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Composite criteria using clinical and FDG PET/CT factors for predicting recurrence of hepatocellular carcinoma after living donor liver transplantation

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Abstract

Objectives Fluorodeoxyglucose (FDG) PET/CT is effective for predicting recurrence of hepatocellular carcinoma after liver transplantation. This study aimed to design composite criteria for predicting post-transplantation recurrence using clinical and FDG PET/CT factors.

Methods We retrospectively enrolled 239 patients who underwent living donor transplantation in two independent centers between 2005 and 2013. On PET, maximum tumor-to-background ratio (TBR_{max}) was measured. Significant predictors for recurrence were selected by logistic regression and survival analyses. With varying cutoff values for the selected factors, composite criteria were designed to maximize the predictive performance for recurrence, and tenfold cross-validation was performed. Predictive values were compared between the composite criteria and the conventional recipient selection criteria.

Results Tumor size, number, alpha-fetoprotein, and TBR_{max} were selected as significant predictors in both logistic regression and multivariate survival analyses. In combination of these factors, the highest diagnostic performance was sensitivity of 75.7% and specificity of 88.5% with cutoff values of tumor size < 6.0 cm, tumor number < 8, alpha-fetoprotein < 465 ng/mL, and TBR_{max} < 2.8. The composite criteria exhibited the highest performance for predicting recurrence and recurrence-free survival among the tested criteria including conventional ones.

Conclusions The composite criteria adding FDG PET findings to clinical factors are effective in selecting appropriate liver cancer patients who are candidates for liver transplantation.

Key Points

- *In patients with HCC, tumor uptake on FDG PET/CT, tumor size, number, and serum AFP level are recognized individual predictors for tumor recurrence after LT.*
- *A composite criterion set, combining tumor size, number, serum AFP level, and maximum tumor-to-background ratio (TBR_{max}), predicts post-LT recurrence most effectively when compared with conventional criteria sets in selecting candidates for living donor LT.*

Yeon-koo Kang and Joon Young Choi contributed equally to this study.

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Keywords Hepatocellular carcinoma · Transplantation · Positron emission tomography · Recurrence

Abbreviations

AFP	Alpha-fetoprotein
HCC	Hepatocellular carcinoma
LT	Liver transplantation
RFS	Recurrence-free survival
SUV	Standardized uptake value
TBR_{max}	Maximum tumor-to-background ratio
UCSF	University of California San Francisco

Introduction

In early but unresectable hepatocellular carcinoma (HCC), liver transplantation (LT) is a radical potentially curative treatment. Particularly in patients with unresectable HCC and underlying cirrhosis, complete tumor removal and hepatic function recovery can be achieved by LT [1–3]. Due to limited organ resources, appropriate candidate selection, including prediction of post-LT tumor recurrence, is important as tumor recurrence is a major cause of failure [4, 5].

Size and number of tumors are common selection criteria for LT. According to the Milan criteria, a single tumor smaller than 5 cm or 2–3 tumors smaller than 3 cm each are eligible for LT [6]. More recent studies have reported that the Milan criteria may be too strict [7–11] and proposed more expanded criteria such as the University of California at San Francisco (UCSF) criteria [11], the "Up-to-seven" criteria [12], and the Tokyo criteria [13]. However, despite several previous studies, the candidate selection criteria for LT in HCC remain controversial [8, 10, 12, 14, 15]. Additionally, with the increase of living donor LT that is often performed in high-risk patients, revision of selection criteria is requested. Pathologic characteristics such as T-stage, histologic grade, and microvascular invasion are effective predictors [5, 16]; however, these can be fully evaluated only after surgery. Serum alpha-fetoprotein (AFP) is another effective predictor [17, 18], and was included in the Samsung criteria [19].

In patients awaiting liver transplantation, fluorodeoxyglucose (FDG) PET/CT is a valuable tool for detecting recurrence of HCC [20]. FDG PET/CT is also effective for predicting tumor recurrence in LT for HCC [17, 21–24]. Its predictive value was not inferior to that of conventional predictive factors based on tumor size and number. It is expected that a more effective prediction of recurrence and patient selection can be achieved by combining FDG PET factors and conventional predictive factors.

In this study, our aim was to design a composite criterion set by including all effective clinicopathologic factors and image findings on FDG PET, for predicting HCC recurrence after LT. Data were analyzed from two independent transplantation centers.

Materials and methods

Patients

Patients who underwent living donor LT for HCC in Seoul National University Hospital between 2005 and 2013 or in Samsung Medical Center between 2008 and 2013 were retrospectively enrolled in this study. The inclusion criteria were (1) pathologically confirmed HCC, (2) time intervals between FDG PET/CT and LT less than 4 months, and (3) post-LT follow-up more than 2 years in case of no recurrence. The study design and waive of informed consents were approved by our Institutional Review Board (H-1603-154-751).

The Milan criteria and the UCSF criteria were considered as the initial candidate selection for LT. However, living donor LT was performed for patients beyond the criteria when a patient and his/her directed donor strongly desired LT, and when there was no radiological evidence of macrovascular invasion or extrahepatic metastasis. Routine post-LT surveillance was based on contrast-enhanced CT, every 3 months in the first year, and every 6 months from the second year. MRI was complementarily used in some cases. Recurrence of a lesion was confirmed based on the imaging studies, and recurrence-free survival (RFS) was defined as the time interval between LT and confirmation of recurrence. Information on clinicopathologic factors was obtained from medical record review: sex, age, pre-LT AFP, the largest tumor diameter (cm), number of tumors, microvascular invasion, T-stage, histologic grade, and necrotic portion (%) of tumors. Size and number of tumors were measured on contrast-enhanced CT and/or MRI.

FDG PET/CT and image analysis

Patients fasted at least 6 h, and PET/CT was performed 60 min after intravenous injection of FDG (5.18 MBq/kg) using Biograph mCT40 or mCT64 (Siemens Healthcare), Gemini (Philips Healthcare), and Discovery LS or STE (GE Healthcare). CT was performed without contrast enhancement, and PET images were acquired from the skull base to the upper thigh. PET/CT images were analyzed by using vendor-supplied analysis software, and standardized uptake value (SUV) was measured. For a patient, maximum SUV (SUV_{max}) of tumor was measured by drawing a volume-of-interest (VOI) for a tumor with reference to PET, contrast-enhanced CT, and/or MRI images. In case of multiple lesions, the highest SUV_{max} was used as a representative value. Maximum tumor-to-blood pool ratio (TBR_{max}) was calculated as the ratio between SUV_{max} of tumor and mean SUV of blood pool, which was measured in three different levels of the inferior vena cava using spherical VOIs (1-cm^3 size).

Designing composite criteria and statistical analysis

Logistic regression and survival analysis for recurrence were performed to select effective predictors, which were determined by logistic regression in case of discrepancy between the two tests. In these analyses, decile values for each factor were used due to wide variations and non-normality that was shown on the Lilliefors test. For survival analyses, the Kaplan-Meier analysis and log-rank test were used for univariate analysis and the Cox proportional hazard analysis was performed for multivariate analysis. The selected factors were included in designing composite criteria. ROC graphs were drawn with varying cutoff value for each selected factor, and the combination of cutoff values that produces the highest Youden index was selected as the final composite criteria. For validation of the criteria design, tenfold cross-validation was used; patients were randomly assigned to ten groups and composite criteria designed from data of nine groups were tested in the other validation group.

All continuous values were expressed as mean ± SD or median and interquartile range for those with non-normal distribution. In group comparison, the chi-square test was used for categorical parameters and the Student *t* test or Mann-Whitney test was used for continuous parameters. Diagnostic performances were compared by McNemar's test. All statistical analyses were performed using MedCalc (Ver. 15.8, MedCalc Software bvba) or Excel (Ver. 2013, Microsoft Corp.), and a *p* value less than 0.05 was considered significant.

Results

Recurrence of HCC and predictive factors

A total of 239 patients (210 men and 29 women; age 56 ± 8 years, range 22–78 years) were enrolled in the study. Clinicopathologic characteristics are summarized in Table 1. FDG PET/CT was performed 0.8 ± 0.8 months (range 0.0–3.7 months) before LT. Patients were followed up for 53.0 ± 30.3 months (5.0–130.8 months), and HCC recurred in 74 patients (31.0%) at 13.0 ± 10.7 months (0.9–42.0 months) after LT. There was no significant difference in age, sex, and viral infection status between the recurrence and non-recurrence groups. Among the tested clinicopathologic factors, AFP, tumor size, tumor number, vascular invasion, T-stage, and histologic grade were significantly different (Table 1). TBR_{max} was also significantly higher in the recurrence group ($p < 0.001$, Table 1).

Design of composite criteria

Among the tested factors, AFP, tumor size, tumor number, and TBR_{max} were selected for designing composite criteria, as they were significant in both logistic regression analysis for recurrence prediction and multivariate survival analysis for recurrence-free time. T-stage was not selected due to its dependency on tumor size and number. Youden's indexes of vascular invasion and histologic grade were 0.399 (sensitivity 59.5%, specificity 80.5%) and 0.185 (sensitivity 58.1%, specificity 60.4%), respectively. They were not selected because they are pathologic factors that can be determined postoperatively or by invasive procedures. In logistic regression analysis, all the four factors were independent and significant factors for predicting recurrence (Table 2). Particularly, TBR_{max} exhibited the highest odds ratio and the lowest *p* value (odds ratio = 1.45, $p < 0.001$). In univariate survival analysis, all the four factors were significant for predicting RFS with high significance (Table 2). Also in multivariate analysis, all the four factors were selected as independent and significant predictors; among them, TBR_{max} exhibited the highest hazard ratio (1.33, $p < 0.001$).

Based on the results, all the four factors were included in designing composite criteria. With varying cutoff values of each factor, an ROC graph was drawn (Fig. 1). The highest diagnostic performance for predicting recurrence was sensitivity of 75.7% and specificity of 88.5% (Youden's index = 0.642), for which the optimal cutoff values were AFP < 465 ng/mL, tumor size < 6.0 cm, tumor number < 8 (up to 7), and $TBR_{max} < 2.8$ (Supplemental Table). A patient who met all these conditions was deemed to meet the composite criteria. In tenfold cross-validation, average sensitivity, specificity, and Youden's index of the composite criteria were 73.9 ± 15.9% (range 50.0–100.0), 84.6 ± 0.7% (range 62.5–100.0), and 0.585 ± 0.139 (range 0.375–0.842), respectively.

Diagnostic performance of composite criteria

The composite criteria exhibited the highest Youden index and the highest sensitivity for predicting recurrence among the compared criteria (Table 3). Also in tenfold cross-validation, the composite criteria exhibited the highest mean Youden index compared with other criteria (Table 4). When the composite criteria were used in overall group, 164 patients were within and 75 were beyond the criteria. The composite criteria exhibited significantly higher sensitivity or specificity than most of other criteria, without significant loss of the other measure of diagnostic performance. Although the Samsung criteria exhibited a significantly higher specificity than the composite criteria (0.952 vs. 0.885, $p = 0.001$), the sensitivity was much lower than that of the composite criteria (0.500 vs. 0.757, $p < 0.001$). In survival analyses using these criteria, the recurrence rate was only 11% in patients within the composite criteria, whereas it was 75% in those beyond the criteria (Fig. 2). The composite criteria exhibited the highest chi-square value and hazard ratio among the compared criteria (Table 5).

Images of representative cases are shown in Fig. 3.

Table 1 Clinicopathologic characteristics and predictive factors for recurrence

Characteristics	Total	Recurrence	Non-recurrence	p[a]
N	239	74 (31%)	165 (69%)	
Age[b], years (range)	56 ± 8 (22–78)	55 ± 10 (22–75)	56 ± 7 (33–78)	0.977
Sex, M:F	210:29	67:7	143:22	0.526
Viral status				0.079
HBV	209 (87.4%)	64 (86.5%)	145 (87.9%)	
HCV	20 (8.4%)	4 (5.4%)	16 (9.7%)	
NBNC	10 (4.2%)	6 (8.1%)	4 (2.4%)	
AFP[c], ng/mL	18.6 (6.0–131.6)	124.0 (14.0–810.0)	12.7 (5.4–55.4)	< 0.001
Tumor size[c], cm	2.5 (1.8–4.0)	4.1 (2.5–6.5)	2.2 (1.7–3.4)	< 0.001
Tumor number[c]	2 (1–4)	3 (2–6)	2 (1–3)	< 0.001
Vascular invasion	76 (31.8%)	44 (59.5%)	32 (19.4%)	< 0.001
Necrosis[c]	15% (0–80)	23% (1–80)	10% (0–86)	0.217
T-stage				< 0.001
T1/T2	205 (85.8%)	50 (67.6%)	155 (93.9%)	< 0.001
T3/T4	34 (14.2%)	24 (32.4%)	10 (6.1%)	
Histologic grade, *n*				< 0.001
1/2	131 (54.8%)	31 (41.9%)	100 (76.3%)	
3/4	108 (45.2%)	43 (58.1%)	65 (39.4%)	
TBR_{max}[c]	2.08 (1.85–2.61)	2.81 (2.18–3.53)	1.99 (1.80–2.17)	< 0.001

AFP, alpha-fetoprotein; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *NBNC*, neither HBV nor HCV; *TBR*, tumor-to-background ratio

[a] Tested by *t* test for age, chi-square test for categorical data, and Mann-Whitney test for other continuous variables

[b] Mean value ± SD

[c] Expressed in median value and interquartile range

Discussion

In this study, we evaluated various clinicopathologic factors to design composite criteria for predicting recurrence after LT, and four factors, i.e., AFP, tumor size, tumor number, and TBR_{max}, were selected as significant. In the composite criteria, a patient with AFP < 465 ng/mL, tumor size < 6.0 cm, tumor number < 8, and TBR_{max} < 2.8 is classified as eligible for LT. The composite criteria exhibited higher predictive values for recurrence and recurrence-free survival than the conventional criteria. A simple number of 500 ng/mL instead of 465 ng/mL could be used as a practical cutoff value for AFP, as it also exhibited a high predictive value (Supplemental Table, Youden's index 0.6342).

However, there is a debate about extending the criteria beyond Milan or UCSF, particularly in living donor LT [8]. Although some other clinicopathologic factors such as AFP, vascular invasion, and poor differentiation have been suggested as predictive factors [17, 18, 25], they have not been included in the candidate selection criteria. One limitation is

Table 2 Logistic regression and survival analysis for recurrence-free survival

Predictive factor	Logistic regression		Univariate survival analysis		Multivariate survival analysis	
	Odds ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
AFP	1.20 (1.06–1.36)	0.005	4.2 (2.6–6.7)	< 0.001	1.18 (1.07–1.29)	< 0.001
Tumor size	1.17 (1.03–1.34)	0.018	6.4 (4.0–10.2)	< 0.001	1.16 (1.05–1.28)	0.003
Tumor number	1.12 (1.00–1.24)	0.049	5.3 (3.0–9.28)	< 0.001	1.07 (1.00–1.15)	0.046
TBR_{max}	1.45 (1.24–1.68)	< 0.001	6.4 (3.9–10.5)	< 0.001	1.33 (1.19–1.48)	< 0.001

AFP, alpha-fetoprotein; *TBR*, tumor-to-background ratio

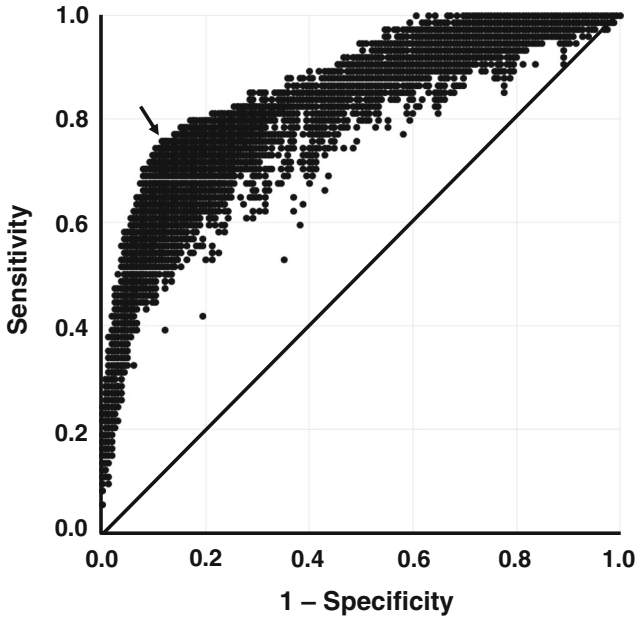

Fig. 1 Receiver-operating characteristic graph with varying cutoff values of each factor. The combination of cutoff values resulting in the highest diagnostic performance is marked by an arrow (sensitivity of 75.7% and specificity of 88.5%)

that pathological features can be accurately evaluated only from the explanted liver or by invasive procedures. In HCC, high FDG uptake is also related to poor prognosis [26, 27]. As recurrence after LT is caused by micrometastasis that has not been detected on preoperative imaging [28, 29], HCC with high FDG uptake might be more prone to metastasis because of high aggressiveness. FDG uptake is also inversely related to tumor differentiation and high uptake is shown in poorly differentiated cancer cells [30]. FDG uptake is a significant predictive factor for recurrence of HCC after LT [21–24, 27] and an effective factor for selecting candidates for LT [31].

In this study, AFP, tumor size, tumor number, and TBR_{max} were significant individual predictive factors in univariate survival analysis, in accordance with previous studies [18, 23–25, 27]. All these four factors remained significant in logistic regression and multivariate survival analyses. The combination appears to be reasonable because each of them represents different aspects of disease status; tumor size and number are markers for physical tumor burden, AFP is a marker for biochemical tumor burden, and FDG uptake is a marker for the degree of malignancy of tumor cells. In a previous study, AFP and FDG uptake were significant factors, whereas tumor size did not remain significant in multivariate analysis [27]. The difference might be the different cutoff values for each factor. In the present study, the optimal cutoff value of each factor was determined to maximize diagnostic performance by using multifactor ROC graph analysis. This analysis is similar to conventional ROC curve analysis, which is used for determining cutoff value of a single factor. Because we attempted to combine multiple factors, diagnostic value of all possible combinations was tested and displayed in the ROC graph.

The main purpose of the present study was to design composite criteria that can overcome the limitations of conventional criteria for patient selection. One of the major criticisms for the Milan and the UCSF criteria is that they are relatively strict for living donor LT [8, 11]. The Up-to-seven criteria and the Tokyo criteria are expanded criteria, and they showed higher specificity than the Milan and the UCSF criteria in the present study. However, their sensitivity for recurrence prediction was only 51.4–54.1%. Although the Samsung criteria that include serum AFP level as well as tumor size and number exhibited the highest specificity of 95.2%, the sensitivity was only 50%. It means that 50% of the recipients who are within the criteria will experience recurrence of HCC. In contrast, the composite criteria exhibited the highest sensitivity (75.7%), a very high specificity (88.5%), and the highest predictive value in survival analyses for RFS.

In the present study, TBR_{max}, the SUV ratio between the tumor and the blood pool, was used as a metabolic activity index on FDG PET. Although SUV_{max} is a widely used index in PET of many cancers, it is vulnerable to measurement errors, individual conditions, and scanner characteristics. In contrast, ratios of SUV between a tumor lesion and reference tissues are robust and often used in the analysis of FDG

Table 3 Sensitivity and specificity of each criterion for predicting recurrence after LT

Criteria	Within/beyond (*n*)	Youden's index	Sensitivity	p^*	Specificity	p^*
Composite	164 / 75	0.642	0.757	–	0.885	–
Milan	127 / 112	0.319	0.689	0.302	0.630	< 0.001
UCSF	142 / 97	0.352	0.649	0.096	0.703	< 0.001
Up-to-seven	172 / 67	0.377	0.541	< 0.001	0.836	0.216
Tokyo	186 / 53	0.423	0.514	< 0.001	0.909	0.503
Samsung	194 / 45	0.452	0.500	< 0.001	0.952	0.001

*In comparison with the composite criteria, by the McNemar test

Table 4 Tenfold cross-validation results for diagnostic performance of composite criteria in comparison with other criteria

Criteria	Sensitivity, % (range)	Specificity, % (range)	Youden's index (range)
Composite	73.9 ± 15.9	84.6 ± 11.7	0.585 ± 0.170
	(50.0–100.0)	(62.5–100.0)	(0.375–0.842)
Milan	65.5 ± 21.1	62.5 ± 11.0	0.280 ± 0.270
	(33.3–100.0)	(47.1–85.7)	(−0.111–0.579)
UCSF	59.1 ± 18.4	68.4 ± 10.8	0.275 ± 0.236
	(33.3–100.0)	(47.1–85.7)	(−0.101–0.632)
Up-to-seven	52.8 ± 19.0	83.6 ± 10.3	0.364 ± 0.183
	(16.7–80.0)	(68.4–100.0)	(0.000–0.655)
Tokyo	51.4 ± 22.1	90.5 ± 9.6	0.419 ± 0.228
	(16.7–100.0)	(68.8–100.0)	(0.111–0.895)
Samsung	49.5 ± 19.1	94.9 ± 5.1	0.444 ± 0.206
	(16.7–80.0)	(85.7–100.0)	(0.111–0.800)

*Values are expressed as mean ± SD

PET. In HCC, TBR_{max} is usually calculated as the SUV ratio between tumor and the normal liver or blood pool [21, 26, 27]. Because the liver is the diseased organ in HCC, blood pool was selected as the reference tissue in this study.

There are some limitations in this study. Firstly, it was retrospectively designed and there was some heterogeneity in patient management protocols, particularly the time intervals between LT and FDG PET. Local treatment before LT was also not controlled. Additionally, there were no independent criteria for decision of LT, and the decision was affected by conventional criteria. It may have caused a bias in comparing diagnostic performance. Secondly, multicenter data were not obtained, although a large cohort of 239 patients from two independent centers was used. Third, there may have been a variation of SUV according to different PET/CT scanners, although TBR_{max} was used instead of SUV in this study to

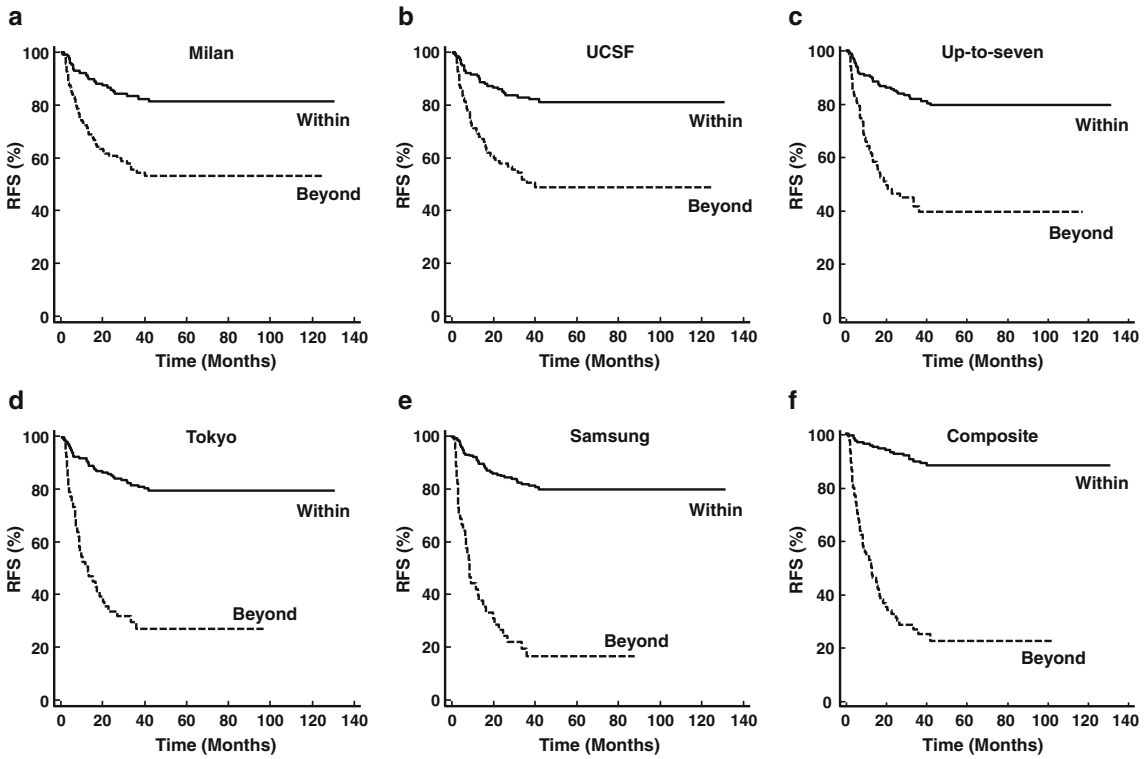

Fig. 2 Kaplan-Meier survival curves according to each patient selection criteria. In comparison with other criteria (**a**–**e**), the composite criteria exhibited the highest predictive value for recurrence-free survival (**f**)

Table 5 Prediction of recurrence-free survival by prediction models

Prediction model	*N*	Mean RFS (mo)	Recurrence rate (%)	Hazard ratio (95% CI)	χ^2	*p*
Milan criteria				3.10 (1.95–4.92)	22.68	< 0.001
Within	127	109.4 ± 4.1	18.1			
Beyond	112	72.5 ± 5.5	45.5			
UCSF criteria				3.39 (2.11–5.47)	28.67	< 0.001
Within	142	109.0 ± 3.9	18.3			
Beyond	97	67.9 ± 5.9	49.5			
Up-to-seven criteria				4.09 (2.37–7.06)	43.24	< 0.001
Within	172	107.0 ± 3.7	19.8			
Beyond	67	53.2 ± 6.4	59.7			
Tokyo criteria				5.76 (3.07–10.82)	73.86	< 0.001
Within	186	107.6 ± 3.5	19.3			
Beyond	53	34.6 ± 5.4	71.7			
Samsung criteria				7.84 (3.82–16.10)	112.45	< 0.001
Within	194	108.0 ± 3.4	19.1			
Beyond	45	23.6 ± 4.6	82.2			
Composite criteria				11.40 (6.54–19.85)	132.44	< 0.001
Within	164	117.8 ± 2.9	11.0			
Beyond	75	33.2 ± 4.7	74.7			

RFS, recurrence-free survival

compensate such variation. Finally, recurred lesions were not pathologically confirmed, which may have caused a little diagnostic error.

In conclusion, AFP, tumor size, tumor number, and TBR_{max} on FDG PET/CT are independent factors for predicting recurrence of HCC after living donor LT. Composite criteria for candidate selection could be suggested by simple numbers: AFP < 500 ng/mL, tumor size < 6.0 cm, tumor number < 8, and TBR_{max} < 2.8. The composite criteria using these factors exhibited excellent predictive values for predicting recurrence compared with conventional criteria. The composite criteria are expected to be effective in selecting appropriate patients who can benefit from LT.

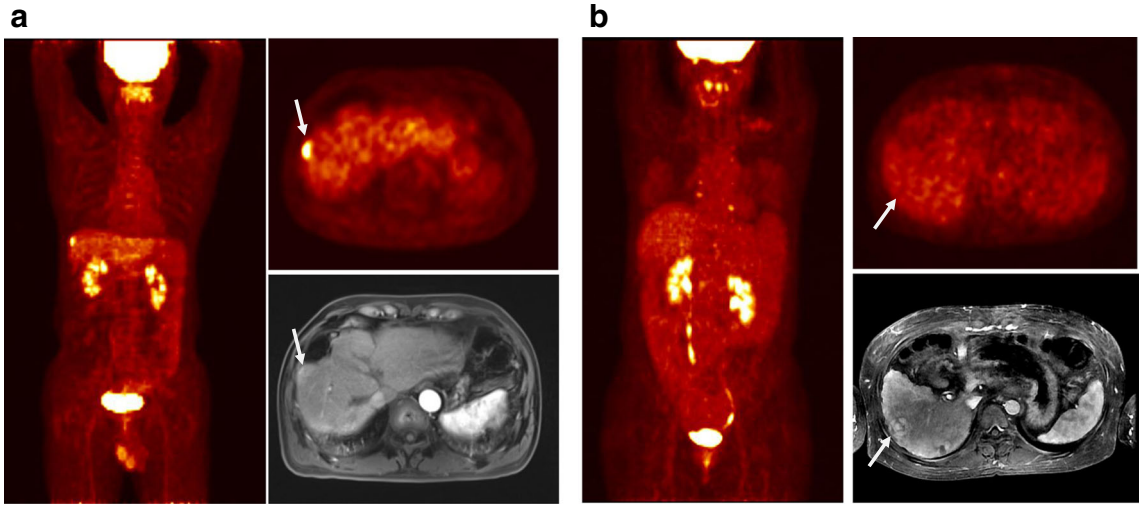

Fig. 3 The representative cases. **a** A 65-year-old man with HCC whose tumor number was 3, the largest tumor size was 2.5 cm (arrow), AFP was 86.1 ng/mL, and TBR_{max} was 5.18. He was within the Milan criteria, but above the composite criteria. He experienced recurrence 16.0 months after LT. **b** A 43-year-old woman with HCC whose tumor number was 5, the largest tumor size was 2.9 cm (arrow), AFP was 59.4 ng/mL, and TBR_{max} was 1.72. Although she was above the Milan criteria, she was within the composite criteria. She survived for 73.3 months without recurrence

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Jin Chul Paeng, MD, PhD.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in articles of different purposes and different study designs: Lee et al. J Nucl Med 2009;50:682, Hong et al. J Hepatol 2016;64:852, Kim et al. J Nucl Med 2016;57:1045.

Methodology
- retrospective
- diagnostic or prognostic study
- multicenter study

References

1. Doyle MB, Vachharajani N, Maynard E et al (2012) Liver transplantation for hepatocellular carcinoma: long-term results suggest excellent outcomes. J Am Coll Surg 215:19–28
2. Moreno P, Jaurrieta E, Figueras J et al (1995) Orthotopic liver transplantation: treatment of choice in cirrhotic patients with hepatocellular carcinoma? Transplant Proc 27:2296–2298
3. Ringe B, Pichlmayr R, Wittekind C, Tusch G (1991) Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg 15:270–285
4. Roayaie S, Schwartz JD, Sung MW et al (2004) Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl 10:534–540
5. Klintmalm GB (1998) Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. Ann Surg 228:479–490
6. Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334:693–699
7. (2006) Consensus conference: indications for Liver Transplantation, January 19 and 20, 2005, Lyon-Palais Des Congres: text of recommendations (long version). Liver Transpl 12:998–1011
8. Broelsch CE, Frilling A, Malago M (2005) Should we expand the criteria for liver transplantation for hepatocellular carcinoma–yes, of course! J Hepatol 43:569–573
9. Duffy JP, Vardanian A, Benjamin E et al (2007) Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 246:502–509
10. Majno P, Mazzaferro V (2006) Living donor liver transplantation for hepatocellular carcinoma exceeding conventional criteria: questions, answers and demands for a common language. Liver Transpl 12:896–898
11. Yao FY, Ferrell L, Bass NM et al (2001) Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33:1394–1403
12. Mazzaferro V, Llovet JM, Miceli R et al (2009) Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 10:35–43
13. Akamatsu N, Sugawara Y, Kokudo N (2014) Living donor liver transplantation for patients with hepatocellular carcinoma. Liver Cancer 3:108–118
14. Hiatt JR, Carmody IC, Busuttil RW (2005) Should we expand the criteria for hepatocellular carcinoma with living-donor liver transplantation?–no, never. J Hepatol 43:573–577
15. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A (2012) Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 13:e11–e22
16. Jonas S, Bechstein WO, Steinmüller T et al (2001) Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology 33:1080–1086
17. Hong G, Suh KS, Suh SW et al (2016) Alpha-fetoprotein and (18)F-FDG positron emission tomography predict tumor recurrence better than Milan criteria in living donor liver transplantation. J Hepatol 64:852–859
18. Kwon CH, Kim DJ, Han YS et al (2007) HCC in living donor liver transplantation: can we expand the Milan criteria? Dig Dis 25:313–319
19. Kim JM, Kwon CH, Joh JW et al (2014) Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. Transplant Proc 46:726–729
20. Refaat R, Basha MAA, Hassan MS et al (2018) Efficacy of contrast-enhanced FDG PET/CT in patients awaiting liver transplantation with rising alpha-fetoprotein after bridge therapy of hepatocellular carcinoma. Eur Radiol 28:5356–5367
21. Lee JW, Paeng JC, Kang KW et al (2009) Prediction of tumor recurrence by ^{18}F-FDG PET in liver transplantation for hepatocellular carcinoma. J Nucl Med 50:682–687
22. Yang SH, Suh KS, Lee HW et al (2006) The role of 18F-FDG-PET imaging for the selection of liver transplantation candidates among hepatocellular carcinoma patients. Liver Transpl 12:1655–1660
23. Kim YI, Paeng JC, Cheon GJ et al (2016) Prediction of post-transplantation recurrence of hepatocellular carcinoma by using metabolic and volumetric indices of ^{18}F-FDG PET/CT. J Nucl Med 57:1045–1051
24. Kornberg A, Freesmeyer M, Bärthel E et al (2009) ^{18}F-FDG-uptake of hepatocellular carcinoma on PET predicts microvascular tumor invasion in liver transplant patients. Am J Transplant 9:592–600
25. Shin WY, Suh KS, Lee HW et al (2010) Prognostic factors affecting survival after recurrence in adult living donor liver transplantation for hepatocellular carcinoma. Liver Transpl 16:678–684
26. Hyun SH, Eo JS, Lee JW et al (2016) Prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with Barcelona clinic liver Cancer stages 0 and a hepatocellular carcinomas: a multicenter retrospective cohort study. Eur J Nucl Med Mol Imaging 43:1638–1645
27. Lee JW, Oh JK, Chung YA et al (2016) Prognostic significance of ^{18}F-FDG uptake in hepatocellular carcinoma treated with transarterial chemoembolization or concurrent chemoradiotherapy: a multicenter retrospective cohort study. J Nucl Med 57:509–516
28. Imamura H, Matsuyama Y, Tanaka E et al (2003) Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 38:200–207

29. Schlitt HJ, Neipp M, Weimann A et al (1999) Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. J Clin Oncol 17:324–331
30. Seo S, Hatano E, Higashi T et al (2007) Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, P-glycoprotein expression, and outcome after resection in hepatocellular carcinoma. Clin Cancer Res 13:427–433
31. Kornberg A, Witt U, Schernhammer M et al (2017) Combining ^{18}F-FDG positron emission tomography with Up-to-seven criteria for selecting suitable liver transplant patients with advanced hepatocellular carcinoma. Sci Rep 7:14176