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Incidence of Brain Metastases on Follow-Up ^{18}F-FDG PET/CT Scans of Non-Small Cell Lung Cancer Patients: Should We Include the Brain?

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ABSTRACT

PURPOSE

The brain is the most common site of distant metastasis from lung cancer. Thus MRI of the brain at initial staging is routinely performed, but if this exam is negative a follow-up exam is often not performed. This study evaluates the incidence of asymptomatic brain metastases in non-small cell lung cancer patients detected on follow-up ^{18}F- FDG PET/CT scans.

MATERIALS AND METHODS

In this IRB approved retrospective review, all vertex to thigh ^{18}F- FDG PET/CT scans in patients with all subtypes of lung cancer from August 2014 to August 2016 were reviewed. A total of 1,175 ^{18}F- FDG PET/CT examinations in 363 patients were reviewed. Exclusion criteria included brain metastases on initial staging, histological subtype of small-cell lung cancer, and no follow up ^{18}F- FDG PET/CT examinations. After applying our exclusion criteria, a total of 809 follow-up ^{18}F- FDG PET/CT scans in 227 patients were included in the final analysis. The original report of each ^{18}F- FDG PET/CT study was reviewed for the finding of brain metastasis. The finding of a new brain metastasis prompted a brain MRI which was reviewed to determine the accuracy of the ^{18}F- FDG PET/CT.

RESULTS

Five out of 227 patients with 809 follow-up ^{18}F- FDG PET/CT scans reviewed were found to have incidental brain metastases. The mean age of the patients with incidental brain metastasis was 68 years old with a range of 60 to 77 years old. The mean time from initial diagnosis to time of detection of incidental brain metastasis was 36 months with a range of 15 to 66 months. Using MRI as the gold standard, our false positive rate was zero.

CONCLUSION

By including the entire head during follow-up ^{18}F- FDG PET/CT scans of patients with non-small cell lung cancer, brain metastases can be detected earlier while still asymptomatic. But, given the additional scan time, radiation, and low incidence of new brain metastases in asymptomatic patients, the cost to benefit ratio should be weighed by each institution.

Keywords:

^{18}F- FDG PET/CT, non-small cell lung cancer, incidental, brain metastasis, brain MRI

TEXT

Introduction:

The brain is the most common site of distant metastasis from lung cancer with an incidence of 9-17% at the time of initial diagnosis (*1,2*) with adenocarcinoma being the most common histological subtype to metastasize to the brain (*1,3*). Current National Comprehensive Cancer Network (NCCN) guidelines recommend the use of ^{18}F- FDG PET/CT for the initial staging of lung cancer (*4,5*) and recognize MRI as the best modality for detecting brain metastases (*1,6*). Accordingly at our institution, all patients diagnosed with lung cancer are staged with a vertex to thigh ^{18}F- FDG PET/CT and brain MRI with contrast before initiation of treatment.

Currently, no NCCN clinical practice guideline recommendations for routine use of ^{18}F- FDG PET/CT for assessing treatment response or post treatment follow-up for lung cancer have been established. However, the value of ^{18}F- FDG PET/CT for assessment of response to therapy is widely recognized (*4,7*) with Centers for Medicare and Medicaid Services Coverage approval including at least three post-therapy ^{18}F- FDG PET/CT scans per patient and per tumor type (*8*). All lung cancer patients at our institution are followed by ^{18}F- FDG PET/CT examinations regardless of tumor subtype. Our institutional protocol typically obtains follow-up brain MRI scans only for patients with brain metastases on initial staging or for suspicious symptoms. Whole body ^{18}F- FDG

PET/CT imaging technique “from eyes to thighs” is accepted in the procedure guidelines for tumor imaging (*9,10*); at our institution, like others, all patients who receive an ^{18}F- FDG PET/CT examination are imaged from vertex of the skull rather than base of skull.

Over the past decade, lung cancer therapies have evolved with the wide-spread use of targeted therapies and most recently, the introduction of immunotherapies with a resulting increase in 5-year survival rates of lung cancer patients (*11,12*). However, it is estimated that approximately 30-50% of patients with non-small cell lung cancer will develop brain metastases during the course of their disease (*13*). This is most likely related to the limited penetration of chemotherapeutic agents through the blood/brain barrier (*13,14*).

Previous studies assessing the incidence of brain metastases on ^{18}F- FDG PET focused on initial staging performed on scanners with lower resolution than modern scanners (*2*). Since MRI of the brain is standard for initial staging of lung cancer, staging ^{18}F- FDG PET/CT including the entire brain would not improve detection of brain metastases. Therefore, this study focuses on follow-up ^{18}F-FDG PET/CT scans to assess the utility of including the whole brain to evaluate the incidence of detecting asymptomatic brain metastases in patients with non-small cell lung cancer.

Methods and Materials:

In this IRB approved retrospective review, a comprehensive list from August 2014 to August 2016 of all initial staging and follow-up ^{18}F- FDG PET/CT exams performed for all subtypes of lung cancer was retrieved. A total of 1,175 ^{18}F- FDG PET/CT examinations in 363 patients were reviewed. Any exams with brain metastases on initial staging, histological subtype of small-cell lung cancer, and/or no follow up ^{18}F- FDG PET/CT examinations were excluded. After excluding these scans and all initial staging scans, a total of 809 follow-up ^{18}F- FDG PET/CT scans in 227 patients were included in the final analysis (Figure 1). As a referral center many of the initial staging scans were completed at outside facilities and were therefore not captured in the retrieval process.

The original dictated report of each ^{18}F- FDG PET/CT examination was reviewed for the finding of brain metastasis. All scans were read by one of two board-certified nuclear radiologists. A comprehensive chart review through our electronic medical record system was performed for each patient with incidentally discovered brain metastasis. The data extracted from the chart review included histological subtype of tumor, treatment regimen, date of original diagnosis, surgical resection of original mass, and results of initial brain MRI. Demographic data was also collected.

^{18}F- FDG PET/CT imaging covered from vertex of skull to thighs on all patients. Patients were instructed to fast for a minimum of four hours prior to the intravenous injection of ^{18}F- FDG. Before ^{18}F- FDG injection, fingerstick blood glucose levels of the patients were measured. ^{18}F- FDG was administered

intravenously at a weight-based dose of 3.7 MBq/kg with a minimum of 185 MBq and maximum of 370 MBq. After the injection, patients rested in a quiet room for approximately one hour before scanning. A General Electric Discovery 690 time-of-flight scanner (Milwaukee, WI) was used for all patients with the low dose CT scan performed before the PET acquisition. CT scans were performed without intravenous contrast and with oral contrast.

PET scans were imaged with either six or seven bed positions, including the brain, with each bed position acquired in 2.5 minutes. Our average total scan time was typically fifteen to eighteen minutes and our median CT radiation exposure including the head was a total DLP of 168 mGy-cm. All patients were imaged with the arms up if tolerated.

The ^{18}F- FDG PET/CT finding of a new brain metastasis always prompted a follow-up contrast-enhanced brain MRI which was reviewed to determine the accuracy of the ^{18}F- FDG PET/CT. Our typical brain MRI for metastatic workup includes pre- and post-contrast images in at least two planes with 0.2 mL/kg of gadobenate dimeglumine injected intravenously for post-contrast images.

Results:

A total of 227 patients with 865 total ^{18}F- FDG PET/CT examinations were reviewed. Of these 865 scans, 56 were for initial staging and 809 were follow-up examinations. Of the 809 follow-up scans, 5 exams reviewed demonstrated new brain metastases, and thus, 5 out of 227 patients were incidentally found to have

a brain metastasis on their follow up ^{18}F- FDG PET/CT examinations (Table 1). The mean age of the patients with incidental brain metastases was 68 years old with a range of 60 to 77 years old. Three out of five were women. All incidentally found brain metastases were supratentorial-two in the right frontal lobe, one in the left frontal lobe, one in the left caudate nucleus, and two in the right occipital lobe. The distribution of histologic subtypes was three adenocarcinoma, one adenosquamous cell carcinoma, and one squamous cell carcinoma. The initial staging brain MRI of all 5 patients were reviewed and confirmed to be negative for metastasis.

The mean time from initial diagnosis of lung cancer to time of brain metastasis in the five patients diagnosed with incidental brain metastasis was 36 months, with a range of 15 to 66 months. All incidental ^{18}F- FDG PET/CT findings of brain metastases were promptly followed up with contrast-enhanced brain MRI. Using the MRI as the gold standard, all metastases were confirmed and therefore the false positive rate was zero. Four out of five patients had a solitary metastasis on ^{18}F- FDG PET/CT that was confirmed to be a true solitary metastasis on subsequent contrast-enhanced brain MRI. One out of five patients had multiple metastases on ^{18}F- FDG PET/CT that was confirmed to be true multiple metastases on subsequent follow-up contrast-enhanced brain MRI. Three patients' brain metastases were found due to the decrease in metabolic activity associated with vasogenic edema (figure 2). One patient's brain metastasis was seen as a hypermetabolic lesion (figure 3). Another patient's

metastasis was a combination of hypermetabolic lesion with surrounding hypometabolic vasogenic edema.

All five patients were receiving conventional chemotherapy when the brain metastases were found and from retrospective record review, were also asymptomatic. Two out of five had their original lung cancer resected. The patients who had their primary pulmonary lesion resected received radiation therapy to their surgical beds and adjacent lymphadenopathy. All had a negative contrast-enhanced brain MRI at their initial staging workup.

The three patients with solitary metastasis were treated with surgical resection of their brain metastases with two receiving stereotactic radiation therapy (SRT) to their surgical bed. The pathology of the resected metastases were confirmed to be true metastases and not new primary malignancies. The other patient with solitary metastasis received SRT alone to the metastatic lesion. The patient with multiple brain metastases was treated with whole brain radiation therapy.

Discussion:

In older studies, the reported incidence of brain metastases on ^{18}F- FDG PET/CT range between 1.5% and 5.3% (*9,15-17*) for all types of cancer. During the initial conception of this study, a primary goal was clinical relevance. Hence, we selected lung cancer, a disease that frequently metastasizes to the brain, and focused on brain metastases that would have otherwise not been detected. Also,

the increased spatial resolution of a modern time-of-flight PET/CT scanner could potentially increase the sensitivity for brain metastasis detection. Changing therapy regimens for lung cancer and longer survival times also could affect the incidence of brain metastases on follow-up ^{18}F- FDG PET/CT. To our knowledge, this is the first study reporting the incidence of brain metastasis in a large cohort of patients with lung cancer who underwent routine follow-up ^{18}F-FDG PET/CT. The observed incidence of brain metastasis was approximately 2% in our patient population (5 in 227 patients), and was 0.6% of ^{18}F- FDG PET/CT follow up scans reviewed (5 in 809 scans). One can expect that sensitivity and specificity will improve with further advancements in the technology of ^{18}F- FDG PET/CT and ^{18}F- FDG PET/MRI.

All patients with incidental brain metastases were asymptomatic. This is concordant with current literature indicating that approximately 50% of brain metastases are asymptomatic at time of diagnosis (*1,18*). Discovering brain metastasis prior to patients becoming symptomatic is critical in order to prevent complications like seizures which could occur during hazardous activities such as driving. All brain metastases were supratentorial and therefore would not have been detected with a base of skull to thigh protocol.

In our study, the most common histological subtype associated with the development of brain metastasis was adenocarcinoma. This is in line with prior findings where adenocarcinoma was demonstrated to be the most common histology to subsequently develop metastases to the brain (*13,19*). This may be

related to the fact that adenocarcinoma is the most common histological subtype of lung cancer overall.

Perhaps the most interesting finding in our study was the latency at which these brain metastases occurred. The average time for development of incidental brain metastasis after initial diagnosis of lung cancer was 36 months, with one patient developing brain metastasis 66 months after initial diagnosis. This may be related to advancing lung cancer treatments such as targeted chemotherapy and immunotherapy (*11,12*). Additionally, this prolonged latency period after initial diagnosis may be because standard chemotherapy agents do not significantly cross the blood/brain barrier (*13,14*). With our institutional protocol, this equates to an additional 2.5 minutes to total exam time related to the single additional bed position, and an approximately 168 mGy-cm increase in radiation exposure from the CT component of the scan. Given the mortality rate and utilization rate of radiation therapy for lung cancer, this additional radiation exposure is very likely of no clinical significance.

A central limitation of this is that it is a single center study; therefore, protocol differences compared to other centers may alter detection rates of brain metastases and the cost to benefit ratio. A second limitation is prevalence of brain metastases in our study population may have been underestimated, as our patient population was not being screened by serial contrast enhanced brain MRI. The follow-up ^{18}F- FDG PET/CT scans without evidence of brain metastasis over a long time frame supports that our results are highly accurate.

Additionally, the prevalence of brain metastases seen on ^{18}F- FDG PET/CT in our study population was similar to that of previous studies, suggesting that our sensitivity is accurate.

In conclusion, by including the entire head during a ^{18}F- FDG PET/CT scan for follow-up of non-small cell lung cancer, brain metastases can be detected early while asymptomatic with a very low false positive rate (zero in this study). However, given the additional scan time, increase in radiation exposure, and the generally low incidence of new brain metastases in asymptomatic patients, the cost to benefit ratio of this technique modification should be weighed by the multidisciplinary care team at each institution.

FINANCIAL DISCLOSURE

We do not have any conflicts of interest to disclose, financially or otherwise, that may directly or indirectly influence the content of the manuscript submitted.

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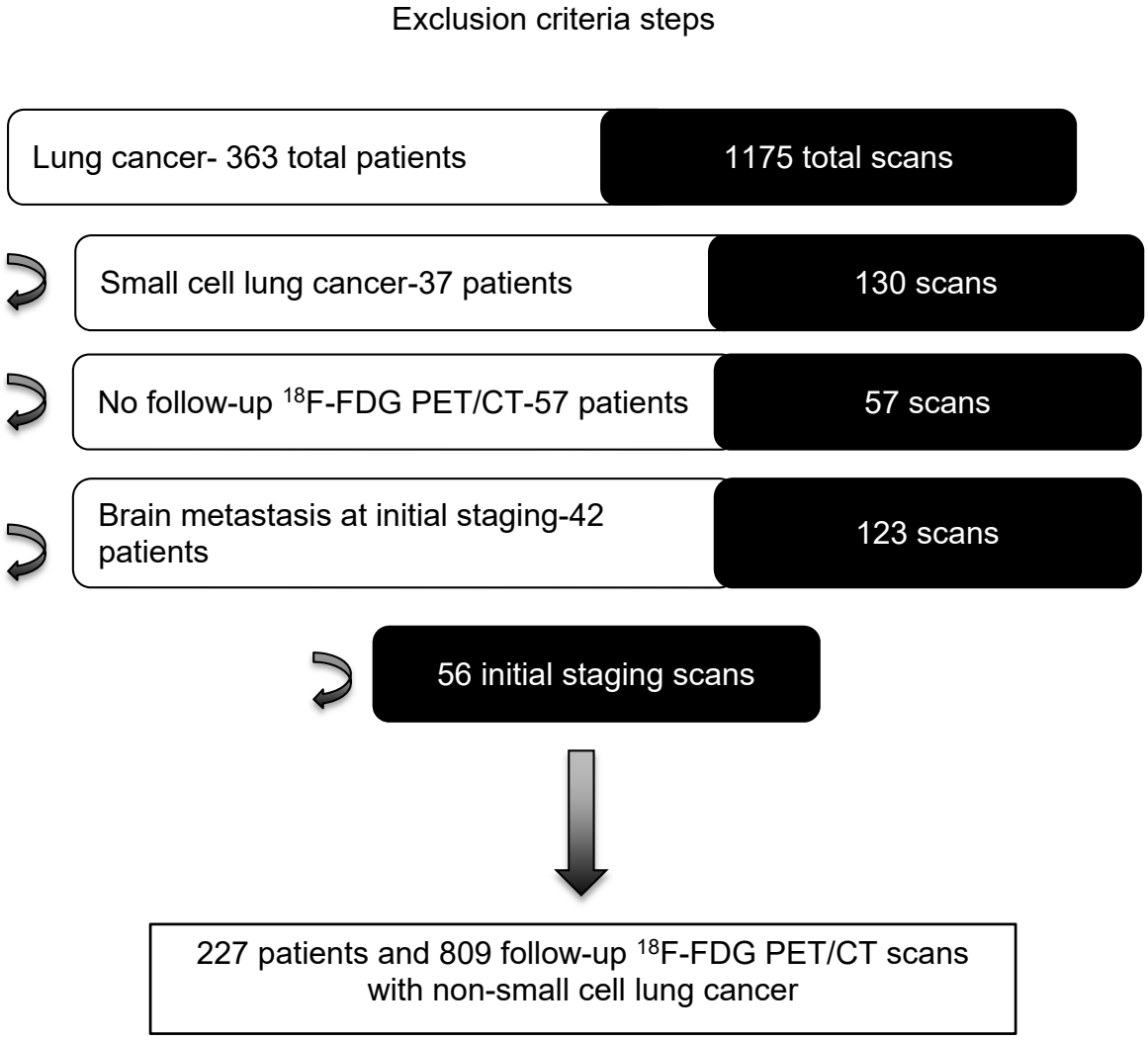
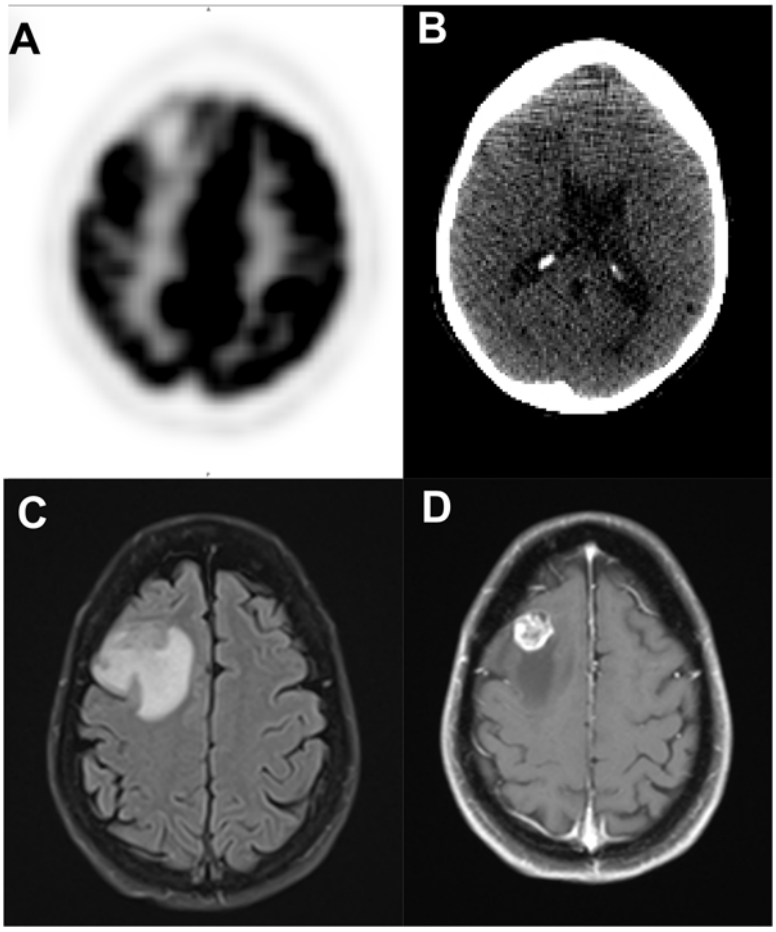
FIGURE 1



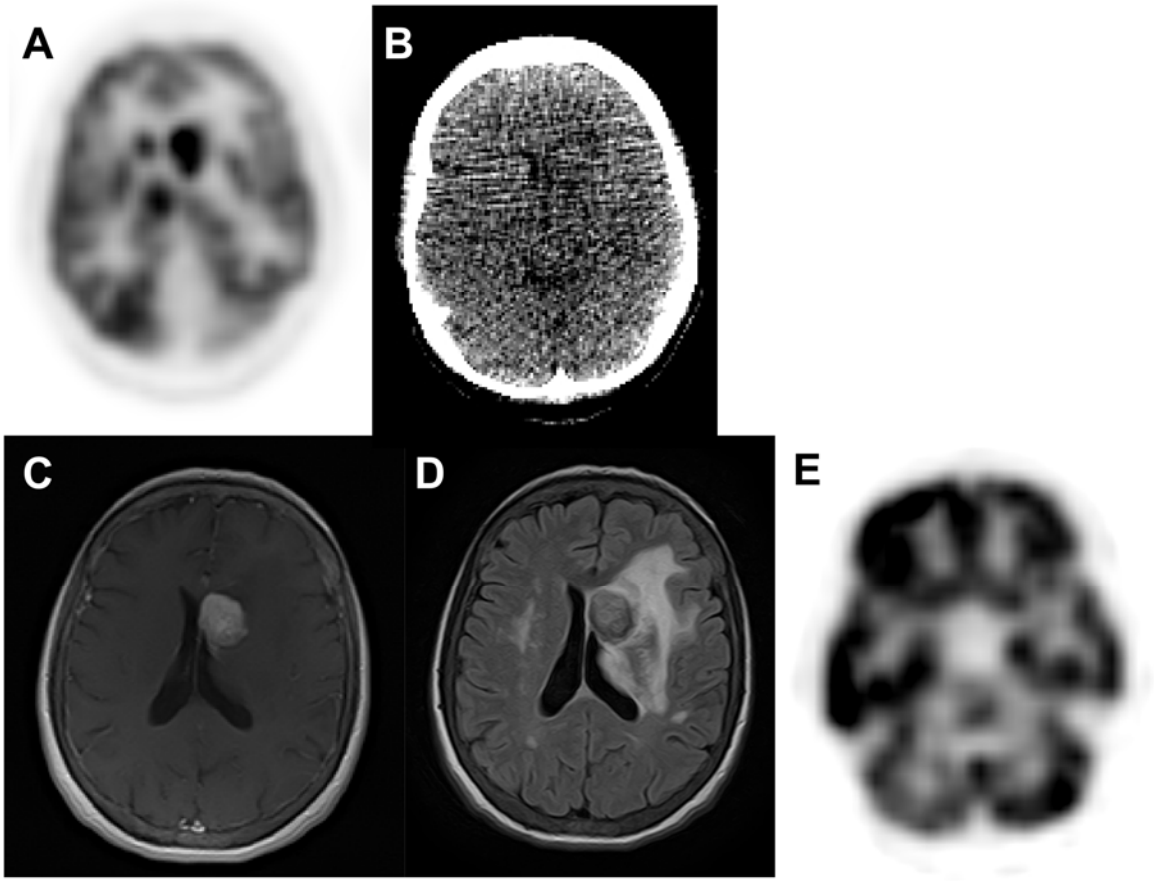
A total of 1,175 ^{18}F- FDG PET/CT examinations in 363 patients were reviewed. Exclusion criteria included brain metastases on initial staging, histological subtype of small-cell lung cancer, and no follow up ^{18}F- FDG PET/CT examinations. After applying our exclusion criteria in addition to eliminating all initial staging scans (only follow-up scans included), a total of 809 follow-up ^{18}F-FDG PET/CT scans in 227 patients were included in the final analysis.

FIGURE 2



Axial ^{18}F-FDG PET image of the brain demonstrates focal hypometabolism in the right frontal lobe (2A) corresponding to vasogenic edema on low-dose CT images (2B). Subsequent axial T2-FLAIR and contrast-enhanced MRI images confirm the metastasis with adjacent vasogenic edema (2C-D).

FIGURE 3



Axial ^{18}F-FDG PET and low-dose CT images of the brain demonstrate a hypermetabolic lesion in the left caudate (1A-B). Subsequent contrast enhanced MRI axial imaging of the brain confirmed the metastasis (1C). Axial T2 FLAIR imaging demonstrates surrounding vasogenic edema (1D). PET also shows crossed-cerebellar diaschisis with decreased activity in the contralateral right cerebellum (1E).

TABLE 1

	Age	Gender	Cancer Type	Time until incidental brain metastasis (months)	# Metastases seen on FDG-PET/CT	# Metastases seen on subsequent MRI
Patient 1	60	Male	Adenosquamous	27	One	One
Patient 2	60	Female	Adenocarcinoma	19	One	One
Patient 3	67	Female	Squamous Cell	53	Multiple	Multiple
Patient 4	77	Female	Adenocarcinoma	66	One	One
Patient 5	77	Male	Adenocarcinoma	15	One	One
Average	68			36		