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Usefulness of Whole-Body ^{18}F-FDG PET in Patients with Suspected Metastatic Brain Tumors

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The aim of this study was to evaluate the diagnostic value of whole-body ^{18}F-FDG PET imaging in the differentiation of metastatic brain tumor from primary brain tumor and in the localization of the primary lesion in patients with metastatic brain tumor. **Methods:** The subjects consisted of 127 patients (77 men, 50 women; mean age ± SD, 55 ± 12 y) with brain masses that were suspected to be metastatic brain tumors on radiologic studies: 77 with confirmed metastatic brain tumor and 50 with primary brain tumor. Whole-body ^{18}F-FDG PET was performed on all patients. When the abnormal lesion was detected outside the brain, we interpreted the brain lesion as metastatic brain tumor. **Results:** In 61 of the 77 patients with metastatic brain tumor, primary lesions were detected using whole-body ^{18}F-FDG PET. Of the remaining 16 patients (all false-negative cases), 7 were classified as metastases of unknown origin. In 47 of the 50 patients with primary brain tumor, whole-body ^{18}F-FDG PET did not show any other abnormal lesions. The sensitivity, specificity, positive and negative predictive values, and accuracy of PET for the detection of primary origin were 79.2%, 94.0%, 95.3%, 74.6%, and 85.0%, respectively. The most common primary origin of metastatic brain tumors on PET examination was lung cancer (48/61, 78.7%). The concordance rate between ^{18}F-FDG PET and conventional radiologic work-up was 80% in identifying primary lesion. Unknown bone or bone marrow metastases and unsuspected distant metastases were found in 14 patients (18%) and 24 patients (31%), respectively, on PET examination. **Conclusion:** Screening the patients with suspected metastatic brain tumors using whole-body ^{18}F-FDG PET could be helpful in differentiating metastatic brain tumor from primary brain tumor and in detecting the primary lesion.

Key Words: whole-body PET; FDG; metastatic brain tumor

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Brain metastases occur in 20%−40% of systemic cancer, and the incidence is increasing because of several factors, including the increased overall incidence of cancer and the increased longevity of cancer patients (*1*). Brain metastases now account for about one half of all brain tumors. Detection of the primary lesion is important in the management of metastatic brain tumor because there are significant differences in survival times between different primary tumors. In addition, accurate staging and detection of the primary tumor are often critical to the appropriate choice of treatment (*2*).

For detection of the primary lesion, extensive evaluations have been performed. However, in 16%−35% of patients with metastatic brain tumors who first present with symptoms of the central nervous system, the site of the primary cancer remains unknown (*3*). Metastatic brain tumors must be differentiated as early as possible from primary brain tumors because of the seriousness of the symptoms and signs and the patient's poor general condition. However, conventional systemic evaluation for metastatic brain tumor is a complicated, time-consuming, and costly procedure. Conventional studies are also limited in their ability to detect small-sized tumors. For the diagnostic approach and management of patients who have metastatic tumor masses in the brain, a more convenient, sensitive, and specific diagnostic tool is required to determine the origin and other metastatic sites.

Whole-body ^{18}F-FDG PET has been used in differentiating and characterizing indeterminate lesions, in differentiating recurrent disease from therapeutic effects, in staging and evaluating the extent of disease, and in monitoring the success or failure of therapy in a variety of cancers (*4*−*15*). Several clinical reports have suggested that ^{18}F-FDG PET is also useful for detecting the unknown primary tumor in various metastatic cancers (*16*−*19*). Although ^{18}F-FDG PET has potential usefulness in differentiating metastatic brain tumors from primary brain tumors, and in localization of primary lesion, there have been few reports with supporting evidence (*3*,*20*).

The aim of this study was to evaluate the diagnostic value of ^{18}F-FDG PET in differentiating metastatic brain tumor from primary brain tumor and in localizing the primary origin in patients with metastatic brain tumor.

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TABLE 1
Patient Characteristics

Parameter	Metastatic brain tumor	Primary brain tumor
Patients (*n*)	77	50
Mean age ± SD (y)	56.6 ± 9.4	53.3 ± 14.0
Sex (M:F)	53:24	24:26
Symptoms*		
Headache	47 (61)	24 (48)
Motor weakness	23 (30)	10 (20)
Anorexia, N/V	14 (18)	8 (16)
Sensory disturbance	12 (16)	1 (2)
Diplopia, decreased VA	9 (12)	3 (6)
Dizziness	9 (12)	2 (4)
Other	9 (12)	7 (14)

*Values are given as number with percentage in parentheses.
N/V = nausea and vomiting; VA = visual accuracy.

MATERIALS AND METHODS

Patient Population

The enrolled subjects were 127 patients (77 men, 50 women; mean age ± SD, 55 ± 12 y) with brain masses who had suspected radiologic evidence of metastatic brain tumors. All patients were examined with brain CT, brain MRI, and whole-body ^{18}F-FDG PET including the brain region for evaluation of the brain mass between May 1997 and May 2001. In cases of strongly suspected metastatic brain tumor that showed multiple rim-enhancing masses with central necrosis and surrounding edema on brain MRI, the patients were also examined with conventional systemic imaging work-up such as chest radiography, mammography, chest and abdominal CT, abdominal sonography, pelvic CT, pelvic MRI, and bone scanning to find the primary cancer.

Among the patients, 77 were classified as having metastatic brain tumors and 50 as having primary brain tumors by pathologic or clinical findings. Metastatic brain tumors were confirmed by pathologic examination of the brain lesion in 18 patients and by pathologic examination of the primary lesion in 40 patients. Of the 50 patients with primary brain tumors, 30 were confirmed pathologically. The remaining 19 metastatic and 20 primary brain tumors were assessed by 2 or more conventional imaging studies and by clinical and radiologic follow-up of disease progression. When the primary foci were already known or were detected during the follow-up period, or when new brain lesions developed despite treatment for brain lesion, we classified the brain lesion as brain metastasis. The brain lesion, whose extracranial foci could not be detected on the first visit and during the follow-up period for 1 y, was classified as the primary brain tumor.

Both groups of patients complained primarily of symptoms such as headache, motor weakness, anorexia, nausea, vomiting, and sensory disturbance. No symptomatic difference was noted between the 2 groups. Table 1 shows the patient characteristics.

^{18}F-FDG Whole-Body PET

Patients underwent ^{18}F-FDG PET after fasting for at least 6 h. Whole-body FDG PET was performed using an ECAT-Exact 47 PET scanner (CTI/Siemens, Knoxville, TN). For attenuation correction in both whole-body and regional images including the brain, transmission scanning with triple ^{68}Ge ring sources was performed for 2 min with each bed in whole-body transmission and for 20 min in regional transmission before emission scanning.

Patients were injected intravenously with 370 MBq ^{18}F-FDG. After 60 min, whole-body images were obtained for 6 min with each bed; then brain and regional images, which required further evaluation, were obtained with the 2-dimensional acquisition mode. Transaxial images were reconstructed using a Shepp–Logan filter (cutoff frequency, 0.35 cycle per pixel) and corrected for attenuation using the attenuation map obtained with the transmission images. The transaxial images were realigned to yield sagittal and coronal images. Section thickness was 3.2 mm.

Data Analysis

Two expert nuclear physicians interpreted the images visually to reach a consensus. If necessary, the maximal standardized uptake value (SUV) of the lesion was calculated to determine the malignant state. The ^{18}F-FDG PET result was considered positive when a lesion showed the maximal SUV of >3.0 or when a lesion showed abnormally increased ^{18}F-FDG uptake compared with that of the surrounding normal tissue. The ^{18}F-FDG PET result was considered as a metastatic brain tumor when ^{18}F-FDG showed positive uptake in other sites in addition to the uptake in the brain. When abnormal ^{18}F-FDG uptake occurred only in the brain, the result was interpreted as the primary brain tumor.

RESULTS

In 61 of the 77 patients with metastatic brain tumor, primary lesions could be detected using ^{18}F-FDG PET, but it remained undetected in the other 16 patients for whom metastatic brain tumor was revealed by pathologic examination. For 7 of these 16 patients, the primary origins were not found in other studies during the follow-up period and, hence, the brain lesions were classified as metastases of unknown origin.

In 47 of the 50 patients with primary brain tumor, ^{18}F-FDG PET showed no abnormal lesion outside of the brain. For the other 3 patients with suspected metastatic brain tumors, PET findings were false-positive. The PET findings in these cases demonstrated hypermetabolic foci in the gastric wall, neck, and hilar region, but they were confirmed as primary brain tumor (central nervous system lymphoma, astrocytoma, and glioblastoma) by biopsy. The sensitivity and specificity of PET for detection of primary origin were 79.2% and 94.0%, respectively. The corresponding positive and negative predictive values and accuracy of ^{18}F-FDG PET were 95.3%, 74.6%, and 85.0%, respectively. The

TABLE 2
Results of ^{18}F-FDG PET Study on Diagnosis of Brain Tumors

PET findings	Primary brain tumor	Metastatic brain tumor
Lesions only in brain	47	16*
Additional uptake in other organs	3	61

*Seven of these patients had metastases of unknown origin.

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TABLE 3
Results of Whole-Body ^{18}F-FDG PET Study According to Primary Tumors in Patients with Metastatic Brain Tumor

Primary tumor	No. of patients
True-positive findings	
Lung cancer	48
Malignant lymphoma	2
Gastric cancer	2
Nasopharyngeal cancer	2
Rectal cancer, pancreatic cancer, renal cell carcinoma, malignant melanoma, osteosarcoma, abdominal sarcoma, adenoid cystic carcinoma	1*
False-negative findings	
Renal cell carcinoma	3
Hepatoma	2
Gastric cancer, malignant melanoma, choriocarcinoma, lung cancer in hilum	1*

*One each.

results of PET study for the diagnosis of brain tumor are summarized in Table 2.

Among the 61 primary origins of metastatic brain tumors on PET study, 48 patients (78.7%) had lung cancer (Table 3). Primary cancers, which were not found on PET, consisted of 3 renal cell carcinomas, 2 hepatomas, and 1 each of gastric cancer, malignant melanoma, choriocarcinoma, and lung cancer in the hilum. In the 7 patients for whom metastatic brain tumor was found histologically, neither PET nor radiologic work-up had revealed the primary tumor on follow-up studies, and metastases of unknown origin were diagnosed. Radiologic work-up included all anatomic imaging studies performed as diagnostic methods, such as chest radiography, mammography, chest and abdominal CT, abdominal sonography, pelvic CT, and pelvic MRI. Figure 1 presents a case of detection of metastatic brain tumor, primary tumor, and unsuspected metastases to bone marrow on PET image.

Comparisons of diagnostic value between whole-body ^{18}F-FDG PET and radiologic work-up were possible in 70

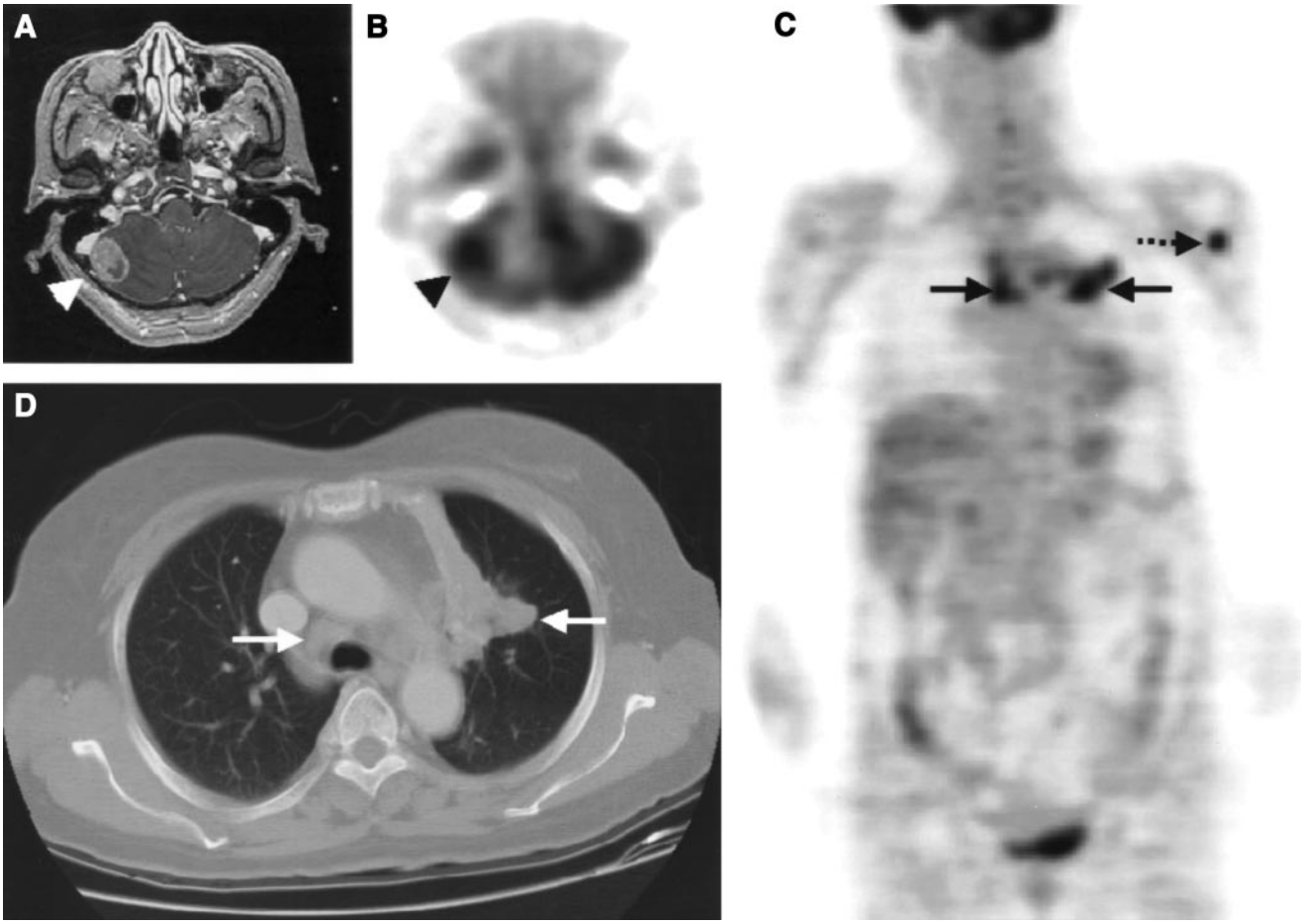


FIGURE 1. A 61-y-old woman with squamous cell carcinoma in lung and metastasis to brain. (A) Brain MR image shows enhanced mass in right cerebellar hemisphere (white arrowhead). (B) ^{18}F-FDG PET image shows hypermetabolic lesion in same site as on MR image (black arrowhead). (C) Whole-body ^{18}F-FDG PET image shows hypermetabolic lesions in right hilum, left lung (solid-line arrows), and left proximal humerus (dotted-line arrow). (D) Chest CT image certifies PET findings in chest region (white arrows) but not in humerus.

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TABLE 4
Relationship Between Radiologic Work-Up and ^{18}F-FDG PET for Detection of Primary Lesion in Patients with Metastatic Brain Tumor

^{18}F-FDG PET	Radiologic work-up	
	+	−
+	56	5*
−	5†	4

*Two malignant lymphoma, 2 lung cancer, and 1 malignant melanoma.
†Two hepatoma, 1 renal cell carcinoma, 1 malignant melanoma in anus, 1 hilar mass.

patients. In 56 of the 70 patients, primary tumors were identified on both whole-body ^{18}F-FDG PET and radiologic work-up (concordance rate, 80%) (Table 4). In 10 patients, the primary lesion was found only on either PET (Fig. 2) or radiologic studies. Whole-body ^{18}F-FDG PET detected the primary origin and metastases in 6 cases that were not detected on radiologic studies: 1 of metastatic malignant melanoma, 1 of abdominal wall sarcoma, 2 lymphomas, and 2 nasopharyngeal cancers. The diagnoses of the remaining 4 patients, whose whole-body PET and conventional work-up findings were negative, were confirmed histologically as metastatic brain tumor by craniotomy or stereotactic biopsy.

Whole-body ^{18}F-FDG PET scans revealed metastatic lesions in unsuspected sites, including the bone marrow. Such PET study disclosures included additional bone marrow or bone metastases (or both) in 14 patients (18%) and disseminated, metastatic lesions in 2 or more regions among the head and neck, chest, abdomen, and pelvis in 24 patients (31%).

DISCUSSION

Although CT and MRI examinations have facilitated the diagnosis of brain tumors, there is often uncertainty with metastatic or primary brain tumors. In addition, when CT or MR images suggest the presence of a metastatic brain tumor, several kinds of diagnostic work-up are performed for systemic evaluation. These include chest radiography; mammography; abdominal sonography; bone scanning; chest, abdominal, and pelvic CT; and bone marrow examination. However, these procedures are time-consuming and costly, and many usually prove unnecessary. A more simple and efficient diagnostic tool that can investigate systemic status safely and reliably is needed.

^{18}F-FDG PET can acquire the whole-body image, including the brain, in one study. Whole-body ^{18}F-FDG PET can be used on patients suspected of having metastatic brain tumor for the detection of an unknown primary focus and can help in the selection of the most suitable work-up for evaluation of the primary lesion. Using this information, patient status can be evaluated and the most appropriate treatment plan can be formulated. Our data demonstrated that ^{18}F-FDG PET correctively identified the primary lesion in 61 of 77 patients with metastatic brain tumor and correctly excluded a metastatic brain lesion in 47 of 50 patients with primary brain tumor. Such results represent high accuracy and predictive values. Several clinical reports have suggested

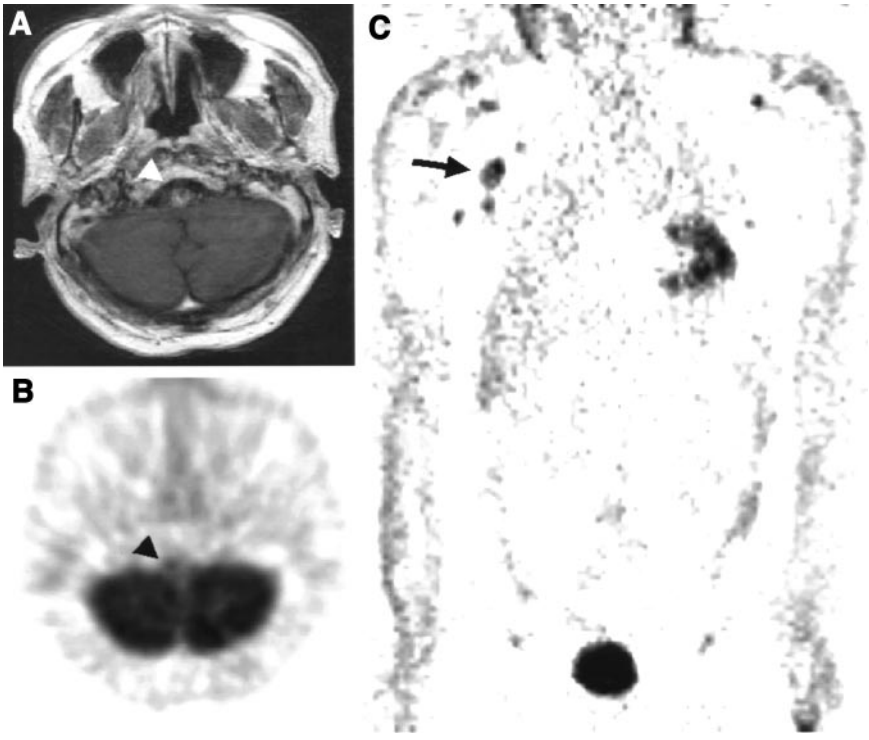


FIGURE 2. A 52-y-old man with malignant melanoma and metastasis to medulla oblongata. (A) Brain MR image shows small-sized, enhanced mass in medulla oblongata (white arrowhead). (B) ^{18}F-FDG PET image shows hypermetabolic lesion in same site as on MR image (black arrowhead). (C) Whole-body ^{18}F-FDG PET image shows hypermetabolic lesions in right axilla area (solid-line arrow) and left hilum (not shown). Radiologic work-up did not reveal any lesion.

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that ^{18}F-FDG PET is useful for detecting the unknown primary tumor in various metastatic cancers (*16*–*19*). Especially in metastatic brain tumor, Gupta et al. (*20*) reported that PET localized 82% of the primary tumor sites; this result is very similar to our own.

It has been recognized that common malignant tumors that metastasize to the brain are lung cancer, colorectal cancer, melanoma, and breast cancer in sequence (*21*). In this study, lung cancer was also the most common primary origin, being found in 48 of 61 patients (78.7%) on PET. In 46 of the 48 patients, this primary lesion was also found on radiologic work-up such as chest radiography and chest CT. However, the need for PET scanning still remains, because the nodal involvement and the extent of metastasis to other regions need to be revealed for staging and for making therapeutic decisions. In the cases of lung cancer, surgeons try not only to perform less invasive treatment for brain metastasis (using, for example, a γ-knife) but also to operate aggressively on the primary foci and lymph nodes (when metastases do not occur at contralateral and distant sites) to maintain or improve the quality of life.

Accurate separation of localized and disseminated metastases is an important consideration for selecting optimal treatment. In this study, whole-body ^{18}F-FDG PET detected the primary origin and metastases in 6 cases that were not detected in radiologic studies: 1 of metastatic malignant melanoma, 1 of abdominal wall sarcoma, 2 lymphomas, and 2 nasopharyngeal cancers. These results confirm that ^{18}F-FDG PET has the ability to detect metabolically active small, superficial, or submucosal lesions that are difficult to detect on clinical examination and conventional imaging. In addition, ^{18}F-FDG PET could detect more lesion sites than conventional radiologic studies did. The ^{18}F-FDG PET results demonstrated that 14 patients (18%) had metastases to multiple bones and bone marrows, whereas 24 patients (31%) had disseminated, metastatic lesions. Gupta et al. (*20*) reported similarly that unsuspected metastatic tumor sites were seen in 29% patients.

Lassen et al. (*17*) reported that, although initial patient history, clinical examination, chest radiologic and histologic examination might be sufficient in some cases, whole-body ^{18}F-FDG PET could be useful in patients with unknown primary tumor and should be performed before further diagnostic procedures. Gupta et al. (*20*) reported that whole-body ^{18}F-FDG PET proved to be an accurate, useful, and reliable initial test for the work-up of patients with suspected or proven intracranial metastases. Go et al. (*21*) reported that although, in terms of cost–benefits, whole-body ^{18}F-FDG PET would make the method less suitable as a substitute for dissemination studies in general, it may speed up the diagnostic process and be useful as a screening method for the search of metastases, allowing other studies to be focused on the lesion.

Our results included 16 false-negative cases, although for 7 of these cases the primary origin was not found on any follow-up studies. The remaining cases included 3 renal cell carcinomas, 2 hepatomas, 1 choriocarcinoma, 1 gastric cancer, 1 malignant melanoma in the anus, and 1 lung cancer in the hilum. Our data also included 3 false-positive cases in patients with primary brain tumor. The PET findings in these cases revealed focal hypermetabolism in the gastric wall, neck, and hilar region, but they were confirmed as primary brain tumor. ^{18}F-FDG PET scans generally show normal physiologic uptake in the liver, stomach, gastrointestinal tract, and urinary system (*22*), and under certain conditions the physiologic uptakes in these organs are often heterogeneous. Sometimes, it is difficult to differentiate abnormal uptake from variant physiologic uptake in these organs (*23*). Besides, inflammation, a process involving increased cellular metabolism and increased ^{18}F-FDG uptake, can be indistinguishable from malignancy and thus produce false-positive cases. These interpretive pitfalls of ^{18}F-FDG PET can lead to false-positive and false-negative results.

CONCLUSION

Whole-body ^{18}F-FDG PET was useful in differentiating metastatic brain tumor from primary brain tumor with high diagnostic certainty, especially in terms of specificity and positive predictive value. Whole-body ^{18}F-FDG PET can be used as a screening method for differentiating metastatic brain tumor from primary brain tumor as well as for detecting primary tumors and other metastatic sites.

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