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ORIGINAL ARTICLE

Diagnostic Accuracy of Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography with Computer Tomography in Detection of Hepatocellular Carcinoma and Its Extrahepatic Metastases

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a global health concern, ranking seventh in cancer incidence and third in cancer-related mortality. Extrahepatic metastases occur in 37% of cases, with common sites such as lungs, lymph nodes, and bone. While contrast-enhanced triphasic computed tomography and magnetic resonance imaging are standard for HCC staging, they have limitations in detecting metastases. PET/CT, combining PET's metabolic imaging with CT's anatomical detail, offers a comprehensive approach without patient movement facilitating accurate lesion localization. This study aimed to assess the efficacy of PET/CT in the detection of hepatocellular carcinoma and its extrahepatic metastases.

Methods: Our study involved 18 pathologically proven HCC patients collected between October 2022 and November 2023. Cases underwent various interventions. Post procedure CT follow-up was performed on all patients, and PET/CT was conducted in clinically suspected extrahepatic metastases cases. Written informed consent was obtained, and the study protocol received institutional ethics approval.

Results: PET/CT has 100% sensitivity and 33.3% specificity for HCC focal lesions. It ranges from 50% to 100% sensitivity and specificity for various metastases such as lymph nodes, vertebral, and pulmonary. For instance, lymph nodes show 87.5% sensitivity and 100% specificity, vertebral metastases exhibit 66.67% sensitivity and 93.33% specificity, while pulmonary metastases display 50% sensitivity and 100% specificity.

Conclusions: Our study demonstrates the role of PET/CT in HCC management, enabling early detection of metastases and guiding treatment. Despite variations in diagnostic accuracy, PET/CT remains important for assessing disease spread and recurrence.

Key words: HCC; metastases; PET/CT.

INTRODUCTION

Hepatocellular carcinoma (HCC) is considered as the seventh most prevalent cancer worldwide and stands as the third leading cause of cancer-related mortality [1]. The primary risk factors include chronic hepatitis B or C virus infection, alcoholic cirrhosis, nonalcoholic steatohepatitis, diabetes (with metabolic syndrome potentially serving as the underlying risk mechanism), and cirrhosis regardless of its cause [2].

Extrahepatic HCC incidence accounts for 37% of cases, with frequent metastases observed in lungs, lymph nodes, and bone [3]. While dynamic computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) are commonly utilized for HCC staging, they exhibit limitations in detecting distant metastases [4,5].

Positron emission tomography/computed tomography (PET/CT) facilitates a seamless acquisition of PET and CT images without patient movement, offering inherently co-registered data

[6]. PET with fluoro-2-deoxy-D-glucose (FDG) has demonstrated utility in furnishing essential qualitative and quantitative metabolic information crucial for tumor diagnosis and staging [7].

PET imaging relies on the labeling of biologically significant molecules with positron-emitting radionuclides, enabling the detection of emitted gamma photons by the PET scanner. The diagnostic efficacy of 18F-FDG PET stems from the heightened glycolytic activity characteristics of most malignant tumors, driven by their substantial energy requirements due to rapid growth [8,9]. PET-CT proves to be a highly efficient noninvasive imaging tool capable of scanning the entire body, facilitating improved detection of hidden metastatic lesions and accurate staging [10].

This study aimed to assess the efficacy of PET/CT in the detection of hepatocellular carcinoma and its extrahepatic metastases.

METHODS

This clinical trial study involved 18 cases, aged between 42 and 64 years, meeting the specified inclusion and exclusion criteria. They were diagnosed with HCC by imaging modalities such as triphasic CT and MRI and by histopathology, who were admitted to the Radiology Department at Zagazig University Hospitals and underwent different methods of intervention either by ablation by radiofrequency or microwave or by transarterial chemoembolization by lipiodol / doxorubicin embolization or drug eluting beads between October 2022 and November 2023. Post-procedure computed tomography (CT) follow-up was performed on all patients on a routine basis and PET/CT was performed in suspected patients included in the study.

Prior to participation patients provided written informed consent. The study protocol received approval from the institution's medical ethics committee (reference number ZU-IRB#10652/2-4-2023), adhering strictly to the Declaration of Helsinki for the protection of participants in medical research.

Included in the study were 18 cases

Inclusion Criteria:

- Patients with HCC and suspected extra-hepatic metastases; the suspicion of extrahepatic metastasis was conducted for patients in cases of highly elevated alpha fetoprotein (AFP) levels > 1000 ng%, suspected chest metastasis by CT examination, or patients with persistent low back or musculoskeletal pain proved by suspicious magnetic resonant imaging findings.

Exclusion Criteria:

Patients with hypersensitivity to radiographic contrast agents, high blood glucose levels (>200 mg/dl), and renal impairment (glomerular filtration rate <30).

Procedure:

Patient history was obtained, focusing on pain, swellings, and previous treatments. Laboratory investigations included kidney function tests, renal function tests, AFP levels, and measurement of blood glucose levels.

Patients were prepared for the examination by fasting for 6 hours to ensure serum glucose levels did not exceed 180 mg/dl before tracer injection. They were advised to avoid vigorous activity 24 hours prior to the procedure and to remove all metallic items. An intravenous cannula was inserted in the patient's arm for an 18 F-FDG injection.

Dosage Administration:

- One liter of negative oral contrast agent (approximately 5% mannitol) was administered about one hour before the study.
- Approximately 0.15 mCi/kg of 18F-FDG was injected 45-90 minutes before the examination.

Examination Time:

- Study duration was approximately 20-30 minutes.

PET Technique:

- PET was performed immediately following the CT study without patient movement.
- Scanning started from the skull base and extended caudally to the upper thighs, with 3-5 minute acquisitions at each of the six to seven planned bed positions.

PET/CT Fusion:

- Trans-axial PET and CT images were reconstructed and reformatted into coronal and sagittal images.
- Fusion images, combining both data types, were generated using specialized software.

Images Interpretation:

- Independent interpretation of images by a consultant radiologist and a consultant nuclear medicine physician.
- Studies were reviewed separately before evaluating the fused images.

Analysis of Findings:

- Lesions characterized as malignant on PET/CT and confirmed as such were considered true positives.

- Lesions characterized as benign without evidence of malignancy were also considered true positive.
- Positive PET/CT lesions without evidence of malignancy on biopsy or other modalities were considered false positives.
- Negative PET/CT lesions with evidence of malignancy on biopsy or other modalities were considered false negatives.

Reference Standard:

Our standard of reference was histopathological examination or imaging follow-up and clinical evaluation together with affirmation of diagnosis by other modalities such as triphaisc CT and MRI.

Statistical Analysis

- SPSS (Statistical Package for the Social Sciences) version 26 was used to analyze the data. Absolute frequencies were used to characterize categorical variables. The chi-square for trend test was performed to examine the relationship between the two sets of ordinal data. Wilcoxon signed rank and Monte Carlo tests also were used. Depending on the data type, quantitative variables were described using mean values, standard deviations, median values, and interquartile ranges. The Spearman rank correlation coefficient was employed to measure the degree to which two continuous variables were correlated with one another and in what direction.

RESULTS

The study involved 18 male participants aged between 42 and 64 years, with a mean age of 50.61 years. PET/CT imaging exhibited robust sensitivity and negative predictive value for detecting various lesions associated with hepatocellular carcinoma (HCC) metastases. Specifically, for HCC focal lesions, PET/CT demonstrated a sensitivity of 100%, a specificity of 33.3%, a positive predictive value of 88.24%, a negative predictive value of 100%, and an accuracy of 88.89%.

In the case of lymph nodes (LNs), PET/CT showed a sensitivity of 87.5%, specificity of 100%, positive predictive value of 100%, negative predictive value of 90.91%, and an accuracy of 94.44%. Peritoneal metastases were identified with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy all reaching 100%.

Vertebral metastases were detected with a sensitivity of 66.67%, specificity of 93.33%, positive predictive value of 66.67%, negative predictive value of 93.33%, and an accuracy of 88.89%. Ribs and sternal metastases, along with pelvic and femoral metastases, were identified with 100% sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

Muscular metastases were similarly identified with 100% across all measures. Pulmonary metastases exhibited a sensitivity of 50%, specificity of 100%, positive predictive value of 100%, negative predictive value of 94.12%, and an accuracy of 94.44%. Thyroid metastases were found with a specificity and negative predictive value both at 94.44% and an accuracy of 94.44%.

Breast metastases were detected with 100% across all measures. Portal vein metastases showed a sensitivity of 66.67%, specificity of 100%, positive predictive value of 100%, negative predictive value of 93.75%, and an accuracy of 94.44%. Visceral metastases exhibited a sensitivity of 100%, specificity of 94.12%, positive predictive value of 50%, negative predictive value of 100%, and an accuracy of 94.44%.

Table (1): Distribution of the cases studied according to demographic data (n=18).

Demographic Data	No.	%
Sex		
Male	18	100.0
Female	0	0.0
Residence		
Urban	12	66.7
Rural	6	33.3
Age (years)		
Min. – Max.	42.0 – 64.0	
Mean ± SD.	50.61 ± 7.27	
Median (IQR)	48.50 (44.0 – 55.0)	

Table (2): Agreement (sensitivity, specificity and accuracy) for PET CT.

	Other Modalities				Sensitivity	Specificity	PPV	NPV	Accuracy
	Negative		Positive						
	No.	%	No.	%					
HCC	**(n=3)**		**(n= 15)**						
Negative	1	33.3	0	0.0	100.0	33.3	88.24	100.0	88.89
Positive	2	66.7	15	100.0					
LN	**(n= 10)**		**(n= 8)**						
Negative	10	100.0	1	12.5	87.50	100.0	100.0	90.91	94.44
Positive	0	0.0	7	87.5					
Peiton	**(n= 17)**		**(n= 1)**						
Negative	17	100.0	0	0.0	100.0	100.0	100.0	100.0	100.0
Positive	0	0.0	1	100.0					
Verteb	**(n= 15)**		**(n= 3)**						
Negative	14	93.3	1	33.3	66.67	93.33	66.67	93.33	88.89
Positive	1	6.7	2	66.7					
Ribs	**(n= 15)**		**(n= 3)**						
Negative	15	100.0	0	0.0	100.0	100.0	100.0	100.0	100.0
Positive	0	0.0	3	100.0					
Sternum	**(n= 17)**		**(n= 1)**						
Negative	17	100.0	0	0.0	100.0	100.0	100.0	100.0	100.0
Positive	0	0.0	1	100.0					
Pelv.fem	**(n= 13)**		**(n= 5)**						
Negative	13	100.0	1	20.0	80.0	100.0	100.0	92.86	94.44
Positive	0	0.0	4	80.0					
MSK	**(n= 16)**		**(n= 2)**						
Negative	16	100.0	0	0.0	100.0	100.0	100.0	100.0	100.0
Positive	0	0.0	2	100.0					
Lung	**(n= 16)**		**(n= 2)**						
Negative	16	100.0	1	50.0	50.0	100.0	100.0	94.12	94.44
Positive	0	0.0	1	50.0					
Thyroid	**(n= 18)**		**(n= –)**						
Negative	17	94.4	–	–	–	94.44	0.0	100.0	94.44
Positive	1	5.6	–	–					
Breast	**(n=17)**		**(n= 1)**						
Negative	17	100.0	0	0.0	100.0	100.0	100.0	100.0	100.0
Positive	0	0.0	1	100.0					
PV	**(n= 15)**		**(n= 3)**						
Negative	15	100.0	1	33.3	66.67	100.0	100.0	93.75	94.44
Positive	0	0.0	2	66.7					
Viscera	**(n= 17)**		**(n= 1)**						
Negative	16	94.1	0	0.0	100.0	94.12	50.0	100.0	94.44
Positive	1	5.9	1	100.0					

PPV: Positive predictive value
NPV: Negative predictive value

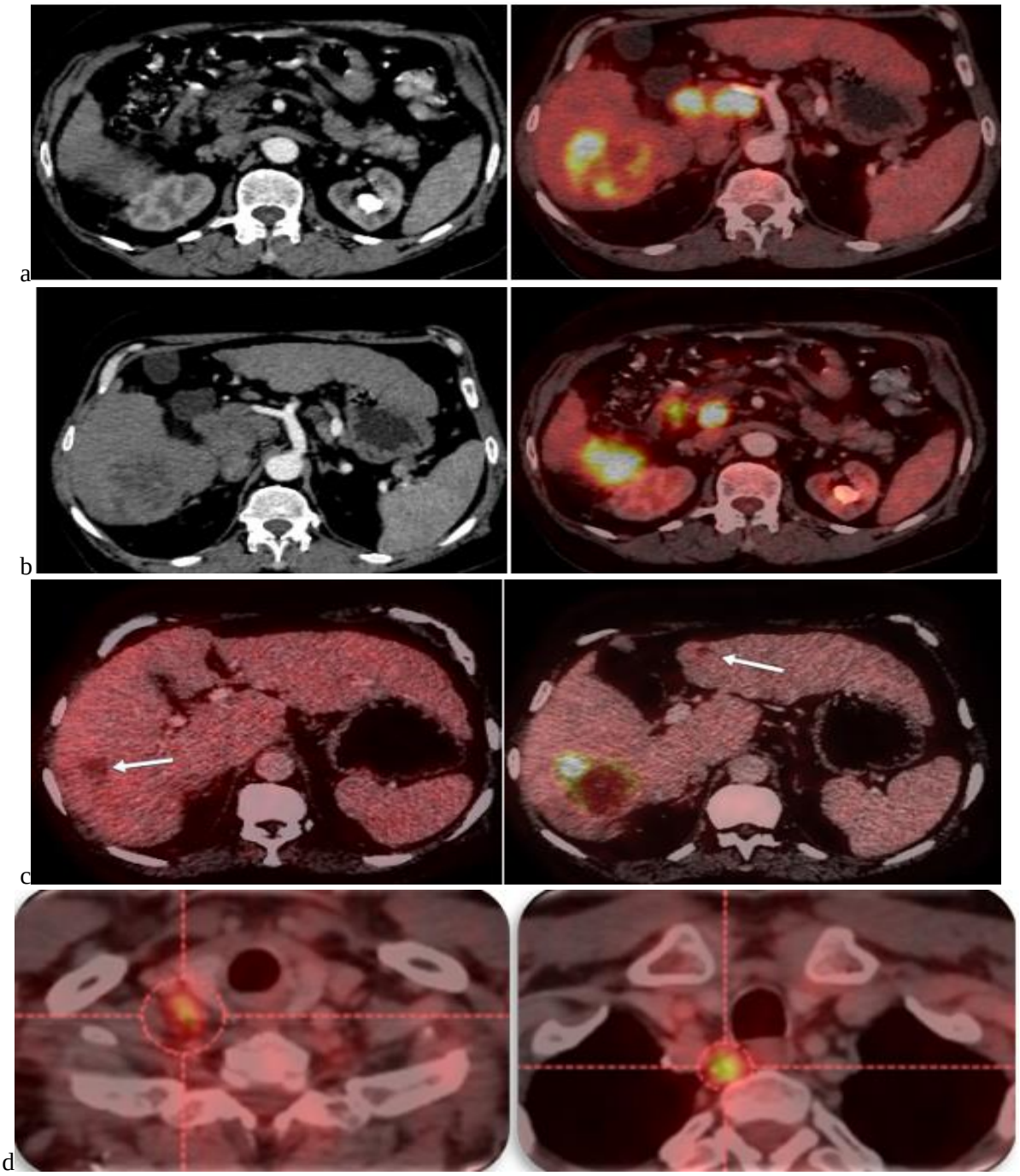

Figure (1): A, B and C axial images showing the liver of cirrhotic configurations showing:
-Right hepatic lobe hypermetabolic rather well-defined mass lesion implicating segment VI is seen as exophytic indenting and almost inseparable from the related anterolateral aspect of the right renal upper pole, measuring roughly 5.6x6.7 cm along its maximum axial diameters and achieving up to 19.3 SUV max.
-Such lesion is seen heterogeneously enhancing at the arterial phase with washout at port-venous and delayed phases.
-Other few smaller metabolically inactive ill-defined predominately hypodense focal lesions are seen dispersed along the hepatic parenchyma, reaching up to 20x23 mm.
d-axial images showing right retro-clavicular and right para-tracheal mildly active lymph nodes are seen, measuring up to 17 mm along the axial diameter and achieving up to 4.24 and 5.2 SUV max respectively.

DISCUSSION

Hepatocellular carcinoma remains a prevalent malignancy globally [11], and with advancements in treatment leading to prolonged survival, the incidence of extrahepatic metastases has seen an increase [12]. The primary objective of this study was to evaluate the efficacy of PET/CT in the detection of hepatocellular carcinoma (HCC) and its extrahepatic metastases.

18F-FDG PET is a well-established imaging modality for various malignancies, has shown limitations in detecting primary HCC due to variable FDG uptake [13,14]. However, it has demonstrated utility in identifying extrahepatic metastases, consistent with findings from previous studies [15]. Our study corroborates previous research indicating that 18F-FDG PET/CT effectively identify extrahepatic metastases, particularly in locations such as the lung, lymph nodes, bone, and adrenal gland [16].

Comparative analyses with existing literature revealed variations in sensitivity and specificity for different metastatic sites. For instance, our study demonstrated higher sensitivity (87.5%) and specificity (100%) in detecting lymph node metastases compared to previous research Kawaoka *et al*. (17), while sensitivity for pulmonary metastases was lower (50%) but with higher specificity (100%). These differences may be attributed to variations in patient cohorts, imaging protocols, and disease characteristics [17].

In terms of HCC diagnosis, our study yielded higher sensitivity (100%) but lower specificity (33.3%) compared to previous reports. This discrepancy underscores the complexity of HCC imaging and the need for further refinement in diagnostic approaches. Nevertheless, PET/CT remains a valuable tool in defining HCC, particularly in assessing disease spread and recurrence post-treatment [18,19].

Consistent with previous literature Sun *et al*. [20], our study highlights the utility of PET/CT in detecting residual activity or recurrence of HCC after treatment. Early identification of recurrent lesions, whether intrahepatic or extrahepatic, is crucial for timely intervention and improved patient outcomes.

Moreover, PET/CT fusion imaging has shown superiority over conventional diagnostic methods in detecting skeletal and lymph node metastases of HCC. This underscores the importance of integrating PET with CT for comprehensive evaluation and accurate staging of HCC which agrees with Nagaoka *et al* [21].

Limitation of the study is lack of availability of PET/CT modality in many clinical facilities also financial cost is considered.

CONCLUSIONS

Our study reaffirms the significant role of PET/CT in the detection and management of HCC and its metastases. Despite some variations in sensitivity and specificity across different metastatic sites, PET/CT remains a valuable imaging modality for guiding treatment decisions and monitoring disease progression in patients with HCC. Further research and technological advances are warranted to enhance the accuracy and clinical utility of PET/CT in HCC management.

Conflict of interest: The authors declared that they have no conflicts of interest with respect to the authorship and publication of this article.

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