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ORIGINAL ARTICLE

Predictors of Macrovascular Invasion and Extrahepatic Metastasis in Treatment Naive Hepatocellular Carcinoma: When Is [^{18}F] FDG PET/CT Relevant?

Khangembam Bangkim Chandra[1] · **Abhinav Singhal**[2]

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Abstract

Purpose Hypermetabolic macrovascular invasion (MVI) and extrahepatic metastasis (EHM) occur in aggressive hepatocellular carcinoma (HCC) and carry unfavorable prognosis. [^{18}F] FDG PET/CT, despite having low sensitivity in primary HCC, is valuable in patients with aggressive HCC for detection of hypermetabolic MVI and EHM. The study aimed at identifying the parameters that could predict hypermetabolic MVI and/or EHM in treatment naive HCC patients for tailored approach to utilize [^{18}F] FDG PET/CT.

Methods Data of 131 treatment naive HCC patients (median age, 60 years; range, 21–80 years; 90.8% males) who underwent [^{18}F] FDG PET/CT were retrospectively analyzed to determine the proportion of patients with hypermetabolic MVI and/or EHM. Logistic regression analysis was performed to define independent predictors of hypermetabolic MVI and/or EHM.

Results 78/131 (59.5%) patients had hypermetabolic MVI and/or EHM. 52/131 (39.7%) patients had EHM. 56/131 (42.7%) patients had hypermetabolic MVI of which, 30 had concomitant EHM with majority (90%; 27/30) having distant metastasis. 26/131 (19.8%) patients had hypermetabolic MVI without EHM while 22/131 (16.8%) patients had EHM without hypermetabolic MVI of which, majority (95.5%; 21/22) had distant metastasis. Hypermetabolic MVI was associated with EHM ($\chi^2 = 7.868$; p value = 0.007). AFP > 93.7 ng/ml, SUVmax > 3.5, and maximum tumor size > 5.0 cm were the independent predictors of hypermetabolic MVI and/or EHM.

Conclusion In treatment naive HCC patients with AFP > 93.7 ng/ml or maximum tumor size > 5.0 cm, [^{18}F] FDG PET/CT can be valuable.

Keywords Hepatocellular carcinoma · Macrovascular invasion · Extrahepatic metastasis · [^{18}F] fluorodeoxyglucose · Positron emission tomography/computed tomography

Introduction

Macrovascular invasion (MVI) is seen in 10 to 40% of patients with hepatocellular carcinoma (HCC) [1–3] and extrahepatic metastasis (EHM) in one-third of patients [4, 5], at the time of diagnosis. Positron emission tomography-computed tomography (PET/CT) with glucose metabolism marker ^{18}F-fluorodeoxyglucose ([^{18}F] FDG) is now widely recommended for detection of distant metastases in a variety of solid malignancies and has also shown promise in differentiating benign and malignant thrombus. However, [^{18}F] FDG PET/CT is not a routinely used imaging modality in HCC because [^{18}F] FDG uptake is seen in less than 40% of HCC cases and majority of well differentiated HCCs are non [^{18}F] FDG avid [6]. Relatively higher cost of the modality, exposure to ionizing radiation from [^{18}F] FDG and CT, and limited availability of the imaging equipment (especially in developing nations) are additional concerns. These highlight the need for reliable clinical criteria to select HCC patients who are more likely to harbor advanced disease and thus may benefit from whole-body evaluation with [^{18}F] FDG PET/CT.

HCC is the most common primary liver cancer comprising 75–80% of cases. Globally, liver cancer is the sixth

✉ Abhinav Singhal
drabhinavsinghal@live.in

[1] Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India

[2] Department of Nuclear Medicine, National Cancer Institute, All India Institute of Medical Sciences, New Delhi, India

most commonly diagnosed cancer and fourth leading cause of cancer-related deaths. Its incidence and mortality rates are 2 to 3 times higher in males, making it the fifth most commonly diagnosed cancer and second leading cause of cancer-related deaths in males [7]. The Barcelona Clinic Liver Cancer (BCLC) staging system enables prognosis prediction and treatment allocation, and is the recommended system endorsed widely as it has been repeatedly and extensively validated [6, 8]. Patients with MVI and/or EHM fall in the BCLC advanced stage (BCLC stage C) and have poor prognosis with expected median survival of 6–8 months [9, 10].

Previous studies have reported certain predictors of vascular invasion in HCC patients. The most consistent of these include tumor size, tumor grade/differentiation, and serum alpha fetoprotein (AFP), while others such as tumor numbers, serum gamma-glutamyl transferase, protein induced by vitamin K absence or antagonist-II, aspartate aminotransferase, prothrombin time, and platelet counts have also been sparingly reported [11–14]. Predictors of EHM most consistently reported in the literature include intrahepatic tumor stage, tumor markers, and vascular invasion, while positivity for viral markers, incomplete capsule, and platelet count have also been sporadically mentioned [15–18]. Although the presence of vascular invasion or EHM carries a bad prognosis, the prognosis is even worse when the two coexist [19]. Hence, a modality which can detect both vascular invasion and EHM (locoregional and distant) in single sitting may be beneficial for optimal patient management.

The imaging modalities generally recommended for the work up and staging of HCC include multi-phase contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) [6, 8]. Though [^{18}F] FDG PET/CT is not routinely advised, it has shown high accuracy for detection of vascular invasion in HCC and its differentiation from benign thrombus [20–22]. Although [^{18}F] FDG PET/CT has low sensitivity for detection of primary HCC, it is valuable for detection of EHM due to high diagnostic efficacy, since the latter tends to occur in aggressive tumors which show higher glucose metabolism [23, 24]. Thus, a tailored approach to utilize [^{18}F] FDG PET/CT in treatment naive HCC patients based on certain parameters which can assess pretest probability of hypermetabolic MVI and EHM can be more beneficial for optimal patient management. This is especially relevant since HCC is a radiological diagnosis [6, 8] and in majority of the cases, pathological information regarding tumor grade/differentiation that could suggest indication for [^{18}F] FDG PET/CT is unavailable. This study aimed at identifying the parameters that could predict hypermetabolic MVI and/or EHM in treatment naive HCC patients so as to enable a tailored approach towards utilizing [^{18}F] FDG PET/CT.

Methods

This study had an observational analytic cross-sectional design. The Institutional Ethics Committee approved the study. Due to the retrospective nature of the study, the requirement for informed written consent was waived.

Patients

Data of consecutive patients with histopathologically proven and/or radiologically diagnosed HCC who underwent [^{18}F] FDG PET/CT between February 2018 and February 2019 were retrospectively assessed. A total of 202 patients were initially listed. Patients with pathologically proven fibrolamellar or mixed histology, known non-HCC malignancy and those who had been previously treated for HCC were excluded. After the exclusion, a total of 131 treatment naive patients were finally included in the study.

PET/CT Acquisition

All patients were fasting for at least 6 h before the PET/CT acquisition. Blood glucose before [^{18}F] FDG injection was less than 150 mg/dl in all patients. [^{18}F] FDG was injected intravenously at a dose of 10 mCi (370 MBq) following which, patients were asked to rest in a quiet room. After an uptake period of 45–60 min, patients were kept in supine position on the scanner table for PET/CT acquisition. All studies were acquired on a dedicated 128-slice time-of-flight (TOF) PET/CT scanner with lutetium-based crystals (Discovery 710, GE Healthcare, Milwaukee, WI, USA). Unless otherwise contraindicated (such as renal disease, contrast allergy), non-ionized iodinated contrast (OMNIPAQUE™ or VISIPAQUE™) was injected intravenously at a dose of 1.7 ml/kg and flow rate of 3 ml/s. CT acquisition was started from vertex to mid-thigh approximately 2–3 min after the start of contrast infusion using the following parameters: 120 kVp, auto mAs, 5 mm helical thickness, 0.6 s rotation time, 39.4 mm/rotation, 0.984 pitch, 2.5 mm slice thickness reconstruction, 15.7 cm field of view, and a matrix of 512 × 512. As a routine, a separate lung CT was acquired at 3.75 mm helical thickness and 1.25 mm slice thickness reconstruction. After the CT acquisition, emission PET data were acquired from vertex to mid-thigh in 3-D mode at 2 min per bed position. PET data were acquired with a matrix size of 128 × 128 with a slice thickness of 3.3 mm. PET data were reconstructed with VUE Point FX (3-D ordered subset expectation maximization with TOF and point spread function correction; 2 iterations and 24 subsets). CT data were used for anatomical correlation and attenuation correction. Reconstructed attenuation-corrected PET images,

CT images, and fused PET and CT images were available for review in axial, coronal, and sagittal axes along with maximum intensity projection (MIP) with 3-D cine mode functionality. All the images were analyzed on a dedicated GE AW 4.7 server workstation.

PET/CT Image Analysis

[^{18}F] FDG PET/CT studies were reviewed by two experienced nuclear medicine physicians. Both readers were aware of the clinical diagnosis and findings of conventional regional imaging. For primary HCC, hepatic lesions were assessed for size and [^{18}F] FDG avidity. Maximum unidimensional tumor measurement in axial plane was used for size estimation. Hepatic lesions showing [^{18}F] FDG uptake more than normal liver parenchyma were considered "[^{18}F] FDG avid" tumors. In case of multifocal tumors, if one or more lesions showed [^{18}F] FDG uptake more than normal liver parenchyma, then the patient was regarded as having [^{18}F] FDG avid tumors. For semiquantitative analysis, a 3-D region of interest (ROI) was drawn over the hepatic lesions to generate standardized uptake value maximum (SUVmax) corrected to lean body mass. Intravascular contrast filling defects or soft tissue densities (in portal vein, hepatic venous outflow tract including the inferior vena cava, or paraumbilical vein) showing [^{18}F] FDG uptake more than aorta at the same axial slice were considered as hypermetabolic MVI. Extrahepatic lesions with non-physiologic [^{18}F] FDG uptake were considered as metastasis. For lung lesions, the characteristic pattern of metastasis on CT (well-circumscribed, rounded soft tissue attenuation lesions, absence of calcification, peripheral location, "feeding vessel sign," multiple nodules, "cannon ball" lesions) was considered metastasis irrespective of [^{18}F] FDG uptake. All analyses of the above imaging findings were done keeping in mind the physiologic biodistribution of [^{18}F] FDG and imaging context of benignity. A consensus decision was arrived whenever a discrepancy arose.

Outcome of Interest

Proportion of patients who had the outcome of interest, i.e., hypermetabolic MVI and/or EHM on [^{18}F] FDG PET/CT, was determined after confirmation with imaging follow-up and/or histopathology (when available). For hypermetabolic MVI, interval enlargement of the thrombus, vessel wall disruption, and parenchymal infiltration on follow-up imaging in those patients who did not have histopathological analysis were considered confirmatory. However, in patients who received loco-regional therapy such as stereotactic body radiation therapy (SBRT), shrinkage and/or recanalization of the thrombus on follow-up imaging was also considered confirmatory for hypermetabolic MVI. For EHM, in patients who did not have histopathological confirmation, progression of the lesions or partial regression/stable status of the lesions (on systemic therapy) were considered confirmatory.

Statistical Analysis

Descriptive statistics such as median (minimum–maximum) and frequency (percentage) were used to describe the patient characteristics. Continuous variables were tested for normality with Shapiro–Wilk test. Chi-square test or Fisher's exact test was used (as appropriate) to assess the categorical variables between patient groups defined by the presence or absence of outcome of interest, and the association between hypermetabolic MVI and EHM. Mann–Whitney *U* test was used to compare the continuous variables between the patient groups. Receiver operating characteristic (ROC) curve was used to ascertain the optimal cut-off values of AFP, maximum tumor size, and SUVmax of primary HCC lesions to distinguish the patient groups. Univariate and multivariate logistic regression analyses were used to identify independent predictors of hypermetabolic MVI and/or EHM. Statistical packages IBM SPSS 22.0.0 (IBM Corp., Somers, NY, USA) and XLSTAT 2019.1 (Addinsoft Inc., New York, USA) were used for the statistical analyses. A 2-tailed p value of < 0.05 was considered significant.

Results

Patient Characteristics

A total of 131 treatment naive HCC patients were included for the final analysis of which, 30 (22.9%) had histopathological confirmation of the primary tumor. Median age was 60 years (21–80 years). Majority of the patients were males (119/131; 90.8%). Viral etiology (hepatitis B and C) was seen in 48/131 (36.6%) patients. 96/131 (73.3%) patients had cirrhotic liver. Non-ionized iodinated intravenous contrast was administered in 117/131 (89.3%) patients. 93/131 (71.0%) patients had multifocal primary HCC lesions. Median AFP level was 200.9 ng/ml (2.2–1,260,830). [^{18}F] FDG uptake in primary HCC was seen in 108/131 (82.4%) patients. Median SUVmax of primary HCC lesions was 5.2 (1.9–23.8) while the median maximum tumor size was 7.0 cm (2.0–26.5).

Patient Groups

Patients were divided into two groups based on the presence or absence of the outcome of interest. Out of 131 patients, 78 (59.5%) patients had hypermetabolic MVI and/or EHM while the remaining 53 (40.5%) patients had disease localized to the liver. 52/131 (39.7%) patients had

EHM of which, only regional lymph node metastasis was seen in 4, only distant metastasis in 27, and combined regional lymph node plus distant metastasis in 21 patients, respectively. Hypermetabolic MVI was noted in 56 of 131 (42.7%) patients of which, 30 had concomitant EHM. 26/131 (19.8%) patients had hypermetabolic MVI without EHM while 22/131 (16.8%) patients had EHM without hypermetabolic MVI. Presence of hypermetabolic MVI showed significant association with EHM ($\chi^2 = 7.868$; p value = 0.007). 6/131 (4.6%) patients had non-metabolic intravascular filling defects (without hypermetabolic MVI elsewhere), among them 3 had EHM. 5/131 (3.8%) patients had both non-metabolic intravascular filling defects and hypermetabolic MVI. Overall characteristics in the patient cohort are detailed in Table 1. Representative images are shown in Figs. 1, 2 and 3.

Cut-off Values of AFP, SUVmax, and Maximum Tumor Size

AFP and maximum tumor size are the most consistently defined predictors of MVI or EHM in the literature [11–18]. In studies utilizing [^{18}F] FDG PET/CT for HCC, the semiquantitative parameter SUV have been reported as a robust predictor of MVI or EHM [23, 25]. Accordingly, in the present study, ROC analysis was performed to derive the cut-off values of these parameters to distinguish the patient groups (Table 2). The cut-off values of all the three parameters (AFP > 93.7 ng/ml, SUVmax > 3.5, and maximum tumor size > 5.0 cm) were statistically significant (p value < 0.001) at 59.5% prevalence of outcome of interest with the best diagnostic efficacy trade-off.

Predictors of Hypermetabolic Macrovascular Invasion and/or Extrahepatic Metastasis

As shown in Table 3, out of the various parameters, AFP > 93.7 ng/ml (p value < 0.001), [^{18}F] FDG uptake in primary HCC (p value < 0.001), SUVmax > 3.5 (p value < 0.001), and maximum tumor size > 5.0 cm (p value < 0.001) were found to be statistically significant predictors of hypermetabolic MVI and/or EHM on univariate logistic regression analysis. On multivariate analysis, AFP > 93.7 ng/ml (p value < 0.006), SUVmax > 3.5 (p value < 0.034), and maximum tumor size > 5.0 cm (p value < 0.001) remained as independent predictors of hypermetabolic MVI and/or EHM.

Discussion

Hypermetabolic MVI was seen in 42.7% and EHM in 39.7% of the patients in our study. This is in concordance with previously reported results in the literature [1–5]. This study suggested AFP, maximum tumor size, and SUVmax of primary HCC as the independent predictors of hypermetabolic MVI and/or EHM. This finding is consistent with the current literature where AFP and tumor size are the most consistently reported predictors of vascular invasion and EHM [11–18]. Jun et al. derived the cut-off value of 400 ng/ml for AFP to predict EHM [17]. The cut-off value of AFP derived in our study was 93.7 ng/ml. This discrepancy could be explained by the fact that the outcome variable in our study was a composite of hypermetabolic MVI and/or EHM rather than EHM alone. Akkiz et al. found AFP cut-off of 121 ng/ml useful to predict macrovascular portal vein invasion [26]. This value is comparable to that derived in our study. The cut-off value of maximum tumor size derived in our study

Table 1 Patient characteristics

Characteristics	Liver restricted disease ($n = 53$)	Hypermetabolic MVI and/or EHM ($n = 78$)	p value
Age in years (median, range)	58 (25–79)	60 (21–80)	0.524
Sex (male/female)	49/4	70/8	0.761
Etiology (viral/non-viral)	18/35	30/48	0.712
Cirrhosis (yes/no)	41/12	55/23	0.427
Multifocality (yes/no)	35/18	58/20	0.331
[^{18}F] FDG uptake in primary HCC (yes/no)	34/19	74/4	< 0.001*
AFP in ng/ml (median, range)	47.0 (2.2–278,072.8)	840.4 (2.4–1,260,830.0)	< 0.001*
Max tumor size in cm (median, range)	5.0 (2.0–20.0)	9.0 (2.0–26.5)	< 0.001*
SUVmax of primary HCC (median, range)	3.5 (1.9–23.8)	6.5 (2.7–20.8)	< 0.001*

MVI macrovascular invasion, *EHM* extrahepatic metastasis, *[^{18}F] FDG* [^{18}F] fluorodeoxyglucose, *HCC* hepatocellular carcinoma, *AFP* alpha fetoprotein, *Max* maximum, *SUVmax* standardized uptake value maximum

*p values are significant

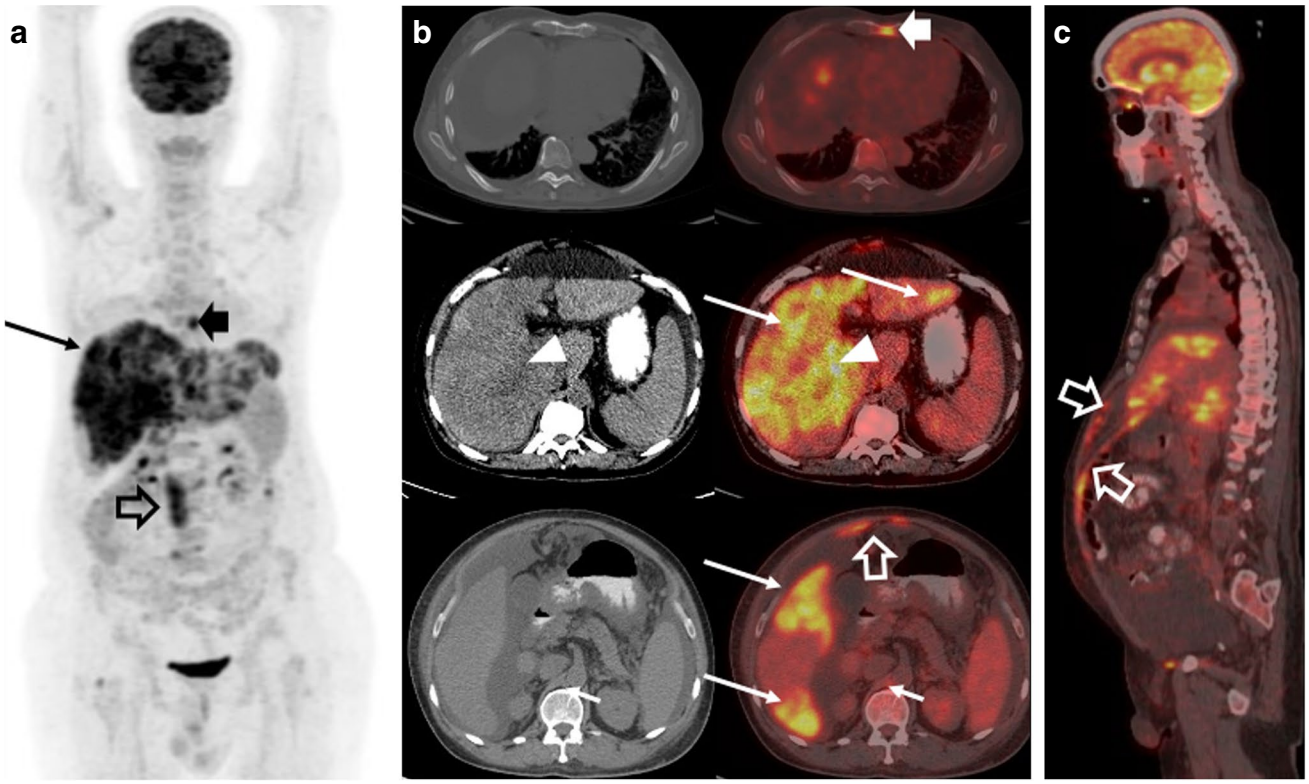

Fig. 1 Sixty-seven years old male patient diagnosed as alcohol-related chronic liver disease with alpha fetoprotein level of 77,143.8 ng/ml. Co-existing chronic kidney disease ruled out feasibility of contrast-enhanced CT. [^{18}F] FDG PET/CT without intravenous contrast agent shows extensive multifocal disease involvement of both lobes of the liver (long thin arrows in **a** and **b**) with hypermetabolic macrovascular invasion (arrowheads in **b**). Focal [^{18}F] FDG avidity suggestive of metastasis with no discernible CT lesion seen involving the sternum (thick arrows in **a** and **b**). Also noted, hypermetabolic metastatic deposits in the peritoneum (hollow arrows in **a**, **b**, and **c**) along with retrocrural lymph node metastasis (short thin arrows in **b**). **a** Maximum intensity projection (MIP); **b** cross sectional [^{18}F] FDG PET/CT images; **c** sagittal [^{18}F] FDG PET/CT image

was 5.0 cm which is concordant with previously reported values in the literature [12, 15, 18, 19, 23, 26, 27]. Also, the cut-off value of SUVmax (3.5) derived in our study is similar with previously reported results [23]. Lin et al. could predict macroscopic vascular invasion in HCC patients planned for liver transplantation using SUVmax ratio of tumor to normal liver as predictor variable [25]. This is in agreement with our study although we used SUVmax of tumor (rather than SUVmax ratio to normal liver) as the predictor variable.

Although majority of the previous studies assessed the utility of [^{18}F] FDG PET/CT to detect EHM or MVI separately [20–24], we adopted a different approach, in that, we attempted to find the predictors of advanced disease (BCLC stage C) on [^{18}F] FDG PET/CT, since the management of patients with hypermetabolic MVI and EHM are similar, in general, as per current standard of care. In our study, 59.5% (78/131) of patients had hypermetabolic MVI and/or EHM. An interesting finding was that out of these 78 patients, almost 1/3 (22/78; 28.2%) had EHM only, 1/3 (26/78; 33.3%) had hypermetabolic MVI only, and another 1/3 (30/78; 38.4%) had EHM along with hypermetabolic MVI. More than half (30/56; 53.6%) of patients with hypermetabolic MVI had EHM of which, majority (27/30; 90%) had distant metastasis with or without concomitant regional lymph node metastasis. A significant association between hypermetabolic MVI and EHM (p value = 0.007) was thus seen, which is in agreement with previous reports [15–17, 19, 28]. Also, among the patients who had EHM only, 95.5% (21/22) had distant metastasis with or without concomitant regional lymph node metastasis.

Lee et al. suggested that patients with primary HCC tumor size > 5.0 cm and average SUV > 3.4 should be considered for EHM [23]. Their results suggested clinical utility of [^{18}F] FDG PET/CT in that subset of patients. Yokoo et al. found that among the staging parameters in existing HCC staging systems, large tumor size, vascular invasion, and high AFP levels were independently associated with EHM and suggested that patients with these high risk factors should be extensively evaluated for EHM [28]. Trojan et al. suggested that [^{18}F] FDG PET/CT could be valuable as a non-invasive staging tool in HCC patients with tumor size > 5.0 cm or markedly elevated AFP levels [29]. Our

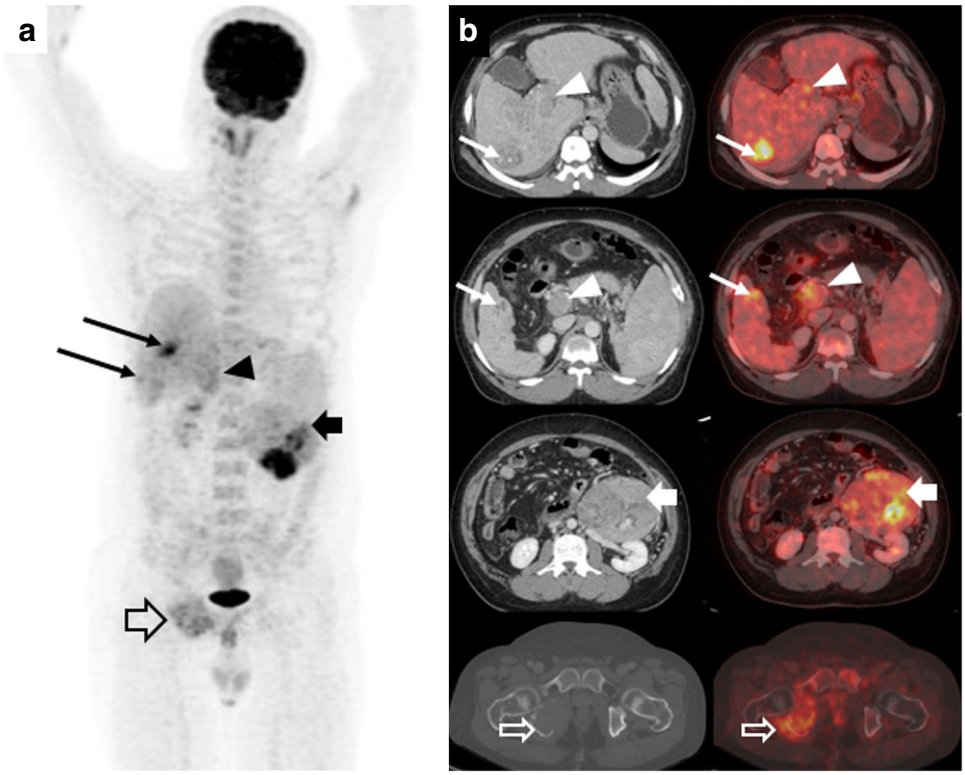

Fig. 2 Forty-five years old male patient diagnosed as chronic liver disease due to hepatitis C virus infection with hepatocellular carcinoma on biopsy. Serum alpha fetoprotein level was 67.9 ng/ml and conventional regional imaging revealed multifocal hepatic lesions (largest, 5.0 cm), expansile portal vein thrombus, and large left adrenal mass. [^{18}F] FDG PET/CT shows [^{18}F] FDG avid multifocal hepatocellular carcinoma (thin arrows in **a** and **b**), hypermetabolic macrovascular invasion (arrowheads in **a** and **b**), and large left adrenal metastasis (thick arrows in **a** and **b**). [^{18}F] FDG PET/CT shows an unexpected right ischium bone metastasis seen as lytic lesion with soft tissue component and [^{18}F] FDG avidity. Patient subsequently received stereotactic body radiation therapy for worsening bone pain in this region and oligometastatic nature of the bone lesion. **a** Maximum intensity projection (MIP); **b** cross sectional [^{18}F] FDG PET/CT images

study adds strength to the evidence leading to these recommendations. We found that maximum tumor size > 5.0 cm or AFP level > 93.7 ng/ml in treatment naive HCC patients could predict presence of advanced disease detectable on [^{18}F] FDG PET/CT. Moreover, more than half of the patients who had hypermetabolic MVI detected on [^{18}F] FDG PET/CT had EHM with majority of them having distant metastasis. Some patients with distant metastasis might need metastasis targeted additional loco-regional therapy such as SBRT due to detection of metastasis in critical locations such as spine, brain, and pelvic bone. In addition, coexistence of vascular invasion and EHM carries a worse prognosis than presence of either of them alone [19]. In view of these findings, [^{18}F] FDG PET/CT may be beneficial in treatment naive HCC patients who have AFP level > 93.7 ng/ml or maximum tumor size > 5.0 cm. Fortunately, these parameters are easily determined during initial clinical work-up of a newly diagnosed HCC patient. Hence, it is prudent to select candidates fulfilling these conditions for [^{18}F] FDG PET/CT, resulting in a rational utilization of the modality. It might thus prevent under-staging of new HCC patients due to inability of conventional regional imaging modalities to detect unexpected distant metastasis as previously reported [24, 28]. Further studies based on our proposal may be worthwhile for external validation and establishment of diagnostic accuracy of [^{18}F] FDG PET/CT in this context. Furthermore, hypermetabolic MVI was associated with EHM on post-hoc analysis. However, the number of patients with isolated non-metabolic intravascular filling defects or soft tissue densities without hypermetabolic MVI elsewhere or EHM was extremely small in our study (3 patients). Further large prospective studies are suggested to ascertain the utility of whole-body evaluation with [^{18}F] FDG PET/CT in patients who have MVI on conventional regional imaging.

In our study, [^{18}F] FDG uptake in primary HCC lesions was seen in 82.4% of patients which is higher than that mentioned in the current literature [6]. This may be explained by the following reasons. First, our study cohort mainly consisted of aggressive or advanced disease patients as suggested by the high median AFP (200.9 ng/ml), SUVmax

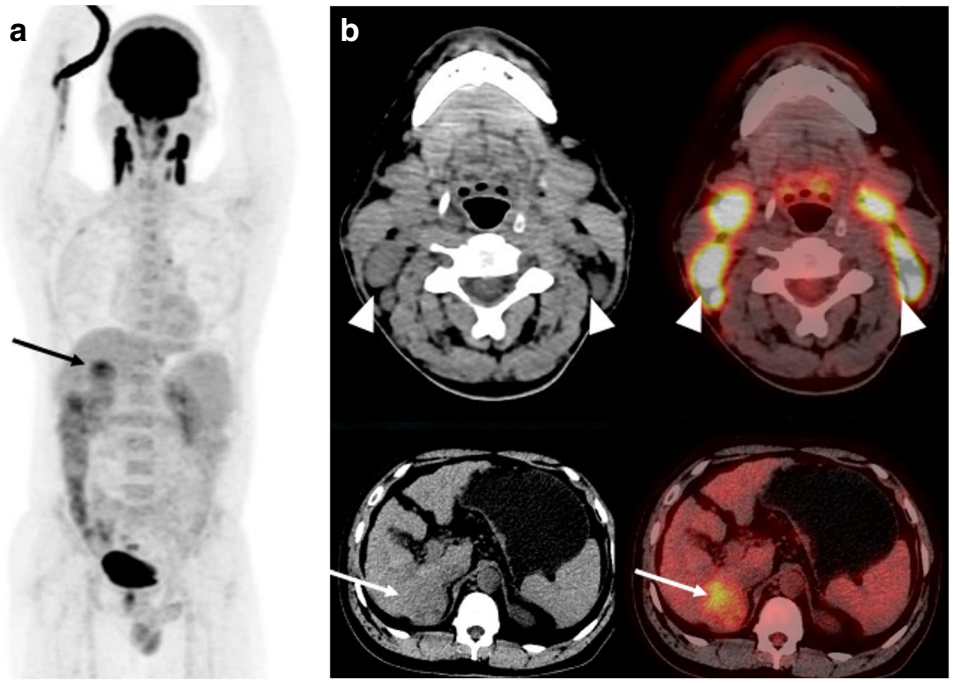

Fig. 3 Forty-two years old male patient diagnosed as chronic liver disease due to hepatitis C virus infection with moderately differentiated hepatocellular carcinoma on biopsy. Serum alpha fetoprotein level was 92.2 ng/ml and maximum tumor size on conventional regional imaging was 4.0 cm. On [^{18}F] FDG PET/CT, the liver shows cirrhotic features with [^{18}F] FDG avid primary hepatocellular carcinoma in segment VI (arrows in **a** and **b**). Note is also made of multiple [^{18}F] FDG avid enlarged bilateral cervical lymph nodes (arrow heads in **b**) symmetrically distributed on both sides of the neck suggestive of benign nature. Fine needle aspiration cytology of the cervical lymph nodes diagnosed granulomatous etiology. **a** Maximum intensity projection (MIP); **b** cross sectional [^{18}F] FDG PET/CT images

(5.2), maximum tumor size (7.0 cm), and high proportion of patients having multifocal tumors (93/131; 71.0%). Second, in our analysis which was patient based (rather than lesion based), if any lesion showed [^{18}F] FDG uptake among multifocal HCC lesions, the patient was regarded as having [^{18}F] FDG avid tumor.

The most important limitation of this study is its retrospective nature. Various other potentially valuable laboratory parameters such as liver function tests, gamma-glutamyl transferase, platelet count, viral markers, inflammatory markers, and Child–Pugh score and performance status were, thus, not consistently available for all patients and could not be included for the analysis. Another limitation is the non-availability of pathological confirmation of EHM and hypermetabolic MVI in all patients detected on [^{18}F] FDG PET/CT. Although ideal, subjecting all such patients to biopsy has its own logistic and ethical constraints, depending on the characteristics and locations of the findings. Also, non-ionized iodinated intravenous contrast could not be administered in 14/131 patients due to contraindications.

Table 2 Receiver operating characteristic curve (ROC) analysis

Parameter	Criterion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Accuracy (%)
AFP (ng/ml)	> 93.7	75.6	60.4	73.8	62.7	0.719	69.5
SUVmax	> 3.5	89.7	50.9	72.9	77.1	0.742	74.0
Tumor size (cm)[#]	> 5.0	84.6	60.4	75.9	72.7	0.787	74.8

[#]Tumor size (cm) denotes maximum tumor size in centimeters

PPV positive predictive value, *NPV* negative predictive value, *AUC* area under the curve, *AFP* alpha fetoprotein, *SUVmax* standardized uptake value maximum

p value < 0.001 at 59.5% prevalence of outcome of interest (defined in text)

Table 3 Predictors of macrovascular invasion and/or extrahepatic metastasis by logistic regression analysis

Parameter	Univariate analysis				Multivariate analysis			
	B	Odds ratio	95% CI	*p* value	B	Odds ratio	95% CI	*p* value
Age	0.005	1.005	0.975–1.036	0.743				
Sex	− 0.336	0.714	0.204–2.504	0.599				
Etiology	0.195	1.215	0.586–2.519	0.600				
Cirrhosis	− 0.357	0.700	0.312–1.568	0.386				
AFP > 93.7 ng/ml	1.554	4.732	2.224–10.069	< 0.001*	1.341	3.822	1.476–9.899	0.006*
[^{18}F] FDG uptake in primary HCC	2.336	10.338	3.266–32.720	< 0.001*				
Multifocality	0.400	1.491	0.696–3.197	0.304				
SUVmax > 3.5	2.207	9.087	3.664–22.536	< 0.001*	1.451	4.268	1.119–16.279	0.034*
Maximum tumor size > 5.0 cm	2.126	8.381	3.671–19.132	< 0.001*	1.791	5.993	2.207–16.272	< 0.001*

CI 95% confidence interval, *AFP* alpha fetoprotein, *[^{18}F] FDG* [^{18}F] fluorodeoxyglucose, *SUVmax* standardized uptake value maximum

*p values are significant

Conclusion

Hypermetabolic macrovascular invasion and extrahepatic metastasis in newly diagnosed HCC patients are not uncommon. Hypermetabolic macrovascular invasion is associated with extrahepatic metastasis in more than half of the patients. Majority of the extrahepatic metastasis are distant metastasis with or without concomitant regional lymph node metastasis. In the initial work-up of newly diagnosed HCC patients, [^{18}F] FDG PET/CT can be valuable in the presence of AFP > 93.7 ng/ml or maximum tumor size > 5.0 cm.

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Author Contribution Both authors contributed to the study concept and design, scan review, data mining, data entry, and analysis. The first draft of the manuscript was written by Khangembam Bangkim Chandra while proofreading and editing of the draft manuscript was performed by Abhinav Singhal. Both authors read and approved the final manuscript.

Data Availability Original raw data is available on reasonable request to the corresponding author.

Declarations

Conflict of Interest Khangembam Bangkim Chandra and Abhinav Singhal declare no conflict of interest.

Ethical Statement All procedures involving human participants were in accordance with the Declaration of Helsinki 1964 as revised in 2013 and its later amendments or comparable ethical standards. The Institutional Ethics Committee, Institute of Liver and Biliary Sciences, New Delhi, approved the retrospective study (ref no: IEC/2019/69/MA03).

Informed Consent The Institutional Ethics Committee waived the requirement for informed written consent.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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