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Diagnostic Utility Of [18f] Psma-1007 Pet/Ct In Patients with Hepatocellular Carcinoma

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Abstract

HCC is the most common primary liver malignancy in Mexico. Cirrhosis is the most significant risk factor. PET-CT with 2-[18F] Fluorodeoxyglucose (2-[18F] FDG) has limited sensitivity (40-50%) for early-stage detection, prompting the search for alternative radiotracers. PSMA has demonstrated diagnostic potential due to its expression in tumor- associated vasculature. PSMA has been proposed as diagnostically equivalent to 2- [18F] FDG in HCC patients.

This study evaluated the diagnostic efficacy of [18F] PSMA-1007 PET-CT versus 2- [18F] FDG in nine patients with HCC confirmed by CT and pathology reports (study No. 2019/0110). Visual analysis determined study positivity, SUV-max values, and tumor-to- background ratio (T/N). A chi-square test assessed the association between tumor differentiation and tracer uptake. Results indicate that [18F] PSMA-1007 PET/CT is an effective non-invasive imaging tool for HCC, aiding in histological grading.

Keywords: Hepatocellular Carcinoma, [18F] PSMA-1007, 2-[18F] FDG, Medical Imaging.

Abbreviations

HCC: Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the leading primary liver cancer and a major cause of cancer-related mortality worldwide. In developed countries like the United States, HCC ranks as the ninth leading cause of cancer-related deaths. In Mexico, HCC-related mortality increased from 4.16 per 100,000 inhabitants in 2000 to 4.74 per 100,000 in 2006. Despite advances in prevention, diagnosis, and treatment, HCC incidence and mortality continue to rise. Cirrhosis remains the most significant risk factor, regardless of etiology. Chronic hepatitis B and C infections are also independent risk factors. Prognosis varies by disease stage, with five-year survival rates ranging from 70% in early stages to <20% in advanced stages.

Tumor classification considers size, vascular invasion, lymph node involvement, and metastasis. Imaging modalities for detection include ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), alongside serological markers like alpha-fetoprotein (AFP), monitored every six months. Treatment options vary, but only orthotopic liver transplantation (OLT) and surgical resection offer curative potential. OLT is available for patients meeting Milan or University of San Francisco criteria.

This study aims to determine the potential of [18F] PSMA-1007 PET-CT in HCC patients through a comparative analysis with 2-[18F] FDG, potentially offering a novel diagnostic tool for early detection and a theranostic approach based on PSMA targeting.

Materials and Methods

A descriptive, cross-sectional, and retrospective study was conducted by reviewing electronic medical records of patients diagnosed with HCC who underwent PET-CT with 2-[18F] FDG and [18F] PSMA-1007 between January 2016 and August 2019.

Collected variables were analyzed using Microsoft Excel. PET-CT scans were evaluated by nuclear medicine specialists. Descriptive statistical analyses were performed. Nominal variables were expressed as frequencies and percentages, while continuous variables were reported as means and standard deviations or medians and percentiles, depending on distribution. Statistical analysis was conducted using IBM SPSS version 22.

Results

Data were collected from 12 patients who underwent PET-CT with 2-[18F] FDG and [18F] PSMA-1007 within the study period. Nine patients (75%) met inclusion criteria.

Baseline characteristics (Table 1) include a mean age of 53.5 years (range: 24-71), with five male (56%) and four female (44%) patients. Post-PET-CT evaluation revealed four non- metastatic and five metastatic cases. PET-CT images were acquired for all nine patients using both radiotracers.

Table 1: Demographic Characteristics of Population

CHARACTERISTICS	n = 9
Age in years (mean + SD)	53.5 + 20.01 (24-71)
Sex Female	4 (44%)
Male	5 (56%)
Histological Grade of HCC Grade I/II	6
Grade III/IV	3
Non-metastatic	4 (44%)
Metastatic	5 (66%)
Regional Lymphadenopathy	1
Non-regional Lymphadenopathy	4
Extranodal Metastases Lung	2
Bone	1
Soft Tissue	1

Qualitative Variables Reported in Frequencies and Percentages. Quantitative Variables Reported in Means and SD.

Table 2: Biodistribution of [18F] PSMA-1007 y 2-[18F] FDG

PSMA	FDG
Tear glands Salivary glands Liver Spleen Kidneys	Brain parenchyma Waldeyer's ring Soft tissues Muscular system Left ventricle Intestine
Elimination via biliary, intestinal and urinary tracts	Elimination through urinary tract

Table 3. Suvmax And T/N Ratio of the Different Histological grades of HC in PET/CT with [18F]PSMA-1007 and 2-[18F] FDG (n=9)

PSMA	GRADE I (n=2)	GRADE II (n=4)	GRADE III (n=2)	GRADE IV (n=1)
SUVmax Lesion	24.97 + 13.25	21.54 + 9.38	2.50 + 0.42	9.7
SUVmax Liver	7.65 + 0.63	10.0 + 5.23	13.85 + 9.54	14.17
Tumor/Normal Tissue Index (T/N)	3.34 + 2.01	3.0 + 2.20	0.25 + 0.20	0.68
Diameter (mm)	36.5 + 0.70	63.5 + 15.84	114.5 + 26.16	21

FDG	GRADE I (n=2)	GRADE II (n=4)	GRADE III (n=2)	GRADE IV (n=1)
SUVmax Lesion	3.81+ 0.69	6.2 + 3.34	17.9 + 6.03	11.9
SUVmax Liver	2.67 + 0.03	2.75 + 0.95	3.15 + 0.35	3.79
Tumor/Normal Tissue Index (T/N)	1.42 + 0.24	2.38 + 1.13	5.83 + 2.57	3.14
Diameter (mm)	36.5 + 0.70	63.5 + 15.84	114.5 + 26.16	21

A) PSMA (+) B) FDG (-) C) PSMA (-) D) FDG (+) E) PSMA (+) F) FDG (-)

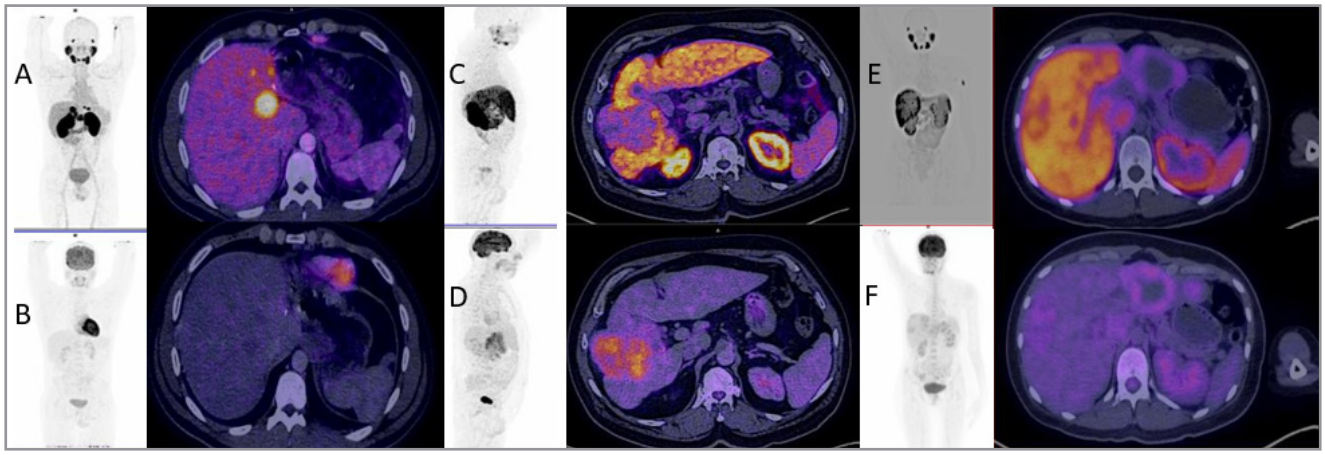

Figure 1: PET/CT 18F

For each study, sex, age, histological grade, SUVmax in lesions, SUVmax in normal liver, and tumor-to-background ratio were recorded. Histological differentiation did not influence tracer uptake. Subgroup analysis divided patients by differentiation grade: Group 1 (grades I/II, n=6) and Group 2 (grades III/IV, n=3).

Group 1 patients showed higher PSMA uptake, reflected in PET/CT images, whereas Group 2 demonstrated increased 2-[18F] FDG uptake. Chi-square analysis confirmed a significant association between differentiation grade and [18F] PSMA-1007 uptake (Pearson chi-square = 9.00, p = 0.029), but no significant association for 2-[18F] FDG (Pearson chi-square = 5.625, p = 0.131).

Discussion

The results obtained demonstrate an association between the differentiation level of hepatocellular carcinoma (HCC) and the uptake of [18F] PSMA-1007. However, this conclusion cannot be drawn for 2-[18F] FDG.

This finding establishes that in patients with HCC evaluated using a PET-CT technique with [18F] PSMA-1007, the degree of differentiation significantly influences the results. The data also indicate that well-differentiated and moderately differentiated patients exhibit higher [18F] PSMA-1007 uptake compared to poorly differentiated and undifferentiated patients.

In the case of the radiopharmaceutical 2-[18F] FDG, no conclusive results were obtained. However, it is essential to analyze in greater detail the findings in patients with histological grade 2, as they showed positive results for both 2-[18F] FDG and [18F] PSMA-1007. A Mann-Whitney test was conducted to analyze the T/N index obtained with each radiopharmaceutical.

This test was used to compare the T/N index value obtained through PET imaging under a standardized protocol using [18F] PSMA-1007 against 2-[18F] FDG, determining whether statistically significant differences exist between the two radiotracers in patients with histological grade 2 HCC. The independent variable was the radiopharmaceutical used, and the dependent variable was the T/N index value. The Mann-Whitney U statistic was 7, with a P-value of 0.773, implying that significant differences could not be determined.

A priori analysis indicated that a sample size of 42 is required to achieve a power of 0.8 and a significance level of 0.05. Thus, conclusive results would necessitate an analysis of 42 patients with grade II HCC.

The challenges of early diagnosis in patients using conventional imaging methods— including differentiating benign findings from early-stage tumors, precise tumor staging, and treatment response assessment—remain significant diagnostic hurdles. Although computed tomography (CT) and magnetic resonance imaging (MRI) have been the cornerstone of HCC diagnosis and staging, efforts to improve staging and patient follow-up have led to the evaluation of molecular imaging in HCC.

2-[18F] FDG, which allows for the assessment of glucose metabolism, is the most widely used oncological tracer due to the half-life of 18F (110 min) compared to other positron emitters. Most tumor cells exhibit increased glucose metabolism due to elevated glucose levels, increased expression of glucose transport proteins, and higher levels of intracellular enzymes that promote glycolysis, such as hexokinase and phosphofructokinase.

In most malignant cells, relatively low glucose-6-phosphatase levels lead to the intracellular accumulation and trapping of 2-[18F] FDG, enabling the visualization of increased 2- [18F] FDG uptake compared to normal cells. PET imaging with 2-[18F] FDG has been useful for differentiating malignant tumors from benign lesions based on metabolic activity differences, detecting malignant recurrence, staging tumors, and monitoring therapy response in various malignancies.

Differentiated hepatocytes typically exhibit relatively high glucose-6-phosphatase activity, allowing intracellular dephosphorylation of 2-[18F] FDG and its efflux from the liver. Experimental studies have demonstrated that gluconeogenesis decreases

while glycolysis increases during hepatic carcinogenesis. However, studies indicate that 2-[18F] FDG accumulation in HCC is variable due to differing glucose-6-phosphatase activity levels. Approximately one-third of HCC cases do not accumulate 2-[18F] FDG, leading to false- negative PET images.

Thus, 2-[18F] FDG PET is not a reliable screening tool for detecting small HCCs in at-risk patients and does not provide sufficient information on intrahepatic or distant disease. Consequently, efforts have been made to identify alternative tracers for detecting at-risk patients, staging, and monitoring regional therapy in HCC.

Monoclonal antibodies (mAbs) have identified PSMA expression in endothelial cells associated with 66% of gastric cancers, 85% of colorectal carcinomas, and 100% of bladder cancers. Nearly 95% of hepatocellular and renal cancers, as well as approximately 75% of ovarian and breast cancers, have shown positive PSMA staining in tumor vasculature. Additionally, 57% of melanoma samples, 43% of bladder cancers, and less than 30% of mesothelioma samples stained positively for PSMA. None of the 32 normal tissue samples examined demonstrated PSMA expression in normal epithelium or vasculature. These findings provide further evidence that targeted therapy could be based on the selective expression of PSMA by tumor endothelial cells.

When compared with previous studies and case reports by Arun Sasikumar et al., a case report described a 78-year-old male with an incidental HCC detected by 68Ga-PSMA PET- CT, supporting that 95% of HCCs stain positively for PSMA in immunohistochemistry studies. Additionally, Cigdem Soyda in January 2017 reported a 72-year-old male patient with an incidental well-differentiated hepatocellular carcinoma, and Hian Liang Huang et al. in 2018 reported another incidental case of well-differentiated hepatocellular carcinoma, both detected using 68Ga-PSMA PET-CT. These findings suggest that PSMA PET imaging could be a useful tool for HCC detection and even open the possibility of theranostic applications. To date, no studies using 18F-PSMA had been conducted, opening new possibilities for this radiotracer as an emerging diagnostic imaging method for improved initial staging, treatment response assessment, and recurrence detection in this pathology.

Conclusion

HCC is a highly prevalent malignancy with a poor prognosis, with most cases presenting at advanced stages, limiting treatment options. Early diagnosis through imaging studies could improve survival. PET-CT with 2-[18F] FDG has a limited role in initial staging, prompting the search for alternative radiotracers that offer improved detection, particularly in early stages.

Incidental reports of well-differentiated HCCs showing uptake on PET-CT with 68Ga- PSMA, and the findings of this comparative study between [18F] PSMA-1007 and 2- [18F] FDG, suggest comparable results. Patients with more differentiated histological grades (Grades I-II) were all positive on PET-CT with [18F] PSMA-1007 and negative in more dedifferentiated histological grades (Grades III-IV).

Our study demonstrated that PET/CT with [18F] PSMA-1007 with a T/N ratio >1.11 supports the diagnosis of HCC, whereas T/N values <0.68 are considered negative. Studies positive for 2-[18F] FDG were found in cases with higher dedifferentiation (Grades III-IV). Therefore, PET/CT with [18F] PSMA-1007 may be an effective non-invasive imaging tool for HCC diagnosis, providing insight into tumor malignancy. Additional studies with a larger sample size are warranted.

Conflict of Interest

The authors declare no conflict of interest.

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