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RESEARCH ARTICLE
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THE DIAGNOSTIC ACCURACY OF PET/CT IN DIFFERENTIATING BENIGN FROM MALIGNANT ADRENAL GLAND NODULES IN CANCER PATIENTS WITH SUSPICIOUS ADRENAL NODULES USING HISTOPATHOLOGICAL AS GOLD STANDARD.

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Abstract

Background: The adrenal gland, known for its metastatic propensity, often hosts accompanying lesions, making the distinction between malignancy and benign adenomas crucial in oncologic patients. Accurate characterization is vital, enabling informed management decisions and prognostic evaluations while minimizing unnecessary biopsies.

Objective: The study aimed to determine the diagnostic accuracy of Positron Emission Tomography/Computed Tomography (PET/CT) in differentiating between benign and malignant adrenal nodules in cancer patients with suspicious adrenal nodules, using histopathology as the gold standard at a Tertiary Care Hospital in Karachi.

Methodology: The study, designed as a cross-sectional investigation, took place at the Department of Radiology, Jinnah Postgraduate Medical Centre (JPMC), Karachi. Conducted over six months, from 26-03-21 to 26-09-21, the research involved the prospective collection of data from 123 patients meeting diagnostic criteria. Verbal consent was obtained, and the data was analyzed using simple descriptive statistics for quantitative variables and frequency percentages for qualitative variables. Sensitivity, specificity, positive and negative predictive values, along with diagnostic accuracy, were calculated for the assessment of the study's objectives.

Results: The study incorporated a total of 123 patients meeting the specified inclusion and exclusion criteria. The mean age of participants was 50.14±10.49 years, with a gender distribution of 63 (51.2%) males and 60 (48.8%) females. Analysis of the data revealed that among these patients, the diagnostic performance of PET/CT for identifying malignant adrenal nodules, using histopathology as the gold standard, resulted in a sensitivity of 89.7%, specificity of 86.6%, positive predictive value of 92.1%, negative predictive value of 82.9%, and an overall diagnostic accuracy of 88.6%.

Conclusion: PET/CT demonstrated good sensitivity and specificity for the characterization of adrenal masses.

Keywords: Adrenal nodules, Positron Emission Tomography, Diagnostic accuracy, Oncologic patients

INTRODUCTION

The adrenal glands are susceptible to a range of pathological conditions, including primary and secondary neoplasms, hyperplasia, and various other disorders. [1]. Tumors that originate from the adrenal cortex can either be benign or malignant, secreting or not secreting. It is a common site of metastasis in patients with cancer [2]. Up to 50% of adrenal lesions in patients with known primary non-adrenal cancers are malignant disease [3]. The most common malignant lesions that metastasise to the adrenal gland include lung, liver, colon, lymphoma, melanoma, breast, kidney, oesophagus, pancreas and stomach cancer [4]. However, diagnosis of an adrenal lesion as malignant or benign can be problematic. Characterization of these adrenal lesions is therefore critical to stage the primary disease, direct therapy and predict prognosis [5]. These lesions are usually called incidentalomas, but this term reflects their mode of discovery rather than their nature [6]. They are found in 4% of abdominal computed tomography (CT) scans and are benign in nature. Although CT and MRI are typically used to characterize a lesion, a small but important number of adrenal lesions are found to be indeterminate on cross-sectional images [7].

In recent years, 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) (18F-FDG PET/CT) has gained an increasing role in oncology, including the diagnosis of adrenal masses in patients with cancer or patients with a previous history of cancer [8]. Few studies have shown that 18F-FDG PET/CT could also provide information regarding the nature of indeterminate adrenal masses on CT [9]. However, its role in the evaluation of adrenal masses in noncancer patients is still debated due to a lack of robust studies [10,11].

Several reports have documented the effectiveness of stand-alone fluorine-18F-FDG PET to differentiate benign from malignant adrenal lesions [12]. Interest has focused on the ability of integrated in-line PET/CT to definitively characterize these lesions given that this technique combines the anatomical and densitometrical applications of CT and the functional and metabolic advantages of PET [13]. PET/CT can also be used as a non-invasive method to help assess the lesion, facilitating diagnosis and treatment decisions [14]. Vikram et al study found sensitivity and specificity of PET/CT to be 67% and 93% [15]. Okada et study found that a SUV(max) cut-off value of 2.5 corresponded to a sensitivity of 89%, specificity of 94%, accuracy of 91%, positive predictive value of 94% and negative predictive value of 88% [16].

Objective: The study aimed to determine the diagnostic accuracy of PET/CT in differentiating between benign and malignant adrenal nodules in cancer patients with suspicious adrenal nodules, using histopathology as the gold standard at a Tertiary Care Hospital in Karachi.

METHODOLOGY

Study Design and Setting:

The research, designed as a cross-sectional study and was carried out at the Department of Radiology, Jinnah Postgraduate Medical Centre (JPMC), located in Karachi.

Duration of Study:
The research spanned six months, initiated after the approval of the synopsis on March 26, 2021, and concluded on September 26, 2021.

Sample Size Calculation:
The sample size of 123 patients was determined by considering a sensitivity of 89% and specificity of 90% for adrenal malignant nodules on PET/CT. The prevalence was estimated at 31.25%, with a margin of error (d) of 10% for sensitivity and specificity, and a confidence interval of 95%.

Sampling Technique:
Non-probability consecutive sampling was employed to select participants.

Sample Selection Criteria:
Inclusion Criteria:
The study focused on individuals exhibiting suspicious adrenal nodules within the context of cancer patients, adhering to the operational definition. Inclusivity criteria allowed for the enrollment of participants of either gender falling within the age range of 30 to 80 years.

Exclusion Criteria:
Exclusion criteria encompassed non-consenting individuals and those with specific medical histories, such as a record of taking anticoagulants like warfarin, a history of pheochromocytoma, Conn's syndrome, or Addison's disease. Additionally, individuals with uncontrolled hypertension (systolic BP > 160 mmHg and diastolic BP > 90 mmHg), a history of diabetes mellitus type II, confirmed pregnancy by both history and dating scan, and those with a history of stroke, renal impairment, chronic obstructive pulmonary disease, asthma, or congestive heart failure were systematically excluded from the study.

Data Collection Procedure:
After obtaining approval from the College of Physicians and Surgeons Pakistan, consenting cases meeting the inclusion criteria were enrolled from the OPD of the Department of Radiology, JPMC, Karachi. Permission from the institutional ethical review committee was secured before conducting the study. Informed consent was obtained from all patients, and a brief history for demographic information was collected. Patients with suspicious adrenal nodules on PET/CT were evaluated for malignancy by a nuclear physician, and those with adrenal to liver max SUV ratio cutoff value ≥ 2.5 were labeled as positive. Subsequently, patients were followed for histopathology, and nodules with Weiss score ≥ 3 on pathology specimens were labeled as malignant. Quantitative and qualitative variables were recorded in a performa attached as an annexure.

Data Analysis Procedure
Data analysis was performed using SPSS Version 20. Mean and standard deviation were calculated for continuous variables such as age, while frequency and percentages were calculated for gender, residence status, malignant adrenal nodules on PET/CT (Positive/Negative), and malignant adrenal nodules on histopathology (Positive/Negative). Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of PET/CT for the diagnosis of malignant adrenal nodules, with histopathology as the gold standard, were calculated. Stratification was conducted based on age, gender, and residence status, followed by post-stratification calculations of sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy.

RESULTS
This study included a large cohort of 123 patients from the Department of Radiology at the Jinnah Postgraduate Medical Centre (JPMC), Karachi, who fulfilled the strict inclusion and exclusion

criteria. The age range in this patient group was rather diverse, with a mean age of 50.14±10.49 years and a minimum age of 30 to a maximum age of 80 years. In the study cohort of 123 patients, the frequency distribution of malignant adrenal nodules based on histopathology revealed that 78 individuals (63.4%) had a malignant adrenal nodule, while 45 individuals (36.6%) did not, as illustrated in (figure 1). In the study cohort of 123 patients, the frequency distribution of malignant adrenal nodules based on PET/CT revealed that 76 individuals (61.8%) had a malignant adrenal nodule, while 47 individuals (38.2%) did not (figure 2).

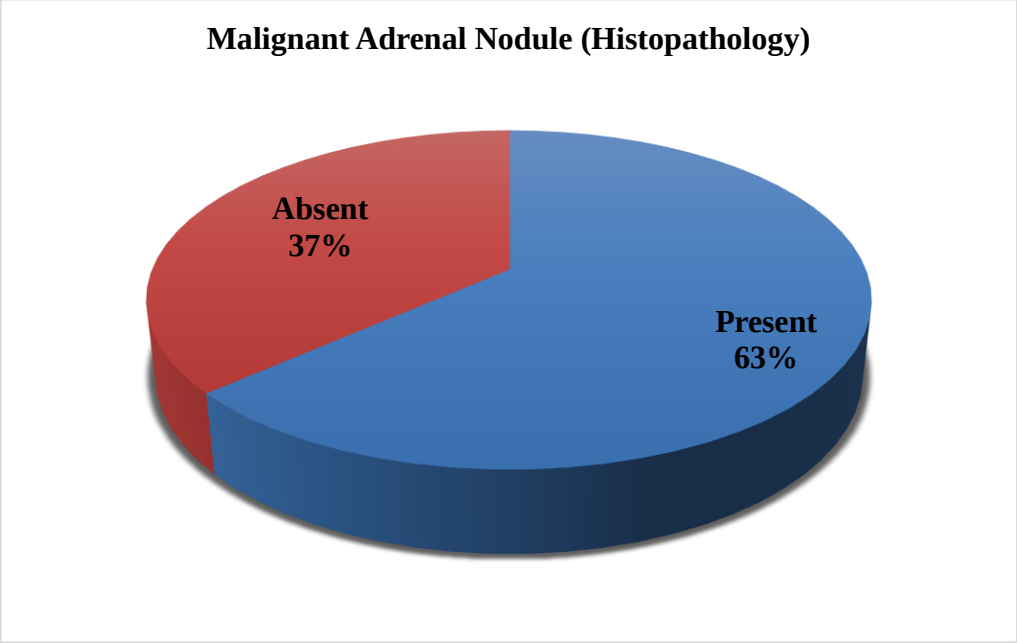

Figure 1: Frequency Distribution of Malignant Adrenal Nodule on Histopathology

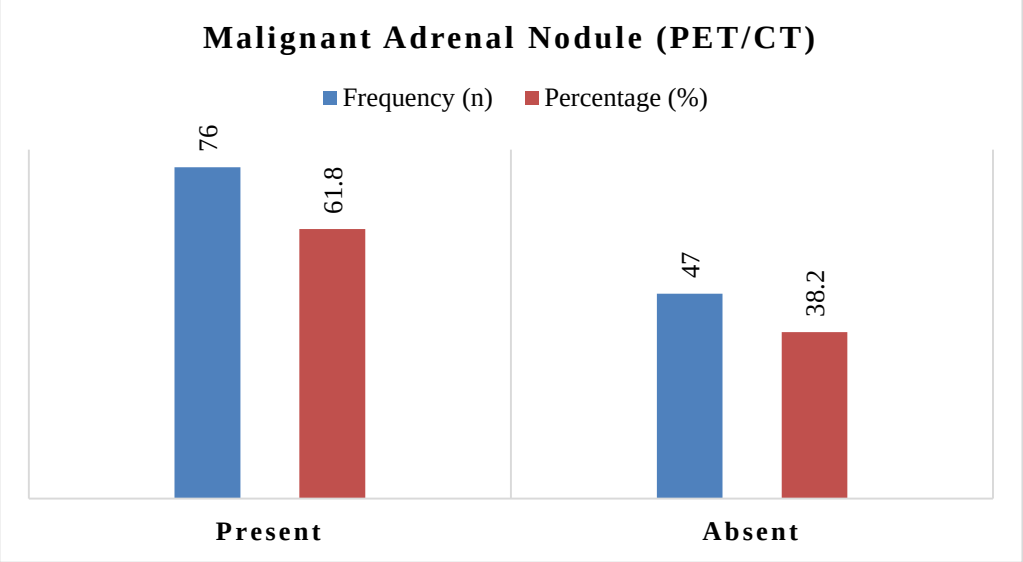

Figure 2: Frequency Distribution of Malignant Adrenal Nodule on PET/CT

In the study population of 123 patients, the frequency distribution based on age groups indicated that 35 patients (28.5%) fell within the 30-50 years range, while 88 patients (71.5%) were in the 51-80 years range (figure 3). Figure 4 illustrates the gender distribution among the 123 participants in the study, indicating that 51.2% (63 individuals) were male, while 48.8% (60 individuals) were female. Additionally, the table displays the residence status of the participants, revealing that 58.5% (72 individuals) resided in urban areas, whereas 41.5% (51 individuals) had a rural residence.

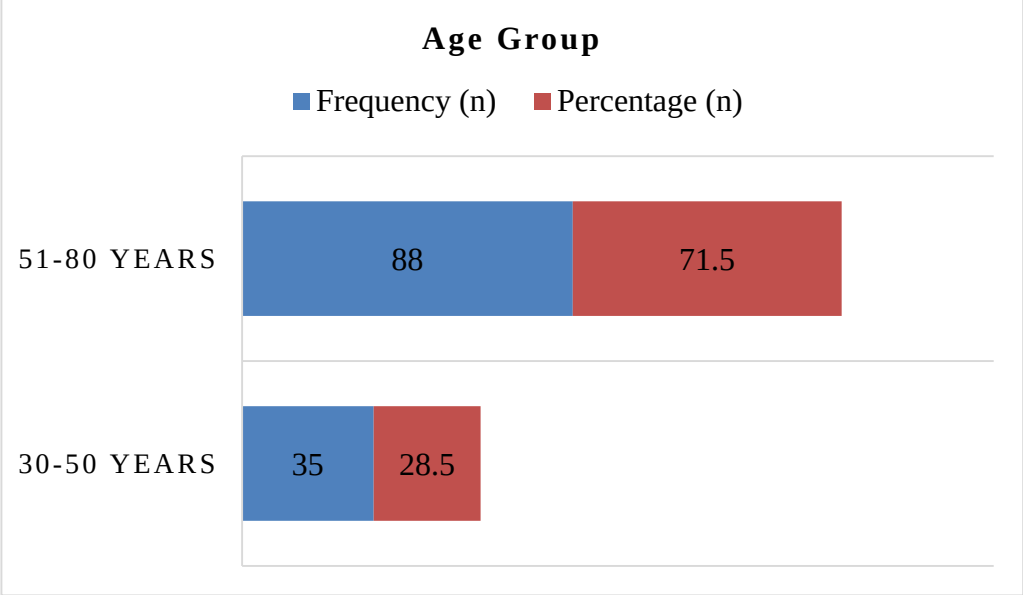

Figure 3: Frequency Distribution of Age Groups

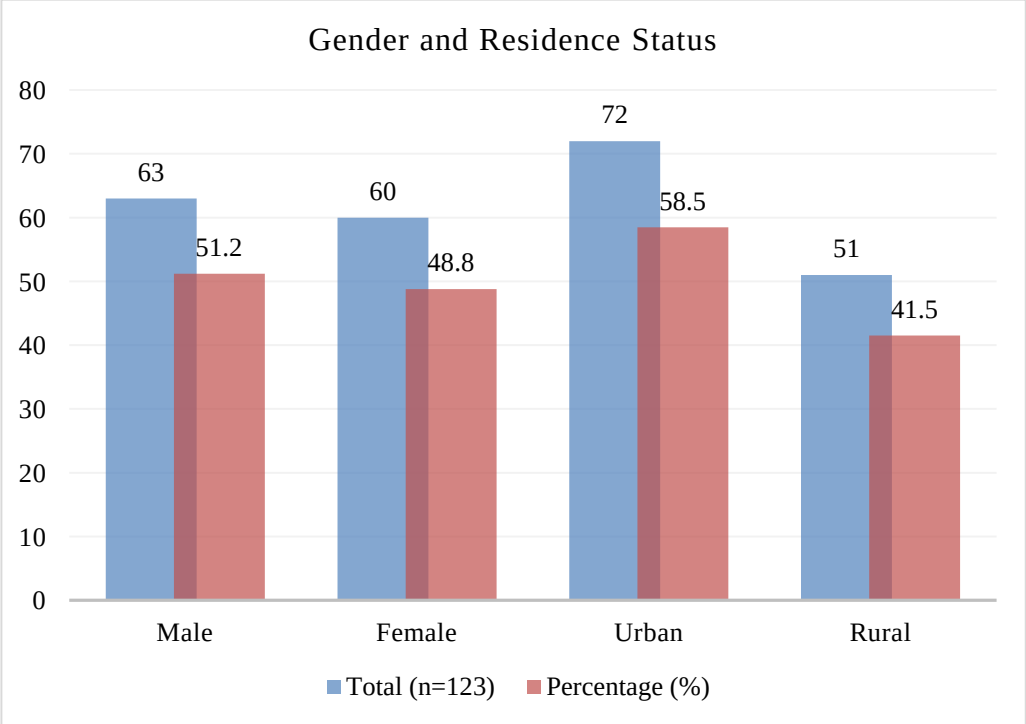

Figure 4: Patient Demographics

Among the 123 patients assessed, the diagnostic performance of PET/CT in identifying malignant adrenal nodules, with histopathology as the gold standard, revealed a sensitivity of 89.7%, specificity of 86.6%, positive predictive value of 92.1%, negative predictive value of 82.9%, and an overall diagnostic accuracy of 88.6% (table 1, 2).

Table 1: Contingency Table for PET/CT vs. Histopathology in Malignant Adrenal Nodule Diagnosis

PET/CT	**Histopathology**	**Total**
Positive	70 (TP)	06 (FP)
Negative	08 (FN)	39 (TN)
Total	78	45

Table 2: Comprehensive Diagnostic Metrics for PET/CT in Malignant Adrenal Nodule Diagnosis

Metric	**Formula**	**Result**
Sensitivity	TP / (TP + FN) x 100	89.7%
Specificity	TN / (TN + FP) x 100	86.6%
Positive Predictive Value (PPV)	TP / (TP + FP) x 100	92.1%
Negative Predictive Value (NPV)	TN / (FN + TN) x 100	82.9%
Diagnostic Accuracy	(TP + TN) / Total x 100	88.6%

The diagnostic performance of PET/CT in identifying malignant adrenal nodules, assessed through age-based stratification, yielded distinct outcomes. Among individuals aged 30-50 years, PET/CT demonstrated a sensitivity of 88.2%, specificity of 83.3%, positive predictive value of 83.3%, negative predictive value of 88.2%, and an overall diagnostic accuracy of 85.7%. In the 51-80 years age group, PET/CT exhibited a sensitivity of 90.5%, specificity of 88.8%, positive predictive value of 94.8%, negative predictive value of 80%, and an overall diagnostic accuracy of 89.7% (table 3).

Table 3: Diagnostic accuracy of PET/CT for the diagnosis of malignant adrenal nodule by taking histopathology as gold standard according to age

Age (Years)	**PET/CT**	**Histopathology**		**Total**	**Sensitivity**	
		Positive	**Negative**			
30-50	Positive	15 (TP)	03 (FP)	18	SEN SPE PPV NPV DA	88.2% 83.3% 83.3% 88.2% 85.7%
	Negative	02 (FN)	15 (TN)	17		
	Total	17	18	35		
51-80	Positive	55(TP)	03(FP)	58	SEN SPE PPV NPV DA	90.5% 88.8% 94.8% 80% 89.7%
	Negative	6 (FN)	24 (TN)	30		
	Total	61	27	88		
Note: Sensitivity (SEN), Specificity (SPE), PPV (Positive Predictive Value), NPV (Negative Predictive Value), DA (Diagnostic Accuracy)						

The stratified analysis based on gender, assessing the diagnostic metrics of PET/CT in comparison to histopathology as the gold standard, revealed distinct outcomes. In the male group, PET/CT demonstrated a sensitivity of 90%, specificity of 86.9%, positive predictive value of 92.3%, negative predictive value of 83.3%, and an overall diagnostic accuracy of 88.8%. Similarly, in the female group, PET/CT exhibited a sensitivity of 89.4%, specificity of 86.3%, positive predictive value of 91.8%, negative predictive value of 82.6%, and an overall diagnostic accuracy of 88.3% (table 4).

Table 4: Diagnostic accuracy of PET/CT for the diagnosis of malignant adrenal nodule by taking histopathology as gold standard according to gender

Gender	**PET/CT**	**Histopathology**		**Total**	**Sensitivity**	
		Positive	**Negative**			
Male	Positive	36(TP)	03 (FP)	39	SEN SPE PPV NPV DA	90% 86.9% 92.3% 83.3% 88.8%
	Negative	04 (FN)	20 (TN)	24		
	Total	40	23	63		
Female	Positive	34 (TP)	03 (FP)	37	SEN	89.4%
	Negative	4 (FN)	19 (TN)	23	SPE	86.3%

	Total	38	22	60	PPV NPV DA	91.8% 82.6% 88.3%
Note: Sensitivity (SEN), Specificity (SPE), PPV (Positive Predictive Value), NPV (Negative Predictive Value), DA (Diagnostic Accuracy)						

Stratification based on residence status in relation to sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of PET/CT in diagnosing malignant adrenal nodules, using histopathology as the gold standard, revealed the following findings: Among patients residing in urban areas, the values were 86.6%, 88.8%, 92.8%, 80%, and 87.5%, respectively. Conversely, for patients residing in rural areas, the corresponding values were 93.9%, 83.3%, 91.1%, 88.2%, and 90.1% (table 5).

Table 5: Diagnostic accuracy of PET/CT for the diagnosis of malignant adrenal nodule by taking histopathology as gold standard according to residence status

Residence Status	**PET/CT**	**Histopathology**		**Total**	**Sensitivity**	
		Positive	**Negative**			
Urban	Positive	39 (TP)	03 (FP)	42	SEN	86.6%
	Negative	06 (FN)	24 (TN)	30	SPE	88.8%
	Total	45	27	72	PPV	92.8%
					NPV	80.0%
					DA	87.5%
Rural	Positive	31 (TP)	03 (FP)	34	SEN	93.9%
	Negative	2 (FN)	15 (TN)	17	SPE	83.3%
	Total	33	18	51	PPV	91.1%
					NPV	88.2%
					DA	90.1%
Note: Sensitivity (SEN), Specificity (SPE), PPV (Positive Predictive Value), NPV (Negative Predictive Value), DA (Diagnostic Accuracy)						

DISCUSSION

Adrenal incidentaloma is defined as an adrenal mass detected incidentally with a size of 1 cm or larger and could be detected in approximately 4–6% of the patients who received imaging studies such as CT or MRI. Although most incidental lesions are adenomas, the adrenal gland is common site for metastasis in patients with cancer with the rate of metastasis being between 25 and 75% depending on the type and size of the primary tumour [17]. Hence, accurate differentiation of adrenal lesions of cancer patients could be essential for prognostication and treatment choices, especially when such lesions are the only abnormality detected. Non-invasive anatomical imaging techniques have been used to differentiate metastases from benign adrenal adenoma. CT has ability to measure attenuation, on both unenhanced images and on delayed contrast-enhanced images, to differentiate benign from malignant lesions. However, the diagnosis based on attenuation measurement is often not feasible in unenhanced or delayed contrast-enhanced CT. Better diagnostic accuracy could be expected when chemical shift MRI is used, but the signal intensity of benign and malignant lesions overlaps considerably [18]. FDG PET/CT is a functional imaging modality that could help characterize these adrenal lesions. Several previous reports have shown the usefulness of 18F-FDG–PET/CT to differentiate benign from malignant adrenal lesions [19, 20].

Our study included a total of 123 patients who met the inclusion and exclusion criteria. Mean age in our study was 50.14±10.49 years. 63 (51.2%) were male and 60 (48.8%) were female. Out of 123 patients, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of PET/CT for diagnosis of malignant adrenal nodule by taking histopathology as gold standard was found to be 89.7%, 86.6%, 92.1%, 82.9% and 88.6%. Across 29 studies (2421 patients),

the pooled sensitivity for 18F-FDG PET or PET/CT was 0.91 [95% CI (0.88–0.94)] with heterogeneity ($\chi 2 = 141.8$, $p = 0.00$) and a pooled specificity of 0.91 [95% CI (0.87–0.93)] with heterogeneity ($\chi 2 = 113.7$, $p = 0.00$) [21]. Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 9.9 [95% CI (7.1–13.7)] and negative likelihood ratio (LR–) of 0.09 [95% CI (0.07–0.13)]. The pooled diagnostic odds ratio was 105 [95% CI (63–176)] [22]. In metaregression analysis, study design, publication year, study location (western vs others), interpretation criteria of PET or PET/CT images, quantification of PET or PET/CT [SUVmax (maximum standardized uptake value) vs SUV (standardized uptake value) ratio], patient group, and analysis method (patient-based vs lesion-based) were the sources of the study heterogeneity. However, in multivariate metaregression, no definite variable was the source of the study heterogeneity [23].

Another study reviewed the radiology reports and images of patients with known malignant disease who had undergone PET/CT for cancer staging or surveillance and who had adrenal nodules at least 1 cm in diameter. Thirty adrenal lesions were malignant. Twenty-five of the 30 malignant nodules had positive PET results. Twelve of 82 benign nodules were PET positive with a sensitivity of 83.3% and specificity of 85.4%. Patients with four of five malignant nodules with negative PET results had received previous therapy. The positive predictive value for detection of malignant lesions was 67%, and the negative predictive value was 93%. Adrenal masses that are not FDG avid are likely to be benign with a high negative predictive value. Especially in patients undergoing therapy, however, there is a small but statistically significant false-negative rate. A considerable proportion of benign nodules have increased FDG activity [24].

Another study found overall number of 24 adrenal masses was diagnosed. Positive PET/CT results were found in 14 adrenal masses. All were finally considered to be metastases by serial imaging follow-up ($n = 8$) and histopathological analysis by surgery ($n = 1$) and percutaneous biopsy ($n = 5$). Accordingly, no false positive result was obtained. Negative PET/CT results were observed in 10 adrenal masses, 9 of them were finally confirmed to be benign by serial imaging follow-up. The remaining mass was finally confirmed to be metastasis by percutaneous biopsy and hence, it represented the false negative result. 93% sensitivity, 100% specificity and 96% accuracy for identifying adrenal metastases were obtained [25].

SUV(max) in adrenal malignant lesions (7.4 +/- 3.5) was higher than that in adrenal benign lesions (2.1 +/- 0.5, $p < 0.05$). The CT attenuation value of adrenal malignant lesions (27.6 +/- 11.9 HU) was higher than that of adrenal benign lesions (10.1 +/- 12.3 HU, $p < 0.05$). In differentiating between adrenal benign and malignant lesions, a CT threshold of 10 HU corresponded to a sensitivity of 57%, specificity of 94%, accuracy of 74%, positive predictive value of 92% and negative predictive value of 65%. An SUV(max) cut-off value of 2.5 corresponded to a sensitivity of 89%, specificity of 94%, accuracy of 91%, positive predictive value of 94% and negative predictive value of 88%. The T/L SUV(max) ratio was 1.0 +/- 0.2 for adrenal benign lesions and 4.5 +/- 3.0 for adrenal malignant lesions. And T/L SUV(max) ratio cut-off value of 1.8 corresponded to a sensitivity of 85%, specificity of 100%, accuracy of 91%, positive predictive value of 100% and negative predictive value of 83% [26].

CONCLUSION

In conclusion, the utilization of integrated 18F-FDG PET/CT for adrenal imaging in oncologic patients offers a precise and non-invasive means of distinguishing between benign and metastatic adrenal masses. This approach enhances patient triage by reducing unnecessary surgical interventions on benign masses and contributes to improved prognosis by enabling the early detection of malignancies.

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