Original Article

Brain-Included ^{18}F FDG PET/CT Acquisition Protocol: Cancer-Specified Clinical Impact of Newly-Diagnosed Brain Metastasis in Extra-Cerebral Cancer Patients

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Abstract

Background: Evolution of individualized radiosurgical therapeutic methods for brain metastasis as an ominous prognostic finding may encourage a more extensive application of neuroimaging in patients with extracerebral cancer. The aim of the present study was to investigate the added value of brain-included 18 F FDG PET/CT acquisition protocol based on primary cancer type and clinical indication.

Materials and Methods: A retrospective review was performed on 3945 18 F FDG PET/CT reports of patients with extra-cerebral cancer underwent brain-included PET/CT study. Cerebral lesions suggestive of brain metastasis were subsequently verified by MRI, MRI+MRS, surgical pathology and a 1-year clinical formal follow up. The detection rate of new brain metastasis and related impact on disease status were then investigated in each cancer type based on clinical indication.

Results: Of a total 3933 eligible patients, 44 (1.12%) were finally verified to have new cerebral metastasis. The most common primary sources were lung cancer (19/385, 4.93%), cancer of unknown primary (CUP) (5/168, 2.97%) and breast cancer (8/468, 1.71%). The most common clinical indications were initial staging (17/44, 43.1%) and restaging (19/44, 36.4%). Change in disease status occurred in 12 out of 44 patients (27.3%), more frequently occurred in lung cancer (n=4), in all indications and breast (n=3) cancers at restaging (n=7, 43.8%).

Conclusion: PET/CT acquisition protocol study may be best optimized based on the type of primary cancer and timing of evaluation. Brain-included field of view may be recommended for lung cancer regardless the clinical indication, cancer of unknown primary and breast cancer at restaging.

Keywords: Brain Metastasis, brain-included 18F FDG PET/CT, Clinical Indication, Cancer Type, Change Status

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Introduction

Increasing incidence of brain metastasis in addition to the advent of individualized surgical and radiosurgical therapeutic methods may highlight the role of neuroimaging modalities in early detection of clinically silent cerebral metastasis and related impact on quality of life and survival in extracerebral cancer patients. Currently, there is no consensus on routine screening of cerebral metastasis in neurologically asymptomatic patients, expect for lung cancer and metastatic melanoma[1]. Whole body 18 FDG PET/CT, as the most comprehensive imaging modality in oncology has gained wide acceptance in clinical practice. The most prevalent primary origins of brain metastasis, including lung, breast, melanoma, colorectal and kidney[2] often constitute the vast majority of patients' population at most PET/CT center, worldwide. However, evidence for optimizing PET/CT field of view and potential value of brain-included acquisition in oncologic studies are scarce. The results of preliminary studies most of which were performed on the small population with stand-alone PET did not advocate the routine inclusion of brain in 18F FDG PET studies due to the little clinical impact[3]. Despite the inherently low sensitivity of brain PET due to high physiologic cerebral 18F FDG uptake obscuring small sized brain metastasis[4]. But recent large-scaled studies using high resolution hybrid PET/CT scanner, with or without contrast enhancement, have been indicated that brain-included whole body PET/CT may provide additional valuable information about previously unsuspected brain metastasis in certain cancer[5-8] which may potentially contribute to a timely treatment and better survival. Few studies have been investigated the added value of PET-detected brain metastasis on the basis of cancer type and timing of evaluation[6-7, 9-11]. Our observations on over 3000 brain-included PET/CT study advanced a proposal for a cancer-specified stratification method to optimize PET/CT acquisition protocol. The aim of the present study was to investigate the added value of brain-included PET/CT study in detection of previously unidentified cerebral metastasis and related impact on disease status based on the primary cancer type and clinical indication.

Methods

Patients: The Institutional Review Board at Shahid Beheshti University of Medical Science approved this retrospective study and waived the need for informed consent.

A retrospective review was performed on 4004 patients underwent brain-included whole body PET/CT studies in Masih Daneshvari Hospital between May 2012-Mar 2015. Of these, 8 patients were referred for non-oncologic neurological indications, 63 were known case of primary (n=25) or metastatic (n=38) cerebral tumor and hence were excluded from the study. A total of 3933 patients with extra-cerebral cancer were considered for inclusion in this study. Brain metastasis was reported in 65 patients, 21 of which lost to complete clinical formal follow up. Finally 46 patients constituted the study cohort. All demographic and cancer related characteristics including age, gender, primary cancer type and reason for referral were recorded.

PET/CT acquisition protocol: Whole body F-18 FDG PET/CT was performed using an integrated PET/CT scanner (GE 690 Discovery, 64 Slice, Time of Flight). Fasting period was considered at least 8 before injection for adults. Blood glucose level was below 150 mg/dl at the time of radiotracer injection. Sixty minutes (± 10%) after IV administration of 4.6MBq/Kg (0.12 mCi/Kg F-18 FDG, CT acquisition commenced craniocuadally from high vertx to mid-thigh (or to toe as indicated) with a multidetector CT scanner and the following parameters: auto mAs 50-120, 120 kV, noise factor 19, 2.5 mm thickness. Thirty minute before imaging acquisition, 40cc meglumin 76% (containing 370mg Iodine /cc) in 1500 water was administered as oral contrast in adults. The PET data were then collected in the reverse direction immediately after CT acquisition with time of 3 minutes per bed position. The PET raw data were corrected for attenuation, dead time, random and scatter coincidence, and subsequently reconstructed by iterative method and HD (high definition) technique. No premedication was administrated before injection.

Image interpretation: All the image data set of selected patients including AC and NAC PET, CT and fused PET/CT were retrieved on PACS and reviewed

by a team comprised of an experience radiologist and a nuclear medicine physician on advantage window Volume Share 4.5, side-by side and reached at consensus for the presence of cerebral metastasis. Disease status, including staging based on TNM staging system or Ann-arbor, treatment response evaluation (<6 months by the end of chemotherapy and <2 months by the end of radiation therapy) based on PERCICST or Deauville score, restaging, and recurrence were then determined according to the patients' medical chart and baseline imaging, including PET/CT data, with and without considering PET-detected cerebral metastasis. Brain metastasis was considered as a focus or foci of abnormal increased or decreased radiotracer accumulation more or less than 20% of the surrounding tissue or the opposite side with or without associated morphologic abnormality on CT component including edema, midline shift or abnormal density. Single (<3) vs. multiple (≥3) metastasis were determined on the basis of the impact on treatment strategy.

Standard of reference: Forty-Six PET/CT detected brain metastasis were correlated with the results of clinical formal follow up (n=38, 82.6%), surgical biopsy (n=5, 10.87%) and MRI/MRS 3 (6.52%). Based on the oncologist final decision, the impact of true positive PET-detected brain metastasis on cancer status were then investigated.

Statistical Analysis: Descriptive quantitative variables were expressed as either frequency or mean (±SD). Chi-square test was used to compare change in disease status and treatment strategy among primary cancer types and indication. *p* value <0.05 was considered to indicate a statistically significant difference (SPSS 23).

Results

Demographics: Of 46 patients with a total of 96 lesions, 44 (1.12%) patients were finally verified to have at least one cerebral metastatic lesion (positive predictive value=95.65%) (25 female [56.8%), 19 male [43.2%]; mean age 59.25±11.87 years). Eighty-seven point five patients were >50 years old. Mean age did not show significant different between male (61.10±10.91 years) and female (57.84±13.10) (p=0.36).

Image characteristics: The most common metabolic pattern of cerebral metastasis was focus of abnormal increased radiotracer uptake (n=40, 90.9%). Three out of 6 (50%) cerebral metastasis of colorectal and 1 of prostate origin presented with foci of absent metabolic activity. Twenty six patients (59.1%) had single lesion (<3) and the remainder demonstrated multiple lesions (40.9%). Except for breast cancer, most primary cancer revealed single cerebral metastasis at PET/CT scan. Most lesions did not have any abnormal CT associated abnormality (n=52, 54.16%), while 37 (38.54%) had edema, 5 (5.2%) demonstrated midline shift and 2 presented with hemorrhage (2.2%). The anatomical distribution pattern of the new cerebral lesions were as the following: supratentorial n=81 (84.37%), infratentorial n=9 (9.37%) and both supra and infratentorial lesion n=6 (6.25%). No significant different was found in imaging characteristics of cerebral metastasis based on primary cancer type and clinical indication. Table 1 summarized the imaging characteristics of PET-detected cerebral metastasis based on primary cancer type and indication.

Detection Rate in General: The overall detection rate of new cerebral metastasis was found to be 44 out of 3933 (1.12%). The most frequent primary source of PET-detected brain metastasis were lung cancer (19/385, 4.93%), followed by cancer of unknown primary (5/168, 2.97%), breast cancer (8/468, 1.71%), genitourinary cancer 4/427 (0.94%), colorectal cancer 6/695 (0.86%) and lymphoma 2/859 (0.23%).

Detection Rate based on primary cancer type: Previously unidentified brain metastasis in patients with lung cancer were most frequently recognized at staging (11/19, 57.89%) and resting (6/19, 31.57%) exams. In breast cancer, the highest yield obtained at restaging studies (6/8, 75%). New cerebral metastasis in patients with colon cancer was most frequently seen in patients underwent treatment response evaluation (4/6, 66.66%).

Detection Rate based on clinical indication: On a per indication basis, new cerebral metastasis was most frequently identified at initial restaging (n=16/44, 36.36%), followed by staging (n=14/44, 31.82%), and treatment response evaluation (n=9/44, 20.45%). The most common primary cancer harbouring unidentified cerebral metastatic lesion at initial staging was lung (n=11/17, 64.7%). At restaging, the highest detection

Table 1: Image characteristics of PET-detected cerebral metastasis based on primary cancer type.

	Lung (no.)	Breast (no.)	CUP* (no.)	GYN* (no.)	Colorectal (no.)	Lymphoma (no.)	Total (no. %)
Metabolic pattern							
Increased	19	8	5	3	3	2	40 (90.9%)
Decreased	0	0	0	1	3	0	4 (9.1%)
CT associated abnormality							
Edema	4	6	2	2	2	1	17 (38.6%)
Midline Shift	3	0	0	0	0	0	3 (6.8%)
Hemorrhage	0	0	0	1	0	0	1 (2.3%)
No	12	2	3	1	4	1	23 (52.3%)
Location							
Supratentorial	17	5	4	4	5	2	37 (84.1%)
Infratentorial	2	2	0	0	0	0	4 (9.1%)
Both	0	1	0	2	1	0	3 (6.8%)
Number of Lesion							
<3	12	1	3	3	5	2	26 (59.1%)
3≤	7	7	2	1	1	0	18 (40.9%)

*CUP= cancer of unknown primary
**GYN= genitourinary cancer

rate occurred in lung (n=6/16, 37.5%) and breast cancer (n=6/16, 37.5%). Treatment response evaluation using brain-included PET/CT demonstrated the highest yield in colon and lung cancers (n=4/9, 44.44% and 2.9, 22.22%, respectively).

Change in Disease Status: Newly detected cerebral metastasis changed cancer status in 12 patients (12/44, 27.3% per patients with unidentified cerebral lesion, 12/3933, 0.3% per total patients) as upstaging in 10/33 (30.30%) and under treatment progressive disease in 2/9 (22.22%).

Change in Disease Status based on primary cancer type: Change in disease status most frequently occurred in patients with lung (4/12, 33.33% per cohort with change in disease status, 4/19, 21.05% per patients with lung cancer and brain metastasis) and breast cancer (3/12, 25% per cohort with change in disease status, 3/8, 37.5% per patients with lung cancer and brain metastasis). In all 2 patients with lymphoma harbouring unidentified cerebral lesion, disease status changed at initial exam and post treatment studies.

Change disease status based on indication: Brain-included PET/CT study demonstrated the highest impact on disease status at restaging exams (7/16, 43.75%) in breast cancer (n=3/7, 42.85%) and lung cancer (n=2/7, 28.75%), followed by staging (3/17, 17.64%) in lung cancer. brain-included PET/CT changed disease status while evaluating treatment response in only 2 patients, one of them had lung cancer (n=1, 50%).

Table 2 outlined cancer characteristics in cohort with PET-detected cerebral metastasis based on primary

Table 1: Mean, standard deviation, minimum and maximum age of participants in test and control groups.

	Lung	**Breast**	**Colorectal**	**Lymphoma**	**CUP***	**GYN****	**Total**
Detection Rate	19/385 (4.93%)	8/468 (1.71%)	6/695 (0.86%)	2/859 (0.23%)	5/168 (2.97%)	4/427 (0.94%)	44
Initial Staging	11 (57.89%)$^{+}$ (64.5%)$^{++}$	1 (12.5%) (5.9%)	0	1 (50%) (5.9%)	0	1 (7.1%) (25%)	14 (31.82%)
Restaging	6 (31.6%) (37.5%)	6 (75%) (37.5%)	2 (33.33%) (12.5%)	0	0	2 (12.5%) (50%)	16 (36.36%)
Treatment Response Evaluation	2 (10.5%) (22.2%)	1 (12.5%) (11.1%)	4 (66.7%) (44.4%)	1 (50%) (11.1%)	0	1 (11.11%) (25%)	9 (20.45%)
Diagnosis	0	0	0	0	5 (100%)	0	5 (11.36%)
Total	19 (43.18%)	8 (18.18%)	6 (13.61%)	2 (4.54%)	5 (11.36%	4 (9.1%)	44
Change in Disease Status							
Initial Staging	1 (9.1%) (33.3%)	0	0	1 (100%) (33.3%)	0	1 (50%) (33.33%)	3 (25%)
Restaging	2 (33.3%) (28.6%)	3 (50%) (42.9%)	1 (50%) (14.3%)	0	0	1 (50%) (14.3%)	7 (58.33%)
Treatment response evaluation	1 (50%) (50%)	0	0	1 (100%) (50%)	0		2 (16.16%)
Diagnosis	0	0	0	0	0	0	0
Total	**4 (33.33%)**	**3 (25%)**	**1 (8.33%)**	**2 (16.66%)**	**0**	**2 (16.66%)**	**12**

*CUP= cancer of unknown primary
**GYN= genitourinary cancer
+First row: within primary cancer type
++Second row; within indication

cancer type and clinical indication.

Figure 1 illustrated a focus of abnormal increased FDG uptake in right cerebellar hemisphere, compared to the opposite side, incidentally detected by brain-included PET/CT study in a 57 Y/O women with a history of breast cancer in right breast underwent radical mastectomy being work up for restaging. All baseline imaging were negative for distant malignant lesion. PET/CT with standard field of view were also negative for active malignant lesion. Brain MRI (not shown) demonstrated a hypointense lesion on T1 with a uniform enhancing pattern which demonstrated high signal intensity on T2 images.

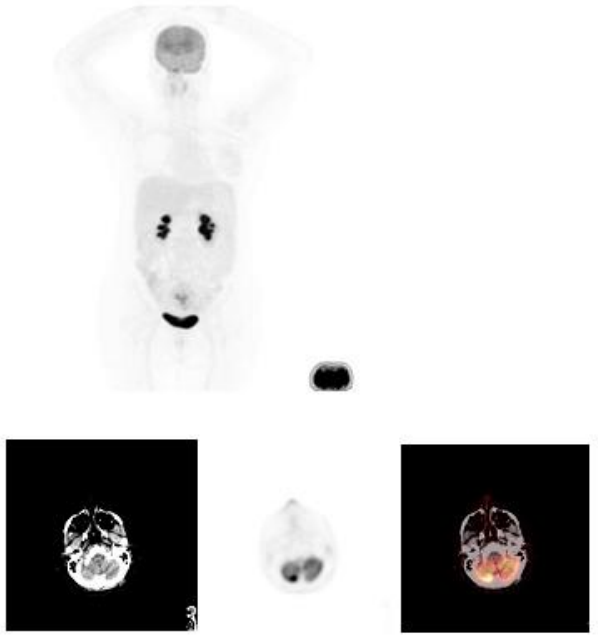

Figure 1. Right cerebellar metastasis incidentally detected in a 57 Y/O women with breast cancer and correlated with MRI, being work up for subsequent treatment strategy. a) PET and fused PET/CT in axial view (b-d) demonstrated focal intense F-18 FDG uptake with no corresponding on NECT images.

Discussion

The results of the present study provided evidence for the potential value of brain included PET/CT study in patients with lung cancer, regardless the clinical indication, cancer of unknown primary and patients with breast cancer at restaging examination. This study found no clinically significant role for brain-included PET/CT scan in most other cancer types, including patients with lymphoma which constitute the highest percentage of patient population at most PET/CT centers.

The additional value of brain-included PET/CT study in neurologically asymptomatic extracerebral cancer patients still needs to be verified. The results of the preliminary studies revealed that the detection rate of cerebral metastasis using brain-included PET/CT was as low as 1% [3] which was mainly attributed to the inherently low sensitivity of 18 F FDG PET/CT due to high physiologic 18 F FDG uptake. The results of the present study demonstrated an overall detection rate of less than 1% for brain metastasis in most primary cancer type by the application of brain-included PET/CT study which is in line with literature[6,7,9,11]. However, some major confounding factors may contribute in this suboptimal performance. The results of large-scaled epidemiologic studies have been demonstrated that most primary cancer types often being evaluated with PET/CT study, including lymphoma, bladder, ovary and prostate, soft tissue sarcoma less commonly metastasize to the brain [12] which may be responsible for the overall low detection rate of cerebral metastasis at true whole body PET/CT scan. However, this may not be true for certain primary malignancies. Using true whole body PET/CT, current study revealed that previously unidentified brain metastasis was successfully detected in approximately 5% of patients with lung cancer, in 21.05% of whom served as the only site of distant metastasis.

Several studies have been demonstrated that up to 90% of brain metastasis developed within the first year of diagnosis of primary cancer, more than half of which were diagnosed during the first month [13]and hence presumably may consider a key role for neuroimaging modalities at initial staging of patients with lung cancer. In line with literatures, the current results provide evidence for the potential value of brain-included PET/CT at initial staging of lung cancer. Additionally, the application of brain-included

PET/CT scan at restaging examination may be beneficial regarding a 10% 5-year cumulative incidence of brain metastasis.

In patients with breast cancer, as the second most common primary origin of cerebral metastasis, the highest yield of true whole body 18 F FDG PET/CT was obtained at restaging examination. These results are compatible with literature indicating that the highest incidences of brain metastasis in breast cancer are observed after 2 year of initial diagnosis[13]. Regarding little penetration rate of most chemotherapeutic agent, cerebral parenchyma may be the first site of disease recurrence and progression in patent's with breast cancer[14], provide additional confirmatory evidence for the potential value of brain-included PET/CT study at restaging examination in this cohort.

The most common primary origin in patients with cancer of unknown primary has been shown to be lung cancer[15] which have a significant association with brain metastasis in this clinical setting[16]. Current study revealed that in nearly 3% of patients with cancer of unknown origin, true whole body PET/CT scan correctly identified new brain metastasis and may hence provide potentially valuable prognostic information to exclude a small minority of patients with favorable prognosis[17].

There results for other type of primary cancer showed major heterogeneity. Indeed, only for breast and lung carcinoma sufficient data was available allowed further analysis. Some reports demonstrated kidney and bladder tumor as the most prevalent primary origin of brain metastasis (0-11%, and 5.26%- 5.9%, respectively)[6,7,9,11], however, it was not demonstrated in the current study. In addition, brain-included field of view in colorectal cancer had a poor yield (0.86) which was in line with other similar publication (0- 0.7%)[6,7,9,11]. Despite a relatively large patients' population, the detection rate of newly diagnosed brain metastasis in patients with lymphoma was not of clinical significance (0.23%).

There are some major drawbacks in the current study. The clinical impact of newly PET-detected brain metastasis on change in treatment strategy and survival was not evaluated in this study. The added value of PET-detected brain metastasis in primary cancer other than lung, breast and cancer of unknown primary still needs to be verified by large-scale multicenteric studies. Furthermore, the potential role of clinical risk factors of brain metastasis, including the histologic subtype, tumor grading, specific tumor mutation and receptor expression in patients' stratification for brain-included PET/CT did not investigated in the current study.

Conclusion

Patients' stratification for brain-included PET/CT study may be best achieved considering primary cancer type and timing for evaluation. Regarding a significant detection rate of cerebral metastasis, brain included PET/CT study may be recommended as the standard acquisition protocol in patients with lung cancer, regardless the clinical indication, cancer of unknown primary and breast cancer at restaging examination. Providing little additional information, brain-included field of view should not be applied as a routine practice for other primary cancer types, particularly lymphoma in most clinical scenarios.

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