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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Jong Park, PhD, Associate Professor, Division of Cancer Prevention and Control, H. Lee Moffitt Cancer Center, College of Medicine, University of South Florida, Tampa, FL 33612, United States

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EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Gastrointestinal Oncology
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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
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Baishideng Publishing Group Inc
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Suite 501, Pleasanton, CA 94588, USA
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MINIREVIEWS

Role of pre-transplant 18F-FDG PET/CT in predicting hepatocellular carcinoma recurrence after liver transplantation

Onur Yaprak, Sencan Acar, Gokhan Ertugrul, Murat Dayangac

Onur Yaprak, Gokhan Ertugrul, Murat Dayangac, Medipol University Hospital, Center for Organ Transplantation, Istanbul 34214, Turkey

Sencan Acar, Atasehir Memorial Hospital, Center for Organ Transplantation, Istanbul 34758, Turkey

ORCID number: Onur Yaprak (0000-0003-1941-8290); Sencan Acar (0000-0001-8086-0956); Gokhan Ertugrul (0000-0002-8351-4220); Murat Dayangac (0000-0002-1240-7233).

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Correspondence to: Onur Yaprak, MD, Associate Professor, Medipol University Hospital, Center for Organ Transplantation, Goztepe Mah. Metin Sk. No.4, Bagcilar, Istanbul 34214, Turkey. onuryaprak@hotmail.com
Telephone: +90-53-22239566

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Abstract

The last two decades have seen a paradigm shift in the selection of patients with hepatocellular carcinoma (HCC) for liver transplantation. Microvascular invasion and differentiation have been the most significant factors affecting post-transplant recurrence; however, because of inherent disadvantages of pre-transplant biopsy, histological criteria never gained popularity. Recently, the selection criteria evolved from morphological to biological criteria, such as biomarkers and response to loco-regional therapy. With the introduction of multi-modality imaging, combination of computed tomography with nuclear medicine imaging, particularly, 18F-fluorodeoxyglucose positron emission tomography fulfilled an unmet need and rapidly became a critical component of HCC management. This review article will focus on the use of 18F-fluorodeoxyglucose positron emission tomography combined with computed tomography in the pre-transplant evaluation of HCC patients with special discussion on its ability to predict HCC recurrence after liver transplantation.

Key words: 18F-fluorodeoxyglucose positron emission tomography; Hepatocellular carcinoma; Recurrence; Liver transplantation

Core tip: The last two decades have seen a paradigm shift in the selection of patients with hepatocellular carcinoma (HCC) for liver transplantation. With the introduction of multimodality imaging, combination of computed tomography with nuclear medicine imaging

fulfilled an unmet need and rapidly became a critical component of HCC management. This review article will focus on the use of 18F-fluorodeoxyglucose positron emission tomography in the pre-transplant evaluation of HCC patients with special discussion on its ability to predict HCC recurrence after liver transplantation.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Currently, HCC is the sixth most common cancer with more than a half million new cases diagnosed annually, and it is the second leading cause of cancer-related mortality in the world[1]. The global risk of HCC has been largely associated with hepatitis B and C virus infection. In addition, improved survival from cirrhosis and increasing rates of obesity and non-alcoholic fatty liver disease are expected to contribute to the ever-increasing incidence of HCC[2,3]. Because of the strong link between cirrhosis and HCC, liver transplantation (LT) is the best treatment option, since it removes the tumor and the underlying tumor-generating cirrhosis. Recently, HCC has been reported as the most common indication for LT in the United States[4].

Until the landmark study by Mazzaferro *et al*[5] in 1996, the liberal selection of HCC patients for LT resulted in high recurrence rates and poor survival. With the introduction of Milan criteria (MC), excellent long-term outcomes have been achieved that were not different from those of patients without HCC. The MC have been validated in several studies and widely accepted as the benchmark for selection of patients with HCC for deceased donor LT (DDLT). Subsequent studies searching for more liberal morphological criteria have shown that it was possible to extend the size and number of tumors without compromising post-transplant outcome[6-11] (Table 1). Despite being continually expanded, aforementioned morphological criteria have been criticized for a variety of reasons: they were restrictive and precluded numerous patients who otherwise would have benefited from LT with a low risk of HCC recurrence; they relied solely on tumor burden (defined as the size and number of tumors at a certain point) and excluded the factors related to tumor behavior (*i.e.,* tumor differentiation, molecular markers, and response to bridging therapy); they depended on imaging parameters that were inconsistent: in patients within MC, up to 40% had explant pathology that exceeded the MC, and in those beyond MC, up to 34% had explant pathology that was within the MC[12,13]. An earlier study investigating the correlation between pathologic and radiologic staging according to the morphological criteria have found that the accuracy of imaging classification for both Milan and (University of California San Francisco (UCSF) criteria was only 60%[14].

In patients with HCC, vascular invasion has been defined as one of the major determinants of the outcome after LT[15]. Further studies have shown that tumor differentiation has also been an independent predictor of recurrence and survival after the transplant[16,17]. Despite initial hesitancy against the use of pre-transplant tumor biopsy, Toronto criteria have led the way to the use of histological criteria in selection of patients with HCC for LT[12]. However, pre-transplant tumor biopsy has not gained popularity because of its limitations: In spite of the invasive biopsy procedures, the presence of vascular invasion and tumor differentiation may not be detected reliably; the sensitivity of biopsy varies depending on location of the tumor, needle size, and tumor size. Moreover, preoperative needle biopsy may increase tumor seeding and post-transplant recurrence[18]. Nevertheless, this was the beginning of a new era when there was a shift in selection criteria from morphological to the combination of biological and histomorphological criteria[19].

Meanwhile, major transplant centers in Asia started to expand aggressively the morphological criteria with the addition of biomarkers to the patient selection process. While in the West, alpha-fetoprotein (AFP) has been traditionally used as a reference biomarker to screen and support the diagnosis of HCC; in the East, des-gamma-carboxy prothrombin (DCP) was introduced as a significant marker for assessing the biological behavior of HCC, particularly in Japan. Shirabe *et al*[20] reported that selection of HCC patients for LT might improve with the use of DCP measurement because pre-transplant DCP level has been shown to be a significant predictor of microvascular invasion (MVI).

The utilization of a combination of biological and morphological data has been a perfect fit for living donor LT (LDLT), which was not restricted by deceased donor organ allocation system. The Kyoto group reported their selection criteria to include no more than 10 tumors, all less than 5 cm in diameter with DCP levels less than 400 ng/mL[21], while the Kyushu group suggested more extended criteria to include a tumor size of less than 5 cm and DCP levels less than 300 ng/mL with no limitation on the number of tumors[22]. Both centers achieved outstanding post-transplant outcomes. The criteria that incorporated biomarkers with expanded morphological criteria are shown in Table 2[21-24].

As the selection criteria have been continuously expanded, search for new criteria to predict the biological behavior of HCC also continued. To this end, response to loco-regional therapy (LRT) has been suggested as a surrogate marker of tumor biology[19]. Bridging therapies primarily focused on reducing the tumor burden and has

Table 1 Morphological criteria used in selection of patients with hepatocellular carcinoma for liver transplantation

Ref.	Year	Size and number
Milan[5]	1996	1 lesion ⩽ 5 cm, or 2 to 3 lesions each ⩽ 3
University of California San Francisco[6]	2001	1 lesion ⩽ 6.5 cm, 2-3 lesions each ⩽ 4.5 cm with total tumor diameter ⩽ 8 cm
Tokyo University[8]	2008	Up to 5 tumors, each < 5 cm
Asan Medical Center[9]	2008	The largest tumor diameter < 5 cm, tumor number ⩽ 6
Alberta[10]	2008	Total tumor volume < 115 cm
Valencia[11]	2008	Up to 3 tumors, each < 5 cm, and a cumulative tumor burden ⩽ 10 cm
Up-to-seven[7]	2009	7 as the sum of the size of the largest tumor and total number of tumors

Table 2 The use of biomarkers with expanded morphological criteria

Ref.	Year	No. of patients	Criteria	Overall survival	
				Within criteria	Beyond criteria
Kyoto[21]	2007	136	Up to 10 tumors, all ⩽ 5 cm; DCP ⩽ 400 ng/mL	87% (5-yr)	37% (5-yr)
Kyushu[22]	2007	40	Any number, tumor diameter ⩽ 5 cm; DCP < 300 ng/mL	77% (3-yr)	40% (3-yr)
Seoul[23]	2007	140	Any number, tumor diameter ⩽ 5 cm; AFP ⩽ 400 ng/mL	87% (5-yr)	23% (5-yr)
Hangzhou[24]	2008	195	Total tumor diameter ⩽ 8 cm; or total tumor diameter > 8 cm and grade Ⅰ/Ⅱ and AFP ⩽ 400 ng/mL	71% (5-yr)	19% (5-yr)

Table 3 The criteria used for prediction of biological behavior of hepatocellular carcinoma in the pre-transplant setting

Biomarkers (AFP, DCP)[21-24]
The neutrophil-lymphocyte ratio[27]
Pre-transplant liver biopsy[12]
Response to loco-regional therapy[19]
Test of time (3-mo waiting period)[19,26]
Dynamic evaluation (tumor doubling time and change in AFP)[19]
FDG-PET scan

AFP: Alpha-fetoprotein; DCP: Des-gamma-carboxy prothrombin; FDG-PET: Fluorodeoxyglucose positron emission tomography.

been recommended to downstage the HCC patients who exceeded the morphological selection criteria to within the MC to become eligible for DDLT[25]. In addition, long waiting times for DDLT and high dropout rates have led to an active approach to the treatment of HCC with LRT to prevent progression while awaiting LT. The LRTs have also been used in LDLT to exclude patients with unfavorable tumor behavior, such as the patients who are unresponsive to treatment or those with progression upon observation. The interval between therapy and LT was found to help in identifying the patients who have HCC with poor tumor biology with an increased risk of post-transplant recurrence[26].

Despite the ability of cross-sectional imaging studies to reliably diagnose HCC, neither computed tomography (CT), nor magnetic resonance imaging (MRI) have been instrumental as a marker of tumor biology[27] (Table 3). With the introduction of multimodality imaging, combination of CT with nuclear medicine imaging, particularly 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET/CT), fulfilled an unmet need and rapidly became a critical component of HCC management[28]. This review article will focus on the use of 18F-FDG PET/CT in the setting of LT for HCC with special discussion on its ability to predict HCC recurrence after LT.

18F-FDG PET/CT IMAGING IN HCC

The successful application of 18F-FDG to a growing number of oncological indications has led to the widespread use of 18F-FDG-PET/CT in the diagnosis, staging and follow-up of patients with distinct types of cancer. Oncological imaging using 18F-FDG is based on the principle of enhanced glucose metabolism in tumors as compared with normal tissues. However, in normal hepatic parenchyma, where the concentration of glucose-6-phosphatase is high, the rapid clearance of 18F-FDG leads to a reduced discrimination between normal tissue and well-differentiated HCC. Because of the fact that low-grade HCC exhibits a lower FDG avidity, the general reported false-negative rate of 18F-FDG-PET/CT approaches 50% in the imaging of HCC[29]. The 18F-FDG uptake in HCC ranges from 38% to 70% with an overall sensitivity of only about 60%[29-32].

In the liver, PET/CT positivity is determined by examining whether the FDG uptake in tumor is significantly higher than that in the surrounding liver parenchyma. Standardized uptake values (SUV) of the lesions are calculated by plotting a circular region of interest (ROI) at the area of the maximum FDG uptake in the PET images. Numerous studies have defined PET/CT positivity *vs* PET/CT negativity by using the maximum SUV (SUVmax) within ROI. In a retrospective study of 280 patients undergoing LDLT for HCC, Lee *et al*[33] defined the SUVmax values for PET/CT positivity and negativity as 4.46 and 3.08, respectively ($P < 0.001$). However, SUV measurements are prone to be influenced by a variety of factors, including high glucose metabolism in the normal liver tissue, as well as the factors related with scanner and reconstruction parameters. Therefore,

Table 4 The standardized uptake values used to define clinically significant 18F-fluorodeoxyglucose positron emission tomography/computed tomography positivity for hepatocellular carcinoma

Ref.	Year	No. of patients	Study model	SUV values		
				SUVmax	TSUVmax-to-LSUVmax	TSUVmax-to-LSUVmean
Lee *et al*[34]	2009	59	LT	3	1.15	1.35
Song *et al*[35]	2012	83	LRT	4	1.45	1.9
Lee *et al*[36]	2015	280	LDLT	4.4		
Hsu *et al*[37]	2016	147	LDLT	4.8		2
Hong *et al*[38]	2016	123	LDLT		1.1	
Boussouar *et al*[39]	2016	28	LT		1.15	
Bailly *et al*[40]	2016	34	LT		1.15	
Lin *et al*[41]	2017	65	LT	3.8	1.49	1.69

SUV: Standardized uptake values; TSUVmax: Tumor SUVmax; LSUVmax: Normal-liver SUVmax.

many researchers suggested using either tumor SUVmax to normal-liver SUVmax (TSUVmax/LSUVmax) or tumor SUVmax to normal-liver SUVmean (TSUVmax/LSUVmean) values instead of SUVmax to identify PET/CT positivity[34-41] (Table 4).

While 18F-FDG-PET/CT has demonstrated substandard sensitivity in discovering new HCC, it has been useful in detecting extra-hepatic metastases, with detection rates reported as high as 100%[42,43]. 18F-FDG-PET/CT has also been reported to detect post-treatment recurrences earlier and at higher rates than conventional imaging modalities[44]. The sensitivity of 18F-FDG-PET/CT is size-dependent in both extra-hepatic metastases and recurrences. Sugiyama *et al*[42] reported a detection rate of 83% for extra-hepatic metastases > 1 cm, which was only 13% for lesions ≤ 1 cm in diameter. In patients with post-transplant HCC recurrence, Kim *et al*[45] reported that a detection rate of > 90% has been achieved for extra-hepatic metastases when the lesions were larger than 1 cm in diameter. However, 18F-FDG-PET/CT was not able to detect any of the extra-hepatic lesions under 1 cm and demonstrated a low detection rate of less than 10% for intrahepatic recurrences. They reported a detection rate of 100% in bone, 60% in the lungs, and 100% in lymph nodes. 18F-FDG-PET/CT has also been used in the evaluation of patients with unexplained AFP elevation after surgical or interventional treatment[46]. In HCC patients presenting with portal vein thrombosis, 18F-FDG-PET/CT was found more valuable than conventional imaging studies in differential diagnosis of tumor thrombus[47,48].

Considering the limited role of 18F-FDG-PET/CT in the detection of HCC because of its low overall sensitivity, Ho *et al*[49] advocated for the use of 11C-acetate, which showed better detection sensitivity of 87.3% compared to 47.3% using 18F-FDG. In another study from Hong Kong, which evaluated the accuracy of dual-tracer PET/CT in HCC patients who underwent either partial hepatectomy or LT, the sensitivity of 11C-acetate PET/CT was significantly higher than those of 18F-FDG-PET/CT and contrast-enhanced CT for the detection of small HCCs (87.0% *vs* 17.4% and 43.5%, respectively)[50]. Recent studies have concluded that in patients undergoing LT for HCC, although 11C-choline PET had a better detection rate for well-differentiated lesions and the addition of 11C-acetate to 18F-FDG-PET/CT significantly increased the overall sensitivity and specificity for the detection of HCC, the complementary role of 18F-FDG should not be underestimated as a marker of poorly differentiated tumor pathology[51-53].

CORRELATION BETWEEN 18F-FDG PET/CT AND HISTOLOGICAL FINDINGS

In HCC, the growth rate and the activity of glycolytic enzymes are related[54]. Therefore, contrary to well differentiated HCC, poorly differentiated HCC cells have low glucose-6 phosphatase activity and high uptake of 18F-FDG[30]. Recent studies have suggested that maximum standardized uptake values in 18F-FDG PET/CT imaging demonstrated strong correlation with histopathological characteristics of HCC, such as MVI and tumor grade[28,55-57]. The reported accuracy rate of 18F-FDG-PET/CT for detection of MVI invasion and tumor differentiation in HCC ranged between 68.3% to 88.1% and 57.4% to 71.4%, respectively[55].

Considering the risk of tumor seeding and limitations related to multifocality and microscopic heterogeneity within tumor, 18F-FDG-PET/CT is a more valuable tool in the prediction of tumor biology. The maximum standardized uptake value (SUVmax) and ratio of tumor-to-normal liver SUVmax value (SUVmax T/L) have been recognized as objective indices for the definition of 18F-FDG-PET/CT positivity. In a recent study on 65 HCC patients who underwent 18F-FDG-PET/CT before LT, Lin *et al*[41] have found that the SUVmax T/L ratio was an independent predictor of vascular invasion. The optimal cutoff values for SUVmax of the tumor and SUVmax T/L ratio for the prediction of HCC vascular invasion were 3.80 and 1.49, respectively. In another study that reviewed 18F-FDG-PET/CT findings of 34 patients with HCC who underwent LT, Bailly *et al*[40] reported that none of the patients with SUVmax L/T ratio > 1.15 had well differentiated HCC.

A study from Seoul National University investigated the association of the gadoxetic acid-enhanced MR and

Table 5 The use of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in predicting post-transplant hepatocellular carcinoma recurrences

Ref.	Year	Follow-up (mo)	Recurrence		Disease-free survival	Risk of recurrence (95%CI)
			PET/CT (+)	PET/CT (-)		
Yang *et al*[28]	2006	19	13/8	25/3	2-yr, 46.1% *vs* 85.1%	OR = 7.6 (1.9-28.9)
Kornberg *et al*[56]	2009	11.5	19/9	36/1	3-yr, 46.9% *vs* 93.3%	OR = 23.9 (2.1-268.5)
Lee *et al*[34]	2013	26.1	55/22	136/16	3-yr, 57.1% *vs* 86.8%	HR = 3.9 (1.1-13.0)
Hsu *et al*[37]	2016	25.8	30/9	117/9	5-yr, 68.3 *vs* 84.8%	HR = 13.5 (4.7-38.2)
Kornberg *et al*[57]	2017	74	41/24	75/5	5-yr, 38.1% *vs* 93.3%	HR = 22.8 (6.3-83.0)
Ye *et al*[63]	2017	25.7	78/46	25/7	5-yr, 21.9% *vs* 76%	HR = 3.6 (1.3-9.6)

PET/CT: Positron emission tomography/computed tomography.

the 18F-FDG-PET/CT findings with the MVI in patients who underwent LT for HCC[58]. Multivariate analysis revealed that peritumoral enhancement and the ratio of tumor maximum standardized uptake value (SUV) to normal liver mean SUV (TSUVmax/LSUVmean) ⩾ 1.2 had a statistically significant association with MVI, with an odds ratio of 10.6 and 14.2, respectively. With regard to predicting MVI, the sensitivity and specificity was 35.7% and 93.3% for MRI and 64.3% and 86.7% for PET/CT, respectively. For the prediction of MVI, a sensitivity of 78.6% and a specificity of 80% were achieved when both imaging modalities were combined.

CORRELATION BETWEEN 18F-FDG PET/CT AND MORPHOLOGICAL CRITERIA

As the selection criteria for LT shifted towards biological criteria, MC as the current gold standard and other morphological criteria have been challenged with a number of studies using 18F-FDG PET/CT. Kornberg *et al*[59] was the first to investigate the prognostic value of preoperative 18F-FDG PET/CT in liver transplant candidates with HCC. They concluded that PET/CT negative patients with HCC beyond MC might achieve excellent post-transplant disease-free survival (DFS). In a more recent study, they combined the pre-transplant 18F-FDG-PET/CT assessments with Up-to-seven criteria[60]. Among 116 patients with HCC who underwent 18F-FDG-PET/CT prior to LT, 5-year DFS was comparable between patients within Up-to-seven criteria (n = 85) and those beyond Up-to-seven criteria with negative PET/CT (n = 16) (81.0% *vs* 87.1%, P = 0.5).

A Japanese multicenter study including 182 LDLT recipients from 16 Japanese LT centers investigated the significance of pre-transplant 18F-FDG-PET/CT at a much larger scale. While patients beyond MC had a significantly higher recurrence rate at 5 years compared with those within MC (38% *vs* 7%, P < 0.001), a subgroup of "beyond MC" patients with negative PET/CT and low AFP (< 115 ng/mL) showed similar recurrence rate with "within MC" patients (19%, P = 0.1)[61]. Similar data were recently published by the Taiwan group who combined pre-transplant PET/CT results with UCSF criteria for predicting the risk of post-transplant HCC recurrence. In a group of 147 patients with HCC who underwent 18F-FDG-PET/CT and proceeded to LDLT, patients within UCSF criteria and those beyond UCSF criteria with a low FDG uptake had similar post-transplant recurrence rates (3.6% *vs* 11.1%)[37].

Another study from Korea investigated the clinical impact of 18F-FDG-PET/CT in patients undergoing LDLT for advanced HCC, where more than half of the patients were beyond MC. In patients beyond either MC (n = 147) or UCSF (n = 136) criteria, PET/CT negative patients had 5-year DFS rates of 73.3% and 72.8%, respectively. Despite the fact that these figures were significantly lower than those of patients within MC (89.8%), the outcome is highly acceptable when the discussion shifts from "zero recurrence" towards targeting 50% 5-year survival as an acceptable goal in advanced HCC[33].

ROLE OF 18F-FDG PET/CT IN PREDICTING POST-TRANSPLANT HCC RECURRENCE

Seoul National University Hospital was the first to report the effectiveness of pre-transplant 18F-FDG-PET/CT to predict post-transplant HCC recurrence[28]. Further studies have shown that a high 18F-FDG uptake on pre-transplant PET/CT was a strong predictive factor for MVI and tumor recurrence after LT[56,33,62] (Table 5).

In a cohort of 116 liver transplant patients with HCC, Kornberg *et al*[60] reported a 5-year DFS rate of 93.3% in PET/CT negative patients *vs* 38.1% in PET/CT positive patients. PET/CT positive patients showed a recurrence rate of 58.5%, while only 6.7% of the PET/CT negative patients had recurrence. Ye *et al*[63] also investigated the clinical value of pre-transplant PET/CT in the selection and prognostic prediction of patients with advanced

HCC in the LT setting. Patients with a positive 18F-FDG-PET/CT had significantly increased risk of post-transplant recurrence compared to PET/CT negative patients (59.0% *vs* 28.0%, $P = 0.007$). In patients with positive PET/CT, they reported a significantly lower 5-year DFS rate than that of patients with negative PET/CT (76.0% *vs* 21.9%, $P < 0.001$). In another study investigating the role of PET/CT as a prognostic factor for early HCC recurrence after LT, Lee *et al*[62] have shown that median SUVmax of PET/CT-positive tumors in the early, late, and no recurrence groups was 5.2, 3.7, and 3.2, respectively. They concluded that preoperative 18F-FDG-PET/CT was an independent and significant prognostic factor for early tumor recurrence after LT for HCC.

Hong *et al*[38] further developed the concept, hypothesizing that the combination of 18F-FDG PET/CT positivity and serum AFP level might improve the prediction of post-LT outcome for patients with HCC. Using cut-off values of 200 ng/mL for AFP and 1.1 for SUVmax T/L ratio for the definition of "high-risk" HCC, they found that the rate of MVI and poor differentiation was 33% and 92%, respectively in the high-risk group. They reported 5-year DFS rates of 49.1% *vs* 93.4% in PET/CT positive *vs* negative patients and 47.7% *vs* 88.3% in high AFP *vs* low AFP patients. In the high-risk group ($n = 12$), 5-year DFS rate was only 8.4%.

CONCLUSION

In patients with HCC, LT is the best treatment option. The selection criteria for LT have been shifting from morphological to the combination of biological and histomorphological criteria. When combined with serum markers, 18F-FDG-PET/CT represents the "new generation" of biological criteria, which has the potential to further improve the prediction of tumor behavior and to provide a better risk stratification model for HCC.

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