RESEARCH ARTICLE

Diagnostic Value of ^{18}F-FDG PET/CT in Comparison to Bone Scintigraphy, CT and ^{18}F-FDG PET for the Detection of Bone Metastasis

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Abstract

    <u>Purpose</u>: To evaluate the diagnostic value of ^{18}F-FDG PET/CT for detection of bone metastasis in comparison with the efficacies of ^{18}F-FDG PET/CT, CT, ^{18}F-FDG PET and conventional planar bone scintigraphy in a series of cancer patients. <u>Methods</u>: Five hundred and thirty patients who underwent both ^{18}F-FDG PET/CT and bone scintigraphy within 1 month were retrospectively analyzed. The skeletal system was classified into 10 anatomic segments and interpreted blindly and separately. For each modality, the sensitivity, specificity, accuracy, PPV and NPV were calculated and the results were statistically analyzed. <u>Results</u>: Bone metastases were confirmed in 117 patients with 459 positive segments. On patient-based analysis, the sensitivity, specificity, accuracy, PPV and NPV of ^{18}F-FDG PET/CT were significantly higher than bone scintigraphy, CT and ^{18}F-FDG PET ($P<0.05$). On segment-based analysis, the sensitivity of CT, bone scintigraphy, ^{18}F-FDG PET and ^{18}F-FDG PET/CT were 70.4%, 89.5%, 89.1% and 97.8%, respectively ($P<0.05$, compared with ^{18}F-FDG PET/CT). The overall specificity and accuracy of the four modalities were 89.1%, 91.8%, 90.3%, 98.2% and 90.3%, 90.9%, 89.8%, 98.0%, respectively ($P<0.05$, compared with ^{18}F-FDG PET/CT). The PPV and NPV were 89.8%, 87.6%, 85.6%, 97.2% and 85.6%, 93.2%, 92.8%, 98.6%, respectively. Three hundred and twelve lesions or segments were presented as lytic or sclerotic changes on CT images at the corresponding sites of increased ^{18}F-FDG uptake. In lytic or mixed lesions, the sensitivity of ^{18}F-FDG PET/CT and ^{18}F-FDG PET were better than bone scintigraphy, while in osteoblastic lesions bone scintigraphy had a similar performance with ^{18}F-FDG PET/CT but better than ^{18}F-FDG PET alone. <u>Conclusion</u>: Our data allow the conclusion that ^{18}F-FDG PET/CT is superior to planar bone scintigraphy, CT or ^{18}F-FDG PET in detecting bone metastasis. ^{18}F-FDG PET/CT may enhance our diagnosis of tumor bone metastasis and provide more information for cancer treatment.

    Keywords: ^{18}F-FDG - PET-CT - bone scintigraphy - CT - bone metastasis

Introduction

    Diagnostic images have played notable roles in bone metastasis detection of malignancy, such as radiography, planar bone scintigraphy (BS), single photon emission computed tomography (SPECT), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and recently PET/CT (Rybak et al., 2001). BS has been utilized for the evaluation of oncological patients and considered a routine role for the assessment of bone involvements for many decades. However, more recent reports have raised doubts whether BS is as effective enough as was previously perceived. Early metastasis lesions may be missed because the sensitivity of BS relies on the identification of osteoblastic

reaction rather than the detection of the tumor cells. Furthermore, the low spatial resolution and low sensitivity to assess treatment response also restrict the application of BS.

    As the most widely accepted metabolic imaging modality, ^{18}F-deoxyglucose (FDG) PET demonstrates apparent advantages in providing information with regard to metastasis localizations both in soft tissue and skeletal (Fogelman et al., 2005). With tracer accumulation ^{18}F-FDG PET visualizes regions of enhanced metabolic activity and complements other imaging modalities based on structural anatomic changes (Wu et al., 2013). ^{18}F-FDG PET had a better performance in esophagus, thyroid, nasopharyngeal and lung carcinoma (Kato et al., 2005; Shinji et al., 2007; Liu et al., 2010; Chang et al., 2013)

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when compared with the isotope BS. For lymphoma and particularly breast carcinoma, some clinical evidences enhanced the result. But there were conflicting evidences that ^{18}F-FDG PET was less sensitive than BS in breast and colon cancer. It seemed that the diagnosis value of PET was tumor specific (Shie et al., 2008; Choi et al., 2012; Montini et al., 2012). The morphological types of the metastasis lesions appeared to be relevant with FDG uptake, too. ^{18}F-FDG PET might have better sensitivity and specificity in lytic or mixed lesions but inferior values in sclerotic lesions (Yuji et al., 2005). Because of these contradictory reports as to the efficacy of PET scanning, it is thus of utmost importance to elucidate the exact value of ^{18}F-FDG PET in bone metastasis and introduce more powerful modalities.

Progresses in imaging technology, especially PET/CT scanning for guidance, have greatly increased the sensitivity and specificity of tumor imaging. Improved spatial resolution, absolute quantization and complementation of CT and PET are also of potential benefits. PET/CT might own higher performance in the diagnosis of bone metastasis. Most of the current data on the role of ^{18}F-FDG in bone metastasis came from dedicated PET. Some pilot study of PET/CT using ^{18}F-Fluoride has been made. To our knowledge, there is little literature available on the diagnosis of bone metastasis with hardware fusion ^{18}F-FDG PET/CT (Yuji et al., 2005).The objective of the current study was to evaluate the incremental value of ^{18}F-FDG PET/CT in bone involvements. We hope to provide more evidences on detecting bone metastasis of ^{18}F-FDG PET/CT in comparison with planar BS, CT and ^{18}F-FDG PET. We conducted this paper to more realistic stratification in patients with bone metastasis and those who were in fact suffering from advanced cancer.

Materials and Methods

Patient Selection

Five hundred and thirty patients (from October 2007 to October 2010 of Shandong Tumor Hospital) who underwent both ^{18}F-FDG PET/CT and BS within 1 month were retrospectively analyzed. Those had bisphosphonate therapy, local therapy approach with external beam radiotherapy or granulocyte colony stimulating factor (less than one month) were excluded. All procedures followed the clinical guidelines of Shandong Cancer Hospital and were approved by the ethical committee. The patients gave their informed consent for performance of the study and for retrospective evaluation of their files.

The patient population included 41 female and 72 male patients with a mean age of 55.9±12.6 (range 21-85y) years. The primary malignancies included 113 solid tumors (31 patients with lung cancer, 21 patients with breast cancer, 16 patients with esophagus cancer, 15 patients with gastric cancer, 8 each with colon and nasopharynx cancer, 3 each with malignant melanoma, hepatic cancer and Cervix uteri cancer, 2 patients with ovary cancer, and one each with submandibular glands, dacryocystis and Uterine endometrium cancer), as well as 4 patients with lymphoma.

Planar Bone Scintigraphy

Planar images of the entire skeleton in the anterior and posterior positions were acquired 2-3h after intravenous injection of 694.2±109.3MBq 99mTc-methylene diphosphonate (99mTc-MDP) using a dual-head camera (Infinia H3000 WT, GE Medical Systems) equipped with a high-resolution low-energy general-purpose, parallel-hole collimator. No SPECT was used in this analysis.

^{18}F-FDG PET/CT Study

Patients fasted for 4-6h before the ^{18}F-FDG PET/CT examination. Blood glucose level was checked (<10 mmol/L) before the injection of 365.1±44.1 MBq (9.8±1.2 mCi) ^{18}F-FDG intravenously. Patients rested for 60 min. Half-body (from head to midthigh) PET and non-contrast-enhanced CT were performed using a hybrid PET/CT system (Discovery LS, GE Healthcare, USA), combining a GE Advance NXi PET scanner with a 4-slice helical CT. Firstly, the CT scan was performed with 140 kV, 80 mA, 0.8s per tube rotation, a pitch of 6, a slice thickness of 4.25 mm, and a table speed of 22.5 mm/s, without any specific breathing-holding instructions. A PET emission scan was performed immediately after acquisition of the CT, without changing the patient's positioning. From 5 to 9 bed positions were performed with an acquisition time of 4 min for each. PET images were reconstructed with CT-derived attenuation correction using an ordered-subset expectation maximization algorithm. The acquired images were viewed with software providing multiplanar reformatted images of PET, CT and fused data with linked cursors (Xeleris workstation, GE Healthcare, USA).

Image Analysis

Images of BS, CT, ^{18}F-FDG PET, and ^{18}F-FDG PET/CT were interpreted blindly and separately. The images of BS were interpreted by two experienced nuclear medicine physicians, PET and PET/CT images by 2 experienced nuclear medicine physicians, and CT images by one double board-certified nuclear medicine physician and radiologist and one board-certified radiologist.Each image was performed to 10 separate areas (Skull, Cervical spine, Thoracic spine, Lumbar spine, Sacrum with coccyx, Pelvis, Long bone (Upper and lower extremities), Sternum, Ribs, Scapula and clavicle) and each site of abnormally increased uptake of 99mTc-MDP or ^{18}F-FDG was recorded and categorized as normal, malignant or equivocal. Suspected focal bone marrow infiltrations by ^{18}F-FDG PET were compared with morphological changes in the corresponding CT scan (Shinji et al., 2007; Shie et al., 2008). Lesions were diagnosed as metastases if they were associated with characteristic morphological changes on CT. If no abnormalities were on CT at the corresponding location with the PET abnormality, the PET/CT lesion was categorized as equivocal. If there were major disagreements, the lesion was then reevaluated by both readers together. Patients were monitored for at least 6 mo (7.2±2.4 mo; 6-12 mo) and the medical records were reviewed with an attempt to get a final diagnosis of equivocal lesions. Imaging follow-up was performed with histopathology, contemporaneous diagnostic full-dose CT, MRI or BS. For the CT components, each lesion was

Table 1. Incidence of Bone Metastases in Bone Segments and Histological Types

| Bone segments	Bone segments with metastasis (no.)	Histopathologic types	No. of patients
Cervical spine	23	Squamous carcinoma	33
Thoracic spine	119	Adenocarcinoma	43
Lumbar spine	88	Adenosquamous cell carcinoma	4
Sacrum with coccyx	21	Lymphoma	4
Pelvis	63	Undifferentiated carcinoma	15
Long bone	34	Malignant melanoma	3
Sternum	19	borderline tumors	6
ribs	46	Hepatic carcinoma	3
Scapula and clavicle	28	Adenoid cystic carcinoma	1
skull	18	Bronchioloalveolar carcinoma	5
Total	459	Total	117
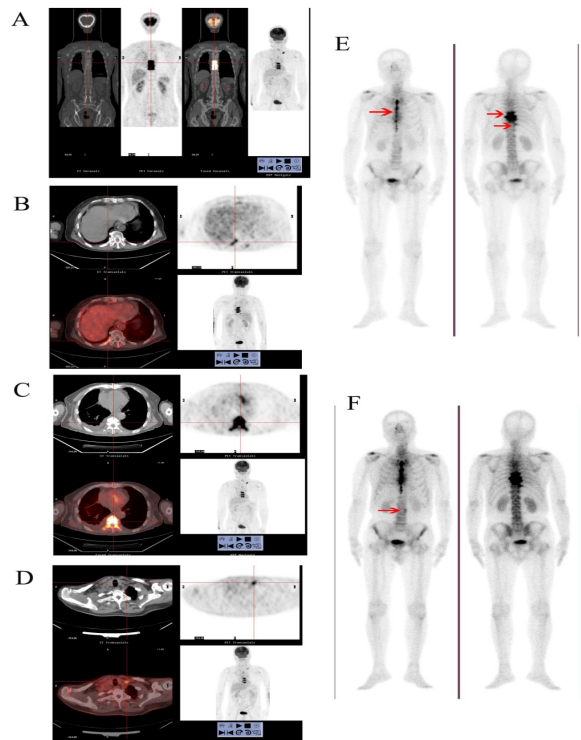
Figure 1. Lesions Missed on CT Components but was Displayed in PET Components in a 65-year-old Male after Lung Carcinoma Resection. T3 vertebra was missed and the T4 vertebra metastasis was precisely detected. (A-D) T3 vertebra: (F-I) T4 vertebra: (A, F)-CT, (B, G)-PET, (C, H)-Fusion images, (D, I)-Coronal view, (E)-Planar bone scintigraphy: anterior and posterior views

further defined as osteolytic, osteoblastic or mixed changes and compared with BS or ¹⁸F-FDG PET results (Osteolytic and mixed lesions combined as a single group).

Statistical Analysis

Comparison of bone metastases by planar BS, CT, ¹⁸F-FDG PET and ¹⁸F-FDG PET/CT was performed using the McNemar test with *P*< 0.05 being statistically significant.

Results

Patient-Based Analysis

Of the 530 patients, 117(22.1%) were finally diagnosed to have bone metastasis based on definitive PET/CT findings, biopsy, and imaging follow-up. Thirty-nine
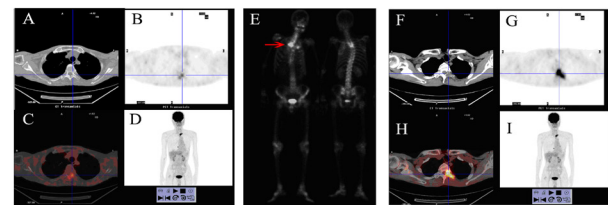

Figure 2. L3 Vertebra were Missed on PET-CT in a 50-year-old Male of Lung Adenocarcinoma: (A-C)18F-FDG uptake in the Sternum, posterior segment of the 10th rib and T7-T9 vertebras. (D) Lymph nodes metastasis. (E-F) 99mTc-MDP bone scintigraphy (anterior and posterior views): Bone involvements in sternum, rib, T7-T9 vertebras and L3 vertebra

patients (7.4%) were newly diagnosed and 78 were referred for evaluation of suspected recurrence or progression. The histopathologic types of the tumors and the positive segments were listed in Table 1. On patient base analysis The sensitivity of CT, BS, PET and PET/CT were 69.2%, 84.6%, 88.0% and 96.6%, respectively (*P*<0.05, compared with PET/CT). The overall specificity and accuracy of the four modalities were 90.8%, 88.4%, 96.1%, 91.3%, 98.8% and 86.0%, 93.6%, 90.6%, 98.3% respectively (*P*<0.05, compared with PET/CT). Our data also showed difference between bone metastasis and tumor cell differentiation. Poorly, median, well and borderline differentiated samples were 66, 29, 20 and 2 respectively, which reflected that the biological behavior of tumor owe to its cell differentiation.

Segment-based analysis

Bone metastases were confirmed in 459 (8.7%) lesions based on the definitive segments, imaging findings, histopathology and imaging follow-up. The spine was the most commonly affected site and the preferable sequence was Thoracic spine > Lumbar spine> Pelvis> Ribs> Long bone> Scapula and clavicle> Cervical spine> Skull> Sacrum with coccyx> Sternum. Four hundred and seventy-eight lesions were found to have increased ¹⁸F-FDG uptake which were classified through consensus of the two readers as being probable or definite bone metastases. Among these 478 lesions, 409 lesions in 103 patients were considered to represent true-positive findings of bone metastases. Corresponding morphologic findings of metastasis were identified at CT for 312 lesions in 81 patients. Ninety-seven of the 409 lesions that didn't show definite morphologic changes at CT were judged to be true-positive for bone metastasis on the basis of findings of progressive disease at follow-up PET (4 lesions in 1 patients), CT (5 lesions in 2 patients), BS (66 lesions in 13 patients) or radiography (3 lesions in 1 patients) or on the basis of concordant MRI imaging results (5 lesions in 2 patients). Because all of the patients with the remaining 14 lesions in 3 patients were found to have other lesions at biopsy or definite morphologic changes on CT images, these lesions were clinically considered, on the basis of all available data, to be true-positive. On the other hand, 69 of the 478 lesions in 36 patients were categorized as non-osseous lesions (60 lesions in 31 patients) or false-positive findings (9 lesions in 5 patients) owing to the fact that no progressive disease was seen during the follow-up period. Ten lesions were missed (false-negative) by combined

^{18}F-FDG PET/CT images which including 5 lesions in the lower extremities, 4 lesions in the spine and 1 lesion in the rib. The sensitivity of CT, BS, PET and PET/CT on the lesion-based analysis were 70.4%, 89.5%, 89.1% and 97.8%, respectively ($P<0.05$, compared with PET/CT). The overall specificity and accuracy of the four modalities were 89.1%, 91.8%, 90.3%, 98.2% and 90.3%, 90.9%, 89.8%, 98.0% respectively ($P<0.05$, compared with PET/CT). The PPV and NPV of the four modalities were 89.8%, 87.6%, 85.6%, 97.2% and 85.6%, 93.2%, 92.8%, 98.6%, respectively ($P<0.05$, compared with PET/CT). Two hundred and twenty-four lesions showed characteristic osteoblastic metastases and 99 lesions were lytic or mixed lesions. In lytic or mixed lesions, the sensitivity of PET was better than BS while in sclerosis lesions the sensitivity of BS were similar to PET/CT but higher than PET alone ($P<0.05$). Figure 1 showed a lesion missed on hybrid CT in 65-year-old male. Figure 2 showed that a third lumbar vertebra lesion was missed on PET/CT when compared with BS though PET/CT offered much more information with simultaneously describes lymph nodes metastasis.

Discussion

Bone metastasis is a critical event in cancer patients. Our data of 530 patients showed that 39 patients were newly discovered of bone metastasis and simultaneously the staging and treatment plans were modified. Interestingly, metastases didn't affect the bones with the same pattern and frequency, but generally, preferred the spine and pelvis which should be paid more attention in advanced cancer patients. The crucial events of bone metastasis enhanced the role of imaging modalities. Many methods have proved their values, but unfortunately, all non-invasive techniques in current use have imperfect abilities.

Our work showed that CT was still a potent tool to identify bone metastasis though BS and PET may have even better performances. The relatively low cost and widespread availability make CT a convenient tool for screening skeleton. Destruction of the bone by tumor invasion causes a different absorption of X-Ray. The amounts, distribution and disturbance of blood vessels in metastasis sites can also be displayed by enhancement scanning. CT components of PET/CT can give precise locations of the metastasis sites and further describe the morphological changes with osteoblastic or lyitc. CT is also a vital choice for initial evaluation the risk of bone fractures (Shie et al., 2008).

BS with 99mTc-MDP, a Technetium based agent, has been used extensively in bone involvements for several decades. BS offers the advantages of total body examination and relatively higher sensitivity than X-ray. Our work showed that BS was still a notable tool in bone metastasis though its lower sensitivity and specificity made it inferior in a diagnostic role when compared with CT or PET-CT. Tracer accumulations of BS may occur in many locations such as trauma, infection and arthropathy when there is a reactive of new bone or osteoblastic activity. The probability that an abnormal scan represents metastasis is directly related to the number of abnormal foci, the clinical symptoms or the history of primary tumors. In many cases, other modalities must be executed in order to further confirm bone metastasis. The poor spatial resolution also restrict the precise location and down-regulated the sensitivity or specificity of BS. BS is rather limited in monitoring treatment of bony metastases due to flare phenomenon and rather delayed changes in bone metabolism. But because of low costs, widely availability and whole body evaluation, BS remains a diagnostic method of choice for initial screening of osseous metastasis though its role and future application may partly substitute by new powerful methods. As an addition of planar acquisition, SPECT has been reported to enhance the quality of planar scintigraphy, in particular improving the spatial resolution. Due to our limited data, we didn't assess the performance of SPECT in this work. Some previous investigations showed that SPECT had a similar sensitivity/specificity as ^{18}F-FDG PET though ^{18}F-FDG PET provided more information beyond the skeletal. The exact difference between SPECT and PET or PET/CT in bone metastasis need further investigated.

Detection of bone metastasis with ^{18}F-FDG PET, and recently PET-CT, is rapidly growing. Shinji (Shinji et al., 2007) reported that PET had a better sensitivity and specificity when compared with SPECT in thyroid cancer. Other clinical evidence also showed that PET was more competitive than BS for esophagus, thyroid, nasopharyngeal and lung cancer (Kato et al., 2005; Shinji et al., 2007; Liu et al., 2010; Chang et al., 2013), just as our data shown. BS and SPECT identify osteoblastic responses while ^{18}F-FDG uptake detecting by PET is related to increase intratumoural glycosis (Masi et al., 2001; Riegger et al., 2012). ^{18}F-FDG PET should have better sensitivity and specificity than SPECT or BS because by imaging tumor metabolism directly with ^{18}F-FDG, detection may occur earlier than abnormal 99mTc-MDP accumulation, required for an identifiable bone reaction (Zaman et al., 2011; Lagaru et al., 2013). But some other reviewed that the sensitivity of PET was lower than BS (Choi et al., 2012; Montini et al., 2012). They regarded PET a possible tool to confirm positive results for conventional scans rather than a means of initial detection. There's still no clearly explanation of the difference between BS and ^{18}F-FDG PET. Some studies concluded that ^{18}F-FDG PET might have better sensitivity and specificity in lytic or mixed lesions but inferior performances in sclerotic lesions (Yuji et al., 2005). Our data also showed that the sensitivity of PET was better than CT or BS in lytic sites but a small lower in osteoblastic sites. Lytic lesions represent continuous removal of the bone and high activity of tumor cells invasion which act as osteoclastic procedure with lysosomal enzymes. In contrast, sclerotic lesions accomplished with fibrosis or collagens deposited don't contain a lot of cells which can take up ^{18}F-FDG as is the case in lytic lesions. Thus, more glycosis of tumor cells in lytic lesions enhance the sensitivity of PET and the deposition of collagen in sclerotic lesions might be record by imaging methods described as morphological changes of intensity modified. This may partly explain those interesting findings that lower sensitivity of PET in colon cancer, or in those lesions which usually had sclerotic metastases. In addition, SUVs were also lower

in sclerotic lesions when compared with lytic lesions (Chang et al., 2013) There are still many disadvantages of 18F-FDG PET in the diagnosis of bone metastasis, too. It's comparatively poor spatial resolution than CT or MRI and low sensitivity in osteoblastic lesions refines its value in bone metastasis (Yuji et al., 2005; Liu et al., 2010). Some lesions near the rib didn't represent bone metastases but rather pleural or adjacent organ involvements (6 lesions in our data). Potential advantages should be made to improve PET ability in detecting bone metastasis.

PET-CT is a wonderful combination of morphological images and functional images (Fuglø et al., 2012). When PET-CT is available, anatomic information obtained at CT may be useful in localizing and distinguishing fractures, cysts or degenerative changes. The improved spatial resolution, lesion contrast, fused tomographic techniques, quantitive analysis and complementary of two pre-existing modalities have made PET-CT more competitive in detecting bone metastasis (Du et al., 2007). Our data showed that PET-CT had the best sensitivity, specificity, accuracy, PPV and NPV in the detection of bone metastasis. Actually other work about 18F-Fluoride PET-CT also showed a powerful role of the combination of PET and CT (Lagaru et al.,2013). When the optimal CT window width and level were used, CT images obtained as part of PET-CT scanning were powerful in yielding the precise location and thus helping avoid misdiagnosis. For most lesions, the data provided by the low-dose CT may obviate the performance of diagnostic CT for correlation purposes and could be used to assess the risk of fractures. As expected, PET-CT was both sensitive and specific for lytic or sclerotic lesions in our data. Combined PET-CT might be the best choice of osseous metastasis and furthermore, it has the ability to provide more information about primary tumors and clinical staging which mean a cost-effective purpose. The attractions of quantitative measurements of 18F-FDG make it possible to monitor therapy responses although to date this has not been extensively explored (Kim et al., 2008; Evangelista et al., 2012). Some patients with unknown origin of bone metastasis might be evaluated by PET-CT guided biopsy due to 18F-FDG avidity, too.

The limitations of our work were related mainly to the population of patients, imaging facility or methods. Though we had a relatively widely spread of primary tumors, most cases were less than fifteen which might confined the representation of our conclusion. The asymmetry image fusion of hardware 18F-FDG PET (4.25mm thickness) and CT (5mm thickness) might misunderstand the precise anatomic position, especially in flat and irregular bone. The CT components of PET-CT still had its limitation when compared with routine CT because of the low dose and non-enhancement scanning in our procedure. Besides, our images of 18F-FDG PET-CT scanned from the skull to mid thigh were not an entirely whole body imaging and might cause an accessorial false negative value of the lower extremities (5/459).

In conclusion, remarkable progress has occurred in clinical application of 18F-FDG PET-CT and when available, is regarded as a better tool than CT, BS or 18F-FDG PET in evaluating bone metastasis (Groheux et al., 2013). Although the clinical role of 18F-FDG PET-CT in the management of bone metastases hasn't fully defined, it is potential to add relevant information and worthy of further study.

Acknowledgements

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