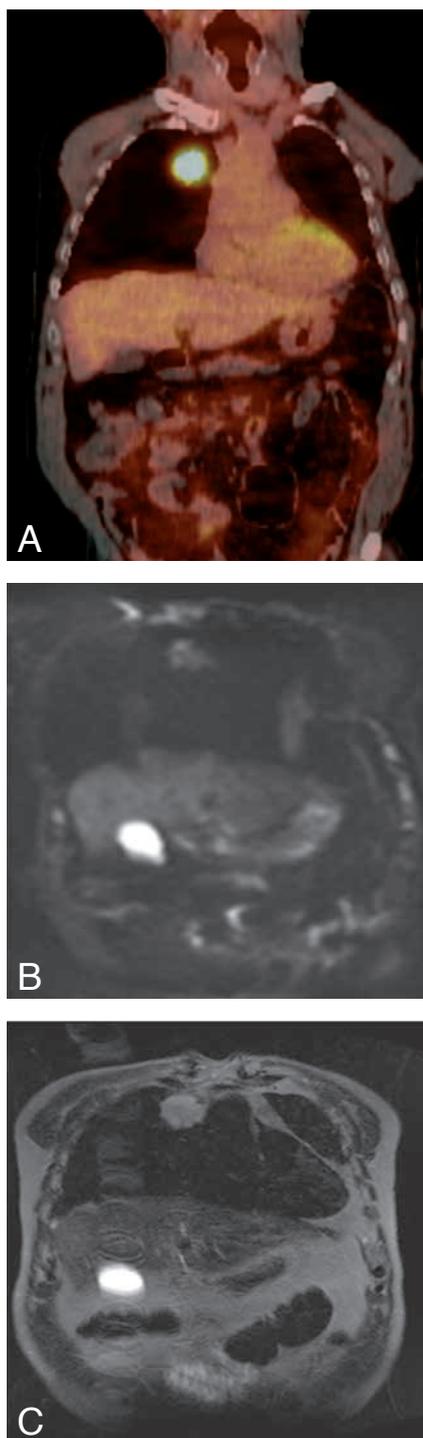


Fig. 2. — 57-year-old male patient with primary lung cancer in the right upper lobe with no metastasis. A. PET-CT image on coronal plane demonstrates pathologic FDG uptake in the mass lesion corresponding to primary lung cancer in the right upper lobe. B. DWI in coronal plane shows impeded diffusion in the mass lesion corresponding to primary lung cancer. C. Fat saturated T2W coronal image demonstrates high signal intensity in the mass lesion corresponding to primary lung cancer.

CT and metabolic information obtained with PET, yielding more precise anatomic information(1, 2, 9, 14, 15).

PET/MR is a new technology which is an integrated hybrid scanner performing simultaneous acquisition of PET and MRI. It may help to solve some of the limitations applying to PET/CT as well as providing a new tool for molecular imaging. Due to the absence of ionizing radiation in MRI, PET/MR will reduce the dose associated with the examination substantially by eliminating the radiation dose from the CT. This will be of importance in the handling of pediatric patients, but also adult cancer patients, where the dose from repeated PET/CT scans can sum up to substantial amounts of ionizing radiation. MRI also provides excellent soft tissue differentiation, and in this aspect is considered superior to CT, allowing more precise radiographic measurements of tumor location, size and invasion especially in areas with complex anatomy, such as the head and neck area and in the pelvis. In addition to routine anatomical MR imaging, a variety of MR acquisition sequences are also available which can yield images of biophysical, pathophysiological or functional properties of tissues. Therefore, by combining MRI and PET imaging, a more thorough information about cellularity and biological activity of the tumor can be achieved and the sensitivity and specificity in oncology staging can be improved. PET/MR will, like PET/CT, improve diagnostic power in several clinical scenarios, but the main indication for PET/MR in oncology remains to be defined. Currently, the clinical experience with PET/MR so far is scarce and no clinical indication for PET/MR has been established. The final clinical use of PET/MR in oncology will depend on the outcome of future prospective clinical studies (16-18).

DWI is a functional magnetic resonance technique, sensitive to the microscopic mobility of water (Brownian motion), due to its thermal movement. It is a completely non-invasive sequence, not requiring the administration of contrast medium and derives its image features from differences in the motion of water molecules through intra- and extracellular spaces (3-7) It yields information about the biophysical properties of tissues, such as cell organization and density, microstructure, and microcirculation (3-7)

The clinical application of whole-body MRI-DWI is under active inves-

tigation. In recent years, significant improvements in hardware and sequence design like echo-planar imaging (EPI) allow whole-body DWI to be used in daily imaging protocols (3, 4). Consequently, whole body MRI together with DWI has then emerged as an excellent candidate for staging and surveillance of patients with neoplastic disease and many authors have compared FDG-PET/CT and WB-MRI in oncology (9-13, 19, 20).

Manenti et al in their study of 45 patients, reported that detection rates of malignancy did not differ between WB-MRI with DWI and PET-CT, therefore concluded that WB-MRI with DWI should be considered as alternative tool to conventional whole-body methods for tumor staging and during follow-up in cancer patients (12).

Also Li et al. reported that DWI WB-MRI is a feasible imaging method in oncology, providing comparable results to PET imaging in 30 oncologic patients evaluated (4).

Similarly, in a systematic review Ciliberto et al concluded that; based on the literature findings, WB-MRI seems to be a valid alternative method compared to PET/CT in oncology (20).

In our study, in WB-DWI has high sensitivity and specificity for the detection of primary and

metastatic lesions (96% and 89%) in comparison to PET-CT. All of the false positive (n = 3) and false negative (n = 2) results corresponded to lymph nodes.

Regarding the mediastinal lymph nodes, we think that the main reason of misevaluation, either for false positive or false negative results, was motion artefacts due to heart beats and diaphragm movements as DWI is very sensitive to incoherent tissue motion resulting in signal loss. This issue has also been noted in several previous studies (10-13, 20). Combining DWI with cardiac triggering may help to solve the problem of cardiac motion-induced signal loss, although this may increase the imaging time as well (20).

In case of the regional lymph nodes which were erroneously determined, the main reason was thought to be low anatomical resolution along with the partial volume-averaging effects, which may have hampered the differentiation of the lymph nodes from the primary lesion itself.

Fat saturated T2W images has the same high sensitivity for the detection of primary and metastatic

lesions, compared to WB-DWI. However, the specificity is significantly lower (56%). In case of misdiagnosed lymph nodes; both false positive (n = 3) and false negative (n = 5), the main reason was probably the inability of morphologic imaging alone in determining the metastasis while size-based assessment typically fails in enlarged lymph nodes from inflammation and in normal-sized lymph nodes with micrometastases. In case of bone lesions (n = 2) and liver lesion (n = 1) the differentiation of malignant from benign was limited.

These short-comings can be minimized by combining the information provided by WB-DWI and conventional sequences. By this way, functional information can be added to the high contrast and spatial resolution. Several previous studies also encourage the combined use DWI with morphological images for accurate evaluation(11, 13, 20).

Limitations

A possible limitation of our study is related to the reference standard used. We assessed the diagnostic performance of WB-MRI considering PET/CT as a reference standard. This is a possible source of bias, because PET/CT has its own limitations, mainly due to the possibility of false-positive or false-negative results, which could affect the diagnostic accuracy calculated for WB-MRI. However, the primary lesions were all confirmed by histopathology and metastatic lesions were confirmed by follow-up over 6 months or biopsy. Therefore, we aimed to overcome this problem.

Another limitation of this study was the relatively small sample size, necessitating future studies. Also, in our study we evaluated different types of tumors together. Comparison of WB-MRI to PET/CT in certain tumour types may be more specific.

Conclusion

In our study, when compared to PET-CT, WB-DWI, demonstrated high diagnostic performance for the detection of primary and metastatic

lesions in patients with newly diagnosed malignancies

With the availability of integrated morphological and functional data, WB-MRI with DWI is emerging as a promising alternative imaging tool in the evaluation of cancer patients and may eventually become complementary to PET-CT in several clinical applications.

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