ABSTRACT

Purpose: The aim of our study was to determine which imaging method was superior in detecting brain metastases by comparing contrast-enhanced MRI and 18F FDG PET / MRI which were obtained simultaneously. Methods: From August 2015 to December 2018, 480 consecutive patients with histopathologic proven primary malignancy (188 men and 292 women; mean age ± standard deviation, 45 years ± 25.4) were retrospectively evaluated. All patients underwent 18F-FDG PET/MRI during follow-up of their malignancies. Results: Brain metastases (BM) were found in 33 (25 Female and 8 Male) of 480 patients. Contrast-enhanced MRI revealed 190 brain metastases (BM) in 33 patients (100%), while 18F-FDG PET data was accurately identified 50 (26.3%) BM lesions in 16 (48.5%) patients. Based on measurements on contrast enhanced MR images, maximum BM lesion size was 40.1mm (mean: 6.64mm ± 6.39mm, range: 0.9mm-40.1mm). Mean lesion size ± SD was 12.88 ± 8.13mm in 18F-FDG PET/MRI detectable lesions. Conclusion: Contrast-enhanced brain MR is more likely to detect brain metastases than 18F-FDG PET / MRI, and is still the gold standard imaging method for the detection of brain metastases.

KEYWORDS PET / MRI, contrast-enhanced MRI, brain metastases
Materials and Methods

Patients
The institutional ethics board (Istanbul training and research hospital domestic ethics committee, 26/07/2019-1924) approved the study, and since the study was a retrospective study, informed consent was not obtained.

The patients were referred to the radiology department for PET/MRI from different departments such as: haematology, radiation oncology, medical oncology, gynecologic oncology, breast, lung and hepatobiliary surgery departments for routine staging and evaluation of treatment in oncologic patients. From August 2015 to December 2018, 480 consecutive patients with histopathologic proven primary malignancy (188 men and 292 women; mean age ± standard deviation, 45 years ± 25.4) underwent 18F-FDG PET/MRI during follow-up of their malignancies, were evaluated retrospectively.

PET/MRI Protocol
All cases were fasted at least 8 hours before the examination. Measurement of blood sugar (BS) was performed with a blood glucose meter (FreeStyle; Abbott Laboratories, Abbott Park, IL) prior to imaging to ensure it was less than 180 mg/dL.

All cases first underwent routine whole-body PET/MRI 60 minutes after intravenous injection of a bodyweight-adapted dose of 18F-FDG (mean dose, 3.5 MBq per kilogram of body weight + 1; range, 185–370 MBq). Patients were positioned head-first, and imaging was performed in the caudo-cranial direction from vertex to mid-thigh. The images were acquired by an integrated 3 T hybrid PET/MRI system (“Biograph mMR, Siemens Healthcare GmbH, Erlangen, Germany”) with a 16-channel head and neck and three 12-channel body coils. These body coils were combined to form a multichannel whole-body coil using total imaging matrix technology. The whole body images were obtained in five to six-bed positions according to the patient’s size.

The PET data were acquired simultaneously during MRI acquisition. For the attenuation correction four-point, Dixon images were acquired in the coronal plane. All patients underwent 18F-FDG PET/ MRI under whole-body MRI protocol (from vertex to mid-thigh). The whole-body MRI protocol consisted of both unenhanced and contrast-enhanced images to provide the most comprehensive oncologic imaging dataset in the routine of our institution. The post-contrast sequences were acquired after a bolus injection of a single dose of 0.2 mL/kg paramagnetic contrast agent with a flow rate of 2mL/s (“Dotarem, Guerbet, Sulzbach/Taunus, Germany”). Non-contrast MRI protocol consisted of “T2-weighted(w) Half-Fourier Acquisition Single-shot Turbo spin-Echo (HASTE)” (TR 1500ms/TE 87ms) in coronal and additionally transverse plane for abdomen, T1-w turbo flashes in the transverse plane (TR 1800ms/TE 2.4m/s), diffusion-weighted images (b0 and 800 s/mm²) using EPI technique in the transverse plane (Σ=30 min). After non-contrast images, triphasic dynamic contrast-enhanced T1 weighted fat-saturated (FS) 3D Volume-Interpolated Breath-hold Examination (VIBE) (TR 4.56ms/TE 2.01ms) covering the upper abdomen, whole-body FS coronal 3D T1-w VIBE Dixon, and late transverse 3D T1-w FS VIBE for the brain (Σ=30 min), and all sections were composed resulting in uninterrupted whole body coverage. Detailed information regarding the whole body 18F-FDG PET/MRI protocol is shown in Table 1. The total scan duration of the PET/MRI examination was 50-60 minutes.

Image Interpretation
All datasets were analyzed using dedicated viewing software (Syngo Via; Siemens Healthcare) for hybrid imaging. Two radiologists blinded to disease stage patients data analyzed the images separately in a random order within two steps. All decisions were made with the agreement of both. First, the non-contrast dataset was evaluated using non-contrast MR images, 18F-FDG PET/ MRI fusion images, and attenuation corrected raw data PET images. The contrast-enhanced dataset was evaluated by reviewing contrast-enhanced MR images. The presence, number, and size of the brain metastatic lesions were recorded for both protocols.

Statistical Analysis
Variables were given as means ± standard deviations. The distribution of variables was analyzed with Kolmogorov Simirnov Test. One way ANOVA test was applied for comparison of non-categorical variables between subgroups. ROC curve was used to determine the cut-off point. Mann-Whitney U test was used to compare independent non-parametric variables. Z test also was applied to compare independent proportions in subgroups. A p-value less than 0.05 was considered to indicate a significant difference. For all statistical analyses, IBM SPSS software, version 22.0 (IBM, Armonk, NY), was used.

Results
Brain metastases (BM) were found in 33 of 480 patients. Consequently, contrast-enhanced MRI recognized BM in 33 patients (100%) while PET data was accurately identified in 16 (48.5%) patients (figure 1 and 2). A total of 190 BM lesions were detected by contrast-enhanced MRI, while only 50 BM lesions out of 190 were detected on 18F-FDG PET/MR images. Moreover, 18F-FDG PET/MR failed to detect any additional metastatic lesions.

Images of 33 patients (25 female and 8 male) having 190 BM lesions were evaluated. Primary malignancy was breast in 16 (48.5%) patients with 32 (16.8%) BM lesions, lung in 7 (21.2%) patients with 40 (21.1%) BM lesions, melanoma in 3 (9.1%) patients with 93 (48.9%) BM lesions, brain in 2 (6.1%) patients with 10 (5.3%) BM lesions, melanoma (p=0.001) and ovary (p=0.005). Also, BM lesions due to primary brain malignancy were significantly larger compared to malignant melanoma (p=0.001) and ovary (p=0.005). Also, BM lesions due to primary brain malignancy were significantly larger than BM lesions due to malignant melanoma (p=0.03) and ovary (p=0.016).

Only 50 (26.3%) BM lesions out of 190 were detected on 18F-FDG PET/MR images. The source of metastatic BM lesions visible in 18F-FDG PET/MR was melanoma in 29 lesions, breast...
### Table 1: Routine institutional MR imaging protocol for whole body PET/MRI.

| Sequence                        | Plane | Slice Thickness (mm) | Gap (mm) | TR/TE (ms) | Matrix     | Resolution (mm²) |
|---------------------------------|-------|----------------------|----------|------------|------------|-----------------|
| DWI (b=0.800 s/mm²)            | axial | 6                    | 0.6      | 7200/81    | 126×128    | 128/100         |
| T1 Weighted Turbo Flash         | axial | 5                    | 1        | 1600/2.46  | 194×320    | 320/81          |
| T2 Weighted HASTE               | coronal | 5                  | 1        | 1500/87    | 320×320    | 320/100         |
| 3D FS VIBE                      | axial | 3                    | 0        | 4.56/2.01  | 195×320    | 320/75          |
| 3D VIBE FS DIXON                | coronal | 1.9                | 0        | 4.02/1.23  | 149×288    | 288/75          |
| 3D FS VIBE for brain            | axial | 1                    | 0        | 9.5/3.69   | 256×320    | 320/80          |

### Table 2: Distribution of BM lesion sizes according to the primary malignancy.

| Primary Malignancy | Lung          | Breast         | Melanoma       | Ovary        | Brain          | Pancreas       | Stomach        | Neuroendocrine |
|--------------------|---------------|----------------|----------------|--------------|----------------|----------------|----------------|----------------|
| Mean ± SD BM Lesion Size (mm) | 7.08 ± 5.64 | 10.37 ± 9.92 | 5.29 ± 3.72 | 2.68 ± 0.89 | 11.25 ± 11.01 | 3.4            | 2              | 5.2            |
| Number of metastatic lesions | 40           | 32             | 93             | 10           | 10             | 1              | 3              | 1              |

**Figure 1** A 50 year old male with metastatic adenocarcinoma of lung. The 6mm cortical metastasis lesion in left temporal lobe is visible in both (a) post-contrast coronal T1 VIBE (b) coronal PET MRI fusion series.

in 11 lesions, lung in 7 lesions, brain in 2 lesions and neuroendocrine tumour subgroup in 1 lesion.

None of the BM lesions from the ovary, stomach, and pancreas was detected on 18F-FDG PET /MRI (figure 3). Mean

**Figure 2** A 69 year old male patient with melanoma. (a) Post-contrast axial T1 VIBE and (b) axial PET MRI fusion images depicted 12mm BM lesion which is visible in both images (white arrow). Tiny BM lesions (3-5mm) are only seen in post-contrast T1 VIBE series as small enhancing foci (asterisks).
lesion size ± SD was 12.88±8.13mm in 18F-FDG PET/MRI detectable lesions, while it was 4.41±3.64 in lesions not detected in 18F-FDG PET/MR images. Lesions detected by 18F-FDG PET/MRI were significantly larger (p=0.000). ROC curve analysis for BM lesion size in predicting its visibility on 18F-FDG PET/MRI showed a cut-off point of 7.3mm, with a sensitivity of 88%, specificity of 91% and AUC of 0.927 (Figure 4).

**Figure 3** A 38 year old female with metastatic invasave ductal carcinoma of breast. Post-contrast axial T1 VIBE series (a) show a 25mm enhancing lesion in right temporal lobe (white arrow). The lesion is not detectable in axial PET/MRI fusion series (b) and is seen as hypometabolic area.

**Figure 4** ROC curve analysis for BM lesion size in prediction of its visibility on PET/MRI.

The detectability of BM lesions on 18F-FDG PET/MRI images is shown in Table 3. The highest detectability was observed in BM lesions from breast and melanoma (34.37% and 31.18%, respectively). There were no statistically significant differences in the detectability rates of the lesions according to the primary malignancy.

**Discussion**

The results of this study confirmed the superioriy of contrast-enhanced brain MR images over 18F-FDG PET/MRI in the detection of untreated BMs from different sources. We allocate this success of contrast MRI to the acquisition of delayed contrasted images, which is effective in detecting small lesions. Contrast-enhanced brain MRI is currently accepted as the gold standard in the detection of brain metastases [4]. This higher success rate is linked to the delayed phase contrast-enhanced series [12-14]. Previous studies have applied various delay times. Kushnirsky et al. have found that 15 min delayed images lead to the detection of at least one more lesion in 43% of the patients [12]. Yuh et al. have found that 20 minutes of delayed examination could be optimal for the detection of lesions smaller than 10mm [13]. Schörner et al. have also shown that 8.5 minutes delayed images increased tumour signal intensity [14]. Time-delayed imaging may be particularly advantageous in the posterior circulation [15,16]. In our study, the evaluation was performed over 15 minutes delayed series as reported by Kushnirsky et al.

To our knowledge, there is only one study in the literature that has compared 18F-FDG PET/MR with contrast-enhanced MRI in the detection of BMs from non-small cell lung cancer [11]. In this study, Deuschl et al. detected 39 BMs in 15 patients with brain MRI while they detected only 15 BMs in 6 patients with 18F-FDG PET/MR. In this study, more lesions were detected in contrast-enhanced MRI as in our study, and no lesions were detected in 18F-FDG PET/MRI in addition to the ones already detected in contrast-enhanced MRI. This study resembles ours in terms of the nuclear tracer used to obtain PET/MRI and the comparison of contrast-enhanced MRI and PET/MRI. However, it included only non-small cell lung cancer patients, whereas our study included a wide variety of malignant tumours.

There are several studies comparing contrast-enhanced MR and 18F-FDG PET/CT in the evaluation of brain metastases, and they reported that contrast-enhanced brain MR was superior to PET/CT in the detection of metastases. The size of BM is an essential factor in the sensitivity of detection in PET, and 18F-FDG PET/CT is insufficient to detect very small lesions [17, 18]. A cut-off point of 7.3mm with a sensitivity of 88% and specificity of 91% was determined for PET discernible lesions in our study, consistent with the results of Deuschl et al. distinguishing smaller lesions from the surrounding hypermetabolic brain tissue is problematic. At the same time, isotropic post-contrast MR sequences provide higher resolution images that can depict even tiny damaged blood-brain barrier foci which occurs in BMs [11].

Li et al. performed a meta-analysis of 5 studies that compared contrast-enhanced brain MRI and 18F-FDG PET/CT in diagnosing brain metastases in lung cancer patients. According to this meta-analysis report, contrast-enhanced MRI was more sensitive than 18F-FDG PET/CT in diagnosing brain metastases of lung cancer [19].

In recent years, studies have especially focused on assessing brain metastases using PET/MRI and whether PET/MRI can be used to distinguish between tumour recurrence or progression and radiation necrosis. Most of these studies have demonstrated that PET/MRI is indeed successful for this purpose [8-10]. Amino acid analogues were used as a tracer in these studies. In our study, brain metastases were evaluated in patients with different tumours and who underwent whole-body PET/MRI with 18F-FDG tracer for routine staging. That is, examinations were not performed with tracer specific for brain metastasis only. As is known, routine studies are usually performed with FDG-PET. BMs of malignancies with lower affinity to 18F-FDG could be missed on 18F-FDG PET. However, we know that contrast-enhanced MRI is superior to detecting metastatic lesions [17], and in our study, delayed contrast-enhanced MRI revealed all metastases.

Our study has some limitations. First, the number of metastases included in the study was relatively low. Second, there are no histopathologic diagnoses for the metastatic lesions. How-
Table 3 Detectability of BM lesions on 18F-FDG PET/MRI based on primary malignancy.

| Primary Malignancy | Lung | Breast | Melanoma | Ovary | Brain | Pancreas | Stomach | Neuroendocrine |
|--------------------|------|--------|----------|-------|-------|----------|---------|---------------|
| Lesions Detected on 18F-FDG PET/ MR in each group (%) | 7 (17.5%) | 11 (34.37%) | 29 (31.18%) | 0 (0%) | 2 (20%) | 0 (0%) | 0 (0%) | 1 (100%) |
| % in Total 18F-FDG PET/MR Detected Lesions | 21.1% | 16.8% | 48.9% | 5.3% | 5.3% | 0% | 0% | 0.5% |

ever, the presence of multiple lesions and a primary tumour focus of the patients and the presence of new brain lesions in follow-up examinations reveal that the lesions are metastases. Third, 18F-FDG has been used as a tracer for obtaining PET / MR sections, and it is stated that amino acid analogues have greater diagnostic efficacy than 18F-FDG. This is due to the fact that normal grey matter has a high physiologic glucose metabolism [20]. Diagnostic studies of PET / MRI in this area can be demonstrated in detail by comparing PET / MRI sections using amino acid analogues and contrast-enhanced brain MR sections.

In the future, further studies that compare PET/MRI sections using amino acid analogues with contrast-enhanced brain MR sections can improve the diagnostic efficacy of PET / MRI.

In conclusion, contrast-enhanced brain MR is more likely to detect brain metastases than 18F-FDG PET / MRI and is still the gold standard imaging method for the detection of brain metastases.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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