Liver transplantation (LT) has become standard of care in patients with non-resectable early stage hepatocellular carcinoma (HCC) in liver cirrhosis. Currently, patient selection for LT is strictly based on tumor size and number, provided by the Milan criteria. This may, however, exclude patients with advanced tumor load but favourable biology from a possibly curative treatment option. It became clear in recent years that biological tumor viability rather than tumor macromorphology determines posttransplant outcome. In particular, microvascular invasion and poor grading reflect tumor aggressiveness and promote the risk of tumor relapse. Pretransplant biopsy is not applicable due to tumor heterogeneity and risk of tumor cell seeding. 18F-fludeoxyglucose (18F-FDG) positron emission tomography (PET), an established nuclear imaging device in oncology, was demonstrated to non-invasively correlate with unfavorable histopathologic features. Currently, there is an increasing amount of evidence that 18F-FDG-PET is very useful for identifying eligible liver transplant patients with HCC beyond standard criteria but less aggressive tumor properties. In order to safely expand the HCC selection criteria and the pool of eligible liver recipients, tumor evaluation with 18F-FDG-PET should be implemented in pretransplant decision process.

Citation of this article: Kornberg A, Schernhammer M, Friess H. 18F-FDG-PET for assessing biological viability and prognosis in liver transplant patients with hepatocellular carcinoma. J Clin Transl Hepatol 2017;5(3):224–234. doi: 10.14218/JCTH.2017.00014.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor and its disease burden is significantly increasing in recent years. Currently, it is the fifth most common cancer and the third most common reason of cancer-related mortality worldwide.1,2 Major hepatic resection is mainly limited by underlying cirrhosis and liver dysfunction. Apart from that, tumor recurrence rates up to 75% have been reported following surgical treatment.3,4 From an oncological point of view, orthotopic liver transplantation (LT) offers best option of cure, since it removes both the tumor with widest possible surgical margins and the tumor-generating liver cirrhosis.5 However, early experiences more than two decades ago were hampered by unacceptably high tumor recurrence rates (32%–54%) and poor survival (5-year survival 20%–40%).6-8 In 1996, Mazzaferro et al. reported on excellent prognosis in 48 patients with a single HCC nodule up to 5 cm, or a maximum of 3 tumor nodules, each not exceeding 3 cm, and absence of macrovascular invasion. Four-year overall and recurrence-free survival rates were 85% and 92% for patients meeting the so-called Milan criteria (MC), but only 50% and 59% for those exceeding them.9 By strictly adhering to the MC, post-LT prognosis was shown to be comparable to LT in non-malignant diseases.10-12 Consequently, the MC have been incorporated as standard for selecting suitable liver transplant candidates in the United Network for Organ Sharing and the Eurotransplant region. Based on the model of end-stage liver disease score, patients with HCC meeting the MC are currently prioritized by exceptional waiting list points, in order to realize timely organ allocation.14,15

In recent years, the MC were increasingly criticised for being too conservative and, thereby, for refraining a significant number of patients from a possible curative treatment option.16 Apart from that, discrepancies between radiographic and histopathologic tumor staging additionally limited clinical applicability.17,18 Therefore, many expanded HCC criteria sets were recently proposed. Yao et al. introduced 2001 the so-called University of California San Francisco (UCSF) criteria (a single tumor up to 6 cm, or up to 3 tumor nodules, each not exceeding 4.5 cm in diameter and total tumor diameter up to 8.5 cm). One and 5-year recurrence-free survival rates were 98.6% and 96.7% in patients meeting, but only 80.4% and 59.5% in those exceeding them.19 In 2008, Herrero et al. reported on acceptable outcome in LT for one HCC nodule up to 6 cm, or up to 3 tumor nodules each not exceeding 5 cm in size, when macrovascular invasion and extrahepatic tumor disease were absent.15 More recently, Mazzaferro et al. proposed the

Keywords: Hepatocellular carcinoma; Liver transplantation; 18F-fludeoxyglucose positron emission tomography; Tumor biology; Tumor recurrence.

Abbreviations: 18F-FDG, 18F-fludeoxyglucose; AFP, alpha-fetoprotein; CI, confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; LDLT, living donor liver transplantation; LRTT, locoregional tumor treatment; LSUVmax, normal liver maximum standard uptake value; LSUVmean, liver mean standard uptake value; LT, liver transplantation; MC, Milan criteria; MRI, magnetic resonance imaging; MVI, microvascular invasion; NCCK, National Cancer Center Korea; NPV, negative predictive value; OS, overall survival; PET, positron emission tomography; PPV, positive predictive value; RFS, recurrence-free survival; RR, recurrence rate; SUV, standard uptake value; TACE, transarterial chemotherapy; TLR, tumor-to-normal liver uptake ratio; TMN, tumor-to-muscle ratio; TNR, tumor-to-nontumor uptake ratio; TSU/max, maximum standard uptake value; TTS, total tumor size; UCSF, University of California San Francisco; UTS, Up-to-seven.

Received: 28 February 2017; Revised: 18 May 2017; Accepted: 5 June 2017

* Correspondence: Arno Kornberg, Department of Surgery, Klinikum rechts der Isar, Technical University Munich, Ismaningerstr. 22, D-81675 Munich, Germany. Tel: +49-89-41405087, Fax: +49-89-41404884, E-mail: ArnoKornberg@aol.com

Copyright: © 2017 Authors. This article has been published under the terms of Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided: “This article has been published in Journal of Clinical and Translational Hepatology at DOI: 10.14218/JCTH.2017.00014 and can also be viewed on the Journal’s website at http://www.jchtnet.com”.

Review Article

18F-FDG-PET for Assessing Biological Viability and Prognosis in Liver Transplant Patients with Hepatocellular Carcinoma

Arno Kornberg*, Martina Schernhammer and Helmut Friess

Department of Surgery, Klinikum rechts der Isar, Technical University Munich, Germany
so-called “Up-to-seven” criteria (UTS; sum of maximum size of the largest tumor in cm and the number of tumors). Based on histopathologic reports of 1112 liver recipients, the authors demonstrated a comparable 5-year posttransplant outcome between patients meeting the MC (73.3%) and those fulfilling the UTS criteria (71.2%), when microvascular invasion (MVI) was absent. In contrast, tumor-free survival rate was only 48.1% at 5 years in patients exceeding the UTS criteria.20 However, the study was based on postoperative histopathologic and not on preoperatively available clinical findings.20

It is nowadays generally accepted that the MC have to be liberalized in order to increase the number of HCC patients that may benefit from LT. However, it is still unclear how far the selection limits may be pushed without excessively increasing the risk of tumor relapse. Currently, a minimum survival probability between 50% and 60% at 5 years post-LT is demanded in order to balance benefit and harm of LT beyond standard criteria.21 In the so-called Metrotricket concept, Mazaferro et al. demonstrated a linear adverse prognostic impact of tumor size, whereas this negative effect tended to stagnate for tumor numbers beyond 3. With other words: when moving beyond the MC, the risk of HCC recurrence is increasingly determined by tumor biology rather than macromorphology.20

Currently, MVI and low tumor differentiation are recognized as most important predictors of biological tumor aggressiveness and poor outcome, along with serum alphafetoprotein (AFP) level and response to neoadjuvant locoregional tumor treatment (LRTT).22–24 Although tumor size and number may correlate with MVI and grading, they only inaccurately describe biological behavior of HCC.25 Pretransplant biopsy is not applicable, due to tumor heterogeneity and the theoretical risk of tumor cell seeding and bleeding.26,27 Therefore, for safely expanding the macromorphometric tumor burden limit, reliable non-invasive clinical surrogate markers of aggressive tumor properties are essential. Apart from different serologic features (AFP; des-gamma-carboxy prothrombin; yglutamyltransferase; protein induced by vitamin K absence or antagonist II), in particular 18F-fludeoxyglucose (18F-FDG) positron emission tomography (PET) was recently shown to correlate with unfavorable biological behavior and poor outcome.22,28 This review reports on current available data about the prognostic impact of 18F-FDG-PET in liver transplant patients with HCC, with a special focus on possible implications for expanding the HCC transplant criteria.

18F-FDG-PET for metabolic evaluation and staging of HCC

PET is a well-established non-invasive diagnostic tool for metabolic staging and monitoring of chemo- or radiotherapy of different malignancies.29,30 Nowadays, it is combined with computed tomography (CT) or magnetic resonance imaging (MRI) for increasing diagnostic accuracy. The most commonly used tracer in oncology is 18F-FDG, which is a glucose analogue. Tumor imaging with this tracer is based on the principle of enhanced glucose metabolism in cancer cells. Like glucose, 18F-FDG is uploaded by the tumor cells via several overexpressed glucose transporters. In normal liver tissue, activity of the enzyme glucose-6-phosphatase, which converts FGDP-6-P to FDG is high, whereas it is very low in liver metastasis, resulting in an increased FDG uptake pattern on PET scan. In contrast, the enzyme activity varies considerably among different types of HCC: Well differentiated HCC nodules exhibit an enzyme activity that is comparable to normal liver tissue. Therefore, low grade tumors tend to have a similar FDG uptake pattern than the surrounding normal liver tissue, finally leading to a low standard uptake value (SUV). On contrary, increased FDG uptake may be visualized in poorly differentiated HCC. Consequently, several studies have reported only a modest (below 50%) sensitivity of 18F-FDG-PET for diagnosing HCC.31–34 Although 18F-FDG-PET/CT is currently not recommended as first line diagnostic tool in suspected HCC, it may be useful for detecting and monitoring moderate to poorly differentiated HCC lesions, advanced stage HCC and extrahepatic metastases by a one-stop non-invasive metabolic imaging. Thus, initial tumor staging and treatment recommendations may change.35

Apart from that, 18F-FDG uptake on PET may provide useful information on biological tumor behavior. In a series of 48 HCC patients, Shiomi et al. demonstrated that the tumor-volume doubling time, an indicator of aggressive tumor growth, correlated significantly with PET results.38 Lee et al. showed that increased 18F-FDG uptake on PET was not only associated with poor tumor differentiation but also with overexpression of pro-cancerogenic gene profiles.39 Thus, important information on prognosis may be delivered by 18F-FDG-PET. In a current meta-analysis including 22 studies and a total of 1721 HCC patients, SUV and tumor-to-non tumor SUV ratio on pre-treatment 18F-FDG-PET both correlated with poor outcome.40

In recent years, several new radiotracers, such as 11C-acetate, were introduced for improving sensitivity and specificity. Despite promising early experiences, dual tracer PET/CT did not yet emerge to a popular diagnostic device in clinical routine.41,42

18F-FDG-PET for predicting tumor viability following LRTT

In contrast, response to neoadjuvant LRTT, such as transarterial chemoembolization (TACE) and radiofrequency ablation, is regarded as one of the most important clinical predictor of favorable outcome following LT for HCC.22,43 Patients with HCC initially exceeding the MC but responding to neoadjuvant LRTT by downsizing or downstaging were shown to have a posttransplant outcome that was comparable to that of patients with standard criteria tumors.44 Post-interventional complete tumor necrosis with subsequent LT may even result in cancer cure.45 By using multiphasic contrast-enhanced CT and MRI, the European Association for the Study of the Liver criteria and the modified Response Evaluation Criteria in Solid Tumors are current standard for assessing tumor response to LRTT.46 However, the use of tumor macromorphology in this context is controversial, since LRTT may lead to cancer devascularization and necrosis without accompanied tumor downsizing. Therefore, 18F-FDG-PET is increasingly studied for evaluating metabolic response to LRTT. Most studies in this context were focusing on non-surgical palliative approaches. They consistently demonstrated that 18F-FDG-PET is an appropriate indicator of response to LRTT and postinterventional outcome.47–51 Only few trials have correlated 18F-FDG-PET data with histopathologic reports after liver resection or LT following LRTT (Table 1). Already in 1994, Torizuka et al. reported on the prognostic value of 18F-FDG-PET in 30 liver transplant patients with 32 HCC nodules following pre-LT
neoadjuvant TACE. Based on visual PET evaluation, the authors have stratified according to the following FDG uptake pattern: Type A tumors showed increased FDG uptake (SUV ratio 1.07–2.66; n = 19); Type B tumors demonstrated similar FDG uptake than surrounding normal liver tissue (SUV ratio 0.77–1.04; n = 6); Type C tumors showed decreased or absent FDG uptake (SUV ratio 0.13–0.58; n = 9). On explant histopathology, viable tumor remained in all Type A and B tumors, whereas more than 90% necrosis was found in type C tumors. The authors concluded that PET might be useful to describe metabolic tumor behavior following TACE in the liver transplant setting. Cascales Campos et al. noted a decrease of the median SUV from pre-TACE 4 (range: 2.79–6.95) to 0 post-TACE (range: 0–4) in 6 liver transplant patients with HCC. On explant pathology, they found a tumor necrosis rate above 80% where SUV decreased to below 3. This interesting correlation could be confirmed in a follow-up trial of 20 liver transplant patients. In a study by Kornberg et al. including 93 liver transplant patients, PET-negativity was found to be the only independent clinical predictor of tumor response to LRTT (HR = 12.4; 95%CI 3.1–49.0; p < 0.001) assessed on explant pathology (>50% tumor necrosis rate). Consequently, the authors concluded that 18F-FDG-PET is useful for selecting patients with advanced HCC that may benefit from LRTT and, thereby, from acceptable posttransplant prognosis.

Although the number of studies is still rather limited, there is an increasing body of evidence that 18F-FDG-PET provides valuable data for prognosis evaluation in the setting of LRTT. With special regard to LT, the switch from enhanced 18F-FDG-uptake pattern to PET-negativity following LRTT might probably indicate transplant eligibility. This, however, has to be assessed in prospective trials.

Table 1. 18F-FDG-PET for predicting tumor viability following LRTT in a neoadjuvant approach

| Authors             | Technique of LRTT | n  | Stratification of subsets | Main study results                                                                 |
|---------------------|-------------------|----|--------------------------|-----------------------------------------------------------------------------------|
| Torizuka et al.     | TACE using iodized oil | 30 | Type A HCC: Increased FDG uptake (SUV 1.07–2.66) | Viable tumor following TACE in type A and B HCC; more than 90% necrosis in type C tumor; tumor necrosis rate <75% in SUV <0.6 and >100% in SUV >0.6. |
|                     |                   |    | Type B HCC: Similar to surrounding liver tissue (SUV 0.77–1.04) | Post-TACE SUV < vs. >3                                                              |
|                     |                   |    | Type C HCC: Decreased FDG uptake (SUV 0.13–0.58) | Decroase of SUV to <3 post-TACE was associated with necrosis rate >80% on explant histopathology. |
| Cascales Campos et al. | TACE             | 6  | Post-TACE SUV < vs. >3   | Decreases of SUV to <3 post-TACE was associated with necrosis rate >70% on explant histopathology and adequate 1- (100%) and 3-year (80%) survival post-LT. |
| Cascales Campos et al. | TACE             | 20 | Post-TACE SUV < vs. >3   | Increases vs. not increased 18F-FDG uptake (PET+ vs. PET- status)                  |
| Kornberg et al.     | TACE and RFA      | 59 | Increased or not increased 18F-FDG uptake | PET- status was identified as the only independent clinical predictor (HR = 12.4; 95%CI 3.1–49.0; p < 0.001) of tumor response (>50% tumor necrosis rate on explant pathology) to LRTT. |
| Kim et al.          | TACE with lipiodol | 91 | Grade I: no 18F-FDG uptake or 18F-FDG uptake lower than in surrounding liver tissue | 18F-FDG uptake correlated with histopathologic grade in treatment-naïve tumors but not in lipiodolized HCCs after TACE; 18F-FDG PET/CT showed a high diagnostic sensitivity and a moderate specificity in evaluating viability of lipiodolized HCC nodules. |
|                     |                   |    | Grade II: 18F-FDG uptake similar to the surrounding liver tissue |                                                                                   |
|                     |                   |    | Grade III: 18F-FDG uptake greater than in the surrounding liver tissue |                                                                                   |

Abbreviations: 18F-FDG, 18F-fludeoxyglucose; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; PET, positron emission tomography; SUV, standard uptake value; TACE, transarterial chemoembolization.
Table 2. 18F-FDG-PET for predicting outcome after curative liver resection for HCC

| Authors          | n  | Stratification of subsets | Major study results                                                                                                                                                                                                 |
|------------------|----|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Torizuka et al.  | 17 | —— —— —— —— —— —— —— —— | Pre-resection SUV was 6.89 ± 3.39 in low grade and 3.21 ± 0.58 in high grade tumors (p < 0.005).                                                                                                                  |
| Kobayashi et al. | 60 | High (≥3.2) vs. low (<3.2) SUVmax | Sensitivity and specificity of SUVmax ≥3.2 for predicting MVI were 77.8% and 74%. It increased to 88.9% and 82.4% by combining SUVmax with lens culinaris agglutinin-a-reactive AFP.                            |
| Baek et al.      | 54 | Low (<6.36) vs. high (≥6.36) TMR  | TMR ratio on pre-resection 18F-FDG PET correlated with MVI (p = 0.005) and tumor differentiation (p = 0.002). TMR ≥6.36 almost reached statistical significance in multivariate analysis for predicting HCC relapse (p = 0.061). |
| Ochi et al.      | 89 | High (≥8.8) vs. low (<8.8) SUVmax | SUVmax correlated significantly with tumor distance to microsatellite lesion pattern (R = 0.57; p < 0.0001). SUVmax was identified as an independent predictor of microsatellite distance >1 cm (HR = 1.60; 95%CI: 1.23–2.26; p = 0.002) and extrahepatic HCC recurrence (HR = 1.24; 95%CI 1.01–1.55; p = 0.033). |
| Hatano et al.    | 31 | High (≥2) vs. low (<2) SUV ratio | Overall 5-year survival rate was 63% in the high and 29% in the low SUV ratio subsets (p = 0.006). SUV ratio correlated significantly with tumor-related mortality (p = 0.001), tumor number (p = 0.002), tumor size (p = 0.001), vascular invasion (p = 0.005) and capsule invasion (p = 0.001). It did not remain as an independent prognostic factor for overall survival in multivariable analysis. |
| Seo et al.       | 70 | Low (<5) vs. high (≥5) SUV Low (<2) vs. high (≥2) TNR | Overall and recurrence-survival rates were significantly lower in the high than in the low FDG uptake groups (p = 0.002; p = 0.0005 for SUV; p = 0.001; p = 0.0002 for TNR). TNR but not SUV was identified as an independent predictor of postoperative recurrence (HR = 1.3; 95%CI 1.03–1.62; p = 0.03) and overall survival (HR = 1.6; 95%CI 1.07–2.38; p = 0.02). |
| Han et al.       | 298| Low (<3.5) vs. high (≥3.5) SUV | Preoperative SUV >3.5 was identified as an independent predictor of high grade tumor (HR = 3.305; 95%CI: 1.214–8.996; p = 0.019), tumor recurrence (HR = 2.025; 95%CI: 1.046–3.921; p = 0.036), and overall survival (HR = 7.331; 95%CI: 2.182–24.630; p = 0.001). |
| Ahn et al.       | 93 | Low (<4) vs. high (≥4) SUVmax Low (<2) vs. high (≥2) TNR | SUVmax and TNR correlated significantly (p < 0.001) with poor tumor differentiation. SUVmax ≥4 and TNR >2 were significant predictors for early recurrence-free survival (p = 0.026; p = 0.015) and overall survival (p = 0.005; p = 0.013). However, PET was no independent prognostic factor. |
| Kitamura et al.  | 63 | Low (<2) vs. high (≥2) TNR | TNR ≥2 was identified as an independent predictor for time interval to HCC recurrence. It was significantly lower in patients with recurrence beyond 1 year (4.4 ± 1.6; p < 0.05) or no recurrence (3.8 ± 1.5; p < 0.01) compared to those with early (within 1 year) tumor relapse (8.4 ± 6.3). Apart from that, TNR was identified as an independent prognostic factor for recurrence patterns according to the MC. It was significantly lower in patients developing tumor relapse within the MC (1.9 ± 1.6; p < 0.05) or no recurrence (1.3 ± 0.5; p < 0.01) compared to patients with tumor recurrence exceeding the MC (2.9 ± 2.6). |

Abbreviations: 18F-FDG, 18F-fludeoxyglucose; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; MC, Milan criteria; MVI, microvascular invasion; PET, positron emission tomography; SUV, standard uptake value; TMR, tumor-to-muscle ratio; TNR, tumor-to-nontumor uptake ratio.
In the past, several studies were able to demonstrate that enhanced \(^{18}\)F-FDG uptake on PET correlates with presence of aggressive histopathologic features assessed on resection specimen (Table 2).\(^{59-62}\) Other liver resection studies have focused on the prognostic role of \(^{18}\)F-FDG-PET with regard to recurrence-free and overall survival (Table 2).\(^{63-67}\) In 2 subsequent trials, the group by Kornberg et al. demonstrated beneficial post-resectional outcome in patients with low tumor to non-tumor SUV ratio (TNR). Apart from that, TNR was even identified as a significant and independent predictor of postoperative recurrence (HR = 1.3; 95%CI: 1.03–1.62; \(p = 0.03\)) and overall survival (HR = 1.6; 95%CI: 1.07–2.38; \(p = 0.02\)). Along with other well-known prognostic factors like AFP level and macroscopic portal vein invasion.\(^{64}\)

In a subset of 298 HCC patients following liver resection, Han et al. identified preoperative SUV >3.5 as an independent predictor of high grade tumor (HR = 3.305; 95%CI: 1.214–8.996; \(p = 0.019\)), tumor recurrence (HR = 2.025; 95%CI 1.046–3.921; \(p = 0.036\)), and overall survival (HR = 7.331; 95%CI: 2.182–24.630; \(p = 0.001\)).\(^{65}\) Analyzing 93 HCC patients, Ahn et al. demonstrated SUVmax \(\geq 4\) and TNR \(\geq 2\) to be significant predictors for both early recurrence-free survival (within 1 year from liver resection; \(p = 0.026\); \(p = 0.015\)) and overall survival (\(p = 0.005\); \(p = 0.013\)). However, FDG uptake had not enough prognostic power for remaining as an independent predictive factor on multivariate analysis.\(^{66}\)

Kitamura and colleagues were able to demonstrate that TNR \(\geq 2\) is an independent predictor for time interval to HCC recurrence (within 1 year vs. beyond 1 year or no recurrence).\(^{67}\) TNR was significantly lower in patients with either recurrence beyond 1 year (4.4 \(\pm\) 1.6; \(p < 0.05\)) or no recurrence (3.8 \(\pm\) 1.5; \(p < 0.01\)) compared to those with early (within 1 year) tumor relapse (8.4 \(\pm\) 6.3). Apart from that, TNR was identified as an independent prognostic factor for recurrence patterns according to the MC. It was significantly lower in patients developing tumor relapse meeting the MC (1.9 \(\pm\) 1.6; \(p < 0.05\)) or no recurrence (1.3 \(\pm\) 0.5; \(p < 0.01\)) compared to patients suffering from tumor recurrence exceeding the MC (2.9 \(\pm\) 2.6). The authors finally concluded that \(^{18}\)F-FDG-PET may be useful for establishing an individualized treatment strategy. They proposed primary liver resection in patients with TNR <2 (low risk of early and extended HCC recurrence), but LT or adjuvant treatment in those with TNR \(\geq 2\) (high risk of early or extended HCC recurrence after hepatic resection).\(^{68}\)

According to the presented data, there seems to be enough evidence that \(^{18}\)F-FDG-PET correlates with tumor biology and outcome in HCC patients following liver resection. In the context of LT, these data may have important clinical implications for applying FDG-PET in an individual decision making process on liver resection for pretransplant bridging.

**Correlation with unfavorable histopathologic features**

Poor tumor differentiation and MVI are highly relevant prognostic features in LT for HCC.\(^{10,22}\) In order to select suitable liver transplant patients with advanced HCC but favorable biology, Cillo et al. have implemented preoperative tumor biopsy decision making.\(^{66}\) However, such a diagnostic approach may not generally be recommended due to heterogenic tumor aggressiveness and risk of tumor cell spread.\(^{23,24,69}\) As shown in Table 3, \(^{18}\)F-FDG-PET is able to non-invasively indicate presence of MVI and poor differentiation. We found a wide range of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In contrast, accuracy rates were rather high in all available studies, ranging from 51.3% to 71.4% for poor grading, and from 63.3% to 88.1% for MVI, respectively. These findings clearly implicate that radiographic results should be augmented by \(^{18}\)F-FDG-PET data for improving pre-LT assessment of biological tumor aggressiveness.

**Predicting posttransplant outcome**

In recent years, there is an increasing number of studies that were focusing on the predictive value of FDG-PET in the liver transplant setting (Table 4). In 2006, Yang et al. from South Korea were the first to correlate preoperative \(^{18}\)F-FDG-PET with outcome in 38 HCC patients following LT.\(^{70}\) In this study, positive PET-status (\(^{18}\)F-FDG uptake in the tumor greater than in surrounding normal liver tissue) correlated significantly with markers of biological tumor activity, such as AFP-level (\(p < 0.001\)) and vascular invasion (\(p = 0.003\)). Posttransplant HCC recurrence rate was 61.5% in \(^{18}\)F-FDG-avid, but only 12% in non-\(^{18}\)F-FDG-avid patients (\(p = 0.003\)). The 2-year recurrence-free survival rates were 85.1% and 46.1% in patients with PET− and PET+ tumors, respectively (\(p = 0.0005\)). In the Milan In subset (n = 26), none of 20 PET-negative (0%) but 4 of 6 PET-positive patients (66.7%) survived.

### Table 3. \(^{18}\)F-FDG-PET for predicting aggressive histopathologic features in liver transplant patients with HCC

| Authors | n | PET−/PET+ (n) | Predicting poor grading (Sensitivity/Specificity/PPV/NPV/ Accuracy) | Predicting MVI (Sensitivity/Specificity/PPV/NPV/ Accuracy) |
|---------|---|---------------|---------------------------------------------------------------|--------------------------------------------------------|
| Yang et al.\(^{70}\) | 38 | 25/13 | 47.8%/85.7%/84.6%/50%/60.5% | 77.8%/79.3%/53.8%/92%/78.9% |
| Kornberg et al.\(^{72}\) | 42 | 26/16 | 83.3%/69.4%/31.3%/96.1%/71.4% | 82.3%/92%/87.5%/88.5%/88.1% |
| Kornberg et al.\(^{73}\) | 91 | 36/19 | 76.4%/70.3%/37.1%/92.9%/71.4% | 81.1%/90.7%/85.7%/87.5%/86.8% |
| Lee et al.\(^{75}\) | 191 | 136/55 | 37.3%/81.7%/75.5%/46%/51.3% | 45.4%/83.9%/66%/69.1%/67.5% |
| Lee et al.\(^{76}\) | 280 | 190/90 | (beyond MC) | 52.6%/62.3%/61.2%/53.8%/57.1% | (beyond MC) |
| Hsu et al.\(^{78}\) | 147 | 117/30 | 100%/80.7%/6.7%/100%/81% | 30.3%/85.7%/56.7%/66.7%/64.6% |

Abbreviations: MC, Milan criteria; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.
developed tumor relapse. In contrast, tumor recurrence rates did not differ between PET− (60%) and PET+ (60%) patients when exceeding the Milan criteria. The same group reported in 2009 on 59 HCC patients that underwent 18F-FDG-PET prior to LDLT (n = 57) or deceased donor (n = 2) LT. In multivariate analysis, only tumor SUVmax (TSUVmax)/normal liver SUVmax (LSUVmax) $\leq 1.15$ ($p = 0.001$) and vascular invasion ($p = 0.014$) were identified as significant and independent predictors of tumor recurrence. The authors critically noted that the significance of the data might be limited by a high rate of preoperative LRTT (75%) and, thereby, altered tumor biology.

Kornberg et al. have specifically assessed the predictive value of pretransplant 18F-FDG-PET for presence of MVI. PET-positivity was found as the only independent clinical predictor of MVI (HR = 14.4; 95%CI 0.003–0.126; $p = 0.001$) in 46 liver transplant patients. Positive and negative predictive values of enhanced 18F-FDG uptake on pretransplant PET were 87.5% and 88.5%. Eight of 16 PET+ patients developed HCC recurrence (50%) but only 1 of 26 PET− patients (3.8%; $p < 0.001$). In the Milan In subset, none of 17 PET-negative (0%) but 1 of 3 PET+ patients (33.3%) demonstrated tumor relapse ($p = 0.004$). In the Milan Out subgroup, tumor recurrence rates were 11.1% and 53.8% in non-18F-FDG-avid and 18F-FDG-avid HCCs, respectively ($p = 0.004$). The authors concluded that pretransplant 18F-FDG-PET is a useful and reliable predictor of MVI and post-LT tumor recurrence. The lack of repeat 18F-FDG-PET after neoadjuvant LRTT was recognized as a major limitation of this trial.

## Table 4. 18F-FDG-PET for predicting outcome after liver transplantation for HCC

| Authors                | n   | n (PET−/PET+) | Overall outcome (PET−/PET+) | Outcome beyond standard criteria (PET−/PET+) |
|------------------------|-----|---------------|----------------------------|---------------------------------------------|
| Yang et al.\(^70\)      | 38  | 25/13         | Overall 2y RFS: 85.1%/46.1% | RR beyond Milan: 60%/57%                     |
| Lee et al.\(^71\)       | 59  | 38/21         | Overall 2y RFS: 97%/42%     | RR beyond Milan: 9%/67%                      |
| Kornberg et al.\(^72\)  | 42  | 26/16         | Overall 3y RFS: 93%/35%     | RR beyond Milan: 11.1%/53.8%                 |
| Kornberg et al.\(^73\)  | 55  | 36/19         | Overall 3y RFS: 93.3%/46.9% | 3y RFS beyond Milan: 80%/44%                 |
| Kornberg et al.\(^74\)  | 91  | 56/35         | Overall RR: 3.6%/54.3%      | 5y RFS beyond Milan: 81%/21%                 |
|                        |     |               |                            | 5y RFS beyond UCSF: 85.7%/19.2%              |
| Lee et al.\(^75\)       | 191 | 136/55        | 5y RFS within Milan: 92.3%/76.3%/5y RFS within UCSF: 91.9%/81.8% | 5y RFS beyond Milan: 73.3%/37.5% 5y RFS beyond UCSF: 72.8%/30.7% |
| Lee et al.\(^76\)       | 280 | 190/90        | 5y RFS within Milan: 92.3%/76.3%/5y RFS within UCSF: 91.9%/81.8% | 5y RFS beyond Milan: 73.3%/37.5% 5y RFS beyond UCSF: 72.8%/30.7% |
| Lee et al.\(^77\)       | 280 | NCCK-In/NCCK-Out 164/116 | NCCK-In/NCCK-Out 5y RFS (clin. staging): 80.7%/45.1% 5y RFS (path. staging): 84%/44.4% 5y OS (clin. staging): 83.6%/59.8% 5y OS (path. staging): 85.2%/60.2% | NCCK–In/NCCK Out + Milan In/beyond NCCK and Milan 5y RFS (clin. staging): 80.7%/75.5%/30.8% 5y RFS (path. staging): 84%/81%/30.8% 5y OS (clin. staging): 83.6%/73.5%/53.9% 5y OS (path. staging): 85.2%/73.8%/57.6% |
| Hsu et al.\(^78\)       | 147 | 117/30        | Overall 5y RFS: 84.8%/68.3% | Risk stratification based on PET and UCSF (low-risk/intermediate risk/high risk) 5y RFS (clin. staging): 85.5%/83.9%/29.6% 5y RFS (path. staging): 94.0%/75.8%/29.6% |
| Hong et al.\(^79\)      | 123 | 87/36         | Overall 5y RFS: 93.4%/49.1% | Risk stratification based on PET and AFP level (low risk/intermediate risk/high risk) Overall 5y RFS: 93.6%/77.7%/8.3% 5y RFS within Milan: 92.6%/73.9%/16.7% 5y RFS beyond Milan: 100%/100%/0% |
| Takade et al.\(^80\)    | 182 | 139/43        | Overall RR: 12%/28%         | Risk stratification based on Milan, AFP and PET (Milan In or Milan Out + AFP <115ng/ml + PET−/Others) 5y OS: 75%/44% |

Abbreviations: AFP, alpha-fetoprotein; NCCK, National Cancer Center Korea; OS, overall survival; PET, positron emission tomography; RFS, recurrence-free survival; RR, recurrence rate; UCSF, University of California San Francisco.
patients, the authors reported on a relative risk of 9.5 and 6.4 for $^{18}$F-FDG-avid patients to reveal poor grading and MVI. In multivariate analysis, only poor differentiation (HR = 44; 95%CI 4.248–455.774; $p = 0.002$) and PET+ status (HR = 23.9; 95%CI 2.143–268.588; $p = 0.01$) were identified as independent promoters of tumor recurrence.\(^7\) The same group focused in 2011 on the prognostic importance of $^{18}$F-FDG-PET in advanced HCC stages (Table 4).\(^7\) In a series of 91 liver transplant patients, the authors were able to demonstrate that patients with PET-negative tumors exceeding the MC or UCSF criteria had a comparable outcome to patients meeting standard criteria. In multivariate analysis, PET status was identified as the strongest clinical predictor of recurrence-free survival (Odds ratio = 21.6; 95%CI 4.9–94.9; $p < 0.001$). In addition, the authors identified PET-positivity as an independent clinical predictor of patients’ drop out from the waiting list due to tumor progression (HR = 5.5; 95%CI 1.5–22.2; $p = 0.01$). They suggested that patients with $^{18}$F-FDG-avid HCC on the waiting list should undergo aggressive LRTT and close re-evaluations in order to prevent their drop-out due to tumor progression.\(^7\)

Lee et al. were the first to describe a specific association of metabolic behavior of HCC on $^{18}$F-FDG PET/CT with risk of early posttransplant tumor recurrence.\(^7\) In a series of 191 patients following LDLT, 20 patients suffered from early (within 6 months) and 18 patients from late (beyond 6 months) tumor relapse, whereas 153 patients remained tumor-free. Overall 3-year survival rate was 0% in patients with early HCC recurrence, compared to 64% and 94% in those with late or no tumor relapse ($p < 0.001$), respectively. In multivariate analysis, only PET+ status was identified as an independent predictor of early tumor recurrence (HR 8.472; 95%CI 3.077–23.325; $p < 0.001$), whereas PET-positivity did not correlate with late HCC recurrence. The authors, therefore, concluded that early and late tumor relapse reveal different biological aggressiveness, which may be reflected by $^{18}$F-FDG uptake pattern on PET.\(^7\)

In recent years, studies have increasingly focused on the prognostic significance of hybrid selection criteria combining $^{18}$F-FDG uptake with morphometric data. In 2015, Lee et al. reported on the so-far largest series in this context, including 280 HCC patients following LDLT.\(^7\) Apart from total tumor size (TTS >10 cm) and MVI, PET-positivity was identified as most significant independent prognostic factor in the Milan Out subset (HR = 3.803; 95%CI 1.876–7.707; $p < 0.001$). Consequently, the authors have stratified their data according to PET findings and TTS, since both features were available prior to LT. In PET-negative Milan Out patients with TTS <10 cm (n = 55), 5-year overall and recurrence-free survival rates were not significantly different (73.4%; 80.4%) from Milan In patients (87.2%; 89.9%), but significantly better than in PET-positive beyond Milan patients exceeding 10 cm in TTS (59.7%; 42.8%; $p < 0.001$). By combining $^{18}$F-FDG-PET with TTS, 37.4% of patients beyond the MC were identified as eligible liver transplant candidates in this series.\(^7\) The prognostic power of this novel expanded HCC criteria set (“The National Cancer Center Korea criteria”; NCCK criteria) in comparison to other established selection approaches has been evaluated by the same transplant group.\(^7\) Enrolling 280 patients following LDLT, 164 of them fulfilled the NCCK criteria (PET-negative + TTS <10 cm) and 132 met the MC. Based on both preoperative and histopathologic staging, 5-year recurrence-free survival rates were significantly higher in patients fulfilling the NCCK criteria (80.7%; 84%) compared to those exceeding them (45.1%; 44.7%; $p < 0.001$). Comparably, tumor-specific outcome was not different when stratified according to the MC (Milan In: 82%; 84.4%; Milan Out: 46.9%; 52.7%; $p < 0.001$). However, the NCCK revealed a higher accuracy of predicting explant pathology by preoperative imaging than the MC (95% vs. 78.9%; Cohen’s Kappa 0.850 vs. 0.583).\(^7\)

Recently, Hsu et al. proposed an expanded HCC selection approach that was based on $^{18}$F-FDG uptake and UCSF criteria.\(^7\) The authors distinguished between high (TNR ≥2; n = 9), low (TNR <2, n = 21) and no FDG uptake (n = 117) subgroups. The 5-year recurrence-free survival was significantly worse in the high (29.6%) than in the low (85%; $p = 0.005$) and the no FDG uptake subsets (85%; $p < 0.001$). In contrast, tumour-specific outcome did not differ between low and negative FDG-uptake patients ($p = 0.337$). Based on PET and pathological UCSF data, the following risk groups were defined: low-risk: UCSF In + negative FDG-PET; intermediate-risk: beyond UCSF + FDG-negative or FDG-positive with TNR <2; high-risk: FDG-uptake ≥2. Recurrence-free survival rates at 5 years post-LT were 94% in the low-risk group, 75.8% in the intermediate-risk group ($p = 0.013$ vs. low-risk) and 29.6% in the high risk subset ($p < 0.001$ vs. low- and intermediate-risk patients). In multivariable analysis, only high risk status based on pathological staging remained as a significant and independent predictor of HCC recurrence (HR = 24.15; 95%CI 5.76–101.23; $p < 0.001$). Discrepant results between clinical and pathological tumor staging and the small sample size in the high-risk subgroup (n = 9) were recognized as study limitations.\(^7\)

Other transplant groups recently suggested that combining $^{18}$F-FDG-PET with AFP level may significantly improve pre-LT selection process. Hong et al. reported on a series of 123 patients that underwent $^{18}$F-FDG-PET prior to LDLT.\(^7\) Only pre-LT available tumor factors were included in this analysis. In multivariable investigation, only PET-positivity (HR = 9.766; 95%CI 3.557–26.861; $p < 0.001$) and serum AFP level ≥200 ng/ml (HR = 6.234; 95%CI 2.643–14.707; $p < 0.001$) were identified as independent prognostic factors of HCC relapse. Accordingly, the authors defined the following risk constellations: low risk: AFP <200 ng/ml + PET− status; intermediate risk: AFP ≥200 ng/ml + PET+ or -AFP <200 ng/ml + PET-positive; high risk: AFP ≥200 ng/ml + PET-positive. Five-year recurrence-free survival rates were 93.6% in the low-risk group (n = 75), 77.7% in the intermediate-risk group (n = 36), but only 8.3% in the high-risk subset (n = 12; $p < 0.001$).\(^7\) They proposed that the MC should be completely replaced by a biology-guided selection approach.

The prognostic value of combining $^{18}$F-FDG-PET with AFP was just recently confirmed by a Japanese multicenter study including 182 HCC patients.\(^8\) Apart from Milan Out status, which was the strongest prognostic factor ($p < 0.001$), only AFP level ≥115 ng/ml + PET− status ($p = 0.008$) and PET-positivity (RR = 2.554; 95%CI 1.101–5.924; $p = 0.029$) were identified as independent promoters of HCC relapse. The following risk groups were defined: group A: meeting the MC (n = 133); group B: beyond MC + AFP level <115 ng/ml + PET− status (n = 22); group C: beyond MC + AFP level ≥115 ng/ml and/or PET+ status (n = 27). Tumor recurrence-rates at 5 years post-LT were comparable between group A and group B (6% vs. 19%; $p = 0.176$) but significantly higher in group C (53%; $p < 0.001$ vs. group A; $p = 0.012$ vs. group B). Based on these findings, the authors defined as novel expanded selection criteria: within the MC or...
beyond MC + AFP level $<115 \text{ ng/ml} + \text{ negative PET-status}$. The 5-year recurrence-free survival rates were 75% and 44% in patients meeting and exceeding them ($p = 0.003$). In addition, its correlation with poor grading and MVI was higher in comparison to previously established HCC transplant criteria (MC, UCSF, UTS; Kyoto, modified Tokyo).

**Conclusions**

Current available studies addressing the prognostic role of $^{18}$F-FDG-PET in liver transplant patients with HCC have several limitations. First, they were of retrospective character and included a relatively small number of patients. Second, most of them have included patients after LDLT and the results may not directly be transferred to recipients of a deceased donor liver allograft. Third, study populations were rather heterogeneous with regard to listing and removal criteria, pretransplant waiting times and applied LRTT concepts. And furthermore, there were significant differences in qualitative and quantitative $^{18}$F-FDG uptake measurements. However, as shown in this review, pretransplant $^{18}$F-FDG-PET provides very useful information on biological tumor viability and posttransplant outcome. Despite the lack of prospective clinical trials, there seems to be enough

---

**Fig. 1. Selection algorithm using $^{18}$F-FDG-PET in HCC patients meeting morphometric standard criteria (A) or exceeding morphometric standard criteria (B).**
evidence that 18F-FDG-PET may identify suitable liver transplant patients with advanced tumor stages but less aggressive behavior. By strictly adhering to established standards of macromorphology-based liver allocation, these patients highly ranked for liver transplantation in the management algorithm of hepatocellular carcinoma. J Gastroenterol Hepatol 2015;30:1379–85. doi: 10.1111/j.1440-1746.2014.08240.x.

Kornberg A, et al: PET in liver transplant patients with HCC

Adler M, de Paauw F, Vereerstraeten P, Fancello A, Lurie J, Starkel P, et al. Outcome of patients with hepatocellular carcinoma listed for liver transplantation within the Eurotransplant allocation system. Liver Transpl 2008;14:526–533. doi: 10.1002/lt.21399.

Elshamy M, Acefo F, Menon KV, Eghtessad B. Hepatocellular carcinoma beyond Milan criteria: Management and transplant selection criteria. World J Hepatol 2016;8:874–880. doi: 10.4255/wjh.v8.i21.874.

Sotiriopolous GC, Malagó M, Molmenti E, Paul A, Nadalin S, Brokaliak E, et al. Liver transplantation for hepatocellular carcinoma in cirrhosis: is clinical tumor classification before transplantation realistic? Transplantation 2005; 79:483–487. doi: 10.1097/01.TP.0000152801.82734.74.

Shah SA, Tan XC, McGilvray ID, Catral MS, Cleary SP, Levy GA, et al. Accuracy of staging as a predictor for recurrence after liver transplantation for hepatocellular carcinoma. Transplantation 2006;81:1633–1639. doi: 10.1097/01.TP.0000226069.66819.7e.

Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti F, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–1403. doi: 10.1053/hep.2001.24563.

Mazzaferrro V, Llovet JM, Miceli R, Bhoori S, Chiavola G, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43. doi: 10.1016/S1470-2045(08)70284-5.

Volk ML, Vigan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant 2008;8:839–846. doi: 10.1111/j.1600-6143.2007.02138.x.

Cillo U, Giuliani T, Polacco M, Herrero Manley LM, Crivellari G, Vitale A. Prediction of hepatocellular carcinoma biological behavior in patient selection for liver transplantation. World J Gastroenterol 2016;22:232–252. doi: 10.3748/wjg.v22.i1.232.

Kaido T. Selection criteria and current issues in liver transplantation for hepatocellular carcinoma. Liver Cancer 2016;5:121–127. doi: 10.1159/0004537749.

Grat P, Stygrowlowski J, Patkowski W, Bik E, Krasnodębski M, Wrónka KM, et al. Limitations of predicting microvascular invasion in patients with hepatocellular carcinoma prior to liver transplantation. Sci Rep 2017;7:39981. doi: 10.1038/srep39881.

Pawluk TM, Delman KA, Vauthay JN, Nagourney DM, Ng IO, Iklé J, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl 2005;11:1086–1092. doi: 10.1002/lt.20472.

Pawluk TM, Glesner AL, Anders RA, Assumpçao L, Mailé W, Cho MA. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. Ann Surg 2007;245:435–442. doi: 10.1097/01.sla.0000250420.73854.7d.

Rowe LR, Mulvihill SJ, Emerson L, Goyez EB. Subcutaneous tumor seeding following needle core biopsy of hepatocellular carcinoma. Diagn Cytopathol 2007;35:717–721. doi: 10.1002/dc.20717.

Kumarman V. Role of liver transplantation for hepatocellular carcinoma. J Clin Exp Hepatol 2014;4:S97–S103. doi: 10.1016/j.jceh.2014.01.002.

Hofman MS, Hicks RJ. How we read oncologic FDG PET/CT. Cancer Imaging 2014;14:66:16–35. doi: 10.1186/1477-4287-14-16. doi: 10.1159/000446680.

Nakajo M, Kajiya Y, Sasaki N, Jomura H, Nishiguchi S, Seki S, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. Transplantation 2006;81:1633–1639. doi: 10.1097/01.TP.0000226069.66819.7e.

Yoon KT, Kim JK, Kim DY, Ahn SH, Lee JD, Yun M, et al. Role of 18F-fluorodeoxyglucose positron emission tomography in detecting extrahepatic metastasis in pretreatment staging of hepatocellular carcinoma. Oncology 2007;72:Suppl 1:104–110. doi: 10.1159/000117175.
Kornberg A. et al: PET in liver transplant patients with HCC

[37] Na SJ, Oh JK, Hyun SH, Lee JW, Hong IK, Song BJ, et al. 18F-FDG PET/CT Can Predict Survival of Advanced Hepatocellular Carcinoma Patients: A Multi-center Retrospective Cohort Study. J Nucl Med 2019;57:730–736. doi: 10.2967/jnumed.118.182202.

[38] Shimoni S, Nishiguchi S, Ishizu H, Iwata Y, Sasaki N, Tamori A, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. Am J Gastroenterol 2001;96:1877–1880. doi: 10.1111/j.1572-0241.2001.00388.x.

[39] Lee JD, Yun H, Lee JM, Choi Y, Choi YH, Lee SH, et al. Analysis of ground-glass appearance of hepatocellular carcinomas with regard to 18F-fluorodeoxyglucose uptake pattern on positron emission tomography. J Eur Nucl Med Mol Imaging 2004;31:1621–1630. doi: 10.1007/s00259-004-1602-1.

[40] Sun DW, An L, Wei F, Mu L, Shi XJ, Wang CL, et al. Prognostic significance of parameters from pretreatment (18)F-FDG PET in hepatocellular carcinoma: a meta-analysis. Atembd Radiol (NY) 2016;41:33–41. doi: 10.1007/s00259-016-0653-9.

[41] Park JW, Kim JH, Kim SK, Kang KW, Park KH, Choi JJ, et al. A prospective evaluation of 18F-FDG and 11C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. J Nucl Med 2008;49:1912–1921. doi: 10.2967/jnumed.107.107516.

[42] Cheung TT, Ho CL, Lo CM, Chen S, Chan SC, Chok KS, et al. 11C-acetate and 18F-FDG PET/CT for clinical staging and selection of patients with hepatocellular carcinoma for liver transplantation on the basis of Milan criteria: surgeon’s perspective. J Nucl Med 2013;54:192–200. doi: 10.2967/jnumed.112.120837.

[43] Bhangui P, Allard MA, Vibert E, Cherqui D, Pelletier G, Cunha AS, et al. Analysis of factors predicting long-term survival of patients with non-[18F]fluorodeoxyglucose-avid advanced hepatocellular carcinoma on clinical staging may achieve long-term recurrence-free survival after liver transplantation. Liver Transplant 2017;23:237–247. doi: 10.1002/lt.24111.

[44] Torizuka T, Yamashita Y, Yoshida Y, Kurihara T, Itoh S, Harimoto N, Ikegami T, et al. Analysis of the 18F-fluorodeoxyglucose-avid extended post-interventional tumor necrosis-implication for outcome in liver transplant patients with advanced HCC. PLoS One 2013;8:e53960. doi: 10.1371/journal.pone.0053960.
Lee SD, Kim SH, Kim SK, Kim YK, Park SJ. Clinical impact of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in living donor liver transplantation for advanced hepatocellular carcinoma. Transplantation 2015;99:2142–2149. doi: 10.1097/TP.0000000000000719.

Lee SD, Lee B, Kim SH, Joo J, Kim SK, Kim YK, et al. Proposal of new expanded selection criteria using total tumor size and (18)F-fluorodeoxyglucose - positron emission tomography/computed tomography for living donor liver transplantation in patients with hepatocellular carcinoma: The National Cancer Center Korea criteria. World J Transplant 2016;6:411–422. doi: 10.5500/wjt.v6.i2.411.

Hsu CC, Chen CL, Wang CC, Lin CC, Yong CC, Wang SH, et al. Combination of FDG-PET and UCSF criteria for predicting HCC recurrence after living donor liver transplantation. Transplantation 2016;100:1925–1932. doi: 10.1097/TP.0000000000001297.

Hong G, Suh KS, Suh SW, Yoo T, Kim H, Park MS, et al. Alpha-fetoprotein and (18)F-FDG positron emission tomography predict tumor recurrence better than Milan criteria in living donor liver transplantation. J Hepatol 2016;64:852–859. doi: 10.1016/j.jhep.2015.11.033.

Takada Y, Kaido T, Shirabe K, Nagano H, Egawa H, Sugawara Y, et al. Significance of preoperative fluorodeoxyglucose-positron emission tomography in prediction of tumor recurrence after liver transplantation for hepatocellular carcinoma patients: a Japanese multicenter study. J Hepatobiliary Pancreat Sci 2017;24:49–57. doi: 10.1002/jhbp.412.