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STAGING OF LUNG CANCER. DO WE NEED A DIAGNOSTIC CT OF THE BRAIN AFTER AN INTEGRATED PET/CT FOR THE DETECTION OF BRAIN METASTASES?

W. De Wever, E. Bruyeer, Ph. Demaerel, G. Wilms, J. Coolen, J. Verschakelen[1]

Brain CT has been recommended in staging of patients with lung cancer because of its usefulness in the detection of metastases. Purpose of this study is to examine if a diagnostic brain CT (CT_1) can be obviated when an integrated PET/CT (PET/CT) is available.
87 consecutive patients underwent a diagnostic brain CT and a whole-body PET/CT within a period of 3 weeks to stage a known primary tumour.
CT examinations were evaluated by two experienced neuroradiologists on the detection of brain lesions (benign and malignant). The results of PET/CT and CT reading were compared and both readings were compared with the clinical results.
Statistical analysis was done by measuring sensitivity, specificity, PPV, NPV and accuracy. The relative accuracies were compared by a McNemar (exact) test for correlated proportions.
Considering the CT_1 as standard of reference, sensitivity, specificity, PPV, NPV and accuracy for the brain CT of PET/CT (CT_2) and PET/CT were respectively 83%, 96%, 77%, 97%, 94% and 69%, 98%, 90%, 95%, 94%. Considering the clinical diagnosis as standard of reference these figures were for CT_1, CT_2 and PET/CT respectively 80%, 100%, 100%, 96%, 96% and 66%, 95%, 77%, 93%, 90% and 66%, 97%, 83%, 93%, 91%. There was no statistical difference between CT_1 and CT_2.
The comparison of the additional CT in PET/CT with a diagnostic CT of the brain did not yield a statistical difference in the detection of brain lesions despite the inferior quality of the CT component of PET/CT. A diagnostic brain CT can be obviated when a PET/CT is available.

Key-words: Lung neoplasms, metastases – Brain neoplasms, secondary - Brain, CT.

Lung cancer is a common disease with approximately 1.3 million new cases per year worldwide and is the leading cause of death in many countries (1, 2). Lung cancer is the commonest primary source of brain metastases (3). The detection of brain metastases at the time of diagnosis of lung cancer has important therapeutic complications. Surgical removal is rarely indicated, but occasionally, in carefully selected patients, it can reduce neurological impairment and prolong survival (4). Incidence rates of brain metastases from lung carcinoma that have been reported in the literature range from as low as 9.7% to as high as 54% (5). An optimal staging is important to determine the best possible therapeutic option, to clarify operability and to have an idea about the outcome for the patient. The ideal staging investigation should be inexpensive and easy to perform, have high sensitivity and specificity, provide accurate results that reflect the patient's true clinical state, and yet cause minimal patient discomfort and morbidity (6).

The role of Computed Tomography (CT) in screening for cerebral metastases in potentially surgically resectable bronchogenic carcinoma patients has been actively debated for decades. Multi-Detector CT has substantially reduced examination time, as well as enabled high-quality multiplanar reconstructions. The use of MRI has contributed to a higher detection rate of central nervous system metastases (5). The clinical gold standard, MRI, provides excellent anatomic details. Standard T1- and T2-weighted MRI is highly sensitive in determining the size and location of brain lesions, as well as mass effect, oedema, haemorrhage, necrosis, and signs of increased intracranial pressure (7).

The efficacy of Positron Emission Tomography (PET) in depicting cerebral metastases is controversial. The sensitivity of PET in revealing cerebral metastases in patients with malignancy has been reported at 68-82% when compared with anatomic imaging (8). The specificity of PET in evaluating cerebral abnormalities is less clear than its sensitivity. In one study published in 1996 with 402 lung cancer patients, researchers reported a 38% specificity of PET alone when compared with anatomic imaging (9).

PET/CT is a new anatomo-metabolic imaging technique. The first integrated PET/CT machine came into clinical practice in 1998, when a prototype was installed at the University of Pittsburgh Medical Centre (10, 11). PET/CT is the combination of two different examination techniques in one machine: CT giving anatomic information and PET giving metabolic information. Due to the concept of integrated PET/CT the technique of the CT component is somewhat different of that of a diagnostic CT of chest, abdomen and brain, and this can influence the quality of the CT images (12). A CT scan of the brain is included in an integrated PET/CT study. The quality of this brain scan is inferior compared to a diagnostic CT of the brain but may detect metastatic disease. The purpose of our study is to examine if a diagnostic brain CT (CT_1) can be obviated when an integrated PET/CT is available.

Patients and methods

Patients

Between February 2004 and June 2006, 123 patients with a malignant

From: Department of Radiology, UZ Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.
Address for correspondence: Dr W. De Wever, M.D., Department of Radiology, UZ Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.
E-mail: walter.dewever@uzleuven.be

Table I. — Etiology of the primary tumour.

Primary tumour	Number	Primary tumour	Number
Lung	49	Oesophagus	6
Abdominal	6	Haematological	13
Urogenital	2	Melanoma	3
Breast	5	Unknown	1
Neurological	2		

primary tumour underwent a whole body integrated PET/CT and a dedicated CT of the brain as part of their staging procedure with a time interval no longer than 3 weeks. After selecting those patients who received an integrated PET/CT and a dedicated CT, both with IV contrast administration, 87 patients (54 men, 33 women, mean age 58 years) were entered into this retrospective study. Forty-nine (56%) patients had primary lung cancer (Table 1). Twenty seven patients (31%) underwent the CT examination of the brain because of neurological symptoms.

The final diagnosis of the presence or absence of brain lesions was made by the clinician and was used as the standard reference in this study. This final diagnosis was based on additional MR examination and/or follow-up during 12 months. There were 27 patients (31%) with neurological symptoms, 8 of them had a lung tumour.

Methods

All PET/CT studies were acquired on a dual-modality PET/CT tomograph (Biograph LSO Duo; Siemens Medical Solutions, Erlangen, Germany). The CT component of the Biograph LSO duo corresponds to a Somatom Emotion Duo (Siemens Medical Solutions, Erlangen, Germany), a 2-row spiral CT system with a maximum continuous scan time of 100 sec. and a maximum rotation speed of 75 rpm. CT images were acquired with 85 mAs, 130 kV, slice thickness of 5 mm, and table feed of 12 mm per rotation. The scanning area for CT was defined on a CT topogram. Whole body spiral CT was performed starting with the head and subsequently covering the neck, thorax, abdomen, and pelvis. To ensure diagnostic CT image quality, 120 mL of a contrast agent containing 300 mg iodine per ml was administered intravenously using an automated injector (1.6 mL/sec, scan delay 100 sec). CT was performed during breath hold at expiration tidal volume.

The PET component of the integrated PET/CT is based on an ECAT ACCEL (Siemens Medical Solutions, Erlangen, Germany), a full ring Lutetium ortho silicate (LSO) based PET system with an in plane spatial resolution of 4.6 mm and an axial field of view of 15.5 cm for each bed position. The scanning area for PET was defined on the CT topogram. Non attenuation and attenuation-corrected images were made. PET imaging was done 75 minutes after injection of FDG which in general gives a good balance between the duration of the examination and the amount of FDG-uptake necessary for interpretation. Patients had been instructed to fast for a minimum of 4 hours prior to starting the examination. Blood samples collected before the injection of the radioactive tracer ensured blood glucose levels in the normal range.

The diagnostic CT of the brain (CT_1) was done using the following scan parameters: 380 mAs, 120 kV, and sequential scan protocol. At the skull base a slice thickness of 2.4 mm, a collimation of 24 x 1.2 mm, a feed of 28.5 mm, and a rotation time of 4 sec. were used. At the brain: these figures were respectively 9.0 mm, 30 x 0.6 mm, 18 mm and 4 sec.

Both CT_1 and the brain CT part of the PET/CT (CT_2) were evaluated by two experienced neuroradiologists searching for suspected brain lesions (brain metastases or primary tumours). The time interval between the evaluations of the 2 CT examinations was at least 2 weeks and conclusions were reached by consensus. The readers were blinded to the clinical information and to the images of the other CT study. The PET/CT of the brain was evaluated by a general radiologist and a nuclear medicine physician in consensus. If CT and/or PET were suggestive for a brain tumour or metastasis, the PET/CT was considered as positive. The results of CT_2 and PET/CT were correlated with those of the diagnostic CT_1 which was used at that moment as standard of reference. The results of CT_1, CT_2 and PET/CT were also correlated with the final diagnosis.

The sensitivity, specificity, accuracy and predictive values of CT_1, CT_2 and PET/CT were calculated using the standard definitions. The relative accuracies were compared by a Mac Nemar (exact) test for correlated proportions (with 95% confidence interval).

Results

The final diagnosis, made by the clinician and based on additional MR examination and/or follow-up during 12 months included 15 patients (17%) with malignant brain lesions (12 brain metastases, 3 primary brain tumours), 12 patients (14%) with benign brain lesions (ischemic lesions) and 60 patients (69%) without lesions. In the group of patients with a lung tumour (49 patients), 6 (12%) patients had malignant brain lesions (all brain metastases), 6 patients (12%) had benign brain lesions and 37 patients (76%) had no lesions. In the group of patients with a lung tumour, there were only 8 patients (16%) with clinical neurological symptoms. Four of these patients showed brain metastases, the other 4 patients didn't show brain lesions.

CT_1 showed 12 patients with malignant lesions (Fig. 1). There were 3 false negatives with CT_1. In the group of patients with a lung tumour (49 patients), CT_1 demonstrated 5 patients with malignant lesions (1 false negative), all brain metastases. CT_1 detected all the patients with a lung tumour with neurological symptoms who had brain metastases. CT_2 showed 10 patients with malignant lesions. There were 5 false negatives with CT_2. In the group of patients with a lung tumour CT_2 demonstrated 4 patients with malignant lesions, there were 2 false negatives (Fig. 2). The four patients with malignant brain lesions detected with CT_2, were also those patients with a lung tumour and with neurological symptoms. PET/CT showed 10 patients with malignant lesions. There were 5 false negatives and 2 false positives with PET/CT. In the group of patients with a lung tumour PET/CT demonstrated 3 patients with malignant lesions, there were 3 false negatives.

Sensitivity, specificity, predictive values and accuracy of CT_2 and PET/CT to detect patients with malignant brain lesions were first

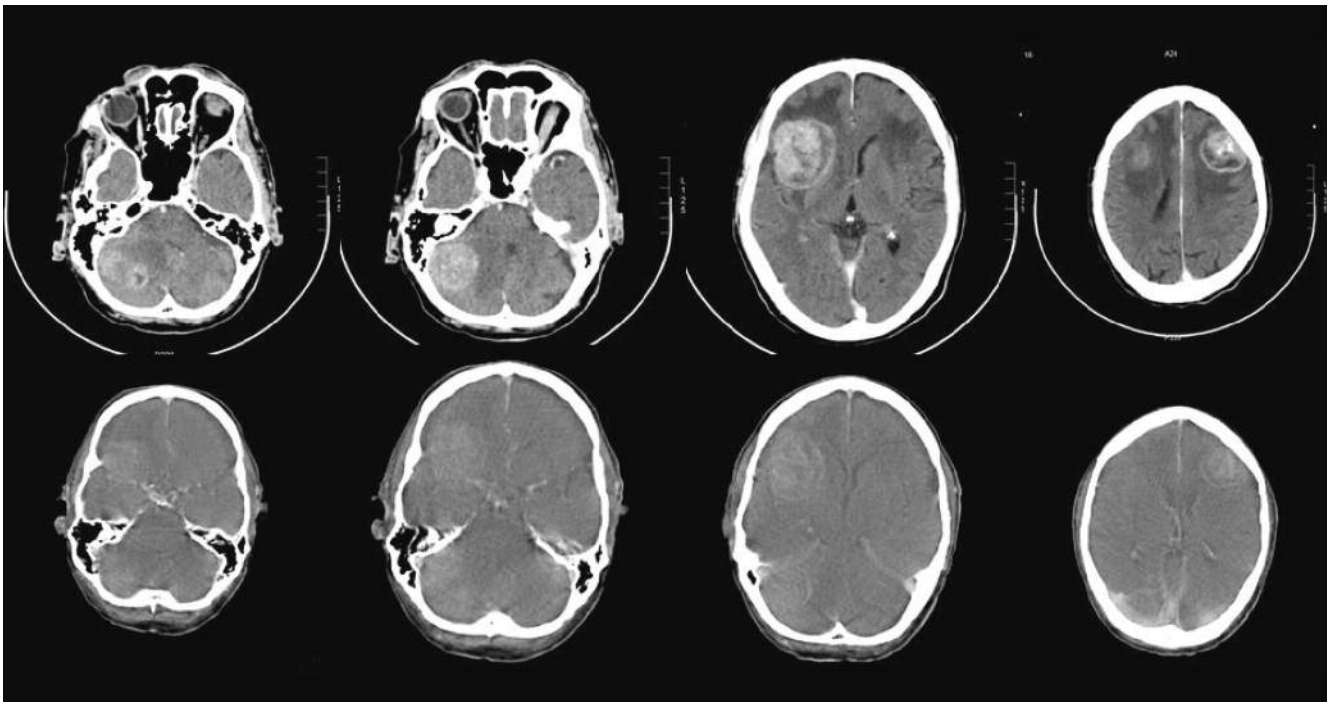

Fig. 1. — 67-year-old man with SCLC in the left upper lobe. Patient developed neurological symptoms. Diagnostic brain CT (upper row) showed multiple brain metastases: two right cerebellar, one right frontal and one left frontal. All these metastases are surrounded by oedema. The CT of the integrated PET/CT (lower row) showed also brain metastases but could not demonstrate one right cerebellar metastasis (first image).

The quality of the CT of the PET/CT is inferior of this of a diagnostic brain CT: lesser contrast opacification and also the surrounded oedema is not so clear visualised, however this can be due to the treatment with corticosteroids in the short time between diagnostic brain CT and integrated PET/CT.

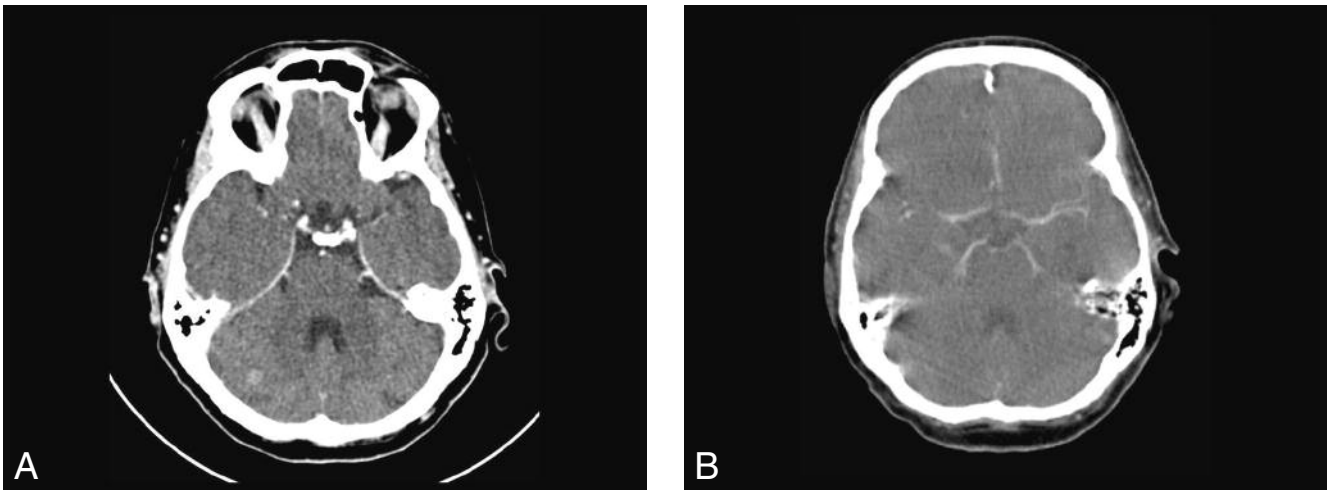

Fig. 2. — 53-year-old woman with oatcell carcinoma with extensive disease. Patient had also brain metastasis. Diagnostic CT of the brain (A) was true positive showing a right cerebellar brain metastasis. This metastasis was not visualised on the brain CT of the integrated PET/CT (B) due to the inferior quality of this CT.

calculated by considering CT_1 as the standard of reference and secondly by considering the final diagnosis as standard of reference (Table II). The relative accuracies are summarized in Table III. We couldn't find a statistically significant difference between CT_1 and CT_2.

Discussion

Recently, it has been shown that in tumour staging of patients with lung cancer, analysis of PET/CT images is superior to the analysis of CT images alone or PET images alone, and to the combined analysis of PET and CT images viewed side by side (13). CT images from PET/CT made with our PET/CT protocol have a lower image (Fig. 1 and 2). The quality of CT and PET/CT images depends on different parameters. Some parameters used for PET/CT, such as CT dose and the use of

Table II. — Sensitivity, Specificity, predictive values and accuracy of CT_1, CT_2 and PET/CT for the detection of malignant brain lesions.

%	Sensitivity	Specificity	PPV	NPV	Accuracy
CT_1 as standard of reference					
All patients with a primary tumour					
CT_2	83	96	77	97	94
Integrated PET/CT	69	98	90	95	94
Patients with a lung tumour					
CT_2	80	97	80	97	96
Integrated PET/CT	60	100	100	95	96
Patients with neurological symptoms					
CT_2	90	94	90	94	92
Integrated PET/CT	80	94	88	88	88
Final diagnosis as standard of reference					
All patients with a primary tumour					
CT_1	80	100	100	96	96
CT_2	66	95	77	93	90
Integrated PET/CT	66	97	83	93	91
Patients with a lung tumour					
CT_1	83	100	100	97	98
CT_2	66	97	80	95	94
Integrated PET/CT	50	100	100	93	93
Patients with neurological symptoms					
CT_1	83	100	100	88	92
CT_2	75	93	90	82	85
Integrated PET/CT	75	93	90	82	85

CT_1: diagnostic CT of the brain
CT_2: brain CT part of the integrated PET/CT.

intravenous (IV) contrast media, that influence image quality, are different from those used for a diagnostic CT (12). An important question is which CT dose has to be chosen for the integrated PET/CT protocol. For a diagnostic CT a dose of about 140 kV and 120 mAs is normally used to obtain images with optimal quality. Due to the concept of PET/CT, this dose cannot be generated with the first PET/CT scanners like ours. Hany et al. (14) compared different CT doses. In this study, 21% of all lesions were classified as undecided with PET alone and could therefore not be specified. By using low-dose CT (10-40 mAs) for image co-registration, an additional 7% of all lesions could be classified. The reduction in false-negative and false-positive results significantly increased the accuracy of PET/CT. When an 80 mAs CT was used, the number of undecided lesions was reduced to 12%. However, using a 120 mAs CT did not further improve lesion classification. Therefore, the authors concluded that PET 80 mAs CT should be used for optimal reduction of the number of undecided lesions. However there are no studies who compares a diagnostic CT of the brain with the brain CT part of a PET/CT in the detection of brain metastases in the staging of patients with a known primary tumour. In this study we tried to examine if we can obviate a diagnostic CT of the brain if a total-body PET/CT is available.

Brain metastases are a common way of general dissemination of lung cancer. The incidence of brain metastases in the initial staging of patients with primary lung cancer has been reported to be between 12% and 18% (15, 16). Also in our study, 12 % of the patients with a lung tumour had brain metastases. The signs and symptoms of brain metastasis are related to the involved brain area. Most patients present with headache or focal neurological deficits. Common focal symptoms include muscle weakness, gait disturbances, visual field defects and aphasia (17) and these symptoms justify further investigation. Preoperative evaluation and follow-up with diagnostic imaging for brain metastases in asymptomatic patients remains a controversial issue (18, 19). International guidelines for staging a lung tumour are proposed by the American Thoracic Society / European Respiratory Society (20). Several authors have recommended that brain CT must be performed in the staging of lung cancer because of its usefulness in the detection of occult metastases (21). Other authors have advocated that the routine use of brain CT is not warranted in patients without neurological signs or symptoms because of the marginal cost-effectiveness (22, 23). In this setting, it is interesting to know whether the brain CT part of the whole-body PET/CT is able to detect symptomatic and occult brain metastases because this brain CT is part of the examination in many institution and has no additional cost.

Therapeutic management of patients with brain metastases includes whole-brain radiotherapy, stereotactic radiosurgery, surgery, and chemotherapy. To select the appropriate therapy, the physician must consider the extent of the brain metastasis, including the number of brain metastases, their size, location, and histology (24). Different studies are made to compare the usefulness of MRI and CT in the detection of brain metastases during preoperative evaluation and postoperative follow-up. Yokoi found in his study

Table III. — Relative accuracies of the different imaging techniques in the detection of malignant brain lesions compared by Mc Nemar exact test (confidential interval 95%).

Mc Nemar test	All patients with a known primary tumour	Patients with a lung tumour	Patients with neurological symptoms
	CT_1	CT_1	CT_1
CT_2	P = 1,000	P = 0,4795	P = 0,4795
Integrated PET/CT	P = 0,6831	P = 0,4795	P = 1,000

CT_1: diagnostic CT of the brain
CT_2: brain CT part of the integrated PET/CT.

that MRI showed a tendency toward a higher preoperative detection rate of brain metastases than CT. The mean maximal diameter of the brain metastases was significantly smaller in the MRI group than in the CT group. However there was no significant difference between the groups in survival time (25). Despite the fact that MRI is the superior test for the detection of brain metastases, CT of the brain has a well-documented accuracy in detecting metastatic lesions and has been described as being of value in the preoperative staging of patients with non-small cell lung cancer who were free of neurological symptoms (3, 26, 27). CT is adequate to exclude brain metastases in most patients but it can miss small lesions especially those who are located in the posterior fossa (28). The CT appearance of brain metastases is non-specific and may mimic other processes, such as infectious disease. Therefore, the CT scan must always be interpreted within the context of the clinical picture of the individual patient, particularly since cancer patients are vulnerable to opportunistic CNS infections or may develop second primaries, which can include primary brain tumours (29). This interpretation within the whole context of the clinical picture was not performed in our study. The readers only knew that the patient had a primary tumour but did not know whether the patients had neurological symptoms or not. Using the final diagnosis as standard of reference we found a sensitivity, specificity, and accuracy for the detection of malignant brain lesions in the global patient group with CT_1, CT_2 and integrated PET/CT of respectively 80%, 100%, 96% and 66%, 95%, 90% and 66%, 97%, 91%. The results of CT_1were better of those of CT_2, however we could not find a significant difference between CT_1 and CT_2. When we examined only the patients with a lung tumour, these results for CT_1 and CT_2 were better. Crane et al found in his study a sensitivity of 98% and a PPV of 98% for CT scans in the detection of brain metastases in patients with or without neurological signs or symptoms. However, CT scans were positive in only 6% of the asymptomatic patients (30). Using as reference criteria clinical judgment supported by a strict follow-up evaluation, Ferrigno et al found in his study a sensitivity, specificity, and accuracy of 92%, 99%, and 98% respectively (19). Also using the clinical judgment and the follow-up as standard of reference, we were not able to demonstrate such a high sensitivity (83%). However, the specificity and accuracy in our study were in the same range. When our patients had neurological symptoms, these figures became better.

The efficacy of PET in depicting cerebral metastases is controversial. Sensitivities between 68%-82% and specificities of about 83% have been reported when compared with anatomic imaging (7, 29). We did not examine the role of PET only in the detection of brain metastases.

In the literature, no detailed information is available about the use of the CT of the brain from a whole-body PET/CT to detect brain metastases. Although in our study no statistical significant difference was found between the diagnostic CT and the CT part of the integrated PET/CT (Table III), the results of the diagnostic CT were somewhat better. The results of the CT part of the integrated PET/CT interpreted apart from the PET information are somewhat better than those of the integrated PET/CT. The reason that PET/CT results are not so good as those of CT_1 and CT_2 can be found in the fact that CT_1 and CT_2 where evaluated by experienced neuroradiologists in consensus and that PET/CT was evaluated by a general radiologist and nuclear medicine physician in consensus.

Conclusion

Brain CT has been recommended in the staging of lung cancer because of its usefulness in the detection of occult metastatic disease. Nevertheless, the routine use of brain CT is probably not warranted in patients without neurological signs or symptoms because of the marginal cost-effectiveness. PET/CT offers an additional CT scan of the brain without additional costs. We have shown that when comparing this CT with a diagnostic CT of the brain, there is no statistically significant difference between these two CT scans in detecting malignant brain lesions, despite the fact that the quality of the CT of the brain of the PET/CT is inferior. So, a diagnostic CT of the brain is very likely not necessary when a whole-body PET/CT has been performed especially in those patients with clinical symptoms. In case of clinical symptoms and a negative PET/CT or in order to obtain a more detailed idea about the multifocality of the brain lesions, an additional MRI of the brain is appropriate.

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