^{68}Ga-Prostate-Specific Membrane Antigen Uptake as a Surrogate Biomarker of Neovascularity in Hepatocellular Carcinoma

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Abstract

^{68}Ga-prostate-specific membrane antigen (^{68}Ga-PSMA) is expressed in the endothelium of tumor-associated neovasculature of various solid malignancies possibly due to tumor-associated angiogenic factors and endothelial cell sprouting. We report a case of a 45-year-old man with known colorectal cancer, cirrhosis, and hepatitis C. Contrast-enhanced computed tomography (CT) showed a hypervascular lesion in the liver, and ^{18}F-*fluorodeoxyglucose* positron emission tomography (PET) did not show any suspicious hepatic uptake. ^{68}Ga-PSMA PET-CT showed predominantly heterogeneous perilesional uptake in a configuration similar to the arterial enhancement pattern on the diagnostic CT. ^{68}Ga-PSMA uptake in *hepatocellular carcinoma* appears to be primarily neoangiogenesis driven, and its morphological and functional characterization can subsequently influence the selection of anti-neoangiogenic chemotherapy agents as well as guiding radionuclide ligand therapy.

Keywords: *^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography, angiogenesis, hepatocellular carcinoma, positron emission tomography/computed tomography*

A 45-year-old male, with an established history of hepatitis C and colorectal cancer treated with surgery 2 years back, showed a hepatic mass on ultrasonography suspicious for metastases. Carcinoembryonic antigen was normal with high alpha fetoprotein values. Contrast enhanced computed tomography (CECT), demonstrated a large predominantly hypodense lesion in segment VII [Figure 1i-k] with enhancement of the lesion in the arterial phase and rapid washout during the delayed phase, i.e., appearances highly suspicious of *hepatocellular carcinoma* (HCC). A subsequent *fluorodeoxyglucose* positron emission tomography/CT (FDG PET/CT) was negative, however, a ^{68}Ga prostate specific membrane antigen (PSMA) PET CT [Figure 1a-h] showed heterogeneous uptake related to the mass. This was predominantly in a peripheral distribution, i.e., in a configuration quite similar to the enhancement pattern seen on arterial phase of CECT. Subsequent biopsy of the lesion confirmed HCC.

^{18}F-FDG PET-CT has a limited role in HCC as only half of the cases are ^{18}F-FDG avid.[1] However, ^{68}Ga-PSMA uptake has been reported in solid malignant tumors including breast cancer, HCC, and renal cell carcinoma[2-4] and is thought to be in tumoral microvessels.[5] Preliminary data indicate that the detection rate of

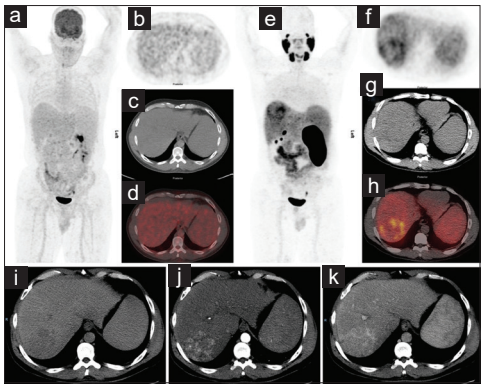

Figure 1: a) FDG MIP and b-d) Transaxial FDG PET-CT images show no abnormal FDG localization in the liver. Triple phase i) un-enhanced j) arterial and k) venous CT images showed a large predominantly arterial enhancing lesion in segment VII with imaging features of Hepatocellular Carcinoma (HCC) e) 68Ga-PSMA MIP f-h) Transaxial 68Ga-PSMA PET-CT images show heterogenous increase tracer uptake in segment VII in a peripheral pattern closely resembling pattern of enhancement on arterial phase imaging (j)

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^{68}Ga-PSMA PET-CT is superior to ^{18}F-FDG in HCC.[6] A recent study by Tolkach *et al*.[7] reported that HCC has high levels of PSMA expression on tumor vessels and canalicular membrane of tumor cells. PSMA plays a major role in regulating angiogenesis and is expressed in the endothelium of tumor-associated neovasculature in these solid malignancies possibly due to tumor-derived angiogenic factors and endothelial cell sprouting.[8,9]

Our case highlights the advantage of ^{68}Ga-PSMA PET-CT in comparison to ^{18}F-FDG PET-CT in characterizing focal hepatic lesions suspicious of HCC. These morphological features on CECT are usually secondary to abnormal handling of contrast material by newly formed vessels in a malignant lesion.[10] Unsurprisingly, the typical pattern of enhancement on CECT imaging in HCC has been shown to correlate with microvessel density.[11] The most interesting aspect of the current images is that the arterially enhancing peripheral component of the index liver lesion displaying higher ^{68}Ga-PSMA uptake indirectly reflects the positive correlation between increased ^{68}Ga-PSMA and lesion neovascularity.

This observation also highlights the potential of ^{68}Ga-PSMA PET-CT in guiding therapeutic options in HCC. This includes suitability and response assessment with antiangiogenic chemotherapy and as a potential guide to radionuclide legend therapy with α/β-emitters. Some recent studies have shown promising response rates of ^{177}Lu- 617 PSMAtargeted radioligand therapy,[12,13] and in the future, PSMA-targeted radioligand therapies can also be considered for other cancers including HCC.

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Conflicts of interest

There are no conflicts of interest.

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