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Efficacy of PET-CT in the prediction of metastatic adrenal masses that are detected on follow-up of the patients with prior nonadrenal malignancy

A nationwide multicenter case–control study

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Abstract

Metastasis is the second most common type of adrenal gland mass. In patients undergoing follow-up for nonadrenal malignancy, adrenalectomy is performed when metastasis to adrenal gland is suspected on the basis of positron emission tomography–computed tomography (PET-CT) imaging. This study investigated the efficacy of PET-CT in the discrimination of metastatic lesions from nonmetastatic lesions in the adrenal glands. In this multicentric study, data was collected from enrolled centers. Forty-one patients who underwent surgery for suspected adrenal metastases were evaluated retrospectively. The following data types were collected: demographic, primary tumor, maximum standardized uptake value of adrenal mass (a-SUVx) and detectability in computed tomography and/or magnetic resonance imaging, and specimen size and histopathology. Six patients were excluded due to unavailability of PET-CT reports and 4 for being primary adrenal malignancy. The rest were divided into 2 groups (metastatic: n = 17, 55% and nonmetastatic: n = 14, 45%) according to histopathology reports. There was no statistical difference between the analyzed values, except the a-SUVx ($P < .05$). The a-SUVx cutoff value was defined as 5.50 by receiver operating characteristic curves and compared with literature. There was no statistical difference when each group was divided as low and high ($P > .05$). It was found that PET-CT was able to discriminate metastatic lesions from primary benign lesions ($P = .022$). PET-CT can discriminate primary benign lesions and metastatic lesions by cutoff 5.5 value for a-SUVx.

Abbreviations: AUC = area under the curve, a-SUVx = maximum standardized uptake value of adrenal mass, CT = computed tomography, MRI = magnetic resonance imaging, PET-CT = positron emission tomography–computed tomography, ROC = receiver operating characteristic, SUVmax = maximum standardized uptake value.

Keywords: adrenal gland, diagnosis, metastasis, PET-CT

1. Introduction

With the advent of new drugs and surgical techniques for the treatment of cancer, the duration of disease-free survival and overall survival has increased for most cancer types. As a result, the detection of metastases at unusual sites is rising. The adrenal glands are one such site due to their rich blood supply, and metastasis is the second most common tumor of the adrenal glands following benign adenomas.[1] Most often, metastases in the adrenal glands arise from melanoma, lung cancer, breast cancer, and renal cell carcinoma, with an incidence of 32% to 73%. In addition to metastases and benign adenomas, primary malignant tumors of the adrenal glands that have a poor prognosis also occur.[2]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Acibadem Mehmet Ali Aydinlar University Clinical Research Ethical Review Board (NO.: 2019-15/28) and individual consent for this retrospective analysis was waived.

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Oncologists use positron emission tomography–computed tomography (PET-CT) during follow-up to detect cancer recurrence and metastasis. During these follow-ups, PET-CT studies can reveal hypermetabolism in the adrenal glands. However, these patients do not always have metastases; sometimes primary tumors (benign or malignant) are mistakenly assessed as metastases. To differentiate these hypermetabolic lesions of the adrenal gland from primary malignancies, noninvasive methods are utilized. Endocrine work-up can reveal whether the mass is a primary malignancy if it is hypersecretive. CT scans and magnetic resonance imaging (MRI) can provide information about the mass based on Hounsfield units and chemical-shift data.[3,4] However, the presence of previous malignancy can interfere with radiological interpretation. PET-CT is also useful in the discrimination of adrenocortical adenomas from malignant lesions; however, small lesions or large necrosis in tumors, metastases from nonhypermetabolic primary tumors (carcinoid tumors, renal cell cancer, etc), and inflammatory processes can give false results.[5]

Therefore, this study investigated the ability of PET-CT to discriminate metastatic lesions located in the adrenal glands from primary masses in patients who were operated for suspected metastases occurring in the adrenal glands.

2. Materials and Methods

In this multicentric study, patients who had a history of previous nonadrenal malignancy and underwent adrenalectomy due to suspicion of metastasis to the adrenal glands were evaluated retrospectively. A call for participation was made to centers via the Turkish Association of Endocrine Surgery, Adrenal Study Group. Since adrenalectomy due to suspicion of distant metastases from previous malignancy is not a common condition, only 6 of the 16 participating centers in Turkey could provide eligible data.

Data on the following parameters were collected from 41 patients: gender, age, primary tumor, history of adjuvant therapy for primary tumor, side of adrenal mass, time between the detection of the adrenal metastasis and the primary tumor, detection of the adrenal mass in CT and MRI, hormonal activity, size, maximum standardized uptake value (SUVmax) of adrenal mass (a-SUVx), and histopathology of the resected specimen.

There were 2 inclusion criteria. First, suspicion of metastasis to the adrenal glands via imaging modalities in patients with a prior history of malignancy other than an adrenal gland malignancy. Second, an adrenal gland specimen which was reported as metastasis by pathology report with a history of malignancy other than an adrenal gland prior to surgery.

There were 2 exclusion criteria: no PET-CT performed prior to adrenalectomy and aged <18 years.

Of the 41 patients who met the criteria, 10 were excluded. The PET-CT reports could not be accessed in 6 patients and preoperative CT/MRI evaluation revealed primary adrenocortical carcinoma features in 4 patients in whom the final histopathology also resulted as primary malignancy of the adrenal gland. The remaining 31 eligible patients were divided into 2 groups (metastatic and nonmetastatic) according to final pathology reports. There were 17 (55%) patients in the metastatic group and 14 (45%) in the nonmetastatic group.

2.1. Statistical analysis

Continuous variables were assessed with Mann–Whitney *U*, Kolmogorov–Smirnov, and Kruskal–Wallis tests, while categorical variables were assessed with the chi-square test. Calculations were performed with IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY). If the *P* value was ≤.05, then it was accepted as statistically significant.

2.2. Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Acibadem Mehmet Ali Aydinlar University Clinical Research Ethical Review Board (no.: 2019-15/28). Individual consent for this retrospective analysis was waived.

3. Results

In terms of gender distribution, there were 4 (23.5%) females and 13 (76.5%) males in the metastatic group, and 7 (50%) females and 7 (50%) males in the nonmetastatic group (*P* = .13). The average age was 55.1 ± 9.7 years in the metastatic group and 55.1 ± 13.2 years in the nonmetastatic group (*P* = .99). While the majority of the primary malignancies were lung cancer in both groups (n = 11, 64.7% in the metastatic group and n = 8, 57.1% in the nonmetastatic group), there was no statistical difference between the groups (*P* = .20). The distribution of primary malignancies is presented in Table 1. The administration of adjuvant treatment for primary cancer was similar in both groups (n = 8 in metastatic, 7 in primary benign group, *P* = .80).

In the metastatic group, the mass was most often located on the left side (n = 9, 52.9%), and this was also observed in the nonmetastatic group (n = 10, 71.4%) (*P* = .29). In 2 patients (in nonmetastatic group) adrenal mass size was not available. There was no statistical difference between groups in terms of adrenal mass size; in the metastatic group, the size was 46.7 ± 34.6 (10–130) mm, and in the nonmetastatic group, the size was 27.8 ± 12.9 (15–55) mm (*P* = .30).

The MRI reports of 21 of the 31 patients were accessible (12 in the nonmetastatic group and 9 in the metastatic group). In the 12 patients in the nonmetastatic group, all the masses were visible by MRI. In the 9 patients in the metastatic group, 7 (77.8%) masses were visible by MRI (*P* = .17).

The CT reports of 23 of the 31 patients were accessible (10 in the nonmetastatic group and 13 in the metastatic group). Among these 23 patients, just 1 (10%) mass was not detected by CT in the nonmetastatic group, and 2 (15.4%) were not detected in the metastatic group (*P* = 1).

Adrenal mass size was compared with visibility by MRI and CT. MRI detected masses in 18 patients and not in 2. Mean size was 43.11 ± 30.8 in MRI detected and 80 ± 7.1 in nondetected (*P* = .12). CT detected masses in 19 patients and not in 3 patients. Mean size was 38.3 ± 31 in CT detected and 71.7 ± 15.3 in not detected (*P* = .09).

In the nonmetastatic group just 2 patients (14.3%) were hormonally active. None were active in the metastatic group (*P* = .20).

PET-CT images of a primary benign adrenal mass and metastasis to an adrenal gland (originating from breast cancer) are shown in Figure 1.

Table 1

Primary malignancies among groups.

	Metastatic group	Nonmetastatic group	Total
Breast cancer	0	3	3
Colon cancer	1	0	1
Endometrium cancer	0	1	1
Gastric cancer	0	1	1
Hepatocellular carcinoma	1	0	1
Lung cancer	11	8	19
Malignant melanoma	1	0	1
Non-Hodgkin lymphoma	0	1	1
Ovarian cancer	1	0	1
Renal cancer	2	0	2
Total	17	14	31

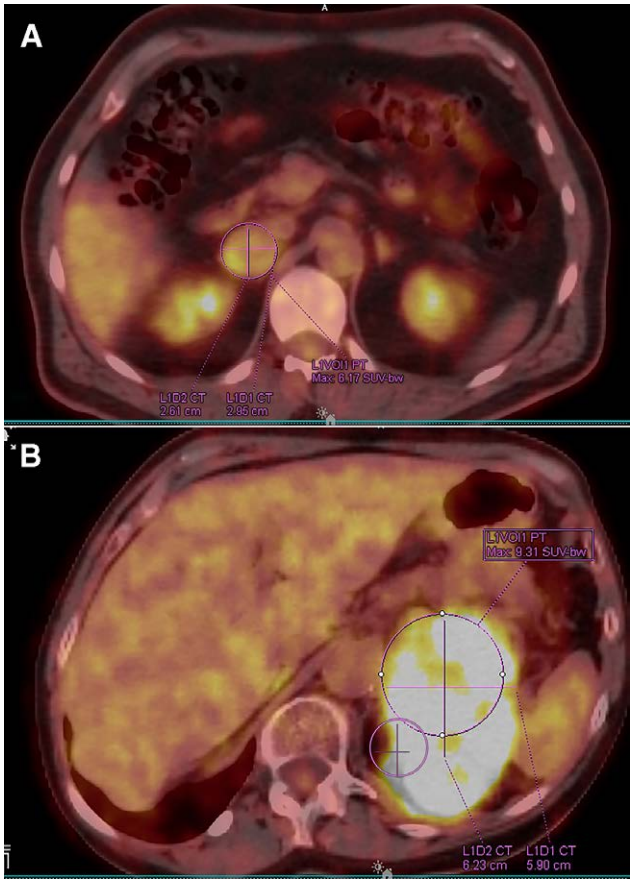

Figure 1. PET-CT imaging of different adrenal masses. (A) A primary benign adrenal mass. The pathology report revealed pheochromocytoma in the right adrenal gland after surgery. The a-SUVmax value was 6.17. (B) A metastatic mass on the left adrenal gland originating from lung carcinoma. The a-SUVmax value was 9.31. a-SUVmax = maximum standardized uptake value of adrenal mass, PET-CT = positron emission tomography–computed tomography.

The mean SUVmax value of the adrenal gland (a-SUVx) was 13.8 ± 11.4 in the metastatic group and 5.4 ± 3.1 in the nonmetastatic group (P = .009).

Receiver operating characteristic (ROC) curves was performed for a-SUVx values of the metastatic and nonmetastatic cases. Area under the curve (AUC) was 0.786 with P = .007 (95% confidence interval: 0.622–0.949; Fig. 2). The most far point from diagonal line on the ROC curve was 8.50 (inclusive) for a-SUVx with 64.7% sensitivity and 14.3% 1 – specificity. Lowest a-SUVx value with statistical significance (P = .022) for differentiating metastasis and nonmetastasis was 5.5 with 76.5% sensitivity and 35.7% 1 – specificity. The distribution of the metastatic and nonmetastatic lesions according to several cutoff values for a-SUVx is presented in Table 2

4. Discussion

Developments in cancer diagnosis and treatment are leading to increases in overall survival; however, the occurrence of metastases in adrenal glands is also rising. Thus, an accurate diagnosis of an adrenal mass is crucial for administering effective treatment. While benign masses under 4 cm can be subjected to follow-up only, suspicious primary malignant or metastatic lesions require surgical intervention. Resection of metastatic lesions can increase the survival of cancer patients in certain conditions.[6]

Histopathological examination provides the most accurate diagnosis of any mass. However, in certain conditions, such as hormone-active adrenal masses (e.g., pheochromocytoma, adrenocortical carcinoma), needle biopsy can cause mortal hazards.[7] In such situations, a noninvasive diagnosis of the mass is necessary. Fortunately, it has been reported that chemical-shift MRI and unenhanced CT can be used to differentiate benign and primary malignant lesions due to the high fat content of the adrenal cortex and most benign adrenal tumors.[4]

However, there are contradictory reports of the ability of PET-CT to differentiate adrenal masses.[8] Metser et al[9] assessed a-SUVx values and found that the best cutoff point for distinguishing malignant lesions from adenomas was 3.1 via ROC curve, resulting in 98.5% sensitivity, 92% specificity, 89.3% PPV, and 98.9% NPV. The current study showed 94.1% sensitivity, 22.2% specificity, 53.3% PPV, and 80% NPV when the cutoff was assumed to be 3 for distinguishing metastatic lesions from primary benign lesions. Metser et al[9] included CT attenuation in the evaluation and increased the sensitivity to 100% and the specificity to 98%.

Similar to this study, Han et al[10] evaluated a-SUVx values and showed good discrimination of malignant lesions from benign lesions, which was related to high glucose use of malignant tumors—the principle of PET imaging. Han et al[10] discriminated benign adrenal lesions from metastatic lesions with a sensitivity of 94% and specificity of 83%. Launay et al[11] also assessed a-SUVx values for the discrimination of adrenal masses and differentiated primary benign lesions from metastatic lesions.

Although Pitts et al[12] assessed a-SUVx values with a cutoff value of 3 and in 87.3% of cases PET results did not affect clinical diagnosis, the majority of cases had a clinical diagnosis rather than a golden (histopathological) diagnosis. In addition, Pitts et al[12] stated that even though PET can discriminate between benign and malignant lesions, this is not essential for the diagnosis of adrenal masses.

Watanabe et al[13] assessed a-SUVx values and showed that metastatic lesions had higher values than adrenocortical adenomas. In their ROC analyses, they calculated the sensitivity as 78% and specificity as 100% when the a-SUVx cutoff value was 5.01 with 0.96 AUC. Altinmakas et al[14] also assessed a-SUVx values obtained from PET-CT with ROC analysis and found AUC as 0.75, determined optimum cutoff value 3.46 which yielded accuracy of 87% and sensitivity of 96%.

Current study has found AUC as 0.79; even sensitivity was 77% for cut off value of a-SUVx as 5.5 and 94% for 3.5 and similar with literature, specificities (64% and 28% respectively) were not that high.

This study has some limitations. The multicentric design will affect the consistency of the PET-CT interpreters and interpretation software. There can be differences among centers in personnel, methods, and software, which leads to nonharmonized data. Retrospective data collection led to alternative imaging data being unavailable for some patients; however, this did not significantly affect the study. A lack of liver SUVmax data in most cases and unavailable PET-CT images resulted in comparative assessments of adrenal to liver ratio of SUVmax not being performed.

5. Conclusion

PET-CT is generally able to discriminate malignant lesions from benign lesions; in this study there was a significant difference in a-SUVx values between primary benign adrenal lesions and metastatic adrenal lesions with cutoff value of 5.5 when histopathology was taken as reference with acceptable sensitivity, specificity, and accuracy.

Author contributions

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Data curation: Adnan Ozpek, Ali Demir, Fatih Tunca, Gürcan Albeniz, Hüsnü Alptekin, Safa Vatansever, Serkan Teksoz.

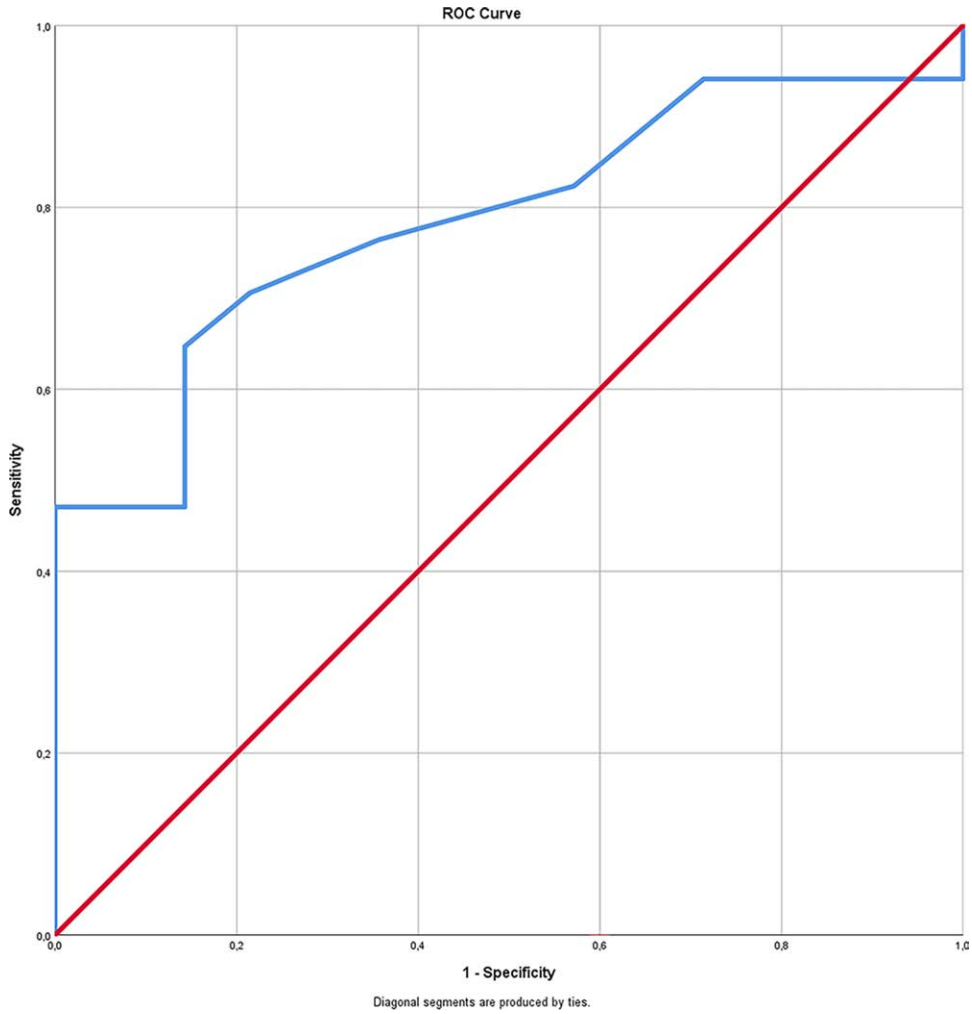

Figure 2. ROC curves for a-SUVx values. Blue line indicates a-SUVx value. Red line indicates diagonal line. AUC was 0.786 with *P* = .007 (95% CI: 0.622–0.949). a-SUVx = maximum standardized uptake value of adrenal mass, AUC = area under the curve, CI = confidence interval, ROC = receiver operating characteristic.

Table 2

Distribution of metastatic and nonmetastatic cases for a-SUVx cutoff values.

a-SUVx cutoff value	Nonmetastatic group	Metastatic group	Total	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	*P* value
<8.5	12	6	18	84.62	66.67	64.71	85.71	74.19	**.005**
≥8.5	2	11	13						
<7	11	5	16	80.00	68.75	70.59	78.57	74.19	**.006**
≥7	3	12	15						
<5.5	9	4	13	72.22	69.23	76.47	64.29	70.97	**.022**
≥5.5	5	13	18						
<5.01	9	4	13	72.22	69.23	76.47	64.29	70.97	**.022**
≥5.01	5	13	18						
<4.5	6	3	9	63.64	66.67	82.35	42.86	64.52	.233*
≥4.5	8	14	22						
<3	4	1	5	61.54	80.00	94.12	28.57	64.52	.148*
≥3	10	16	26						
Total	14	17	31						

Only statistically significant values are in bold.

a-SUVx = standard uptake value at maximum of adrenal gland.

*Fisher exact test was utilized.

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Writing – review & editing: Akif Enes Arikan, Fatih Tunca, Ozer Makay.
They have reviewed and approved the manuscript.

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