Brain metastases detectability of routine whole body ^{18}F-FDG PET and low dose CT scanning in 2502 asymptomatic patients with solid extracranial tumors

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Abstract

As fluorine-18-fluorodesoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is gaining wider availability, more and more patients with malignancies undergo whole body PET/CT, mostly to assess tumor spread in the rest of the body, but not in the brain. Brain is a common site of metastatic spread in patients with solid extracranial tumors. Gold standard in the diagnosis of brain metastases remains magnetic resonance imaging (MRI). However MRI is not routinely indicated and is not available for all cancer patients. Fluorine-18-FDG PET is considered as having poor sensitivity in detecting brain metastases, but this may not be true for PET/CT. *The aim of our study* was to assess the value of ^{18}F-FDG PET/CT in the detection of brain metastases found by whole body scan including the brain, in patients with solid extracranial neoplasms. *A total of 2502 patients* with solid extracranial neoplasms were studied. All patients underwent a routine whole body ^{18}F-FDG PET/CT scan with the whole brain included in the scanned field. Patients with known or suspected brain metastases were preliminary excluded from the study. Hypermetabolic and ring-like brain lesions on the PET scan were considered as metastases. Lesions with CT characteristics of brain metastases were regarded as such irrespective of their metabolic pattern. Lesions in doubt were verified by MRI during first testing or on follow-up or by operation. *Our results showed* that brain lesions, indicative of and verified to be metastases were detected in 25 out of the 2502 patients (1%), with lung cancer being the most common primary. Twenty three out of these 25 patients had no neurological symptoms by the time of the scan. The detection rate of brain metastases was relatively low, but information was obtained with a minimum increase of radiation burden. *In conclusion*, whole body ^{18}F-FDG PET/CT detected brain metastases in 1% of the patients if brain was included in the scanned field. Brain scanning as a part of whole body scan cannot replace routine imaging techniques, but in case of positive findings provides early and crucial information for further patient management, especially in asymptomatic patients.

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Introduction

Current utilization of fluorine-18-fluorodesoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in oncology is well known and after its clinical introduction in 2000/2001 has replaced the sole use of PET, because it provides both morphological (CT) and functional (PET) information.

The vast majority of patients, referred for ^{18}F-FDG PET/CT are those with lymphomas and solid extracranial tumors without particular indications for brain scanning [1]. This, combined with the well known limitations of ^{18}F-FDG PET in detecting brain neoplasms, raises a controversy whether brain structures should be routinely scanned as part of a whole body examination. Generally, whole body ^{18}F-FDG PET/CT scans leave the brain outside the field of view.

The major drawback of brain scanning is the physiologically high brain ^{18}F-FDG uptake due to high glucose utilization of grey matter tissue, which may exceed the expected uptake of many malignant lesions, thus making diagnosis of brain neoplasms difficult. In an attempt to overcome this problem several techniques have been proposed, like dual time point imaging, or glucose loading [2-4]. These techniques require specific dedicated brain protocols but are time consuming, and thus difficult to use in routine whole body PET scans. On the other hand, CT provides additional anatomical information, able to reveal metastatic disease by itself and if used in the PET/CT scan could detect non functioning brain lesions.

The aim of our study was to assess the value of ^{18}F-FDG PET/CT in the detection of brain metastases from extracranial neoplasms when the whole brain is included in the routine whole body ^{18}F-FDG PET/CT scan.

Table 1. *Data from the 25 patients with verified brain metastases detected in the whole body ^{18}F-FDG PET/CT scan*

ID	Primary cancer	Extracranial PET/CT findings	Metabolic type of brain metastases	Multiple	CT findings, suggestive of brain metastases	Verification
1	Breast cancer	Pleural metastases	Ring-like	Yes	Yes	Progression on CECT
2	» »	No pathologic extracranial findings	Hypermetabolic	No	Equivocal	MRI
3	» »	Contralateral breast Ca, liver metastases,	» »	Meninges	No	MRI, Clinical progression
4	» »	Advanced metastatic spread	» »	Yes	Yes	CECT, Clinical progression
5	» »	LN, Bone metastases	» »	No	Equivocal	Operated
6	» »	No pathologic extracranial findings	Hypometabolic	»	Yes	CECT, Clinical progression
7	Cervical cancer	Local recurrence, LN	»	Yes	»	MRI
8	» »	»	Hypermetabolic	No	Equivocal	Operated
9	Colon cancer	Advanced metastatic spread	» »	Yes	Yes	Clinical progression
10	CUP (cervical LN-adenoCa)	Lung cancer, advanced metastatic spread	» »	»	»	Progression on CECT
11	» »	Lung cancers, advanced metastatic spread	» »	No	»	Operated
12	Head and neck cancer	LN	» »	»	»	Progression on CECT
13	Lung cancer	Lung cancer	Ring-like	Yes	»	MRI
14	» »	Lung cancer, LN, bone metastases	» »	»	»	CECT, Clinical progression
15	» »	Lung cancer, advanced metastatic spread	» »	»	»	CECT, Clinical progression
16	» »	Lung cancer, Lung metastases	Hypermetabolic	»	»	Progression on CECT
17	» »	Lung cancer; Pleural metastases	» »	No	»	Operated
18	» »	Lung cancer	» »	»	Equivocal	MRI - multiple lesions
19	» »	Lung cancer, LN	» »	»	Yes	MRI
20	Melanoma	No pathologic extracranial findings	Ring-like	Yes	»	Clinical progression
21	» »	Lung metastases	Hypometabolic	No	Equivocal	MRI
22	» »	Lung (complete remission on follow up)	Hypermetabolic	»	Negative	MRI
23	Ovarian cancer	Liver metastase,LN	Ring-like	»	Yes	Operated
24	Rectal cancer	Advanced metastatic spread	Hypermetabolic	Yes	»	CECT, Clinical progression
25	Renal cell carcinoma	Local recurrence, lung metastases	Ring-like	No	»	Progression on CECT

**CUP: cancer of unknown primary, LN: lymph nodes, CECT: contrast enhanced CT, MRI: magnetic resonance imaging*

Patients and methods

We adopted a whole body ^{18}F-FDG PET/CT protocol with the brain included in the scanned field. All patients gave their written consent for the whole procedure. Patients were given a low sugar diet on the day before the scan, were kept fast for at least 6h before the scan and refrained from tobacco and alkaloid drinks. The scan was scheduled at least a month after surgery or chemotherapy and three months after radiotherapy. On the day the scan was performed, the patients were examined by a physician. Patients were rested in a dimmed, quiet, warm room usually for 60min, before entering the scan room. 5.18MBq/kg of ^{18}F-FDG was administered through an intravenous (i.v.) line. All patients were scanned with Gemini TF (Philips Healthcare) PET/CT camera from head vertex to mid-thigh using the following parameters: Low dose CT 120keV, 50-100mAs and corresponding PET scan field with 576mm FOV, 4mm pixel size, 60sec per frame, feet first direction. This was our whole body PET/CT protocol. Raw data PET were reconstructed by iterative reconstruction, following the standard manufacturer's reconstruction algorithm for whole body scans. Reconstruction generated three sets of images: non-attenuation corrected, non-scatter corrected and attenuation/scatter corrected with time of flight data.

A total of 2502 patients, with solid extracranial neoplasms who referred for whole body ^{18}F-FDG PET/CT to our center, from August 2009 to December 2010 were examined. Lymphoma patients and patients with known brain metastases or patients operated for brain metastases were also excluded. About one third of the patients were studied prospectively and the rest retrospectively. In case of positive findings in the brain, consistent with metastatic disease, patients and their physicians were asked to give more specific information and imaging data related to their disease. All patients had solid extracranial tumors as shown in Table 1.

Reporting PET and CT images was done both separately and jointly by 2 expert nuclear medicine physicians. Any focal hypermetabolic lesion in the brain PET scan, with an activity, exceeding that of normal grey matter, or surrounded by a hypometabolic rim, or corresponding with a lesion on the CT scan or if clearly exceeded normal brain contours was considered as indicating metastasis. Space occupying lesions in the CT scan unexplained otherwise were also considered as metastases, irrelevant of the ^{18}F-FDG findings.

Table 2. *Relative share (%) of the primary cancer in the 25 cases diagnosed by PET/CT as having brain metastases*

Primary cancer	Diagnosed with brain metastases	Patients scanned	%
Lung cancer	7	307	2.3
Breast cancer	6	770	0.8
Cervical cancer	2	157	1.3
Melanoma	3	88	3.4
Colorectal cancer	2	384	0.5
Ovarian cancer	1	180	0.6
CUP	2	109	1.8
Renal cell carcinoma	1	22	4.5
Head and neck	1	71	1.4
Total for these primaries	25	2088	1.2
Other primary cancers	0	414	0
Total	25	2502	1.0

Results

In 25 out of the 2502 patients we detected brain lesions, indicative of and verified to be metastases. Out of the 25 patients with brain lesions, these lesions were verified by MRI in 8 patients, by clinical follow-up in 11 patients, by surgery in 5 patients and one patient with multiple brain metastatic lesions, seen in the low dose CT scan was not further studied due to rapid clinical deterioration (Table 1).

Twenty three out of these 25 patients were asymptomatic by the time of the scan and had not experienced headache, vomiting, unconsciousness, vertigo, seizures or neurologic deficits. All patients were questioned about such symptoms; however detailed neurologic examination was not performed. The remaining 2 patients complained recently of vomiting of unknown origin.

Among the 25 patients, 13 presented with solitary metastases, 11 with multiple metastases and one with meningeal carcinomatosis (Table 1). In the 3 patients with hypometabolic lesions, the only clue for diagnosis was CT (Fig. 1).

In 22/25 patients we noticed additional extracranial metastatic lesions with or without lymph node metastases and in 3/25 patients we noticed only brain metastases (Table 1). Table 2 shows the relative share of the primary cancer in the 25 cases diagnosed by PET/CT as having brain metastases.

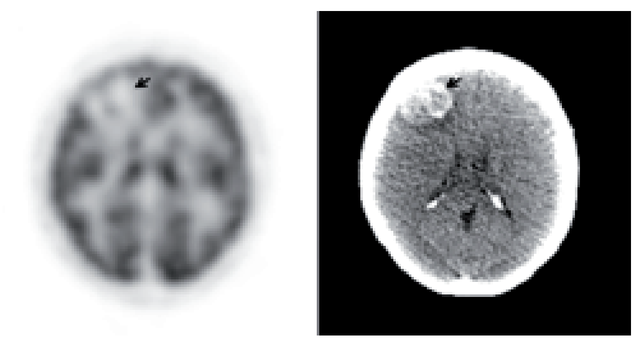

Figure 1. Patient №11 with cancer of unknown primary and supraclavicular metastases from adenocarcinoma. ^{18}F-FDG PET/CT revealed two metastases in the right frontal lobe, clearly delineated on the low dose CT images (arrow), but hypometabolic on PET images (arrow). Patient had neurosurgery with histological confirmation.

Discussion

The patients, diagnosed with brain metastases on PET/CT were exactly 1% of all scanned patients, which obviously is far below what is theoretically expected [5]. Incidence proportion of brain metastases in cancer patients is reported to be 8.5% to 9.6% with patients being diagnosed with routine clinical and imaging techniques but not by autopsy [16, 17]. More than one fourth of the 25 cases with brain metastases were of patients with lung cancer and accounted for 2.3% of all scanned lung cancer patients (16.3%-19.9% expected cumulative rate [16, 17]) e.g. twice the overall rate. It's worth noticing that all lung cancer patients from this group had non-small cell lung cancer. A rather similar situation was noticed in melanoma patients with a 3.4% metastatic rate (6.1%-7.4% expected) [16, 17], while in breast cancer patients the detection rate was low: 0.8%, about 5% of the expected [16, 17]. The observed higher percentage of brain metastases in renal cell carcinoma is misleading due to the limited number of patients (Table 2).

One of the limitations of our study was patient selection, because patients with symptomatic brain metastases are usually examined with CECT or MRI and not with PET/CT and are usually in an advanced stage. As shown in Table 1 both PET and CT findings were complimentary to support the diagnosis of brain metastases.

In patients with solid extracranial tumors, brain metastases occur in 10%-35% of the cases [5]. Most of these lesions are supratentorial (80%) and about 30% are solitary. Gold standard in the diagnosis of brain metastases remains MRI. However MRI is not routinely applied in every cancer patient. Although ^{18}F-FDG PET is known to have poor sensitivity for malignant brain lesions, we find it reasonable to include the brain in the scanned field mainly because of the additional information, provided by the simultaneous low dose CT. Low dose CT as a part of PET/CT does not provide good quality CT images, but is enough for detecting lesions [6] larger than 1cm and not localized close to bone structures [7]. By adding a few low dose CT slices to cover the brain, patient's effective dose is not significantly increased. In order to calculate the increase of the effective dose while including the brain in the scanned field we studied 50 patients in whom we planned the scan with and without the brain in the scanned field. The information for the expected dose length product (DLP) was automatically calculated by the acquisition software and the mean increase in DLP was 10.7%. In order to estimate the effective dose we used the equation *E* (mSv) *k* x *DLP* [18] where E is the effective dose, k is a conversion factor and DLP is obtained directly from the scan planning software. The conversion factor for head CT scan, provided by the American Association of Physicists in Medicine (AAPM) is 0.0021 which resulted in an average increase of the effective dose of 0.14mSv per patient (ranging from 0.08 to 0.19mSv).

Furthermore, PET/CT images could probably help in revealing other brain abnormalities, apart from metastatic spread as reported in the literature [8, 9].

It is likely that incidental detection of brain metastases by whole body PET/CT can change treatment plan (Fig. 2) and especially in patients in whom brain is the only metastatic site and who would have otherwise been read as complete remission as in 3 patients in our series.

We cannot evaluate sensitivity and specificity in our study, mainly because of lack of reference image, but sensitivity would be expectedly low [10, 11] (Fig. 3). A recent study with MRI found 50% sensitivity of PET/CT for brain metastases, compared to MRI on patient basis with PET/CT being superior to PET alone [10]. In the same study sensitivity of PET/CT on lesion basis was disappointing: 13%. Another study with similar design but enrolling only lung cancer patients demonstrated sensitivity of 23% on patient basis [11]. In order to improve detectability one could choose a dedicated brain protocol for brain PET/CT [12] even with CECT, but this would double the scan time and provide a higher absorbed dose to the patient (Fig. 4). Dedicated brain protocol could be used in symptomatic patients, in which however MRI is the mandatory modality. It has to be mentioned that hypometabolic foci should also be taken into consideration when reading a brain scan because it could indicate perifocal-perimetastatic oedema [13]. Studies assessing sensitivity enroll limited number of patients and the study design used is not always routinely applicable [10, 11]. On the other hand, screening studies as the present one claim to enroll more patients and are closer to routine practice, but can only demonstrate detection rate of the specific protocol used. A large screening study found the detectability rate for brain metastases of routine whole body ^{18}F-FDG PET scan alone as low as 0.4% [14]. A recent study in 500 patients focused on PET/CT performance used an extended field of view from vertex to toe and found unexpected brain metastases in 8 patients (1.6%) [15]. However that study also included patients with lymphoma, brain tumors and lung cancer with non-specified histological type, which could add a bias as compared to our results. Clinical symptoms, suggestive of brain pathology are also an issue in comparing results of different authors.

We consider that in patients with solid extracranial tumors and without neurological symptoms inclusion of the brain in the whole body scanned field is a reasonable procedure. When these patients become symptomatic they will be studied by MRI, but delay in diagnosis will be unfavorable for their outcome. Negative scans should not be read as lack of brain metastatic spread and cannot replace further neuroimaging, but positive scans should be considered as true positives and further studied.

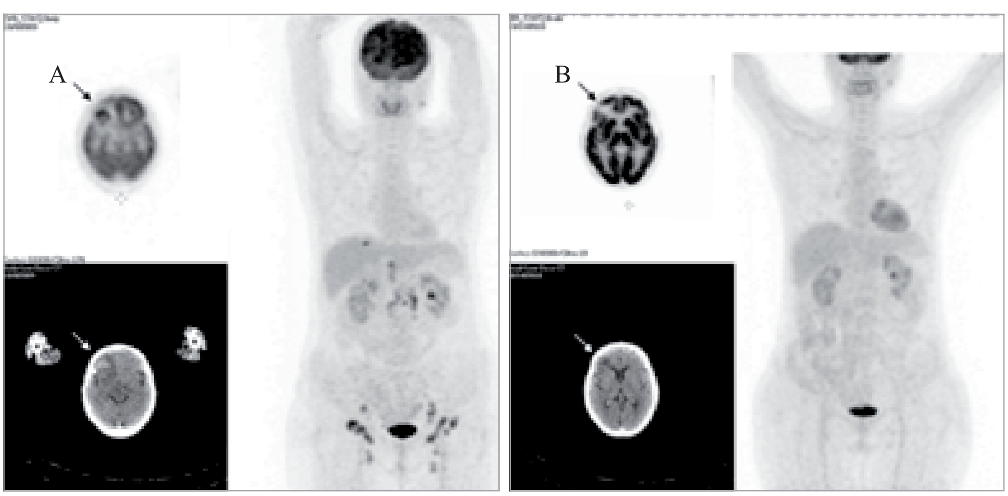

Figure 2. A. Patient No. 23 with ovarian cancer referred for restaging with ^{18}F-FDG PET/CT. The study revealed a solitary ring-like brain metastasis in the right frontal lobe (arrow), a solitary liver metastasis, paraaortal and inguinal lymph nodes involvement. **B.** The same patient after neurosurgery and chemotherapy. Postoperative changes in the brain (arrow). Complete metabolic remission of all extracranial lesions.

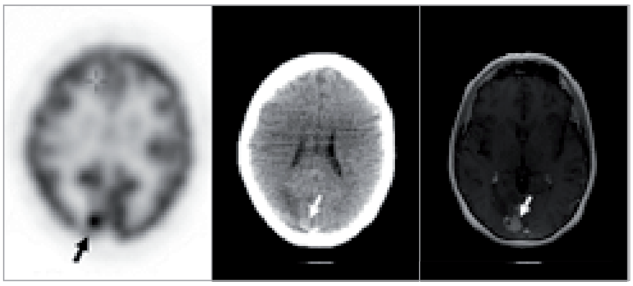

Figure 3. A. Patient No.18 with newly diagnosed solitary brain metastasis by PET/CT, in the right occipital lobe with hypermetabolic appearance on the PET scan (arrows). **B.** MRI revealed the lesion to be metastatic (arrow) and diagnosed at least 20 other subcentimetric lesions.

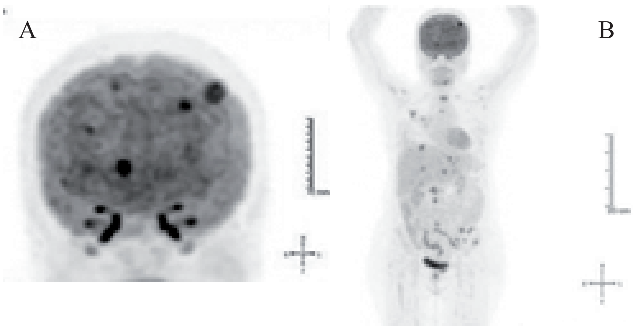

Figure 4. Patient No. 4, brain imaging, using dedicated brain protocol and whole body PET/CT. **A.** Shows numerous lesions, some of them subcentimetric. **B.** Shows a single metastatic focus in the brain. Patient's stage, however, was not changed.

In conclusion, routine whole body ^{18}F-FDG PET/CT scans may detect brain metastases in 1% of asymptomatic patients with solid extracranial tumors, if brain is included in the scanned field. The procedure is simple, has no significant additional radiation burden and if positive provides useful clinical information.

The authors declare that they have no conflicts of interest.

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