Original Research Article

Characterization of adrenal masses with non-enhanced CT and 18F FDG-PET in patients with primary malignancies

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ABSTRACT

Background: Characterizing adrenal lesions in patients with a known primary malignancy has a vital role in treatment and prognostication. A study by Gufler et al proposed a scoring system based on density, contour, homogeneity and size and found a high accuracy in differentiating adrenal adenomas from metastasis in patients with a known malignancy. This study evaluates the sensitivity and specificity of this NECT scoring system and comparing it with that of 18F FDG PET.
Methods: The study was conducted on patients with diagnosed malignancies with adrenal mass, referred for 18F-FDG PET-CT scanning as a part of work up or follows up between October 2014 and March 2016. Whole-body CT and PET images were obtained using standard protocol. NECT scoring and quantitative analysis of FDG uptake in the adrenal lesions (SUVavg analysis) is done separately.
Results: Of the 50 patients studied, 33 patients had benign adrenal lesions and the rest had metastatic lesions. Most common site of primary was lung. NECT score yielded a sensitivity of 88.2%, specificity of 100% and positive predictive value of 100%. SUVavg analysis yielded a 100% sensitivity, specificity and positive predictive value. Comparison of the predictive power of the two tests showed a z score of 2.5 and p value of 0.0124.
Conclusions: 18-FDG PET can be considered as a gold standard for differentiating between metastasis and benign lesions of adrenal glands in patients with known primary. NECT has a comparable specificity as that of FDG PET, however with lower sensitivity.

Keywords: Adrenal lesion, NECT, Non-adrenal primary, 18 FDG PET

INTRODUCTION

Characterizing adrenal lesions in patients with a known primary malignancy has a vital role in treatment and prognostication. Approximately 40-57% of adrenal incidentalomas are benign in these patients.[1] The prevalence of adrenal metastases in patients with known primary malignancy ranges between 32% and 73% in different series.[2] CT, MRI and FDG PET are widely used to characterize adrenal lesions.

In a retrospective study by Gufler et al, the combined morphologic criteria with the density measurements on NECT, found a high accuracy in differentiating adrenal adenomas from metastases in patients with a known malignancy.[3] They proposed a scoring system based on density, contour, homogeneity and size.

This study evaluates the sensitivity and specificity of this NECT scoring system and comparing it with that of 18F FDG PET.

METHODS

The study was conducted after institutional ethics committee clearance on 50 patients with diagnosed malignancies with adrenal mass, referred to our institution for 18F FDG PET-CT scanning as a part of work up or follow up between October 2014 and March 2016. Those patients with primary malignancy of adrenals and those already on chemotherapy or radiation therapy were excluded. 3 patients were excluded as they had bilateral lesions and 2 patients were excluded as they had lesions of fully fat density suggesting myelolipoma. Whole-body CT and PET images were obtained approximately 60minutes after the IV injection of 18F FDG. Images were acquired from the head to the mid-thigh. CT data were acquired first, using the following parameters: section thickness, 1.25mm; pitch, 6:1 (in high-speed mode); gantry rotation speed, 0.8second; tube voltage, 120 kVp; tube current, automatic mode; and field of view, 50cm. Immediately after the CT scans, PET images are obtained in 3D mode. PET image datasets are reconstructed by using an iterative algorithm, after applying CT-based attenuation correction.

NECT scoring and quantitative analysis of FDG uptake in the adrenal lesions (SUVavg analysis) are done separately. CT characteristics used for scoring are combined morphologic criteria with the density measurements on NECT proposed by Gufler et al.[3] The total score is obtained by adding 10% of the density values to the size in centimeters, plus 2 if the contour of the lesion is blurred and plus 1 if the structure is inhomogeneous. Score of less than 7 is taken as benign and more than or equal to 7 as malignant. Size was measured as average of the length, breadth and height of the lesion. Density was evaluated by placing a circle of ROI covering one third of the lesion at the center of the lesion and the noting the average HU displayed. Contour and homogeneity were evaluated subjectively by two of the investigators who were having seven and 16years experience in the field of CT interpretation and a consensus opinion formed.

Histopathology or follow-up imaging data (CT or PET-CT) were used as reference standards for final classification of the adrenal lesions. Stability in size on follow-up imaging after a minimum period of 6months was taken as benign. Interval growth on follow-up imaging or reduction in size in response to treatment was taken as metastasis. The Statistical software namely SPSS 18.0 (Statistical Package for Social Science) was used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs and tables.

RESULTS

A total of 50 patients were included in the study. The mean age of the study population was 63.2years and the maximum number of patients were in the age group 60-69years. There were 38 (76%) males and 12 (24%) females. Of the 50 patients studied, 33 (66%) patients had benign adrenal lesions and 17 (34%) patients had metastatic lesions. 23 patients had primary malignancy in lung. Sites of primary in other cases were breast, cervix, colon, kidney, pharynx, endometrium, melanoma nasal cavity and soft tissue sarcoma. Out of 17 patients with metastasis, 12 patients had lung as primary site. In patients with primary lung malignancy, 52% of the adrenal lesions were found to be metastasis.

Table 1: Distribution of patients based on NECT score and pet SUV avg values.

	NECT score		SUV avg	
	<7	>7	<2.5	>2.5
Metastasis	2	15	0	17
Benign	33	0	33	0

NECT score <7 was taken as benign and >=7 was taken as metastatic. 33(70%) patients with adrenal lesions had a score of <7 and 15 (30%) patients had a score of >=7. Thus, NECT score yielded a sensitivity of 88.2%, specificity of 100% and positive predictive value of 100%. FDG PET SUVavg value <2.5 was taken as benign and >=2.5 was taken as metastases. 66% (33) of patients with adrenal lesions had SUVavg of <2.5 and 34% (17) had that of >=2.5. This yielded a 100% sensitivity, specificity and positive predictive value. Comparison of the predictive power of the two tests, that is the NECT Score and SUV avg showed a z score of 2.5 and p value of 0.0124 (Table 2).

Table 2: Comparison of statistical parameters for NECT score and pet SUVavg.

	Sensitivity	Specificity	PPV	NPV	Accuracy
NECT scoring	88.2	100	100	94	96
PET-CT	100	100	100	100	100

DISCUSSION

The main imaging modalities currently used for the differentiation of adrenal lesions are CT, MRI and PET.

The structural features of most adrenal lesions on imaging are usually not specific enough to characterize them. Suspicious imaging findings on unenhanced CT for malignancy include large size of lesion, irregular

margins, heterogeneous appearance and rapid interval growth. Densitometry of adrenal lesions in non-enhanced CT can detect around 70% of adrenal adenomas as they are known to contain significant intracellular lipid when compared to malignant adrenal lesions. The presence of high intracellular lipid content lowers the CT density of most adenomas. Non-adenomatous lesions usually have low intracellular fat content and their CT attenuation is consequently higher. In clinical practice, 10 HU is the most widely used threshold value for the diagnosis of a lipid-rich adrenal adenoma.[4,5] Upto 30% of adenomas are lipid poor and do not show characteristic attenuation values on non-enhanced CT scans, so it is difficult to differentiate them from malignant lesions.[6-9]

Contrast enhanced CT wash out studies are now widely employed in evaluation of suspicious adrenal lesions. Absolute and relative wash out are calculated using formulas and analysed along with non-enhanced CT characteristics. An absolute percentage washout of 60% or higher shows 86-88% sensitivity and 92-96% specificity for the diagnosis of adenomas by using 15minute delay after contrast administration protocol. After 15minutes, 40% or higher relative percentage washout favours the diagnosis of an adenoma with 96% sensitivity and 100% specificity.[10]

MRI is being effectively used in analysis of adrenal lesions in specific clinical settings. Chemical shift imaging is being considered the mainstay in MR evaluation. Adrenal-to-spleen CSI ratio and adrenal signal intensity index are calculated by specified formulas. A chemical shift imaging (CSI) ratio of less than 0.71 or a signal intensity index of more than 16.5% both indicate a lipid-rich adenoma.[11]

FDG PET yields information about the biochemical processes that precedes gross anatomic changes and is evidently very useful in characterization of adrenal masses. The increased uptake of radio-labelled glucose analog by tumor tissue due to increased glycolysis as compared with normal adrenal tissue is the basis for detection of metastasis by FDG PET.[12,13] This results from an increased number of glucose membrane transporters and increased activity of the principal enzymes that control the glycolytic pathways. Thus, even very small metastasis may be detected with this technique. Some previous reports have described excellent sensitivity of 18F FDG PET in identifying malignant adrenal masses.[14-18] However, studies in which the capability of FDG PET for characterization of adrenal disease has been specifically evaluated differ in reported accuracies, which range from 75% to 100%.[12]

In our study, we compared the effectiveness of NECT and PET in differentiating benign from metastatic adrenal lesions in patients with a known primary malignancy. According to HPE/6months follow up CT/PET CT, 66% lesions were benign and 34% were metastasis (Figure 1, 2). The use of NECT was maximized by using the

scoring system taking into account the size, density, contour and homogeneity. In our study NECT score of <7 was taken as benign and >=7 was taken as metastasis. Two cases of metastasis yielded a score of less than 7 which were the false negatives. Both the lesion was small in size with regular contour and homogenous appearance due to the early stage of the disease. This is in concordance with previous study by Gufler et al, who proposed the scoring which we have adopted for our study.[3] The total score is obtained by adding 10% of the density values to the size in centimeters, plus 2 if the contour of the lesion is blurred and plus 1 if the structure is inhomogeneous. The highest predictive power was calculated at a cutoff value of 7.05, with 100% sensitivity and 96.8% specificity for the detection of metastasis. Lee et al reported the effectiveness of non-enhanced CT densitometry in differentiating adrenal adenomas from non-adenomatous lesions and found that the mean attenuation of adenomas (-2.2HU) was significantly lower than that of non-adenomas (28.9HU).[4] Later, an inverse linear relationship between fat concentration and attenuation on non-enhanced CT images was described by Korobkin et al.[5] In a meta-analysis of published studies it was found that the CT attenuation threshold of 10 HU, would yield test sensitivity of 71% and specificity of 98%.[19]
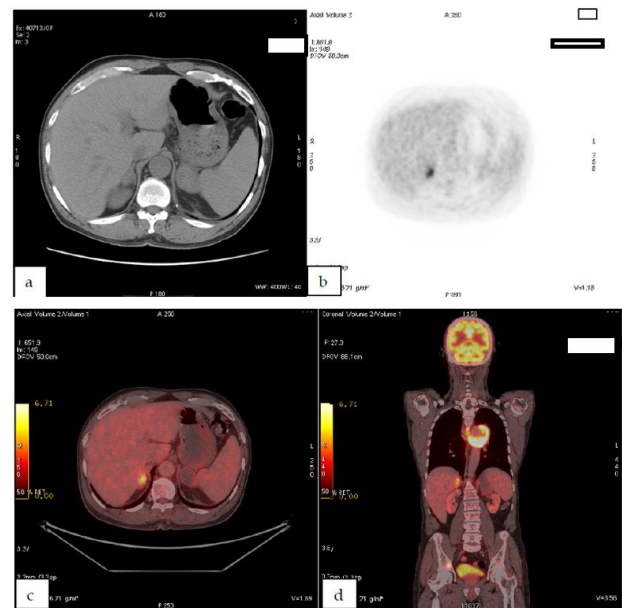

Figure 1: NECT and 18F FDG PET-CT of metastatic right adrenal mass. a) Axial NECT showing a right adrenal lesion with score of 7.8. b) 18F FDG PET axial image showing increased uptake (suvavg 4.4). c) and d) Fused 18F FDGPET CT images (axial and coronal reformatted) showing the increased metabolic activity in the right adrenal lesion and in right iliac bone.

In our study the FDG PET SUVavg of <2.5 was taken as benign and >=2.5 was taken as metastasis. This yielded excellent diagnostic capability and is keeping with

previous studies showing excellent sensitivity for 18F FDG PET in identifying malignant adrenal masses with a 5-10% false-positive rates in cases of adrenal adenomas with relatively high FDG uptake.[14,15,17,20,22] One meta-analysis demonstrates that most adrenal masses can be characterized by using FDG PET with high sensitivity, specificity ,and accuracy.[17] In a study by Metser et al, PET CT had a sensitivity and specificity of 98.5% and 92% respectively, for the differentiation of lipid-poor adenomas and 98.5% and 93% for all adenomas from malignant lesions.[22] They also found that when 3.1 was used as cutoff for the maximum SUV, PET CT had a sensitivity and specificity of 98.5% and 92% in the differentiation of malignant lesions from benign lesions. High values of diagnostic accuracy for adrenal masses using a PET-CT quantitative method, combining an SUV threshold of 3.1 and an attenuation value cutoff of 10 HU was also detected by them. Similar results have been reported by Brady et al in a series of 147 patients with known or suspected lung cancer.[23]
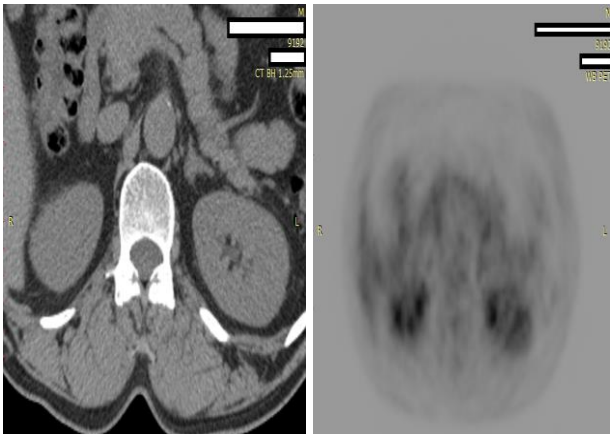

Figure 2: A) Axial NECT image showing a left adrenal lesion with score 4.38 B) 18F FDG PET axial image showing mild uptake (suvavg 1.7) indicating a benign lesion.

Boland et al found that PET CT had sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 99%, 100%, 100%, 93% and 99% for the detection of benign lesions and 100%, 99%, 93% and 100% respectively, for the detection of malignancy.[24] In our study, while the specificity of both NECT scoring system and FDG PET in characterizing adrenal lesions were found to be same, the sensitivity of both had difference which is statistically significant (p value 0.0124). Therefore, it can be said that even if the NECT <7, we have to go for additional imaging, but if the NECT score is >7 we can confidently conclude that it is metastasis.

Advantage of PET CT is that it has a high sensitivity and specificity for the differentiation of benign adrenal lesions from metastatic lesions. But there are some limitations also. A 5% false-positive rate for PET CT has been reported secondary to a variety of causes.[12] Some adrenal adenomas demonstrate increased FDG uptake, at levels even higher than those in the liver.[25] The reason for this is not fully understood but is presumed that the functional state of an adenoma is the factor in determining the intensity of FDG uptake, with increased uptake in functioning adenomas.[26] Pheochromocytoma of the adrenal gland also has been reported to show increased FDG uptake at PET.[17] More recently a study by Lang et al showed that single adrenal uptake on FDG-PET/CT in suspected 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.[27] Adrenal cortical hyperplasia without chronic inflammatory cell infiltration and adrenal endothelial cyst may also simulate metastatic nodules and show increased FDG uptake.[12] Jana et al, reported two cases of false-negative adrenal lesions at FDG PET in patients with a pulmonary carcinoid tumor.[28] Metastatic lesions from pulmonary adenocarcinoma with a predominantly bronchioloalveolar component may also show little FDG uptake at PET CT. The other common causes of false-negative FDG PET results are hemorrhage and necrosis in the lesion.[17,22,26] Nodule size is another factor that contributes to a false-negative interpretation. According to a previous report, most metastatic adrenal nodules of 10mm or less in diameter showed lower uptake than the liver.[18] Sub centimeter metastatic lesions will have less FDG uptake than large lesions and cannot be differentiated as the resolution of PET is currently limited in the range of 4-6mm.

A limitation to our study is the small sample size as the sample size was calculated with a high sensitivity, it may prove inadequate for variables with relatively lower sensitivity. Yet another limitation is that we have not plotted any ROC curves to determine the NECT score cut offs or determine statistical significance of individual variables in the scoring system.

CONCLUSION

From our study it can be seen that FDG PET can be considered as a gold standard for differentiating between metastasis and benign lesions of adrenal glands in patients with known primary. NECT has a comparable specificity as that of FDG PET, however with lower sensitivity. But because of the wider availability, being very much cheaper than FDG PET and due to the advantage that it can be used in patients with co-existent renal failure, NECT may be used in day to day practice to reliably differentiate between the two. Further wider studies with addition of MR chemical shift imaging is recommended in this field.

REFERENCES

1. Dunnick NR, Korobkin M. Imaging of adrenal incidentalomas: current status. AJR. 2002;179:559-68.
2. Terzolo M, Bovio S, Pia A, Reimondo G, Angeli A. Management of adrenalin cidentaloma. Best Pract Res Clin Endocrinol Metab. 2009;23:233-24.
3. Gufler H, Eichner G, Grossmann A, Krentz H, Schulze CG, Sauer S, et al. Differentiation of adrenal adenomas from metastases with unenhanced computed tomography. J Comput Assist Tomogr. 2004;28(6):818-22.
4. Lee MJ, Hahn PF, Papanicolaou N, Egglin TK, Saini S, Mueller PR, et al. Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. Radiology. 1991;179(2):415-8.
5. Korobkin M, Giordano TJ, Brodeur FJ, Francis IR, Siegelman ES, Quint LE, et al. Adrenal adenomas: relationship between histologic lipid and CT and MR findings. Radiology. 1996;200(3):743-7.
6. Korobkin M, Brodeur FJ, Francis IR, Quint LE, Dunnick NR, Londy F. CT time-attenuation washout curves of adrenal adenomas and nonadenomas. AJR. 1998;170:747-52.
7. Szolar DH, Kammerhuber FH. Adrenal adenomas and nonadenomas: assessment of washout at delayed contrast-enhanced CT. Radiology. 1998;207:369-75.
8. Pena CS, Boland GW, Hahn PF, Lee MJ, Mueller PR. Characterization of indeterminate (lipid poor) adrenal masses: use of washout characteristics at contrastenhanced CT. Radiology. 2000;217:798-802.
9. Johnson PT, Horton KM, Fishman EK. Adrenal mass imaging with multidetector CT: pathologic conditions, pearls, and pitfalls. Radio Graphics. 2009;29:1333-51.
10. Caoili EM, Korobkin M, Francis IR, Cohan RH, Platt JF, Dunnick NR, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology. 2002;222(3):629-33.
11. Fujiyoshi F, Nakajo M, Kukukura Y, Tsuchimochi S. Characterization of adrenal tumors by chemical shift fast-low angle shot MR imaging: comparison of four methods of quantitative evaluation. AJR. 2003;180:1649-57.
12. Chong S, Lee KS, Kim HY, Kim YK, Kim BT, Chung MJ, et al. Integrated PETCT for the Characterization of Adrenal Gland Lesions in Cancer Patients: Diagnostic Efficacy and Interpretation Pitfalls. RadioGraphics. 2006;26:1811-26.
13. Elaini AB, Shetty SK, Chapman VM, Sahani DV, Boland GW, Sweeney AT, et al. Improved detection and characterization of adrenal disease with PET-CT. Radiographics. 2007;27(3):755-67.
14. Boland GW, Goldberg MA, Lee MJ, Mayo-Smith WW, Dixon J, McNicholas MM, et al. Indeterminate adrenal mass in patients with cancer: evaluation at PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology. 1995;194(1):131-4.
15. Erasmus JJ, Patz Jr EF, McAdams HP, Murray JG, Herndon J, Coleman RE, et al. Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. AJR. Am J Roentgenol. 1997;168(5):1357-60.
16. Maurea S, Mainolfi C, Bazzicalupo L, Panico MR, Imparato C, Alfano B, et al. Imaging of adrenal tumors using FDG PET: comparison of benign and malignant lesions. AJR. Am J Roentgenol. 1999;173(1):25-9.
17. Yun M, Kim W, Alnafisi N, Lacorte L, Jang S, Alavi A. 18F-FDG PET in characterizing adrenal lesions detected on CT or MRI. J Nucl Med. 2000;42:1795-9.
18. Kumar R, Xiu Y, Jian QY, Takalkar A, El-Haddad G, Potenta S, et al. 18F-FDG PET in evaluation of adrenal lesions in patients with lung cancer. J Nu Med. 2004;45(12):2058-62.
19. Boland GW, Lee M, Gazelle GS, Halpern EF, McNicholas MM, Mueller PR. Characterization of adrenal masses using unenhanced CT: an analysis of the CT literature. AJR. 1998;171(1):201-4.
20. Maurea S, Mainolfi C, Bazzicalupo L, Panico MR, Imparato C, Alfano B, et al. Imaging of adrenal tumors using FDG PET: comparison of benign and malignant lesions. AJR. 1999;173(1):25-9.
21. Perri M, Erba P, Volterrani D, Guidoccio F, Lazzeri E, Caramella D, et al. Adrenal masses in patients with cancer: PET/CT characterization with combined CT histogram and standardized uptake value PET analysis. Ame J Roentgenol. 2011;197(1):209-16.
22. Metser U, Miller E, Lerman H, Lievshitz G, Avital S, Even-Sapir E. 18F-FDG PET/CT in the evaluation of adrenal masses. J Nucl Med. 2006;47(1):32-7.
23. Brady MJ, Thomas J, Wong TZ, Franklin KM, Ho LM, Paulson EK. Adrenal nodules at FDG PET/CT in patients known to have or suspected of having lung cancer: a proposal for an efficient diagnostic algorithm. Radiology. 2009;250:523-30.
24. Boland GW, Blake MA, Holalkere NS, Hahn PF. PET/CT for the characterization of adrenal masses in patients with cancer: qualitative versus quantitative accuracy in 150 consecutive patients. AJR. 2009;192:956-62.
25. Dong A, Cui Y, Wang Y, Zuo C, Bai Y. (18)F-FDG PET/CT of adrenal lesions. AJR Am J Roentgenol. 2014;203(2):245-52.
26. Shimizu A, Oriuchi N, Tsushima Y, Higuchi T, Aoki J, Endo K. High [18F] 2-fluoro-2-deoxy-D-glucose (FDG) uptake of adrenocortical adenoma showing subclinical Cushing's syndrome. Annals Nuc Med. 2003;17(5):403-6.

27. Lang BH, Cowling BJ, Li JY, Wong KP, Wan KY. High False Positivity in Positron Emission Tomography is a Potential Diagnostic Pitfall in Patients with Suspected Adrenal Metastasis. World J Surg. 2015;39(8):1902-8.
28. Jana S, Zhang T, Milstein DM, Isasi CR, Blaufox MD. FDG-PET and CT characterization of adrenal lesions in cancer patients. Eur J Nucl Med Mol Imaging. 2006;33(1):29-35.