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Original Research

FDG-PET predicted unfavorable tumor histology in living donor liver transplant recipients; a retrospective cohort study

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ABSTRACT

Background: Tumor histology affects outcome after liver transplantation (LT) for hepatocellular carcinoma (HCC). This study explores the association between F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) and tumor histology in living donor liver transplantation (LDLT) recipients and their outcome.
Materials and methods: Two hundred fifty-eight patients with primary liver tumors who underwent FDG-PET before LDLT were enrolled in this retrospective study. Unfavorable tumor histology was defined as primary liver tumor other than a well- or moderately differentiated HCC. Thirteen patients had unfavorable tumor histology, including 2 poorly differentiated HCC, 2 sarcomatoid HCC, 5 combined hepatocellular cholangiocarcinoma, 3 intrahepatic cholangiocarcinoma, and 1 hilar cholangiocarcinoma.
Results: FDG-PET positivity was significantly associated with unfavorable tumor histology ($P < 0.001$). Both FDG-PET positivity and unfavorable tumor histology were significant independent predictors of tumor recurrence and overall survival. In a subgroup analysis of patients with FDG-PET-positive tumors, unfavorable tumor histology was a significant independent predictor of tumor recurrence and overall survival. High FDG uptake (tumor to non-tumor uptake ratio ≥ 2) was a significant predictor of unfavorable tumor histology. Patients with high FDG uptake and/or unfavorable tumors had significantly higher 3-year cumulative recurrence rate (70.8% versus 26.2%, $P = 0.004$) and worse 3-year overall survival (34.1% versus 70.8%, $P = 0.012$) compared to those with low FDG uptake favorable tumors.
Conclusions: The expression of FDG-PET is highly associated with histology of explanted HCC and predicts the recurrence. FDG-PET-positive tumors with high FDG uptake may be considered contraindication for LDLT due to high recurrence rate except when pathology proves favorable histology.

1. Introduction

Hepatocellular carcinoma (HCC) is currently the third most common cause of cancer-related mortality [1]. Liver transplantation (LT) offers the chance of cure from both the tumor and the underlying liver cirrhosis [2,3]. The Milan and University of California San Francisco (UCSF) criteria are widely used for selecting HCC patients for LT [4,5]. However, tumors recur with a reported incidence of 15%–20% [6]. This is because both criteria rely on the tumor size and number from clinical investigations alone. Pretransplant tumor staging by imaging modality underestimates tumor burden in up to 23% of patients and there are discrepancies demonstrated between radiographic and histopathologic tumor staging [7,8]. Besides, tumor macromorphology has been identified as equally or more predictive for tumor recurrence.

Currently the important predictors of tumor recurrence after LT are

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the grade of tumor differentiation, certain HCC subtypes, presence of microvascular invasion (mVI), and serum α-fetoprotein (AFP) level [6,9]. The outcome of well- and moderately differentiated HCCs after LT is favorable [10]. Poorly differentiated HCC, sarcomatous HCC, combined hepatocellular cholangiocarcinoma (CHC), and intrahepatic or hilar cholangiocarcinoma (CC) have a significantly higher recurrence rate and a poorer prognosis after LT [11–17]. These unfavorable tumors are difficult to distinguish from favorable HCC on preoperative imaging before LT, and are usually known only after examination of the explanted liver [17–19]. Serum AFP on the other hand might not be elevated in patients with unfavorable tumor histology. Pretransplant liver biopsy can be used to determine tumor histology, but it might not always be feasible. Moreover, it is limited by sample errors.

There is growing evidence that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) independently predicts tumor recurrence in LT patients and yields useful information on tumor biology and post-LT outcome [20–28]. There seems to be enough evidence that the patients with FDG-PET-negative liver tumors can safely undergo LT for tumors exceeding morphology-based selection criteria [29]. FDG-PET-positive liver tumors are associated with aggressive biological properties such as poor differentiation and the presence of mVI that predict a poor outcome after LT [30,31]. The unfavorable histological tumor type of sarcomatous change, CHC, and CC are usually FDG-PET-positive [32,33]. However, the association between FDG-PET and unfavorable tumor histology in LT recipients and their outcome is not well understood. The aim of this study is to investigate the association between FDG-PET and tumor histology and to identify the predictors of post-transplant tumor recurrence and outcome.

2. Patients and methods

2.1. Patients

Between Jan 2000 and Aug 2017, 565 adult patients with malignant liver tumors who underwent living donor liver transplantation (LDLT) were retrospectively evaluated. Although some evolutions have developed, the surgical techniques of donors and recipients were mainly described elsewhere previously in detail [34,35]. The study was approved by the *** Medical Foundation Institutional Review Board, Taiwan (IRB No. 201800057B0) and has been reported in line with the STROCSS criteria [36]. The detailed decision making for primary resection, locoregional therapy (LRT), or LDLT has been previously described [37]. Acceptance for LDLT required the candidate to fit the UCSF criteria, in accordance with Taiwan National Health Insurance Policy. The patients' medical records were reviewed for clinicopathologic information: age, gender, viral markers, serum AFP, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) level, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and histopathological examinations.

2.2. FDG-PET/CT study and semiquantifying FDG uptake level

Detailed protocols for FDG-PET/CT and semiquantifying FDG uptake levels have been previously described [24]. An integrated PET/CT scanner (Discovery ST; GE Healthcare, USA) was used to acquire images. Standardized uptake value (SUV) was calculated as (decay-corrected radioactivity per unit volume)/(injected FDG radioactivity per body weight). The SUV_{max} of the HCC was obtained by manually placing a circular region of interest (ROI) over the tumor's area of highest activity. The tumor to non-tumor uptake ratio (TNR) was calculated as (tumor SUV_{max})/(non-tumor SUV_{mean}), where the non-tumor SUV_{mean} was the average of the SUV_{mean} at 3 ROIs (3 cm in diameter) in non-tumor liver tissue. A negative FDG-PET interpretation was based on no visually tumor uptake higher than the surrounding non-tumor liver tissue or TNR less than 1.2 and positive was defined by TNR ≥ 1.2. In patients with recent LRT, the FDG uptake in the necrotic tumor border (typical peripheral rim-shaped) without corresponding viable tumor on the CT or MRI was interpreted as post-therapy inflammation rather than tumor uptake [38].

2.3. Histopathological study

All explanted livers were histologically evaluated. Tumors were graded using the Edmondson and Steiner system. If histological pattern demonstrated an intermediate presentation between HCC and CC, immunochemical staining was performed. Likewise, if spindle cell change was encountered, positive vimentin and keratin stain and negative stain for hepatic markers would confirm sarcomatous change. The final histological evaluations of the explanted livers were performed by two specific pathologists. We classified poorly differentiated HCC, sarcomatous HCC, CHC, intrahepatic CC, and hilar CC as unfavorable tumor histology in this study.

2.4. Immunosuppressive protocol and follow up after LDLT

Basiliximab (Simulect; Novartis Pharma AG, Switzerland) was intravenously administered (20 mg) twice. Steroid therapy was tapered down and withdrawn after 3 months if no acute cellular rejection occurred. Tacrolimus (Prograf; Fujisawa, Ireland) was maintained trough level at 5–10 ng/mL during the first week after LDLT. Mycophenolate mofetil (CellCept; Roche, Puerto Rico) was continuously administered at 0.5–1 g/day. Patients diagnosed with unfavorable tumor histology, mVI or initially beyond UCSF criteria were given sirolimus (Rapamune; Pfizer, USA) that maintained trough 4–12 ng/mL. No adjuvant therapy was given to prevent recurrence. During the follow-up, the dosage of immunosuppressants was intentionally minimized if liver function was normal or stable. The backbone immunosuppressants were the combination of tacrolimus and sirolimus in most recipients. Abdominal ultrasound was performed every 3 months or if necessary. CT and MRI were arranged if clinically indicated.

2.5. Statistical analysis

Dichotomous variables are expressed as percentages and continuous values as means ± standard deviation, or as medians and interquartile range (IQR) if data were not normally distributed. Fisher's exact or χ^2 test was used to compare categorical variables. Student's *t*-test or Mann-Whitney *U* test was used to compare continuous variables between groups as appropriate. The cumulative recurrence rate and overall survival were estimated using the Kaplan-Meier method with the log-rank test. A Cox proportional hazards regression model was used to assess predictors of posttransplant tumor recurrence and overall survival. Hazard ratios (HRs, crude and adjusted) and corresponding 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve analysis was performed using nonparametric method. Significance was set at $P < 0.05$. SPSS 18 was used for all analyses.

3. Results

3.1. Patients and tumor histology

The enrolled 258 patients (202 men and 56 female) with pretransplant FDG-PET study were 55.5 ± 7.9 years of age (range, 29–71 years). One hundred fifty seven (60.9%) patients had moderately differentiated HCC; thirty (11.6%) patients had well differentiated HCC; fifty eight (22.5%) patients' tumor differentiation was uncertain because of complete tumor necrosis after LRT. The other 13 (5.0%) patients had unfavorable tumor histology: 2 poorly differentiated HCCs, 2 HCCs with sarcomatous change, 5 moderately differentiated CHCs, 1 well differentiated hilar CC, 1 moderately differentiated intrahepatic CC, and 2 intrahepatic CC with sarcomatous change (Table 1).

Table 1
Patients with unfavorable tumor histology and their outcome.

Age(y)/Sex	AFP/CEA/CA19-9	FDG-PET (SUV_{max}/TNR)	Tumor number, differentiation, histology (size)	mVI	Recurrence after LDLT (months)
58/M	9.2/4.7/27.3	–	1 MD CHC (0.8 cm), 2 MD HCC (1.2 cm, 0.7 cm)	+	− (53.8)
64/F	16.0/2.9/63.4	–	1 MD ICC (1.5 cm), 1 MD HCC (6.0 cm),	+	− (26.2)
63/M	32.7/6.3/17.4	–	1 MD CHC (1.3 cm) 4 MD HCC (3.7 cm, 2.5 cm, 1.6 cm, 1.5 cm)	–	− (14.4)
57/M	6.7/3.8/30.4	–	1 MD CHC (2.6 cm), 1 MD HCC (1.2 cm), 3 uncertain HCC (3.8 cm, 3.4 cm, 2.2 cm)	+	− (14.2)
49/M	3.5/4.1/24.8	–	1 sarcomatoid ICC (1.0 cm), 1 MD HCC (1.7 cm)	–	− (12.3)
50/M	7.6/0.9/17.3	+ (8.1/3.6)	1 MD CHC (4.0 cm)	–	+ (11.7)
58/M	7.4/2.0/266	+ (5.0/2.2)	1 WD hilar CC (2.5 cm)	+	+ (1.6)
68/F	98.7/2.3/36.2	+ (6.2/3.0)	1 MD CHC (2.7 cm), 1 MD HCC (2.2 cm)	+	+ (4.2)
58/M	4.0/2.0/41.6	+ (4.5/1.9)	1 PD HCC (2.0 cm), 3 MD HCC (1.0 cm, 0.9 cm, 0.6 cm)	+	− (40.4)
61/F	19.0/0.9/5.0	+ (4.8/2.0)	1 sarcomatoid HCC (1.7 cm)	–	+ (6.6)
60/M	5.8/1.9/19.4	+ (3.2/1.2)	1 sarcomatoid HCC (2.9 cm)	–	+ (4.1)
47/M	15.0/3.6/10.1	+ (5.2/2.1)	1 PD HCC (4.5 cm), 2 WD HCC (1.3 cm, 1.2 cm), 6 uncertain HCC (2.5 cm, 2.5 cm, 2.5 cm, 2.0 cm 2.0 cm, 1.8 cm)	+	+ (8.9)
58/F	5.8/3.7/47.1	+ (4.2/2.2)	1 sarcomatoid ICC (2.5 cm), 1 WD HCC (0.6 cm)	+	+ (6.8)

3.2. Comparison of pretransplant clinical features between favorable and unfavorable tumor groups

None of the pretransplant clinical features of age, gender, hepatitis, Child-Pugh classification, AFP, CEA or CA19-9 level was significantly associated with unfavorable tumor histology (Table 2). Patients with unfavorable tumor histology tend to have FDG-PET-positive tumors in comparison to those with favorable (8/13, 61.5% versus 33/245, 13.5%, $P < 0.001$). Using FDG-PET positivity to predict unfavorable tumor histology, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 61.5%, 86.5%, 19.5%, 97.7%, and 85.3%, respectively.

3.3. Association between FDG-PET and microvascular invasion

The incidence of mVI was 29.1% (75 of 258 patients). There was significant association between FDG-PET positivity and presence of mVI ($P < 0.001$). Using FDG-PET positivity to predict presence of mVI, the sensitivity, specificity, PPV, NPV, and accuracy were 33.3%, 91.3%, 61.0%, 77.0%, and 74.4%, respectively.

Table 2
Comparison of patient demographics and pretransplant clinical features between patients with favorable and unfavorable tumor histology.

Variables	Favorable (n = 245)	Unfavorable (n = 13)	P
Age (years)	55.6 (10.1)	58.1 (8.8)	0.286
Gender (male/female)	193/52	9/4	0.488
Hepatitis (B/C/both/none)	129/76/14/26	4/3/2/4	0.056
Child-Pugh classification (A/B/C)	148/63/33	5/6/2	0.389
Pretransplant LRT (with/without)	212/33	10/3	0.401
Pretransplant AFP (ng/mL)	8.1 (22.0)	7.6 (11.7)	0.605
Pretransplant CEA (ng/mL)	2.0 (2.0)	2.9 (2.0)	0.089
Pretransplant CA19-9 (U/mL)	19.1 (19.8)	27.3 (27)	0.063
FDG-PET (negative/positive)	212/33	5/8	< 0.001

Data expressed as median and interquartile range (IQR).

3.4. Predictors for tumor recurrence and overall survival

The median follow-up was 40.6 months (IQR: 39.2 months). Tumors recurred in 35 patients (13.6%) at a median of 14.7 months after LDLT (IQR: 15.0 months). 24 of those patients died because of the recurrent tumor. Pre-transplant AFP and the potency of immunosuppression were not associated with the risk of recurrence. In univariable analysis, FDG-PET positivity, tumor number, largest tumor size, largest tumor size more than 5 cm, total tumor size, total tumor size more than 10 cm, beyond UCSF criteria, mVI, and unfavorable tumor histology were significant predictors of posttransplant tumor recurrence (Table 3). FDG-PET positivity, mVI, and unfavorable tumor histology were also significant predictors of overall survival (Table 3). A multivariable analysis showed that FDG-PET positivity (adjusted HR: 3.61; 95% CI: 1.76–7.40; $P < 0.001$), mVI (adjusted HR: 2.56; 95% CI: 1.20–5.49; $P = 0.015$), and unfavorable tumor histology (adjusted HR: 4.00; 95% CI: 1.62–9.88; $P = 0.003$) were significant independent predictors of posttransplant tumor recurrence (Table 3). FDG-PET positivity (adjusted HR: 3.21; 95% CI: 1.56–6.61; $P = 0.002$) and unfavorable tumor histology (adjusted HR: 4.46; 95% CI: 1.79–11.08; $P = 0.001$) were also significant independent predictors of overall survival (Table 3).

3.5. Tumor recurrence and outcomes according to FDG-PET and tumor histology

The recurrence rates according to FDG-PET and tumor histology are shown in Table 4. In 245 patients with favorable tumor histology, 212 patients of them were FDG-PET-negative and their recurrence rate was 8.5%. The recurrence rate was higher at 30.3% in patients with FDG-PET-positive favorable tumors. In the 13 patients with unfavorable tumor histology, 5 patients of them were FDG-PET-negative and none had tumor recurrence. Seven of eight (87.5%) patients with FDG-PET-positive unfavorable tumors had tumor recurrence.

In FDG-PET-negative patients, the estimated 3-year cumulative recurrence rates were 8.9% and 0% for favorable and unfavorable tumors, respectively and their difference was not significant ($P = 0.636$, Fig. 1A). The 3-year overall survival were 95.1% and 100% for favorable and unfavorable tumors, respectively and their difference was not significant ($P = 0.624$, Fig. 1B). In patients with FDG-PET-positive tumors, the estimated 3-year cumulative recurrence rates were 32.8% and

Table 3
Cox hazards analysis of clinicopathological data for tumor recurrence and overall survival.

Variables	HR (95%CI) for tumor recurrence	P	HR (95%CI) for overall survival	P
Univariable analysis				
Immunosuppresants (tacrolimus + sirolimus)				
Dosage (mg/day)				
> 2	0.853(0.36–2.05)	0.722	1.224(0.27–2.00)	0.709
Concentration (ng/ml)				
> 6	0.87 (0.40–1.87)	0.712	1.162 (0.46–2.96)	0.754
Pretransplant serum AFP				
Log_{10} ng/ml	1.19 (0.70–2.03)	0.523	1.19 (0.72–1.97)	0.496
> 20 ng/ml	1.19 (0.58–2.44)	0.629	0.85 (0.41–1.78)	0.664
> 100 ng/ml	1.63 (0.57–4.63)	0.361	1.33 (0.47–3.78)	0.598
FDG-PET positivity	6.44 (3.32–12.53)	< 0.001	5.06 (2.63–9.74)	< 0.001
Number of tumors	1.12 (1.01–1.25)	0.030	0.97 (0.84–1.13)	0.704
Number of tumors > 3	1.36 (0.65–2.86)	0.417	0.62 (0.26–1.50)	0.292
Largest tumor size (cm)	1.40 (1.15–1.71)	0.001	1.06 (0.84–1.33)	0.637
Largest tumor size > 5 cm	3.23 (1.33–7.82)	0.010	0.84 (0.20–3.52)	0.816
Total tumor size (cm)	1.13 (1.05–1.21)	0.001	0.99 (0.91–1.08)	0.806
Total tumor size > 10 cm	2.43 (1.13–5.23)	0.023	1.01 (0.39–2.60)	0.985
Beyond UCSF criteria	2.62 (1.35–5.08)	0.004	1.18 (0.59–2.36)	0.644
Microvascular invasion	4.78 (2.38–9.61)	< 0.001	3.04 (1.57–5.91)	0.001
Unfavorable histology	10.17 (4.35–23.77)	< 0.001	9.06 (3.84–21.37)	< 0.001
Multivariable analysis				
FDG-PET positivity	3.61 (1.76–7.40)	< 0.001	3.21 (1.56–6.61)	0.002
Beyond UCSF criteria	1.63 (0.82–3.27)	0.165	–	–
Microvascular invasion	2.56 (1.20–5.49)	0.015	1.85 (0.91–3.77)	0.090
Unfavorable histology	4.00 (1.62–9.88)	0.003	4.46 (1.79–11.08)	0.001

87.5% for favorable and unfavorable tumors, respectively. The patients with unfavorable tumors had a significantly higher cumulative recurrence rate ($P < 0.001$, Fig. 1A). The 3-year overall survival were 68.1% and 12.5% for favorable and unfavorable tumors, respectively. The patients with unfavorable tumors also had a significantly worse overall survival ($P = 0.001$, Fig. 1B).

3.6. Subgroup analysis of patients with FDG-PET-positive tumors

For predicting unfavorable tumor histology using FDG uptake level of SUV_{max} and TNR in the subgroup of patients with FDG-PET-positive tumors, ROC curve analysis was done (Fig. 2). TNR demonstrated acceptable discrimination for predicting unfavorable tumor histology with an area under ROC curve of 0.731 ($P = 0.045$). With the TNR cutoff value of 2.0, the sensitivity, specificity, PPV, NPV, and accuracy were 75.0%, 75.8%, 42.9%, 92.6%, and 75.6%, respectively. In univariable analysis, high FDG uptake (TNR ≥ 2.0) and unfavorable tumor histology were significant predictors of posttransplant tumor recurrence and overall survival in the subgroup (Table 5). A multivariate analysis showed that unfavorable tumor histology was a significant independent predictor of posttransplant tumor recurrence (adjusted HR: 4.03; 95% CI: 1.37–11.84; $P = 0.011$) and overall survival (adjusted HR: 3.70; 95% CI: 1.21–11.33; $P = 0.022$) in the subgroup of patients with FDG-PET-positive tumors (Table 5).

The recurrence rates according to FDG uptake level and tumor histology in the subgroup are also shown in Table 4. We divided patients with FDG-PET-positive tumors into two groups: low FDG uptake (TNR between 1.2 and 2.0) favorable tumors (n = 25) and high FDG uptake and/or unfavorable tumors (n = 16). Patients with low FDG uptake favorable tumors had a 3-year cumulative recurrence rate of 26.2% and a 3-year overall survival of 70.8%. However, patients with high FDG uptake and/or unfavorable tumors had a significantly higher 3-year cumulative recurrence rate of 70.8% ($P = 0.004$, Fig. 3A) and a worse 3-year overall survival of 34.1% ($P = 0.012$, Fig. 3B).

4. Discussion

We found that unfavorable tumor histology was a significant independent predictor for posttransplant tumor recurrence and overall survival. Poorly differentiated HCC is associated with a significantly higher recurrence rate after LT and is considered by some centers as a contraindication to LT [11,39]. Sarcomatous HCC is a rare subtype, featuring both epithelial and mesenchymal tumors histologically [40,41]. The patient prognosis with sarcomatous HCC is poor: the 3-year overall survival rate after resection is 18.2% and after LT is 37.5% [12]. CHC is a rare primary liver tumor displaying histological features of both HCC and CC. Patients with CHC undergoing LT showed inferior survival in comparison with HCC [13]. Intrahepatic CC is currently considered to be a contraindication for LT because of its poor posttransplant outcome [42,43]. A recent review [16] concerning prognosis of incidental and misdiagnosed CC and CHC after LT reported a recurrence rate of 42%. Sarcomatous CC is a rare variant with adenocarcinoma and sarcomatous components [44]. A prognosis review of the literature on sarcomatous CC reported a discouraging survival rate compared with ordinary CC [45]. Median survival times of sarcomatous CC with and without surgery are 11 months and 3 months, respectively.

Table 4
Tumor recurrence rates according to FDG-PET and tumor histology.

	Favorable tumor histology (n = 245)	Unfavorable tumor histology (n = 13)	Total
FDG-PET negative (n = 217)	18/212 (8.5%)	0/5 (0%)	18/217 (8.3%)
FDG-PET positive (n = 41)	10/33 (30.3%)	7/8 (87.5%)	17/41 (41.5%)
Low FDG uptake (n = 27)	6/25 (24.0%)	1/2 (50.0%)	7/27 (25.9%)
High FDG uptake (n = 14)	4/8 (50%)	6/6 (100%)	10/14 (71.4%)
Total	28/245(11.4%)	7/13(53.8%)	

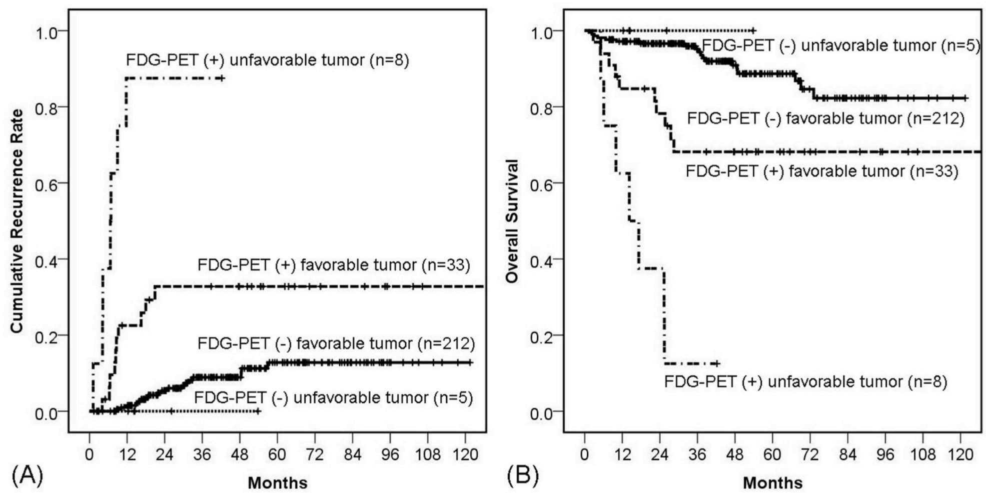

Fig. 1. Kaplan-Meier analysis of cumulative recurrence rates (A) and overall survival (B) according to FDG-PET and tumor histology.

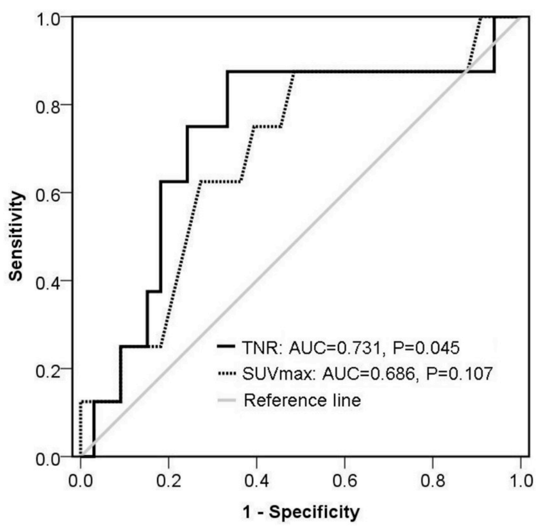

Fig. 2. The receiver operating characteristic curve analysis for predicting unfavorable tumor histology with maximum standardized uptake value (SUVmax) and tumor to non-tumor uptake ratio (TNR).

Table 5
Cox hazards analysis of clinicopathological data for tumor recurrence and overall survival in the subgroup of patients with FDG-PET-positive tumors.

Variables	HR (95%CI) for tumor recurrence	*P*	HR (95%CI) for overall survival	*P*
Univariable analysis				
Pretransplant serum AFP				
Log_{10} ng/ml	1.02 (0.51–2.07)	0.952	1.43 (0.75–2.74)	0.283
> 20 ng/ml	0.77 (0.27–2.20)	0.629	0.76 (0.27–2.15)	0.602
> 100 ng/ml	1.14 (0.26–5.00)	0.864	1.98 (0.57–6.92)	0.283
FDG-PET				
SUV_{max}	1.34 (0.97–1.87)	0.079	1.20 (0.84–1.71)	0.315
TNR	1.80 (0.95–3.40)	0.072	1.57 (0.81–3.07)	0.183
High FDG uptake	3.77 (1.41–10.10)	0.008	3.01 (1.14–7.94)	0.026
Number of tumors	0.92 (0.76–1.12)	0.408	0.83 (0.64–1.08)	0.173
Number of tumors > 3	0.41 (0.12–1.44)	0.164	0.29 (0.07–1.26)	0.097
Largest tumor size (cm)	1.13 (0.84–1.53)	0.423	0.96 (0.70–1.32)	0.801
Largest tumor size > 5 cm	1.77 (0.51–6.16)	0.371	0.95 (0.22–4.14)	0.941
Total tumor size (cm)	0.98 (0.88–1.10)	0.742	0.92 (0.80–1.05)	0.215
Total tumor size > 10 cm	0.82 (0.24–2.85)	0.754	0.58 (0.13–2.54)	0.471
Beyond UCSF criteria	0.90 (0.34–2.37)	0.834	0.75 (0.28–2.04)	0.578
Microvascular invasion	0.96 (0.36–2.51)	0.928	0.91 (0.35–2.40)	0.856
Unfavorable histology	5.70 (2.11–15.44)	0.001	4.94 (1.82–13.44)	0.003
Multivariable analysis				
High FDG uptake	2.61 (0.89–7.64)	0.080	1.93 (0.64–5.78)	0.243
Unfavorable histology	4.03 (1.37–11.84)	0.011	3.70 (1.21–11.33)	0.022

In our series, 13 of 258 (5%) patients had unfavorable tumors and all their tumor histology were identified after LDLT by examination of explanted liver. Some authors [10,39] advocate a pretransplant biopsy to select well- and moderately differentiated HCC for LT and to exclude those with poorly differentiated HCC. However, a routine pretransplant biopsy might not be useful because tumor heterogeneity can lead to a false-negative result. Moreover, ascites, coagulopathy, or inaccessible tumor locations might make a biopsy technically challenging, and there is always the risk of tumor seeding [46,47]. In our study, we found pretransplant FDG-PET was significantly associated with presence of unfavorable tumor histology. Only five (2.3%) of 217 FDG-PET-negative patients had incidental unfavorable tumors and their outcome was not significantly different in comparison to those with favorable tumors. Kornberg et al. [48] analyzed 13 patients with hilar CC after LT and reported that patients with FDG non-avid hilar CC on PET may achieve long-term recurrence-free survival after LT. Therefore, a routine biopsy to exclude unfavorable tumors might not be necessary for FDG-PET-negative patients.

Eight (19.5%) of 41 patients with FDG-PET-positive tumors had unfavorable tumors and their outcome was significant worse than those with favorable tumors. Therefore, identification of the unfavorable tumor before LT is important in the subgroup of patients with FDG-PET-positive tumors. A pretransplant biopsy might be necessary to exclude such patients from LT. In our series, their tumors were all clinically within (or downstage to fit) UCSF criteria based on pretransplant images, and seven of them (87.5%) had a normal pretransplant serum AFP level (< 20 ng/mL). There was no significant difference between favorable and unfavorable groups in pretransplant serum tumor-marker (AFP, CEA, CA 19-9) levels. We evaluated the FDG uptake level of SUV_{max} and TNR and found that TNR ≥ 2 was a significant predictor of unfavorable tumor histology in the subgroup of patients with FDG-PET-positive tumors. Our result is similar to the findings of Ijichi et al. [33] who analyzed 53 patients with liver tumors and reported that preoperative FDG-PET status was significantly associated with tumor differentiation, and that sarcomatous HCC and CHC had a much higher FDG uptake. They concluded that FDG-PET is a useful noninvasive tool

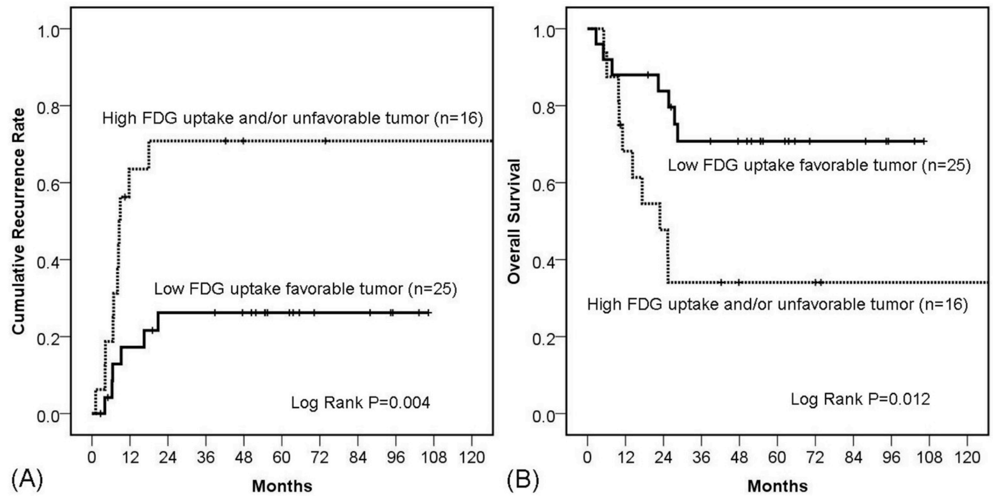

Fig. 3. Kaplan-Meier analysis of cumulative recurrence rates (A) and overall survival (B) according to FDG uptake level and tumor histology in the subgroup of patients with FDG-PET-positive tumors.

for preoperatively diagnosing aggressive primary liver cancer.

FDG-PET has recently been used in some centers to decide whether to perform LT. Studies reported that a negative FDG-PET study can identify suitable LT candidates with advanced tumors but potentially less aggressive behavior. However, there is still no consensus about how to select suitable candidates for LT in patients with FDG-PET-positive tumors. Kornberg et al. [28] suggest using aggressive LRT to convert FDG-PET-positive tumors to FDG-PET-negative status in their selection algorithm. However, there is uncertainty about persistent FDG-PET-positive status after LRT. In our study, we found unfavorable tumor histology is a significant independent predictor of posttransplant tumor recurrence and poor outcome in patients with FDG-PET-positive tumors. Tumors recurred within one year after LDLT in seven of eight patients with FDG-PET-positive unfavorable tumors. High FDG uptake was a significant pretransplant predictor of recurrence because of its association with unfavorable tumor histology. Therefore, we suggest that patients with high FDG uptake tumors on PET should be excluded from LDLT because it is more than likely futile. In addition, patients with low FDG uptake tumors should undergo either a liver resection (when feasible), or a liver biopsy in unresectable cases to exclude those with unfavorable tumors from LDLT. Our findings emphasize our previously stated [49] commitment to using strict selection criteria for HCC and to optimizing pretransplant conditions to ensure a high disease-free survival rate, like for patients without HCC, when selecting patients for LDLT.

A mounting evidence showed heavy immunosuppression has negative impacts on HCC recurrence after transplant [50]. In this study, we did not find the association between the dosage of immunosuppressants and recurrence, even in the patients of PET (−) and favorable pathology (data not shown). This may be because we consistently try to minimize our immunosuppression in the patients with unfavorable HCC. This study has some limitations. First, our patient sample is small. Second, this is a single-center retrospective study. Third, all our patients fit UCSF criteria clinically. There undoubtedly is some patient selection bias. Finally, the significance of the data might be affected by the high rate of LRT, which may alter the tumor biology.

5. Conclusion

FDG-PET is a useful noninvasive pretransplant modality to predict unfavorable tumor histology. The patients with FDG-PET-negative status might be suitable for LDLT without awareness of tumor histology. In patients with FDG-PET-positive tumors, high FDG uptake is a predictor of unfavorable tumor histology and may be considered as contraindication for LDLT due to high recurrence rate except when pathology proves favorable histology.

Registration

This study was registered in concordance with the declaration of Helsinki to researchregistry.com (UIN: 4656).

Ethical approval

Ethical Statement: The Chang Gung Medical Foundation Institutional Review Board approved this retrospective study (No. 201800057B0) and waived the requirement for written informed consent.

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Author contribution

Author Contributions: (I) Conception and design: CC Lin, CL Chen; (II) Administrative support: CC Lin, CL Chen; (III) Provision of study material or patients: CC Yong, YC Chan, CC Wang, WF Li, TL Lin, FY Kuo, YF, LM Lin, Cheng, CL Chen, CC Lin; (IV) Collection and assembly of data: LLL Ling, CC Hsu, AM Elsarawy; (V) Data analysis and interpretation: LLL Ling, CC Hsu; (VI) Manuscript writing: LLL Ling, CC Hsu, CC Lin; (VII) Final approval of manuscript: All authors.

Trial registry number

Researchregistry4656.

https://www.researchregistry.com/browse-theregistry#home/registrationdetails/5c498402c3813e2f9c26cb93/

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Nil.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.07.035.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

Data not available/The data that has been used is confidential.

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