2-[18F]FDG PET/CT

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PET (positron emission tomography) is a noninvasive functional imaging technique based on the detection of photons resulting from the annihilation of positrons emitted by a radioactive substance known as radiotracer or radiopharmaceutical. PET equipments usually incorporate a computed tomography scanner (PET/CT) in order to obtain hybrid functional-anatomical images.

Different radiotracers are used to study different physiologic processes, such as blood flow, bone turnover or expression of certain cell receptors. The most common radiotracer used in clinical practice is 2-deoxy-2-[18F]fluoro-d-glucose (2-[18F]FDG), a glucose analogue binded to a radioactive isotope of fluor that informs about glucose metabolism in the body. As cancer cells have high energy requirements (and, therefore, high glucose consumption), this radiotracer is mostly used to evaluate oncologic processes (disease extension, response to treatment, *etc.*). However, some types of cancer have low 2-[18F]FDG uptake (e.g., well-differentiated or slow-growing neoplasms), and others can have a variable uptake due to the action of certain enzymes in the metabolic route of glucose (e.g., hepatocellular carcinoma).

Keywords: hepatocellular carcinoma ; 2-[18F]FDG ; PET/CT ; liver resection ; standardized uptake value ; lean body mass ; microvascular invasion ; cellular differentiation.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver with estimates of it being the seventh most incident cancer type and the third with the highest mortality in the world in 2020 [1]. Among the curative treatments, surgical resection is preferred in patients without cirrhosis as well as in those without clinically significant portal hypertension and Child–Pugh class A [2]. However, the risk of recurrence after a resection is high (about 70% at five years) [3] with the grade of differentiation, the presence of vascular invasion and the existence of satellite nodules the most important prognostic factors for an early recurrence [4][5]. Predicting the existence of these factors would allow a more patient-specific treatment with a better selection of those individuals who could benefit from surgery and with the highest probability of a long-term survival.

Even if histological confirmation was mandatory before treatment of most neoplasms, it is usually not required and even discouraged as a routine procedure in an HCC mainly due to the risk of bleeding, tumor seeding and the possibility of false negative results [2][6]. Therefore, in most cases, the diagnosis is done with a multiphasic contrast-enhanced CT or MRI. In the last years, different studies have evaluated the capacity of conventional and functional imaging methods to preoperatively identify aggressive features of an HCC especially microvascular invasion (MVI) [7][8]. Unlike in other malignancies, PET/CT with 2-deoxy-2-[18F]fluoro-d-glucose (FDG) is not routinely used as part of the diagnostic and staging workup of an HCC as it shows a low uptake of this radiopharmaceutical especially in well-differentiated lesions [9]. However, FDG uptake in HCC lesions seems to relate to more aggressive biological factors such as higher alpha-fetoprotein levels and to predict MVI and an early recurrence after a curative treatment [10][11][12].

2. Correlation between Metabolic Parameters on PET/CT and Histological Factors of a Poor Prognosis

2.1. Presence of MVI

To identify those metabolic variables predictive of MVI, the metabolic values of the different variables obtained in patients with and without MVI were compared using the Mann–Whitney U test. A qualitative conversion of those with significant differences between patients with and without MVI and without missing values (SULmax, SULpeak, TLRmax, TLRmean and TLRpeak; all at the 60 min images) was performed using p25, p50 and p75 as cut-off values.

In the majority of the cases using a cut-off value in the p50 or p75, a significant relationship between the metabolic activity of the tumor and the presence of MVI was observed. The AUC was calculated for each of these metabolic parameters, being the SULpeak of the lesion at 60 min (SULpeak60) with a cut-off value of 2.26 (p50) the one showing the best results (AUC 0.716). Patients with an SULpeak60 ≥ 2.26 presented bigger HCC lesions and had a greater incidence of MVI (Table 3).

Table 3. Comparison between the two groups of patients according to the metabolic activity based on SULpeak60 with the cut-off in the p50 (2.26).

Variables	SULpeak60 ≥ 2.26 (n = 21)	SULpeak60 < 2.26 (n = 20)	*p*-Value
Sex (M/F)	21/0	18/2	0.232
Age (years), mean (SD)	60.4 (12.8)	62.6 (10.4)	0.547
BMI (kg/m^2), mean (SD)	26.6 (4.0)	27.6 (4.6)	0.450
HCV Ab+, n (%)	2 (9.5)	10 (50)	0.006
HCV RNA+, n (%)	0	2 (10)	1.000
HBV S Ag+, n (%)	7 (33.3)	0 (0)	0.009
AFP (ng/mL), mean (SD)	2091.0 (13109.7)	24 (66.8)	0.359
AFP ≥ 200 ng/mL, n (%)	3 (14.3)	1 (5.6)	0.609
Tumor characteristics on cross-sectional imaging			
Size of the nodule (mm), mean (SD)	5.1 (2.6)	3.2 (1.2)	0.006
Functional preoperative status			
ASA classification (I/II/III/IV)	1/6/14/0	0/13/7/0	0.053
MELD	7.19 (1.8)	7.2 (1.2)	0.985
Intra-operative and post-operative variables			
Open/laparoscopic	13/8	8/12	0.217
Major resection, n (%)	2 (9.5)	1 (5)	1.000
Anatomical resection, n (%)	10 (47.6)	8 (35)	0.530
Pringle maneuver yes/no	18 (85.7)	19 (95.0)	1.000
Perioperative transfusion yes/no	3/18	1/19	0.606
Post-operative complications. Clavien classification (No/I/II/IIIa)	14/4/1/2	14/2/3/1	0.577
Mortality, n	0	0	
Hospitalization time (days), mean (SD)	6.95 (5.5)	7.1 (8.0)	0.982
Pathological variables			
Fibrosis grade (0 + F1 + F2/F3 + F4)	11/10	8/12	0.536
Histological type (HCC/hepatocholangiocarcinoma)	21/0	18/2	0.232
Number of tumors	1.1 (0.4)	1.05 (0.2)	0.174
Multiple tumors, n (%)	4 (19)	1 (5)	0.343
Tumor size (mm), mean (SD)	5.2 (2.8)	3.4 (1.6)	0.013
Tumor size ≥ 30 mm, n (%)	18 (85.7)	10 (50)	0.020
Grade of differentiation (G1 + G2/G3 + G4)	12/9	17/3	0.085
Satellite nodules, n (%)	3 (14.3)	1 (5)	0.606
Microvascular invasion, n (%)	13 (61.9)	4 (20)	0.010
R1 resection, n (%)	5 (23.8)	1 (5.3)	0.186

BMI: body mass index; HCV: hepatitis C virus; HBV: hepatitis B virus; AFP: alpha-fetoprotein; ASA: American Society of Anesthesiologists; MELD: model for end-stage liver disease; HCC: hepatocellular carcinoma.

2.2. Poor Cellular Differentiation

In the same way reported for MVI, to identify those metabolic parameters predictive of a poor cellular differentiation, a comparison of the results obtained for each metabolic variable in patients with and without poorly differentiated tumors (G3 and G4 vs. G1 and G2) was performed using the Mann–Whitney U test. Five metabolic parameters, corresponding with the same ones as previous (SULmax, SULpeak, TLRmax, TLRmean and TLRpeak; all at the 60 min images) were qualitatively converted using p25, p50 and p75 as cut-off values.

In all of the five variables using a cut-off value in the p50 or p75, a significant relationship between the metabolic activity of the tumor and the grade of differentiation was observed. As in the previous section, the AUC was also calculated for each of these variables, now being SULpeak of the TLR at 60 min (TLRpeak60) with a cut-off value of 1.20 (p50) the one with the best performance (AUC 0.744).

Patients with a TLRpeak60 ≥ 1.20 had a higher incidence of a poor cellular differentiation, a higher presence of satellite nodules, a greater incidence of MVI and bigger HCC lesions (Table 4).

Table 4. Comparison between the two groups of patients according to metabolic activity based on TLRpeak60 with the cut-off in the p50 (1.20).

Variables	TLRpeak60 ≥ 1.20 (*n* = 20)	TLRpeak60 < 1.20 (*n* = 21)	*p*-Value
Sex (M/F)	**20/0**	**19/2**	**0.488**
Age (years), mean (SD)	**59.0 (13.5)**	**63.8 (8.8)**	**0.183**
BMI (kg/m^2), mean (SD)	**26.4 (4.3)**	**27.8 (4.3)**	**0.327**
HCV Ab+, n (%)	**3 (15)**	**9 (42.9)**	**0.085**
HCV RNA+, n (%)	**0 (0)**	**2 (22.2)**	**1.000**
HBV S Ag+, n (%)	**5 (25)**	**2 (9.5)**	**0.238**
AFP (ng/mL), mean (SD)	**3046.4 (13,432.9)**	**22.6 (64.4)**	**0.327**
AFP ≥ 200 ng/mL, n (%)	**3 (15)**	**1 (5.3)**	**0.605**
Tumor characteristics on cross-sectional imaging			
Size of the largest nodule (mm), mean (SD)	**5.2 (2.7)**	**3.3 (1.2)**	**0.008**
Functional preoperative status			
ASA classification (I/II/III/IV)	**1/7/12/0**	**0/12/9/0**	**0.210**
MELD	**7.6 (0.9)**	**6.8 (1.9)**	**0.104**
Intra-operative and post-operative variables			
Open/laparoscopic	**11/9**	**10/11**	**0.758**
Major resection, n (%)	**2 (10)**	**1 (4.8)**	**0.606**
Anatomical resection, n (%)	**10 (50)**	**7 (33.3)**	**0.350**
Pringle maneuver yes/no	**17/3**	**20/1**	**0.343**
Perioperative transfusion yes/no	**3/17**	**1/20**	**0.343**
Post-operative complications. Clavien classification (No/I/II/IIIa)	**14/3/1/2**	**14/3/3/1**	**0.727**
Mortality, n	**0**	**0**	
Hospitalization time (days), mean (SD)	**6.9 (5.6)**	**7.0 (7.8)**	**0.945**
Pathological variables			
Fibrosis grade (0 + F1 + F2/F3 + F4)	**11/9**	**8/13**	**0.354**

Variables	TLRpeak60 ≥ 1.20 (*n* = 20)	TLRpeak60 < 1.20 (*n* = 21)	*p*-Value
Histological type (HCC/hepatocholangiocarcinoma)	20/0	19/2	0.488
Number of tumors	1.2 (0.4)	1.05 (0.2)	0.151
Multiple tumors, n (%)	4 (20)	1 (4.8)	0.184
Tumor size (mm), mean (SD)	4.9 (2.6)	3.9 (2.3)	0.265
Tumor size > 30 mm, n (%)	18 (90)	10 (47.6)	0.006
Grade of differentiation (G1 + G2/G3 + G4)	10/10	19/2	0.006
Satellite nodules yes/no	4/16	0/21	0.048
Microvascular invasion, n (%)	12 (60)	5 (23.8)	0.028
R1 resection, n (%)	5 (25)	1 (5)	0.182

BMI: body mass index; HCV: hepatitis C virus; HBV: hepatitis B virus; AFP: alpha-fetoprotein; ASA: American Society of Anesthesiologists; MELD: model for end-stage liver disease; HCC: hepatocellular carcinoma.

2.3. Presence of MVI and/or Poor Cellular Differentiation

For this analysis, only the p50 values of SULpeak60 and TLRpeak60 were used. Proceeding as explained in the previous section, the AUC for both parameters was calculated with TLRpeak60 obtaining the best results (AUC 0.732). Patients with TLRpeak60 ≥ 1.20 had MVI or a poor cellular differentiation in 75% of the cases while these factors were present in only 28.6% of the remaining study population (p = 0.005). This was the only variable available before the surgery that predicted the presence of any of the two histological factors of a poor prognosis (Table 5).

Table 5. Predictors of microvascular invasion or a high grade of differentiation (G3 or G4) using data available before a liver resection.

Variables	Univariate Analysis		
	HR	95% CI	*p*-Value
Sex (M/F)			0.972
Age ≥ 70 years			0.255
BMI ≥ 30 kg/m^2			0.929
Diabetes mellitus			0.282
HCV Ab+, n (%)			0.559
HCV RNA+, n (%)			0.999
HBV S Ag+, n (%)			0.253
MELD ≥ 9			0.168
AFP (ng/mL)			0.535
AFP ≥ 200 ng/mL			0.337
Liver stiffness > 14 kPa			0.140
Preoperative tumor size			0.154
Preoperative tumor size ≥30 mm			0.469
TLRpeak60 p50	7.50	1.87–29.98	0.004

BMI: body mass index; HCV: hepatitis C virus; HBV: hepatitis B virus; MELD: model for end-stage liver disease; AFP: alpha-fetoprotein.

Furthermore, patients with increased values of TLRpeak60 presented a significantly higher incidence of disease recurrence at 12 months compared with the rest of the patients (38% vs. 0%, p = 0.014). No significant differences regarding survival at 12 months were observed.

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