Review Article

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

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Abstract

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. ^{18}F-fludeoxyglucose (^{18}F-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 ^{18}F-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 ^{18}F-FDG-PET should be implemented in pretransplant decision process.

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Abbreviations: ^{18}F-FDG, ^{18}F-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; TMR, tumor-to-muscle ratio; TNR, tumor-to-nontumor uptake ratio; TSUVmax, tumor maximum standard uptake value; TTS, total tumor size; UCSF, University of California San Francisco; UTS, Up-to-seven.

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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 curation, 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.[10–13] 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.[12] More recently, Mazzaferro *et al.* proposed the

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 alpha-fetoprotein (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 ^{18}F-fludeoxyglucose (^{18}F-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 ^{18}F-FDG-PET in liver transplant patients with HCC, with a special focus on possible implications for expanding the HCC transplant criteria.

^{18}F-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 ^{18}F-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, ^{18}F-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 FDG-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 ^{18}F-FDG-PET for diagnosing HCC.[31–34] Although ^{18}F-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.[35–37]

Apart from that, ^{18}F-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 ^{18}F-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 ^{18}F-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 ^{18}F-FDG-PET both correlated with poor outcome.[40]

In recent years, several new radiotracers, such as ^{11}C-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]

^{18}F-FDG-PET for predicting tumor viability following LRTT

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, ^{18}F-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 ^{18}F-FDG-PET is an appropriate indicator of response to LRTT and postinterventional outcome.[47–51] Only few trials have correlated ^{18}F-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 ^{18}F-FDG-PET in 30 liver transplant patients with 32 HCC nodules following pre-LT

neoadjuvant TACE.[52] 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.[52] 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.[53] This interesting correlation could be confirmed in a follow-up trial of 20 liver transplant patients.[54] 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).[55] Consequently, the authors concluded that ^{18}F-FDG-PET is useful for selecting patients with advanced HCC that may benefit from LRTT and, thereby, from acceptable posttransplant prognosis.[55]

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

^{18}F-FDG-PET for predicting outcome after liver resection for HCC

Hepatic resection in liver cancer may be performed with curative intention or in a neoadjuvant concept prior to LT. The major aim of a surgical bridging approach is tumor control in order to prevent cancer progression and patients' drop-out from the waiting list. Besides, it allows for a precise assessment of biological tumor viability by histopathologic analysis of the resection specimen. After detection of aggressive tumor features, like MVI or poor grading, early preemptive LT may be recommended. In contrast, absence of unfavorable tumor features justifies a "wait and see" attitude with LT in case of recurrent tumor.[57,58]

Table 1. ^{18}F-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.*[52]	TACE using iodized oil	30	Type A HCC: Increased FDG uptake (SUV 1.07–2.66) Type B HCC: Similar to surrounding liver tissue (SUV 0.77–1.04) Type C HCC: Decreased FDG uptake (SUV 0.13–0.58)	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.
Cascales Campos *et al.*[53]	TACE	6	Post-TACE SUV < vs. ≥3	Decrease of SUV to <3 post-TACE was associated with necrosis rate >80% on explant histopathology.
Cascales Campos *et al.*[54]	TACE	20	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.
Kornberg *et al.*[55]	TACE and RFA	59	Increased vs. not increased ^{18}F-FDG uptake (PET+ vs. PET− status)	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.*[56]	TACE with lipiodol	91	Grade I: no ^{18}F-FDG uptake or ^{18}F-FDG uptake lower than in surrounding liver tissue Grade II: ^{18}F-FDG uptake similar to the surrounding liver tissue Grade III: ^{18}F-FDG uptake greater than in the surrounding liver tissue	^{18}F-FDG uptake correlated with histopathologic grade in treatment-naïve tumors but not in lipiodolized HCCs after TACE; ^{18}F-FDG PET/CT showed a high diagnostic sensitivity and a moderate specificity in evaluating viability of lipiodolized HCC nodules.

Abbreviations: ^{18}F-FDG, ^{18}F-fludeoxyglucose; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; PET, positron emission tomography; SUV, standard uptake value;TACE, transarterial chemoembolization.

Table 2. ^{18}F-FDG-PET for predicting outcome after curative liver resection for HCC

Authors	n	Stratification of subsets	Major study results
Torizuka *et al.*[59]	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]	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.*[61]	54	Low (<6.36) vs. high (≥6.36) TMR	TMR ratio on pre-resection ^{18}F-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.*[62]	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.*[63]	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.*[64]	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.*[65]	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.*[66]	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.*[67]	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: ^{18}F-FDG, ^{18}F-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 Hatano *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 ≥4 and TNR ≥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 ≥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 ± 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 meeting the MC (1.9 ± 1.6; p < 0.05) or no recurrence (1.3 ± 0.5; p < 0.01), compared to patients suffering from tumor recurrence exceeding the MC (2.9 ± 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 ≥2 (high risk of early or extended HCC recurrence after hepatic resection).[67]

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.

^{18}F-FDG PET for predicting outcome after liver transplantation

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.[68] However, such a diagnostic approach may not generally be recommended due to heterogenic tumor aggressiveness and risk of tumor cell spread.[25,26,69] As shown in Table 3, ^{18}F-FDG-PET is able to non-invasively indicate presence of MV 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%)

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) 58.4%/68.6%/67.2%/60%/63.3%
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.

Table 4. ^{18}F-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	3y RFS: 86.8%/57.1%	-
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.

developed tumor relapse. In contrast, tumor recurrence rates did not differ between PET− (60%) and PET+ (60%) patients when exceeding the Milan criteria.[70] The same group reported in 2009 on 59 HCC patients that underwent ^{18}F-FDG-PET prior to LDLT (n = 57) or deceased donor (n = 2) LT.[71] In multivariate analysis, only tumor SUVmax (TSUVmax)/normal liver SUVmax (LSUVmax) ≥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.[71]

Kornberg *et al.* have specifically assessed the predictive value of pretransplant ^{18}F-FDG-PET for presence of MVI.[72] 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 ^{18}F-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-^{18}F-FDG-avid and ^{18}F-FDG-avid HCCs, respectively (p = 0.004). The authors concluded that pretransplant ^{18}F-FDG-PET is a useful and reliable predictor of MVI and post-LT tumor recurrence. The lack of repeat ^{18}F-FDG-PET after neoadjuvant LRTT was recognized as a major limitation of this trial.[72] In a follow-up trial including 55 liver transplant

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.[73]

The same group focused in 2011 on the prognostic importance of ^{18}F-FDG-PET in advanced HCC stages (Table 4).[74] 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.[74]

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.[75] 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.[75]

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.[76] 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.[76] 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.[77] 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).[77]

Recently, Hsu *et al.* proposed an expanded HCC selection approach that was based on ^{18}F-FDG uptake and UCSF criteria.[78] 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, tumor-specific outcome did not differ between low and negative FGD-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 promoter 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.[78]

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.[79] 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).[79] 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.[80] Apart from Milan Out status, which was the strongest prognostic factor (p < 0.001), only AFP level ≥115 ng/ml (relative risk = 3.077; 95%CI 1.748–7.023; 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

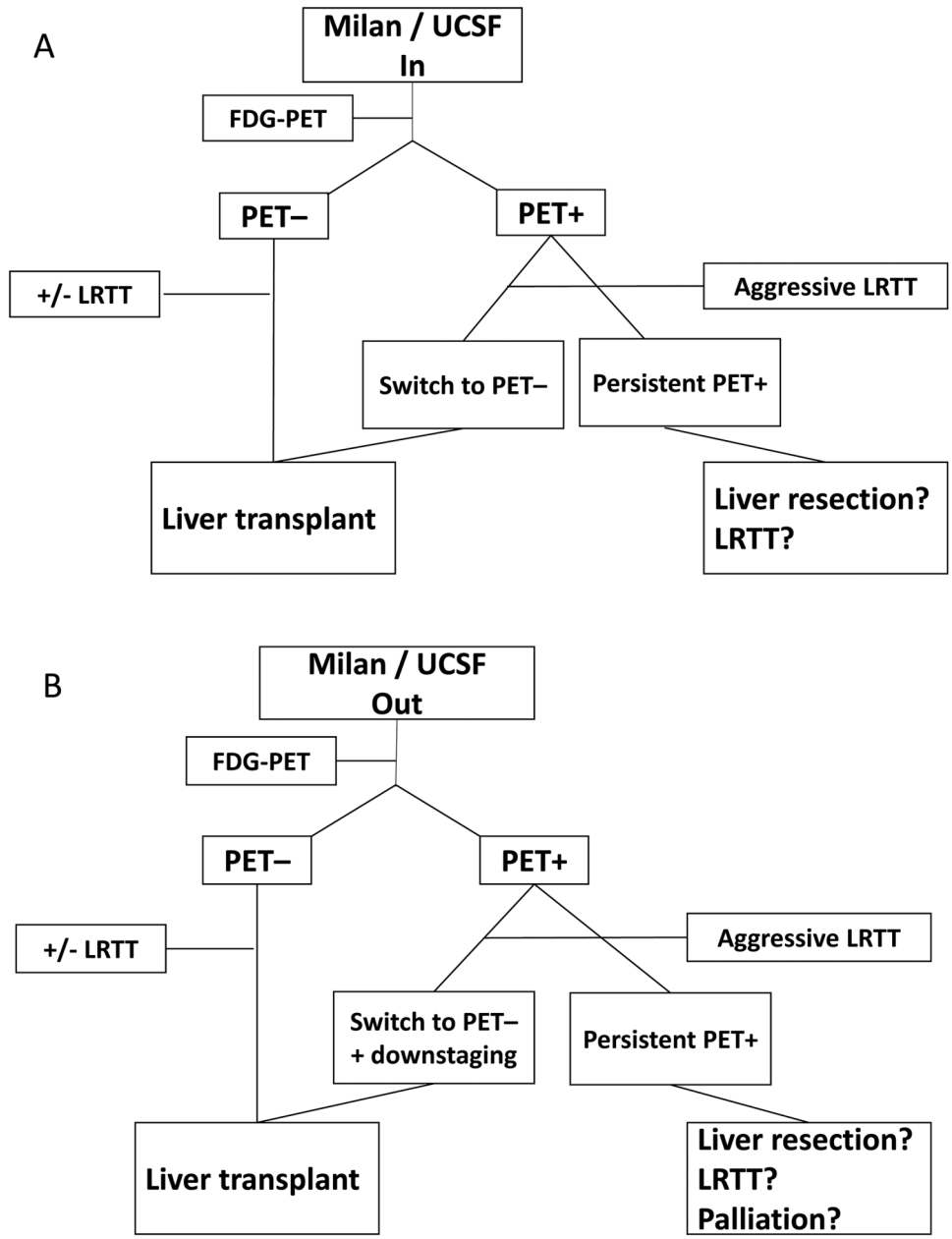

Fig. 1. Selection algorithm using ^{18}F-FDG-PET in HCC patients meeting morphometric standard criteria (A) or exceeding morphometric standard criteria (B).

beyond MC + AFP level <115 ng/ml + 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

evidence that ^{18}F-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 are currently excluded from LT and, thereby, from a major opportunity of cure. Based on the presented data, we suggest a simplified selection algorithm combining morphometric features with ^{18}F-FDG-PET for improving outcome in patients meeting (Fig. 1A) and exceeding (Fig. 1B) standard criteria. Although these selection approaches have to be validated by future studies, our review clearly suggests that ^{18}F-FDG-PET should be implemented in pretransplant decision-making for safely expanding the acceptable tumor burden limits and the pool of suitable liver transplant patients with HCC.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Performed the study, analysed data and wrote the manuscript (AK), analysed data and critically reviewed the manuscript (MS), critically reviewed the manuscript (HF).

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