SUV_{max} as Predictor of Metastatic Disease on ^{18}F-FDG PET-CT in Hepatocellular Carcinoma

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ABSTRACT

Objective: To ascertain the utility of maximum standardised uptake value (SUV_{max}) in ^{18}F-FDG PET-CT in predicting metastatic disease burden in hepatocellular carcinoma (HCC) patients.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Nuclear Medicine and PET-CT Imaging, Institute of Nuclear Medicine and Oncology (INMOL), Lahore, Pakistan, from April to October 2022.

Methodology: ^{18}F-FDG PET-CT data of 87 patients were analysed prospectively. Patients were considered regardless of resection status. The SUV_{max} measurements were performed, and their association with metastases was determined. Molecular docking studies were conducted to determine a mechanism behind the higher SUV_{max} at the metastatic sites.

Results: A higher number of patients (49) was found to have metastasis (1 to 5 in numbers) and demonstrated higher SUV_{max}, especially in cases of pre-surgery and post-transplant state. A positive correlation existed between SUV_{max} of pre-surgery ($r = 0.419$, $p = 0.001$) and post-transplant patients ($r = 0.779$, $p = 0.001$). Molecular docking studies revealed a strong binding affinity (-5.18± 0.25 kcal/mol) between the hexokinase (HK-II) and ^{18}F-FDG.

Conclusion: SUV_{max} positively correlated with metastatic tumour burden. The strong binding affinity between the HK-II and ^{18}F-FDG may be the reason. ^{18}F-FDG PET-CT appeared beneficial in providing prognostic information for HCC in a selected group.

Key Words: *Hepatocellular carcinoma, ^{18}F-FDG, Positron emission tomography, Maximum standardised uptake value, SUV_{max}, HK-II binding, PET-CT, Metastases.*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most frequent aetiology of cancer-associated fatalities and ranked as the sixth most prevalent malignancy in the world.[1] In Pakistan, statistics from a recognised hospital-based data registry show that HCC incidence has gradually increased, accounting for 10.7% of all malignancies.[2] Only 10% of people with risk factors pre-disposing to HCC have access to routine screenings, and most patients are detected relatively late.[3] HCC patients usually have a poor prognosis, and because of the many variables, including the tumour stage, alpha-fetoprotein (AFP), portal vein thrombosis, Child-Pugh score, and an increased likelihood of recurrence, estimating life expectancy is challenging.[4]

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Detecting metastases and actual tumour burden in patients of HCC in early stages is crucial for effective treatment or, at minimum, improving quality of life. The diagnostic parameters in some serological and imaging techniques have been suggested that can estimate tumour burden and show association with the prognosis in HCC patients.[5]

Contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) are commonly used in HCC patients. Positron emission tomography (PET) is a hybrid imaging modality that uses positron-emitting markers labelled with 2-deoxy-2-[18F] fluoro-D-glucose (^{18}F-FDG), a glucose analogue. The dividing and growing cells experience a rise in ^{18}F-FDG uptake because of the rapid glucose metabolism.[6] ^{18}F-FDG PET, in addition to being a whole-body technique, when fused with CT, has high sensitivity in diagnosing and staging malignancies and is utilised as a response assessment tool in managing patients. However, the diagnostic performance of ^{18}F-FDG PET-CT is restricted in HCC because of an inconsistent pattern of ^{18}F-FDG uptake.

^{18}F-FDG accumulation in HCC is heterogeneous depending on the histopathological differentiation of the tumour, and thus ^{18}F-FDG PET-CT has demonstrated a sensitivity of 50-70% for identifica-

tion of primary HCC.[7] Poorly differentiated HCC shows increased ^{18}F-FDG uptake as compared to well-differentiated variety, and it aids in the identification of the distant metastases as poorly differentiated type is more prone to metastasise.[8] The degree of differentiation and degree of FDG uptake by the primary tumour are closely related. ^{18}F-FDG PET-CT imaging has been associated with a degree of differentiation of malignant cells and seemed to provide the risk of tumour relapse and longevity in the HCC patients who underwent surgical resection.[5] The ^{18}F-FDG PET-CT is ranked higher as compared to other techniques in identifying occult metastases and is more accurate as compared to CT in differentiating intrahepatic malignancies (88.9% *vs.* 81.5%).[6] This study analysed the maximum standardised uptake value (SUV_{max}) on ^{18}F-FDG PET-CT among HCC patients and any variation in these values as an indicator of metastatic disease. Also, the possible molecular mechanism was determined behind ^{18}F-FDG accumulation in HCC through computerised molecular docking studies. Keeping in view the metabolic analytical ability of FDG PET-CT, the aim of this study was to ascertain the utility of maximum standardised uptake value (SUV_{max}) in ^{18}F-FDG PET-CT in predicting metastatic disease HCC patients and identify it as a biomarker for metastatic HCC.

METHODOLOGY

A total of 90 patients underwent ^{18}F-FDG PET-CT for HCC at INMOL Hospital during the study period of six months i.e. April to October 2022. The inclusion criteria were adult patients who had confirmed diagnosis of HCC and those who had given consent were included in the study. Patients with dual malignancies were excluded from this study. After applying the inclusion and exclusion criteria, eighty-seven consecutive patients with HCC were analysed.

Each patient had undergone a conventional diagnostic work-up, CECT and was then referred for ^{18}F-FDG PET-CT. Fifty-six patients were referred for ^{18}F-FDG PET-CT before starting their treatment; fourteen patients had liver transplants, and seventeen underwent TACE out of these eighty-seven patients. All enrolled patients provided prior informed consent, and the institution approved the study protocol.

^{18}F-FDG PET-CT scans were acquired on the Discovery XT GE healthcare machine according to the EANM 2.0 guidelines.[9] Patients received 2.7 MBq/kg of radiotracer intravenously with a fasting serum glucose reading <200mg/dl. Both sets of PET and CT images were viewed in isolation and fusion modes using the Fusion software ADW 4.4 version (GE Healthcare), as shown in Figure 1, which also indicates a focal hypermetabolic lesion in the spleen consistent with metastatic HCC. The SUV_{max} values were evaluated by drawing rectangular regions of interest over the pathological sites showing high FDG uptake in liver and metastatic sites.

Molecular docking is a renowned method for determining small molecules' optimal orientation and receptor binding affinity.[10,11] HCC proteins and the ^{18}F-FDG were molecularly docked using free, open-source software, including AutoDockVina from PyRx Virtual Screening and BIOVIA Discovery Studio 2017. (San Diego, CA). Calculations of energy (kcal/mol) and binding affinity were performed using the AutoDockVina screening software. The BIOVIA Discovery Studio 2017 was used for virtual investigation. All water molecules and cofactors were omitted. A ligand library was created after the three-dimensional (3D) structures were collected from the protein data bank (PDB). Eventually, docking investigations were conducted once all structures were optimised using energy minimisation.

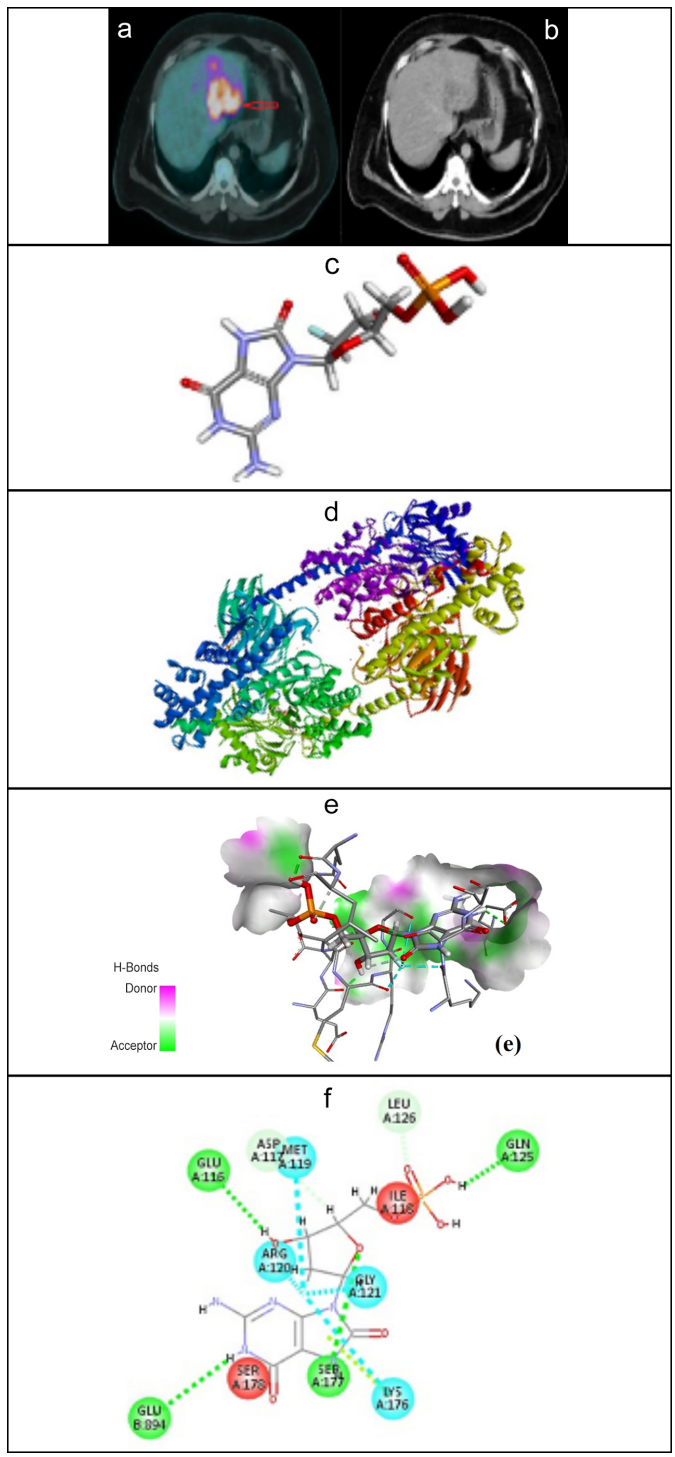

Figure 1: (a) Fused axial PET-CT image of HCC demonstrating high uptake of ^{18}F-FDG in HCC (b) Axial CT image at the same level, (c) Structure of ^{18}F-FDG (d) Structure of human hexokinase-II (e) H-Bonds donor and acceptor regions and (f) key interactions between HK-II and ^{18}F-FDG.

Table I: Analysis of number of metastasis and SUV_{max} value.

Patient Groups	N	Mean Rank	Sum of Ranks	Asymp. Sig. (2-tailed)
Patients SUV (without Metastases)	38	37.25	1415.50	0.028
Patients SUV (with Metastases)	49	49.23	2412.50	
Total	87			
Pearson Correlation		**N**	**Correlation**	**Sig. (2-tailed)**
1. Patients SUV and Number of Metastases		87	0.486	0.000
2. Pre-surgery SUV and Number of Pre-surgery Metastases		56	0.419	0.001
3. Post-Transplant SUV and Number of Post-Transplant Metastases		14	0.779	0.001
4. Post-TACE SUV and Number of Post-TACE Metastases		17	0.297	0.247

The Mann-Whitney test shows patients with evidence of metastasis have higher mean rank correlated with higher SUV_{max} value and Pearson Correlation between the SUV_{max} and number of metastases.

Both parametric and non-parametric different statistical models were used for data analysis. Pearson correlation was found for the parametric data, which included the correlation of SUV_{max} to the total number of metastases in a patient. The p-values <0.05 were statically significant in all patients. The Mann-Whitney U test was conducted for the non-parametric data, which included the correlation of SUV_{max} with whether any evidence of metastatic disease is present in a patient. SPSS version 15.0 software was used. The calculations were performed for both confidence levels of 95% and 99%. The results showed that 73 patients were required for the 95% confidence level and 80 patients for the 99% confidence level analysis. Therefore, for this study, and considering possible dropouts the data were analysed for the maximum number of patients as possible, which was 87.

RESULTS

Of the 87 patients with an average age of 53±9.7 years, 72 (82.76%) were males and 15 (17.24 %) were females, demonstrating an SUV_{max} mean value of 3.48. Fifty-six were pre-surgery cases with a mean SUV_{max} value of 3.45, fourteen were post-transplant cases with a mean SUV_{max} value of 3.67, and seventeen were post-TACE patients with a mean SUV_{max} value of 3.05.

To confirm an association between SUV_{max} and the evidence of metastases, the patients were divided into two groups: patients without any evidence of metastases (38 patients) and patients with a confirmed metabolic disease (49 patients). Then, using the Mann-Whitney test, it was confirmed that the patients with evidence of metastasis have higher mean rank (Table I) correlated with higher SUV_{max} values, demonstrating a statistically significant (p=0.028) difference between the two groups.

Of forty-nine patients with metastases, the total number of metastases for each patient was also counted. This number ranged from 1 to 5, as no patient had more than 5 metastatic sites. Among eighty-seven patients, 38 patients (43.67%) had no metastases, 29 patients (33.33%) had 1 metastatic site only, 15 patients (17.24%) had 2 metastatic sites, 2 patients (2.29%) had 3 and 4 metastatic sites, whereas only 1 patient (1.14%) had 5 metastatic sites. No patient had more than 5 metastatic sites. The Pearson correlation indicated that the SUV_{max} positively correlated to the total number of metastases ($r = 0.486$, $p < 0.001$). The Pearson correlation results indicated a moderately positive correlation present between the SUV_{max} value, suggesting that as the SUV_{max} increases, there is a good probability that there is an increased risk of metastases, as shown in Table I.

The SUV_{max} of pre-surgery, post-transplant, and post-TACE cases was also evaluated to find a correlation between the SUV_{max} and metastases evidence. This analysis would help to determine the usefulness of ^{18}F-FDG PET-CT as a predictive or diagnostic parameter for HCC metastases shown in Table I. First, the Pearson correlation analysis was conducted for the pre-surgery patients. The results were statistically significant and indicated a moderately positive correlation between SUV_{max} and the number of metastases ($r = 0.419$, $p = 0.001$), suggesting that as the SUV_{max} increases, there is a good probability that there is an increased risk of metastases. More interestingly, when the Pearson correlation analysis was repeated for the post-transplant patients, the results showed a statistically significant strong positive correlation between SUV_{max} and the number of metastases ($r = 0.779$, $p = 0.001$). This strong positive correlation suggests that SUV_{max} value as a diagnostic or predictive method for metastasis may be more suitable in the case of post-transplant patients. However, in the case of post-TACE patients, the Pearson correlation analysis showed a weak positive correlation between SUV_{max} and number of metastasis, nevertheless, the results were not statistically significant ($r = 0.297$, $p = 0.247$). This suggests that SUV_{max} might not be an ideal predictive tool for post-TACE patients.

Evaluation of the affinity between HK-II and ^{18}F-FDG was performed to identify the cause for the binding affinity between the two molecules to understand the underlying reason for the accumulation of ^{18}F-FDG in HCC tumour cells. The average molecular binding energy between HK-II and the ^{18}F-FDG was found to be -5.18± 0.25 kcal/mol. The studies were also conducted to propose the binding site, bond length, and interactions between HK-II and ^{18}F-FDG (shown in Figure 1). It was found that different interactions, such as conventional hydrogen bonds and halogen interactions, exist between HK-II and ^{18}F-FDG, as shown in Table II. ^{18}F-FDG could interact with HK-II through SER-177, GLU-894, GLU-116, LEU-126, ASP-117, MET-119, GLY-129, and LYS-176. In general rule, the shorter the bond distance the stronger will be the bond interaction between the two molecules. ASP-117 and GLU-116 showed the strongest hydrogen bonding interaction with the ^{18}F-FDG. The details of the interaction positioning and the bond length present between each interaction are given in Table II.

Table II: Interaction details between the HK-II and ^{18}F-FDG, their category and the bond distance.

Name	Category	Distance A°
A:SER177:OG - FDG:O20	Hydrogen Bond	3.01681
FDG:H25 - B:GLU894:OE1	Hydrogen Bond	2.78411
FDG:H32 - A:GLU116:O	Hydrogen Bond	1.89548
A:LEU126:CA - FDG:O23	Hydrogen Bond	2.25461
FDG:H33 - A:ASP117:O	Hydrogen Bond	1.91025
A:MET119:O - FDG:F16	Halogen	2.75542
A:GLY121:O - FDG:F16	Halogen	3.55288
A:LYS176:O - FDG:F16	Halogen	2.68532

DISCUSSION

As an indicator of metabolic activity, ^{18}F-FDG PET-CT has the prime advantage in the work-up and follow-up of malignant diseases by providing a map of metabolic activity in the tumour and distant locations of metastasis. Due to the increased expression of glucose transporters (GLUT-2) and hexokinase-II (HK-II) activity, most cancers rely on glucose as their prime energy source.[12] Many studies have reported moderate ^{18}F-FDG uptake and strong expression of GLUT-2 and HK-II in the case of hepatocellular carcinoma.[13,14] Hexokinase effectively phosphorylates ^{18}F-FDG to ^{18}F-FDG -6 phosphate by binding to the mitochondrial membrane and phosphorylation prevents ^{18}F-FDG from exiting the cell leading to accumulation there instead.[11,15] This entrapment in tumour cells provides a map of metabolic activity when imaged and enables use of docking studies.

Normal hepatocytes have a high concentration of glucose-6-phosphatase and a low concentration of hexokinase, but HCC cells have the opposite ratio. ^{18}F-FDG can concentrate in HCC but not in healthy cells due to this imbalance.[16] According to reports, the sensitivity of ^{18}F-FDG PET-CT for HCC detection varies from 50 to 70% depending on the amount of this enzyme present in HCC cells.[17] CT and MRI perform better in HCC detection, yet they cannot distinguish well-differentiated from poorly-differentiated HCC. The variability of ^{18}F-FDG uptake has been linked to the differentiation and mitotic activity of HCC, and as biopsy is not the gold standard in cases of HCC, ^{18}F-FDG PET-CT may be utilised as a non-invasive tool for assessing tumour features and behaviour.[18,19]

The present study evaluated SUV_{max} values' usefulness in ^{18}F-FDG PET-CT predicting the prognosis of metastatic disease in HCC. Figure 2 shows an image of a patient with HCC and metastases at various sites. A higher SUV_{max} showed increased evidence of metastatic disease in pre-surgery and post-transplant patients. However, only a moderately positive correlation was found in post-TACE patients, considering that the TACE is offered only to patients without any biochemical and image-based evidence of metastasis. Post-transplant patients showed a strong positive correlation between SUV_{max} and metastases, favouring its use as a diagnostic tool to determine the potential of HCCs recurrence or metastasis. These results also correlate with other studies that found a relationship between SUV_{max} and a higher incidence of metastases for diagnosis.[4]

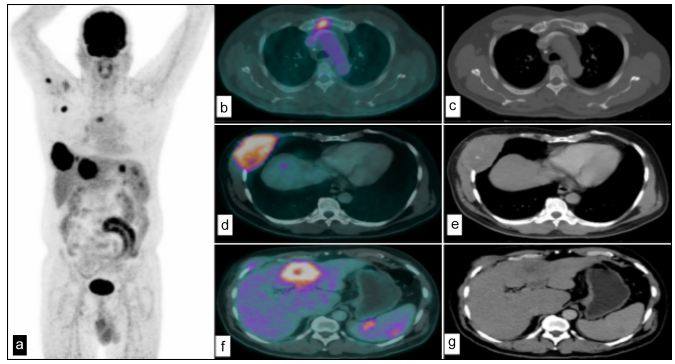

Figure 2: (a) MIP image of a patient with HCC and metastases at various sites. (b) Fused axial PET-CT image with metastatic hypermetabolic focus in sternum. (c) CT image showing a lytic focus in sternum. (d) Fused axial PET-CT image showing hypermetabolic soft tissue density mass involving right sided ribs and intercostal muscles. (e) CT image showing soft tissue density mass involving right sided ribs and intercostal muscles. (f) Primary hypermetabolic HCC lesion in liver. (g) CT image showing irregular shaped hypodense area in liver-primary HCC.

The SUV_{max} has been shown as one of the critical prognostic indicators.[20] Thus, an analysis of ^{18}F-FDG binding affinity with enzymes responsible for its metabolism in the tumour cells was done. The metabolic activity of a tissue can be ascertained from the quantity of ^{18}F-FDG collected in the tissue over a specific time. ^{18}F-FDG accumulation strongly relies on GLUTs and the rate-limiting glycolytic HK-II in most malignancies.[11,21] For effective glucose consumption, it is critical to have enough HK-II protein, particularly in the mitochondrial bond form in cancer cells. In HCC, for example, mitochondrial-bound hexokinase can represent approximately 70% of the total cellular hexokinase, whereas the amount on the mitochondria of normal liver cells is negligible.[22] Therefore, this study conducted molecular docking-based virtual screening between ^{18}F-FDG and HK-II to better understand the possible mechanism behind the ^{18}F-FDG uptake in the tumour cells. The results reported strong binding energy between the molecules of ^{18}F-FDG and HK-II.

Upon binding of a molecule to a target, the total energy of the complex is reduced due to the release of binding energy. Also, any modification of the ligand brought on by its minimum energy in relation to its conformation when bound to the macromolecule is made up for by the release of energy equal to its binding energy. Thus, a ligand has a stronger propensity to connect with a given macromolecule, the more energy is generated during the binding process.[23,24] The negative binding energy suggests that the ^{18}F-FDG was bound to HK-II spontaneously without needing any energy. Furthermore, the hydrogen interactions also existed between the ^{18}F-FDG and HK-II, which indicates why ^{18}F-FDG is accustomed to being bound with HK-II and entrapped in the tumour cells, which eventually results in higher SUV_{max} values. The docking studies in the study population were not performed to show a difference in SUV_{max} uptake values among groups of patients with well-differentiated and poorly differentiated carcinoma, as histopathology of all patients was unavailable. However, docking studies have been performed by Song *et al*. to vali-

date that poorly differentiated HCC hexokinase expression increases, leading to high ^{18}F-FDG uptake and retention in cells, explaining the possible reason behind the higher SUV_{max} in these patients.[25,26]

Further studies involving patients from multiple centres and longer follow-up is suggested to validate these findings. The study population was heterogeneous, comprising pre-surgery, post-transplant, and post-TACE patients due to time constraints. Docking studies could not show a difference in SUV_{max} in patients with well-differentiated and poorly differentiated HCC because histopathology of all patients was not available.

CONCLUSION

A positive correlation was demonstrated between the SUV_{max} and the HCC metastases and suggested that ^{18}F-FDG PET-CT can be presented as a predictive marker to diagnose the metastases of HCCs. The mechanism behind the higher SUV_{max} in tumour cells is likely to be a higher affinity for HHC- II binding in HCC metastases sites.

ETHICAL APPROVAL:

The present study was approved by the Ethics Committee of the Institute of Nuclear Medicine and Oncology, Lahore, Pakistan.

PATIENTS' CONSENT:

All enrolled patients provided prior informed consent.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MNY, WA: Conception, design of the work, and drafting the manuscript.
WA, KR: Data collection, data analysis, and interpretation.
MNY: Critical revision of the manuscript.
AS, MNY: Study supervision, funding, and materials, etc.
All authors approved the final version of the manuscript to be published.

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