ORIGINAL ARTICLE

Detection of Primary Hepatocellular Carcinoma on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography-computed Tomography

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Abstract

Aims and background: Hepatocellular carcinoma (HCC), ranks as the third most prevalent malignancy contributing to cancer-related death on a global scale. Hepatocellular carcinoma is known to be the fifth most frequently diagnosed malignancy of the males while among females, it is ranked as the seventh most common malignancy. The study was conducted to detect the sensitivity of primary HCC using ^{18}F-flourodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) scan.

Materials and methods: This prospective study was conducted to identify the primary HCC in a sample size of 51 patients, in whom FDG PET-CT scan was performed between May 2022 and December 2022.

Results: Among the cohort of 51 patients, primary HCC was detected on FDG PET-CT in 43 individuals representing true-positive cases. Conversely, FDG PET-CT was unable to detect HCC in 8 cases, representing false-negative. Out of 51 patients, 74.5% of HCC cases exhibited multifocal pattern. The maximum standardized uptake value (SUV max) of the primary malignant site ranged from 1.9 to 16.1, with a mean of 3.7 $\pm$ 2.8. The FDG PET-CT revealed abnormal sites of the uptake outside liver in 23 individuals. The research confirmed the tumor recurrence in four previously treated patients. In the conducted investigation, FDG PET-CT showed 84.3% sensitivity for the diagnosis of HCC.

Conclusion: The study demonstrates that FDG PET-CT is a viable option for the detection of HCC. The sensitivity of FDG PET-CT in our population is comparable and in agreement with international data for diagnosis of HCC thereby favoring its reproducibility among geographical and ethnic groups. However, owing to the reduced ability of FDG PET-CT scan to identify well-differentiated/low-grade HCC, the routine use of FDG PET-CT scan may not be considered in cases requiring evaluation of primary disease only.

Keywords: Computed tomography, Hepatocellular carcinoma, ^{18}F-flourodeoxyglucose positron emission tomography-computed tomography, Sensitivity.

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Introduction

Hepatocellular carcinoma (HCC), sometimes referred to as hepatoma, is the predominant histopathological subtype of primary liver cancer originating from hepatocytes. Additionally, it ranks as the third most prevalent malignancy contributing to death associated with cancer on a global scale. Hepatocellular carcinoma is known to be the fifth most frequently diagnosed malignancy of the males while among females, it is ranked as the seventh most common malignancy.[1] Hepatocellular carcinoma often exhibits intrahepatic and extrahepatic metastasis due to the liver's extensive dual blood supply. Cholangiocarcinoma and hepatocellular carcinoma are the principal categories of primary liver malignancies.[2,3] Hepatocellular carcinoma consistently represents a significant proportion, ranging from 70 to 80% of reported liver cancer incidences annually across the globe. Moreover, this malignancy is responsible for a staggering number of fatalities, resulting in over 600,000 deaths.[4,5] According to the data provided by Globocan, HCC is the eighth most frequent malignancy in Pakistan.[6] Hepatocellular carcinoma prevalence varies between 3.7 and 16% per 100,000 individuals. In Pakistan, viral hepatitis is the most prevailing cause of HCC, which is strongly associated with the development of liver cirrhosis. Hepatitis C virus (HCV) is identified as the predominant etiological factor in 60–80% of HCC cases in local population.[7,8] HCC may be broadly classified into four grades determined by the degree of differentiation: grade I (well-differentiated), grade II (moderate differentiated), grade III (poor differentiated), and grade IV (undifferentiated). The

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measurement of serum alpha protein (AFP) levels is often used for the purpose of HCC detection. The AFP test, however, has a 25–72% reduced sensitivity for the identification of HCC.[9,10] Hepatocellular carcinoma does not require histological confirmation, in contrast to other solid tumors. An average subclinical lifespan of 3.2 years is observed in HCC.[11] During this particular period, imaging plays a pivotal role for noninvasive diagnosis of HCC. Imaging is also utilized for the management of HCC, evaluation of treatment efficacy, and differentiation between HCC and various benign nodules commonly observed in cirrhosis, benign lesions or pseudolesions, intrahepatic cholangiocarcinoma, and liver metastases.[12] Two distinct clinical scenarios are often present while making the diagnosis of HCC. Malignant tumors in individuals without chronic hepatic disease may exhibit substantial size and may exhibit vascular invasion, while also potentially lacking adherence to normal monitoring protocols. The noninvasive diagnosis of higher risk individuals can only be achieved by imaging techniques that include recognizable traits. The observed features on CT and MRI scans include arterial enhancement, followed by washout during the delayed or portal venous phase.[13] The MRI and CT sensitivity is reported to be 100% for the detection of substantial lesions. However, for lesions ranging from 1 to 2 cm in size, the sensitivity declines to around 40–75% for CT and 45–80% for MRI.[14,15] Ultrasonographic identification of HCC is more challenging in individuals with chronic hepatic disease because cirrhotic liver showed the area with fatty infiltration and nodular re-growth. There are some restrictions in the pathological analysis of HCC that CT and MRI do not reveal. PET-CT using ^{18}F-flourodeoxyglucose (FDG) radiotracer is noninvasive and effective nuclear medicine imaging modality that gives structural and functional information at cellular level for the detection of diversity of tumor including HCC. ^{18}F-flourodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) evaluation is dependent on the metabolism of the tumor and it has the advantage of whole body examination. Hence, we can detect intrahepatic and extrahepatic metastasis in a single scan. By using FDG PET-CT, the diagnosis of HCC, histological HCC distinction, and therapy impact monitoring. The detection of primary HCC remains challenging because to the elevated levels of FDG activity seen in normal liver tissue (with an average mean of 1.55) and the liver's substantial non-dietary glucose production rate of 2.0 mg/kg/min.[9] This prospective study was conducted to detect sensitivity of primary HCC by using FDG PET-CT scan. Currently, there exist a scarcity of data regarding the utilization of FDG PET-CT for HCC detection. Additionally, application of FDG PET-CT in cancer diagnosis and staging is relatively uncommon because of limited availability, and thus restricted research has been published using this modality.

Materials and Methods

Patients

The Institutional Review Board (IRB) of FMH College of Medicine and Dentistry has provided clearance as per the letter reference number FMH-23/01/2023-IRB-1178 in accordance with the approval issued by the Institutional Ethical Board. This prospective research comprised a cohort of 51 patients diagnosed with HCC who received[16–18] F-FDG PET-CT scans through May 2022 to December 2022. Individuals who meet eligibility criteria were adults diagnosed with HCC who were verified by the histological examination, HCC detected using CT or MRI, patients newly diagnosed with HCC, or patients with recurrent HCC. The study sample did not include patients diagnosed with malignancy other than HCC, uncontrolled diabetes, and patients with a documented history of severe responses to contrast agents, as well as women who were pregnant or lactating.

FDG PET-CT Image Processing and Acquisition

The medical records of the patient's radiation and chemotherapy treatments were documented. Prior to the commencement of the scan, everyone in the study adhered to a fasting period of maximum 6 hours and exhibited blood glucose levels within the range of 70–140 mg/dL. The administration of FDG necessitated the placement of an intravenous cannula. The patients became free of all metallic items. Before commencing the procedure, patients instructed to empty their bladder. In order to mitigate the potential interference of physiological muscle uptake of FDG, the patients were instructed to abstain from engaging in any kind of physical activity prior to the evaluation. After administering a dose of 10–20 milli-curie of FDG and 7–8 megabecquerel per kilogram of body weight, a PET-CT scan was conducted around 45–90 minutes afterwards. The patients were positioned in a supine posture, ensuring their comfort with their arms elevated and their heads immobilized. Initially, a CT was conducted to determine the anatomical location and adjusted for attenuation. The scan included the region from vertex to the feet using the specified parameters. The imaging parameters used for the scan were a peak kilo-voltage of 120, a milli-ampere-second value of 70, and a slice thickness of 3.75 mm. The scan was conducted utilizing a PET-CT scanner that combines a Discovery STE 16 slice CT scanner with a BGO-PET scanner. Following the completion of a CT scan, a PET scan was then performed on the patient without any movement; use a 3-minute acquisition period for every six to eight bed positions. The duration of the PET-CT scan acquisition for the whole body ranged from 25 to 30 minutes. Following the reconstruction of helical PET and CT data, sagittal and coronal images were generated. The generation of PET-CT images included the fusion of two distinct sets of data.

Interpretation Criteria

The PET-CT images were analyzed to identify a hepatic lesion that exhibited positive uptake of FDG. The quantitative analysis of hepatic lesions with aberrant FDG uptake included the establishment of a region of interest (ROI) that encompassed the area with the highest level of activity. The use of this methodology facilitated the establishment of the SUV for all hepatic lesions. According to EANM procedure guidelines for FDG PET-CT, SUV is calculated using the formula SUV = Act_{VOI}(kBq/mL) $Act_{administered}$(MBq)/LBM(kg).[16] The term "Hypermetabolic HCC" was used when there was a detected rise in FDG uptake relative to the surrounding liver parenchyma, whereas the phrase "Hypometabolic HCC" was utilized when FDG uptake was declined. The patients who indicated HCC in their CT, MRI, and PET-CT scans were diagnosed as true-positives for malignancy. Patients diagnosed with HCC who exhibited positive findings on CT or MRI scans, but negative results on FDG PET-CT were mediated to have had false-negative outcomes.

Statistical Analysis

The data were processed using a software known as IBM-spss v-23. The age variable was quantified as a continuous measure by calculating the mean and standard deviation, while categorical data were represented using frequency and percentage. A significance level of 0.05 was deemed appropriate for determining statistical significance in both types of data. The statistical formula sensitivity =

(TP/TP + FN) was used to examined FDG PET-CT scan sensitivity for the detection of HCC.

Results

The present research included the participation of 51 cases of primary HCC who underwent with ^{18}F-FDG PET-CT scan. The distribution of patient gender was as follows: 10.6% of the patients were female (n = 11), while 78.4% were male (n = 40). The group varied between 32 till 70 years in age, with a mean of 51.8 ± 10.4 years (Table 1; Fig. 1). Within the cohort of patients, it was determined that 90.2% of individuals had liver lesions that were confirmed by CT scans, while 1% of cases were validated using MRI, and 7.8% were verified through histopathological examination.

FDG PET-CT Findings

The technique of transarterial chemoembolization (TACE) was previously used for the treatment of a cohort of four patients, while an additional 47 people were recently diagnosed with HCC. Local tumor recurrence was seen in four patients who had undergone earlier TACE, as shown by the findings from FDG PET-CT scan. Among 43 out of 51 patients, a PET-CT scan demonstrated elevated uptake of FDG by hepatic tumors. The range of primary HCC SUV max values was seen to be between 1.9 and 16, with a mean value of 3.7 ± 2.8. Segment IV had a higher uptake of SUV max, with a mean value of 4.67 ± 3.51 and a p-value of 0.04. The FDG uptake in Segment IV exhibited statistical significance. A total of 74.5% (n = 38) patients among 51 were included in the study, with them presenting with multifocal HCC. The occurrence of HCC exhibited variability across different liver segments. Notably, segment VIII had the largest proportion of HCC cases, accounting for 25.5% of the total. Conversely, segments I and II exhibited the lowest frequencies of HCC, with incidences of 2.0 and 3.9%, respectively (Table 2; Fig. 2). Extrahepatic metastases were correctly detected by FDG PET-CT in a cohort of 23 people. The study reveals the presence of metastasis in many anatomical sites among the patients. Specifically, the evidence of metastasis was shown in the stomach, pancreas, gallbladder, and neck in four patients, accounting for 7.8% of the total sample. Intrathoracic metastasis was identified in

Table 1: Demographic data of study patients

Gender	*Frequency*
Male	78.4%
Female	10.6%
Mean age	51.8 ± 10.4

Table 2: Summary of FDG PET-CT findings

Liver segments	*Frequency*	*SUV Mean ± S.TD*	*p-value*
Segment I	2.0%	2.7 ± 1.20	0.62
Segment II	3.9%	4.05 ± 2.57	0.69
Segment III	9.8%	4.2 ± 2.5	0.36
Segment IV	5.9%	3.04 ± 1.26	0.31
Segment V	13.7%	3.55 ± 1.83	0.79
Segment VI	21.6%	4.67 ± 3.51	0.04
Segment VII	17.4%	4.67 ± 3.82	0.07
Segment VIII	25.5%	4.50 ± 3.37	0.06
Liver lesion		*SUV max*	
Multifocal	74.5%	Mean	3.7 ± 2.8

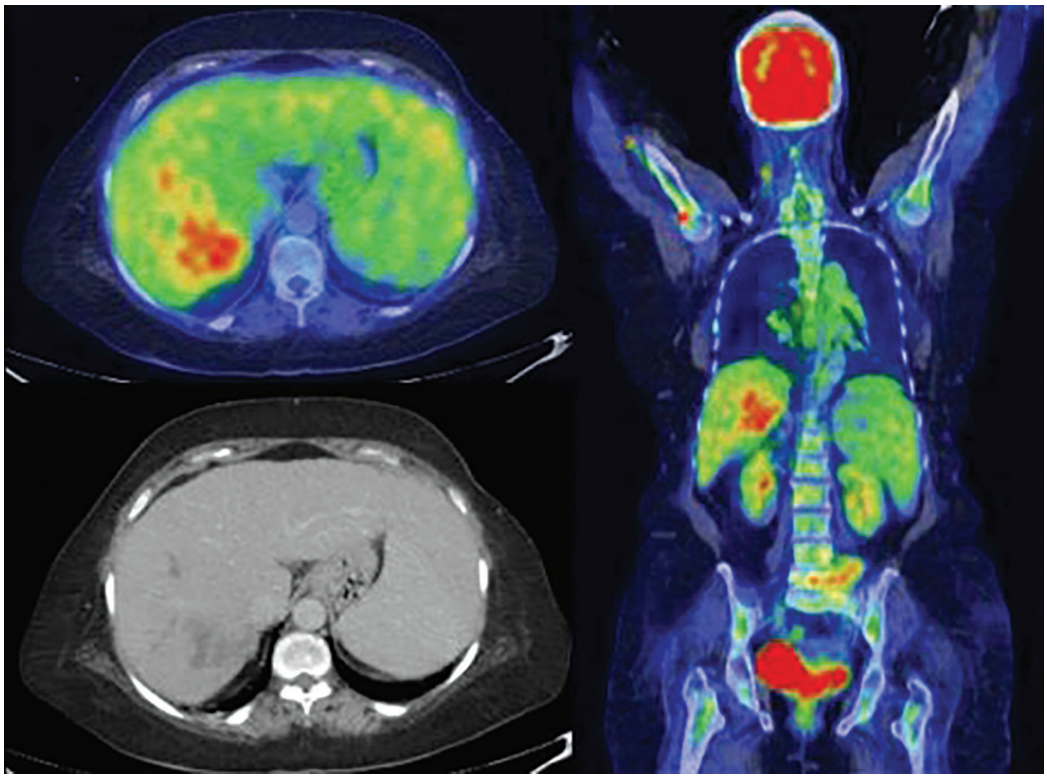
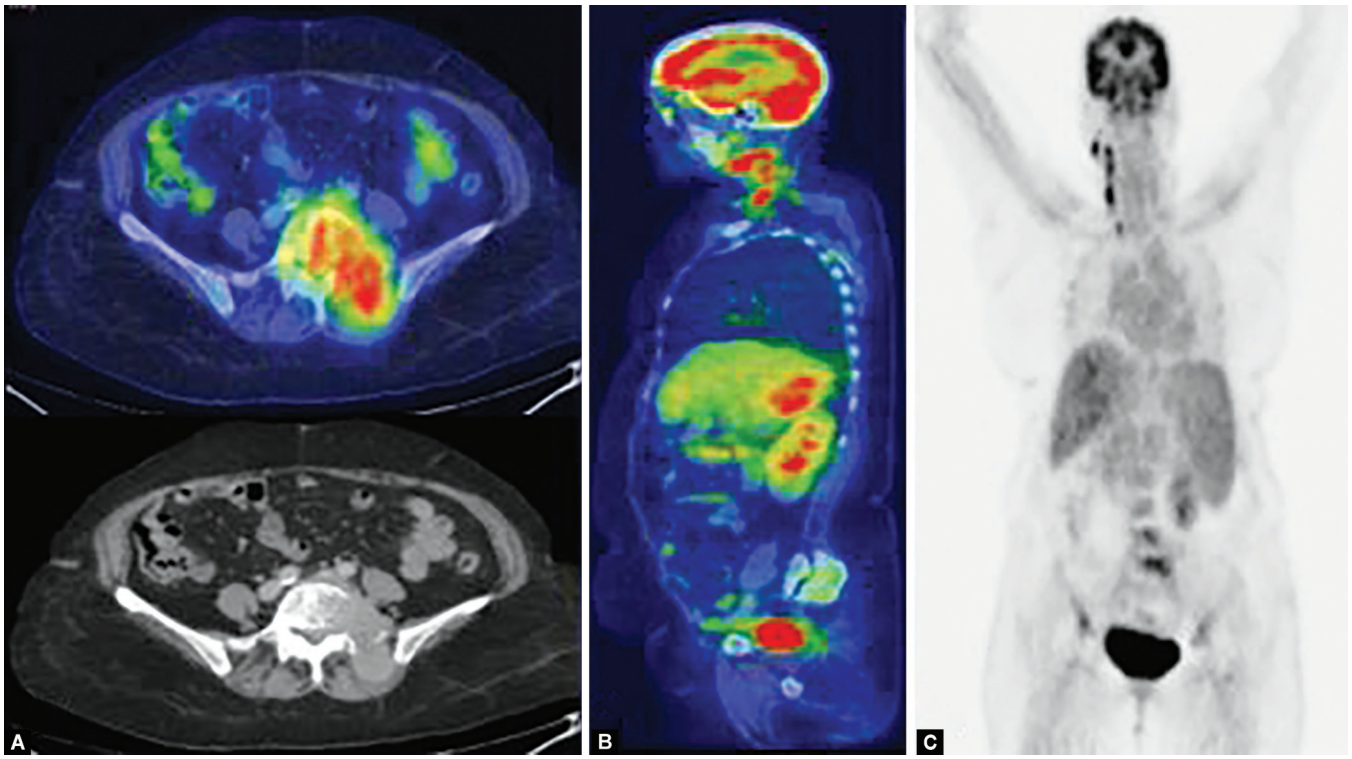


Fig. 1: PET-CT images showing metabolically active hepatic lesions consistent with known hepatocellular carcinoma



Figs 2A to C: (A) Axial PET-CT fused images showing bone metastasis; (B) Sagittal PET-CT fused images showing hepatic lesions and abdominal metastasis; (C) Coronal PET images showing multiple FDG avid skeletal and nodal neck metastasis

Table 3: Sensitivity for detecting HCC using FDG-PET-CT scan

Primary HCC detection on ^{18}F-FDG PET-CT	*No. of patients*	*Frequency*
True positive	43	84.3%
False negative	8	15.7%
Sensitivity 84.3%		

two patients, representing 3.9% of the sample. Furthermore, eight patients (15.6%) exhibited metastasis in right lung nodules, while skeletal metastasis was observed in seven patients, accounting for 13.7% of the sample. Additionally, nine patients (17%) revealed abdominal lymph node metastasis. The patients were categorized into two separate groups based on the degree of difference with high differentiation ($n = 8$) and poor differentiation ($n = 43$). The identification of overall HCC was achieved in 43 out of 51 cases through FDG PET-CT scan, indicating an actual positive result. In eight cases characterized by well-differentiated HCC, the detection of the HCC was unsuccessful with FDG PET-CT, resulting in false-negatives. Based on the findings of this investigation, the calculated sensitivity of FDG PET-CT was determined to be 84.3% for detecting HCC (Table 3).

Discussion

The prevalence of HCC has been shown to be as high as 80% in the regions of South-East Asia and Africa. Current study population is situated in a geographical area characterized by intermediate prevalence rates of HCV and HBV.[17,18] Due to lack of awareness about the risk factors and limited screening for HCC which is around 8.2%, mostly, the individuals are identified when they exhibit symptoms due to advanced HCC; hence, they were not considered eligible for definitive treatment. Nevertheless, the existing data on HCC in local population is constrained, mostly consisting of observations from a solitary institution with a restricted number of participants, predominantly focusing on viral-related HCC. Moreover, there is a lack of relevant data about the frequency and prognostic variables associated with viral marker negative HCC in Pakistan.[19,20]

Management of HCC can be done through a number of medical procedures that are available locally, including liver resection, loco regional therapy, transarterial chemoembolization, transarterial radioembolization, and immunotherapy. The overall survival of patients with HCC has improved over shorter duration due to these treatment options, but the risk of recurring illness persists.[21]

Specifically, the FDF PET-CT has been found to be an efficient imaging technique in the management and identification of HCC, especially in cases when hepatic resection and liver transplantation are being considered. FDG PET-CT is beneficial for multiple purposes, including the diagnostic work-up and decision of treatment of HCC, initial staging of the disease, and the assessment of therapeutic effectiveness.[22]

However, there are no published data from Pakistan available evaluating the pattern of uptake and frequency of HCC detection on FDG PET-CT scan. The current study is an attempt to share the experience of a high reference institution regarding the diagnostic efficiency of FDG PET-CT among patients of HCC. The research was expected to identify the potential value of FDG PET-CT in local settings where the HCC incidence is rising in concordance

with global pattern due to rising exposure to risk factors, an aging population, and lifestyle modifications, including alcohol consumption and metabolic liver disease.[23]

Hepatocellular carcinoma in the early stages often do not exhibit any symptoms, and are mostly detected via routine monitoring. Diagnosing the condition upon manifestation of symptoms enhances the likelihood of encountering a more progressed stage of the disease. According to the findings of our research, it was observed that 84.3% of the patients exhibited infiltrative and poorly differentiated HCC. The findings of our study align with the research done by A Butt et al., who indicated that a significant proportion (62.8%) of Pakistani patients exhibited advanced or infiltrative HCC as a consequence of inadequate monitoring measures.[19]

Based on our research results, the average patient's age was determined to be 51.8 years. These data suggest a higher incidence of HCC among older individuals, with males exhibiting the greatest prevalence. A research investigation conducted by A Bhatti et al. demonstrates consistent results, indicating an elevated male to female ratio and an increased incidence of HCC among individuals aged 55–80 years.[17]

It is vital to possess knowledge about the distinct imaging properties of HCC and other types of liver malignancies in order to effectively strategize for pre-study preparation. The routine application of FDG PET-CT however remains a subject of controversy for the diagnosis of HCC. In the present analysis, the sensitivity of FDG PET-CT scan was evaluated either through comparison with histopathology or by comparing with CT and MRI scans that detected HCC in these patients. Using an FDG PET-CT scan, the overall HCC was identified among 84.3% individuals. In 15.7% individuals with well-differentiated HCC, FDG PET-CT failed to detect the disease, it is seen that FDG PET-CT exhibits a sensitivity of 84.3% for the identification of HCC. This sensitivity value is comparable to the results reported by Kim et al., who demonstrated an 87.6% sensitivity in detecting HCC by PET-CT imaging.[24]

In few previously published articles, the reported sensitivity of PET-CT for the identification of disease is as low as 55%.[25] The analysis done by Park et al. yielded the sensitivity of FDG PET-CT in diagnosing poorly differentiated disease which was 60.7%, whereas for highly differentiated HCC, it was 39.3%.[26]

Current research's detection rate is greater than that of the study by Abdelhalim H et al., which indicated a sensitivity of 76.5%.[22] The augmented detection rate in the present research may be attributed to a larger cohort of patients diagnosed with poorly differentiated HCC, as well as variations in the sample size.

The amount of FDG that accumulates in HCC exhibits variability based on the tumor's histological differentiation. Well-differentiated HCC has a poorer glucose metabolism compounded with relatively with poor FDG uptake. Conversely, HCC with poor histological differentiation has elevated FDG uptake and increased glucose metabolism. Since the physiological pattern of higher FDG activity in normal liver parenchyma and the fact that well-differentiated HCC exhibits FDG uptake analogous to that of normal hepatic cells, the PET-CT demonstrates relatively poor sensitivity in such cases. The findings of the current study also favors a limited sensitivity of FDG PET-CT in detecting well-differentiated HCC. These results align with the conclusions drawn by Trojan et al., who similarly reported that FDG PET-CT does not offer significant utility in identifying well-differentiated HCC.[27]

The uptake of FDG serves as an accurate and reliable indicators for the existence of tumors. The use of SUV max allows for the quantitative assessment of both tumor histology and FDG absorption. According to the findings of many researchers, the SUV max of primary HCC varied from 1.9 to 14.[28] Primary SUV max in the current study showed a similar pattern (mean 3.7 ± 2.8) varied from 1.9 to 16. Those diagnosed with positive HCC had significantly elevated SUV max levels in comparison to those diagnosed with negative HCC.

By unique virtue of combining the CT-based cross-sectional anatomical details with the metabolic map, the application of FDG PET-CT has expanded to include the evaluation of many malignant conditions. For HCC patients, the advantages include the assessment for candidature of local therapy, evaluation of response to such targeted therapies and detection of extrahepatic extent which is crucial prior to liver transplantation. In contrast to morphological imaging techniques, such as ultrasonography, CT, and MRI, FDG PET-CT determines the tumor viability as indicated by the degree of glucose metabolism and thus is independent of tumor morphology or lipiodol deposition. Previous published data yielded the finding that FDG PET-CT demonstrated better accuracy and sensitivity as compared with CECT in the detection of HCC recurrence subsequent to TACE. However, the presence of the beam hardening artifact caused by the high-attenuation lipiodol on CT scans may indeed impede the accurate identification of live tumors inside the lesion. Following TACE, the feeding arteries associated with the remaining tumor exhibit a notable reduction in thickness, which subsequently impacts the extent of tumor amplification. CECT may be able to conceal increased tumor activity because of the presence of highly dense lipidol.[29,30] The current analysis examined a cohort of four cases who had previously had TACE therapy, and it was found that the recurrence of tumors may reliably be detected using FDG PET-CT scans.

Based on this research, 75.4% of the patients had multifocal liver lesions that affected several liver segments. Segment VIII (25.5%) was most consistently impacted, whereas segments I and II had the lowest occurrences of afflicted segments, at 2.0 and 3.9% respectively. According to a study performed by Farahat et al., segments I and II were found to be the least affected segment, accounting for 6.7% of the total impact. Conversely, segment VIII was identified as the most significantly affected segment, representing 26.7% of the overall impact.[31]

The FDG PET-CT technique is considered the most pragmatic approach for detecting extrahepatic metastases. In the course of my research, it was determined via the use of FDG PET-CT that 23 people had extrahepatic metastases. The lungs and the abdominal lymph node are recognized as the two most prevalent locations for extrahepatic metastases. According to the published data, the FDG PET-CT whole body scan has found to exhibit better accuracy in comparison with other diagnostic modalities, such as X-rays, CT scans, and MRI in the identification of pulmonary sites, as well as intrathoracic and abdominal lymph nodes.[32]

Limitations

Our study has limitations that we included only positive patients of HCC. Although the sample size is small, it is similar to other

published studies because there are few cases of HCC studied with FDG PET-CT.

Conclusion

This study demonstrates that FDG PET-CT is a viable option for the detection of HCC in local settings. The PET-CT has demonstrated sensitivity comparable to internationally published research for detecting primary HCC in our population as well, mainly owing to greater capability for detecting high-grade HCC. However secondary to the reduced ability of FDG PET-CT scan to identify well-differentiated/low-grade HCC, the routine use of FDG PET-CT scan may not be considered for the evaluation of primary disease only.

Clinical Significance

The clinical value of contemporary research is vital for the progression of healthcare. Through the use of this study, medical practitioners will better understand the clinical use of the hybrid imaging techniques, which have been shown to provide crucial information for the precise detection of primary liver malignancy and its metastasis. The current study also contributes to the mitigation of healthcare expenses.

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