Original Article

High false positivity in positron emission tomography is a potential diagnostic pitfall in patients with suspected adrenal metastasis

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ABSTRACT

Background:

Although 18F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) is a potentially powerful, non-invasive imaging tool in differentiating adrenal metastasis from benign disease, some adenomas also exhibit high FDG uptake, therefore mimicking metastasis (i.e. false positives). We aimed to evaluate the accuracy of FDG-PET/CT based exclusively on histology and to identify risk factors for adrenal metastasis.

Methods:

Among the 289 consecutive patients who underwent adrenalectomy, 39 (78.0%) patients had suspected solitary adrenal metastasis and had a positive preoperative FDG-PET/CT. The FDG-PET/CT findings were correlated with the histology of the excised adrenal gland. To identify risk factors for adrenal metastasis, characteristics were compared between patients with histologically-proven adrenal metastasis and those without. Youden's index was used to calculate the optimal cut-off value for predicting adrenal metastasis.

Results:

Histology of the excised adrenal tumor confirmed adrenal metastasis in 28/39 (71.8%) patients while non-metastatic lesions comprised mostly benign adrenal cortical adenoma (n=10) and one non-functional pheochromocytoma. Therefore, the overall false positive rate of FDG-PET/CT was 28.2%. History of primary lung malignancy (odds ratio (95%CI)= 20.00 (1.01 – 333.3),

p=0.049) and SUVmax >2.65 (odds ratio (95%CI)=31.606 (2.46 – 405.71), *p*=0.008) were independent risk factors for adrenal metastasis.

Conclusions:

Single adrenal uptake on FDG-PET/CT in suspected solitary adrenal metastasis was associated with a high false positive rate (28.2%). Risk factors associated with adrenal metastasis included a history of known primary lung malignancy and a SUVmax >2.65 at the adrenal lesion of interest on FDG-PET/CT. Based on these findings, a new algorithm was constructed.

INTRODUCTION

The adrenal gland is a common site for metastasis in patients with malignancy. It is estimated that up to 50% of all adrenal masses incidentally detected in patients with history of malignancy would harbor metastases[1-3]. Since adrenalectomy for solitary adrenal metastasis offers survival benefit in selected patients[4-5], establishing whether these adrenal masses are in fact metastatic or not is clinically important. Radio-guided fine needle aspiration of these masses could provide definitive diagnosis of adrenal metastasis but is invasive and may be associated with significant morbidity and high inadequacy[6-7].

18F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) is a relatively new, non-invasive tool that could help to characterize these adrenal masses. Several reports have shown the effectiveness of stand-alone FDG-PET/CT to differentiate benign from malignant adrenal lesions[1,2,8]. It works on the basis that malignant adrenal tissue (i.e. metastasis) tends to have a higher uptake of radio-labelled glucose analog (because of increased glycolysis) than benign or normal adrenal tissue. However, it is not perfect because although most benign adenomas have FDG uptake equal to or below liver (i.e. appearing as little to no uptake), some exhibit FDG uptake greater than the liver (i.e. increased uptake), therefore mimicking metastases. In fact, a recent study has found an unexpected high false positive rate (i.e. an adrenal lesion appearing positive on FDG-PET/CT but ending up benign on histology)[9]. Given that the vast majority of the current literature reporting the accuracy of FDG-PET/CT is based on interval CT follow-up [1,2,10,11] instead of actual histology which should be regarded as the gold standard for determining the nature of an adrenal mass, the present study aimed to first evaluate the accuracy of FDG-PET/CT based exclusively on histology and secondly, to identify potential significant factors associated with adrenal metastasis.

PATIENTS AND METHODS

All consecutive patients who underwent adrenalectomy at our institution by our team from 2001 to 2013 were retrospectively reviewed. To be eligible for analysis, patients had to have a suspected solitary adrenal metastasis and undergone a preoperative FDG-PET/CT within 2 months before adrenalectomy. Those with apparent oligometastatic disease on presentation were not included as they are expected to have a higher chance of adrenal metastasis. All patients underwent routine hormonal evaluations before adrenalectomy including overnight 1-mg dexamethasone test, 24-hour urinary catecholamines and a plasma aldosterone to renin ratio (if hypertensive)[3] as well as a dedicated adrenal protocol CT performed with no contrast, 1-min post-contrast and 15-min delayed post contrast scans before FDG-PET/CT. All scans were reported by dedicated radiologists. The findings on the preoperative FDG-PET/CT were correlated with the final histology of the excised adrenal gland. During the study period, preoperative FDG-PET/CT was not mandatory for all patients with a suspected adrenal metastasis but was increasingly being performed for the purpose of cancer staging (i.e. excluding extra-adrenal metastatic diseases before adrenalectomy). Since the findings of the FDG-PET/CT was not intended to differentiate metastasis from benign disease, the decision for adrenalectomy was based on clinical suspicion of an adrenal metastasis. For the purpose of the study, clinical suspicion of an adrenal metastasis was categorized into 4 groups, namely a new lesion (i.e. an adrenal lesion not apparent from previous CT scans if available), a lesion with interval enlargement (which was defined as >20% increase in any one dimension over one year or by pro rata if duration was not exactly one year), a large lesion (i.e. ≥4.0cm in the largest dimension) and a lesion with indeterminate CT features (such as attenuation by Hounsfield unit > 10 on non-contrast CT scan and / or absolute washout pattern > 60% or relative washout > 40% on contrast

CT scan)[1,3]. Characteristics such as age, sex, main reason for suspecting adrenal metastasis, type of primary non-adrenal malignancy, PET/CT findings and final adrenal pathology of the eligible patients were extracted from patient charts.

FDG-PET/CT technique

All patients were asked to fast for a minimum of 6 hours with serum glucose level confirmed to be < 120 mg/dL before intravenous administration of 370 to 555 MBq of FDG through a peripheral vein. After 60 minutes, FDG-PET/CT images were acquired using a full-ring dedicated PET scanner. Images were acquired from the base of skull to the mid-thigh. The maximum standardized uptake value (SUVmax) for the particular adrenal lesion of interest was recorded by drawing a rectangular three-dimensional region of interest around the nodule.

To identify for potential risk factors associated with adrenal metastasis, preoperative patient baseline characteristics were compared between those with histologically proven adrenal metastasis (malignant group) and those without adrenal metastasis (benign group).

Statistical analysis

Statistical analysis was performed by chi-square or Fisher's Exact test to compare categorical variables, and Mann-Whitney U test was used to compare continuous variables between groups. Variables significant in the univariate analysis ($p<0.10$) were entered into multivariate analysis. To improve clinical utility of significant continuous variables (such as SUVmax and tumor size), Youden's index[12] was used to calculate the best cut-off value for predicting adrenal metastasis. The AUC was used to measure the predictive accuracy. AUC values closer to 1 meant better predictability whereas values closer to 0.5 meant poorer predictability. A bootstrap approach with 1,000 resamples was used to estimate 95% confidence intervals for AUC and to compare two AUCs. All statistical analyses were conducted using SPSS version 18.0 (SPSS, Inc., Chicago,

IL, USA) and R version 2.14.0 (R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

RESULTS

Altogether 289 consecutive patients underwent adrenalectomy. Of these, 50 (17.3%) were suspected solitary adrenal metastasis and 39 (78.0%) patients had a preoperative FDG-PET/CT within 2 months of adrenalectomy. All patients who underwent a preoperative FDG-PET/CT had a single positive adrenal uptake in the suspected lesion and all were tested negative for hormonal hyper-secretion. The patient baseline characteristics (such as age, sex, type of primary malignancy, suspicion and risk of metastasis) between those did (n=39) and those who did not undergo preoperative FDG-PET/CT (n=11) were not significantly different (*data not shown*).

Table 1 shows the baseline characteristics of the 39 patients who underwent preoperative FDG-PET/CT. All patients had a single FDG uptake in their respected adrenal lesion. The mean (±SD) SUVmax of the adrenal lesion was 5.5 ± 3.5 while the mean (±SD) size of adrenal lesion was 4.0 ± 2.3cm. The most common primary malignancy was non-small cell lung cancer (n=16, 41.0%) followed by lymphoma (n=4, 10.3%), esophagus/stomach (n=4, 10.3%), gynecological cancer (n=4, 10.3%), breast (n=2, 5.1%), pancreas (n=2, 5.1%), liver (n=2, 5.1%), colon (n=2, 5.1%), kidney (n=1, 2.6%), sarcoma (n=1, 2.6%) and nasopharyngeal cancer (n=1, 2.6%). Final pathology of the excised adrenal tumor confirmed adrenal metastasis in 28/39 (71.8%) patients while the pathology of the non-metastatic lesions were mostly benign adrenal cortical adenoma (n=10) with one pheochromocytoma (n=1). For this latter patient, the two sets of preoperative 24-hour urinary collections for catecholamines were normal and there were no unexpected intraoperative hemodynamic changes during surgical dissection. Therefore, it was probably a non-functional pheochromocytoma. The SUVmax value in this patient was 7.80. Based on these findings, the true positive and false positive rates of FDG-PET/CT were 71.8% and 28.2%. The risk of adrenal metastasis based on the 4 suspicion categories alone (a newly-found lesion,

progressive size increase, size alone and indeterminate CT appearance) were 9/12 (75%), 11/15 (73.3%), 4/7 (57.1%) and 4/5 (80.0%), respectively.

Table 2 shows the clinical details of the 11 patients with false-positive FDG-PET/CT.

Table 3 shows a comparison of preoperative baseline characteristics between the malignant (n=28) and benign group (n=11). Age, sex ratio, time period, clinical suspicion and side of adrenal lesion were not significantly different between the two groups. The malignant group tended more likely to have history of primary lung malignancy (50% vs. 18.2%, p=0.069), larger sized adrenal lesion (4.3 ± 2.4cm vs. 3.2 ± 2.0cm, p=0.079) than the benign group. The mean SUVmax value was significantly higher in the malignant group (6.4 ± 3.5 vs. 3.6 ± 1.9, p=0.005).

Table 4 shows the multivariate analysis for adrenal metastasis. After adjusting for size of adrenal lesion, history of primary lung malignancy (ß coefficient= 2.476, odds ratio=11.905, 95%CI=1.298 – 111.111, p=0.028) and SUVmax value (ß coefficient= 0.504, odds ratio=1.656, 95%CI=1.086 – 2.524, p=0.019) were independent risk factors for adrenal metastasis. The optimal cut-off value in predicting adrenal metastasis for SUVmax was 2.65 (Youden's index = 0.532; sensitivity 89.3% and specificity 63.6%). In terms of overall predictability (as measured by AUC), SUVmax had an AUC value of 0.792 (95%CI=0.629 – 0.955). Although the AUC for SUVmax was higher (i.e. more predictive) in patients with a history of primary lung malignancy (n=16) than those with a history of primary non-lung malignancy (n=23), the two AUCs were not significantly different (0.893 vs. 0.810, p=0.521).

Based on these findings, we proposed a clinical algorithm for incidentally found adrenal mass in patients with history of malignancy. Figure 1 shows the proposed algorithm.

DISCUSSION

FDG-PET/CT has become increasingly popular for diagnosing solitary adrenal metastasis in patients with a history of primary non-adrenal malignancy. A large meta-analysis and systematic review of 21 studies found that the overall sensitivity and specificity of FDG-PET/CT in differentiating malignant and benign adrenal disease in patients with known primary malignancy were 97% and 91%, respectively[2]. In this particular report, the reported false positive rate was only 5.8% [2]. However, the authors cautioned that in their study, the histological diagnosis for the majority of lesions was not available and the final diagnosis was based mostly on serial imaging (a widely accepted method among non-surgical series). We believe this might be one of the main reasons for the difference in false positive rate between most other studies and ours. Our study found that among patients with a single positive FDG uptake in the suspected adrenal metastasis, the chance of metastasis was only 71.8% and so the false positive rate was 28.2%. In other words, almost 1 in 3 positive on FDG-PET/CT turned out to be non-metastatic. Even if one excluded the non-functional pheochromocytoma (as this is a heterogeneous tumor with malignant potential), the false positive rate was still 10/38 or 26.3%. This false positive rate appeared even higher than that of a recent study that examined the accuracy of FDG-PET/CT based on histology[9]. Interestingly, when one looked at the chance of adrenal metastasis among the 4 clinical suspicion categories, the false positive rate for FDG-PET/CT was actually higher than having either a new adrenal lesion or an adrenal lesion with interval enlargement or “indeterminate” CT features (28.2% vs 25.0%, 26.7%, 20.0%, respectively).

Apart from assessing the accuracy of FDG-PET/CT in differentiating malignant from benign adrenal disease, our study also identified two independent risk factors for adrenal metastasis. Our data found that the history of primary lung malignancy (odds ratio=11.91, 95%CI 1.30 – 111.1)

and SUVmax (odds ratio=1.66, 95%CI=1.09 – 2.52) were significant risk factors for adrenal metastasis. From our analysis, patients with primary lung malignancy had almost 11 times greater chance of harboring an adrenal metastasis than those with non-lung primary malignancy. This is consistent with the finding that lung primary malignancy is the most common malignancy metastasizing to the adrenals[1-3,10-11]. Using an optimal cut-off of 2.65, those with SUVmax >2.65 had a 31.6 times greater chance of adrenal metastasis than those with SUVmax ≤2.65. Our data also showed that SUVmax was a significant factor and there appeared to be no significant difference in predictability (by AUC) (p=0.521) whether the patient had a history of lung or non-lung primary malignancy. With this cut-off of 2.65, the sensitivity and specificity were 89.3% and 63.6%, respectively which appeared slightly less than previous studies. Metser *et al*. found that with a SUVmax cut-off of 3.10, the sensitivity and specificity were 98.5% and 92%, respectively[13]. Using the same cut-off, another study reported the sensitivity and specificity were 91% and 81%, respectively[14]. However, determining SUVmax cut-off among different studies is difficult as it is dependent on many factors including body habitus and composition, timing of the radionuclide injection, plasma glucose concentration and partial volume effects[2]. Therefore, some have advocated the use of qualitative visual assessment alone as a criterion for determining malignancy on FDG-PET/CT[2,11,14,15].

Despite these findings, we would like to acknowledge that this was a retrospective review of a relatively small number of patients who had preoperative FDG-PET/CT and so some of the non-significant findings might have been due to the lack of power of this study. Also although hormonal evaluations were performed for all patients, subtle or intermittent hyper-secretion from a benign adrenal adenoma could not be completely ruled out and may account for the high false positive rate[16].

Conclusion

Our data showed that a single positive adrenal uptake on FDG-PET/CT in patients with known malignancy was associated with an unexpected high rate of false positive (28.2%) and this rate was not significantly lower than normally-used clinical criteria such as having a new adrenal lesion or a lesion with interval enlargement or indeterminate CT features. Factors associated with adrenal metastasis included a history of known primary lung malignancy and a SUVmax >2.65 at the adrenal lesion of interest. A new working algorithm was constructed.

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Table 1. The baseline characteristics of the 39 patients with suspected single adrenal metastasis who underwent FDG-PET/CT scan before adrenalectomy

Parameters	
Mean (± SD) age at operation (years)	57.9 ± 13.3
Sex (Male/Female)	23 : 16
History of primary malignancy	
- Lung	16 (41.0)
- Lymphoma	4 (10.3)
- Esophagus/stomach	4 (10.3)
- Gynecological cancer	4 (10.3)
- Breast	2 (5.1)
- Pancreas	2 (5.1)
- Liver	2 (5.1)
- Colon	2 (5.1)
- Others	3 (7.7)
PET/CT findings or appearance	
- Right / Left	15 (38.5) / 24 (61.5)
- Discrete nodule / hyperplasia	36 (92.3) / 3 (7.7)
- Tumor size (cm)	4.0 ± 2.3
- CT attenuation (HU ≤ 10)	33 (84.6%)
- SUVmax	5.5 ± 3.5

Abbreviations: PET/CT = positron emission tomography/computed tomography; HU – Hounsfield Unit; SUVmax = maximum standardized uptake value

Table 2. Clinical details of the 11 patients with false-positive FDG-PET/CT (i.e. benign histology)

Patient	Clinical history	Clinical suspicion / FDG-PET/CT results	Adrenal histology
1	57-year-old male with a history of pancreatic cancer.	New lesion / hypermetabolic left adrenal lesion (SUVmax=3.70)	Adrenal cortical adenoma
2	56-year-old male with a history of lung cancer	Indeterminate CT washout pattern / hypermetabolic right adrenal lesion (SUVmax=2.90)	Adrenal cortical adenoma
3	28-year-old lady with a history of ovarian cancer	New lesion / hypermetabolic left adrenal lesion (SUVmax=7.0)	Adrenal cortical adenoma
4	82-year old lady with a history of esophageal cancer	Size>4cm / hypermetabolic left adrenal lesion (SUVmax=3.0)	Adrenal cortical adenoma
5	56-year-old lady with a history of lymphoma.	Size>4cm / hypermetabolic left adrenal lesion (SUVmax=2.5)	Adrenal cortical adenoma
6	57-year-old male with a history of nasopharyngeal cancer.	Progressive size increase / hypermetabolic left adrenal lesion (SUVmax=3.3)	Adrenal cortical adenoma
7	62-year-old lady with a history of lung cancer	Progressive size increase / hypermetabolic right adrenal	Adrenal cortical adenoma

		lesion (SUVmax=2.2)	
8	43-year-old lady with a history of breast cancer	Indeterminate washout pattern / hypermetabolic right adrenal lesion (SUVmax=2.5)	Adrenal cortical adenoma
9	73-year-old lady with a history of gastric cancer	HU 34 on non-contrast CT / hypermetabolic left adrenal lesion (SUVmax=7.8)	Non-functional pheochromocytoma
10	72-year-old lady with a history of esophagus cancer	Progressive size increase / hypermetabolic left adrenal lesion (SUVmax=2.9)	Adrenal cortical adenoma
11	55-year old lady with a history of breast cancer	Progressive size increase / hypermetabolic right adrenal lesion (SUVmax=2.8)	Adrenal cortical adenoma

Table 3. A comparison of preoperative clinical characteristics between those with histologically-proven adrenal metastasis (i.e. malignant group) and those without (i.e. benign group)

Parameters	**Benign group (n=11)**	**Malignant group (n=28)**	***p*-value**
Age (±SD) at operation (years)	58.27 ± 14.68	57.78 ± 13.01	0.723
Sex (male/female)	4 / 7	19 / 9	0.146
Time period			0.475
- 2001 – 2004	2 (18.2)	10 (35.7)	
- 2005 – 2009	5 (45.5)	12 (42.9)	
- 2010 – 2013	4 (36.4)	6 (21.4)	
Main reason for suspecting adrenal metastasis			0.804
- New lesion (not apparent in previous CT scan if available)	2 (18.2)	9 (32.1)	0.693
- Interval enlargement (>20% over a year)	4 (36.4)	11 (39.3)	1.000
- Lesion size ≥4cm	2 (18.2)	4 (14.3)	0.379
- Indeterminate CT features*	3 (27.3)	4 (14.3)	0.655
Side of adrenal lesion			0.694
- Right	4 (36.4)	11 (39.3)	
- Left	7 (63.6)	17 (60.7)	
History of primary malignancy#			0.069
- Lung	2 (18.2)	14 (50.0)	
- Non-lung	9 (81.8)	14 (50.0)	

PET/CT findings			
- Discrete nodule / hyperplasia	11 / 0	25 / 3	0.545
- SUVmax#	3.61 ± 1.94	6.42 ± 3.47	**0.005**
- Size of adrenal lesion (cm)#	3.2 ± 2.01	4.3 ± 2.39	0.079

Abbreviations: PET/CT = positron emission tomography/computed tomography; SUVmax = maximum standardized uptake value

* including CT attenuation value > 10 Hounsfield unit and/ or absolute washout pattern > 60% or relative washout > 40%.

these factors were entered into the subsequent multivariate analysis for adrenal metastasis

Table 4. A multivariate analysis for adrenal metastasis

Covariates	**Odds ratio**	**95% confidence interval**	***p*-value**
Primary lung malignancy - No - Yes	 1 11.905	 1.298 – 111.111	**0.028**
SUVmax	1.656	1.086 – 2.524	**0.019**
Size of adrenal mass	1.389	0.853 – 2.262	0.186

SUVmax = maximum standardized uptake value

When SUVmax was entered as a categorical variable using an optimal cut-off of 2.65, the odds ratio (95%CI) became 31.606 (2.462 – 405.714), p=0.008 while the odds ratio (95%CI) for primary lung malignancy became 20.00 (1.010 – 333.33), p=0.049.

A proposed algorithm