Impact of metabolic indices of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography on post transplantation recurrence of hepatocellular carcinoma.

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Abstract

Background Tumor recurrence is the leading cause of death after liver transplantation in patients with hepatocellular carcinoma. There is an ongoing debate as to whether metabolic indices such as tumor to liver standardized uptake value ratio in 18 F-fluorodeoxyglucose positron emission tomography/computed tomography of the primary tumor can identify patients outside the Milan criteria with as low recurrence rates as patients inside Milan and thus should be added to the established prognostic factors. **Methods** This retrospective study analyzes 103 consecutive patients who underwent 18 F fluorodeoxyglucose positron emission tomography/computed tomography before liver transplantation for hepatocellular carcinoma using data of clinical tumor registry. Primary endpoints were overall survival and 10-year cumulative recurrence rates. **Results** Tumor to liver standardized uptake value ratio of the primary tumor was statistically significant higher in Milan out tumors, “up-to-seven” out tumors, grade 3 tumors, alpha-fetoprotein level >400 ng/ml and lesions upwards 5cm in diameter. Factors with statistically significant influence on the 10-year overall survival in the univariate analysis were Milan, up-to-seven” criteria, number of lesions and pT-category. COX regression analysis did not show independently statistically significant factors for 10-year overall survival. Milan, “up-to-seven” criteria, grade, pV, number of lesions, size of lesion, pT-category, tumor to liver standardized uptake value ratio influenced 10-year cumulative recurrence rates statistically significantly. Tumor to liver standardized uptake value ratio, grade and pT-category proved to be independently statistically significant factors for 10-year cumulative recurrence rates. **Conclusions** Our study suggests that tumor to liver standardized uptake value standardized uptake value ratio in 18 F-fluorodeoxyglucose positron emission tomography/computed tomography is an independent prognostic factor in transplanted patients with hepatocellular carcinoma and might be helpful in estimating the risk of recurrence for patients scheduled for liver transplantation.

1. Introduction

Tumor recurrence is the leading cause of death after liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) in cirrhosis. In 1996 Milan criteria were introduced by Mazzaferro et al. [16] and this classification is still recommended by a few guidelines for assigning patients exceptional Meld points or for initial listing for liver transplantation. It is well known that a certain patient population “outside” Milan can be found that show similar low recurrence rates as patients “inside” Milan. There is an ongoing debate as to whether biological markers, such as alpha-fetoprotein (AFP), Des-gammo-carboxy prothrombin (DCP), grading, neutrophil-lymphocyte ratio [7] or downstaging after initial presentation with disease outside the Milan criteria [2, 6, 17, 18, 19, 21, 22] should be considered to refine criteria for transplantation.

The diagnostic potential of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) in the evaluation of transplant candidates is well established for extrahepatic tumor. However, the sensitivity of ¹⁸F-FDG PET/CT for HCC is lower than in metastatic liver cancer or cholangiocellular carcinoma (CCC) [9]. In recent years, the use of volumetric indices in PET/CT has been more frequent because they may reflect location of cancerous tissue as well as metabolic activity. This combination of metabolic activity and computed tomography (CT) images is supposed to discriminate more precisely between physiologic and malignant FDG uptake and may support physicians in the calculation of recurrence risk more accurately.

The study analyzes the value of 18F-FDG PET/CT for the identification of patients with HCC in cirrhosis and the tumor biology after LT.

2. Materials And Methods

This study in human subjects was carried out with consent of the local ethics committee (reg.-no. :2020-1827-Daten) in accordance with national law and the Declaration of Helsinki of 1975 (in the current form)

2.1. Patients

Here we analyze 103 consecutive patients who underwent ^{18}F -FDG PET/CT in our hospital before liver transplantation for HCC from 2009 to 2019. Patient data, HCCs, treatment and follow-up were extracted from standard medical records. Data not found in the standard medical records were completed by contacting clinicians.

Diagnostic procedures were applied following current European guidelines for the diagnosis and treatment of hepatocellular carcinoma [15]. Decisions about diagnosis and treatment were made by the tumor board with participation of hepatobiliary surgeons, radiologists, oncologists, nuclear medicine physicians and radiotherapists.

We analyzed the morphological data of the tumor load in pre-transplant computed tomography scans (CT) or magnetic resonance imaging (MRI) scans, α -fetoprotein (AFP) (ng/ml) level, TNM stage [4], stage of underlying liver disease (Child-Pugh-stage) and use of loco-regional therapy before liver transplantation.

In cases of sufficient liver function bridging procedures, such as liver resection, local ablative procedures (transarterial chemoembolization (TACE), radio frequency ablation (RFA), Yttrium90 radio embolization (^{90}Y RE), tomotherapy, in combination with systemic therapy with tyrosinkinase inhibitor were employed. All these interventions were continued for as long as residual tumor was identified and monitored radiologically in 90 days intervals. In cases of residual vital tumor, the procedures were repeated and combined.

2.2 Calculation of standardized uptake value (SUV) max, standardized uptake value (SUV) mean and tumor to liver ratio (TLR)

Whole-body ^{18}F -FDG PET/CT scan was performed before LT as described recently [25]. The maximum SUV (SUVmax) of a hepatic tumor was measured by drawing a volume-of-interest (VOI) over the target lesion with reference to PET, contrast-enhanced CT, and/or MRI images. In case of multiple lesions, the highest SUVmax was used as a representative value. Tumor to liver SUV ratio (TLR) was calculated as the ratio of SUVmax of the tumor to SUVmean of normal liver tissue (Yaprak et al. 2018, Song et al. 2012). A receiver operating characteristic (ROC) analysis was performed to define the optimal F-18-FDG uptake value cut-off to predict tumor recurrence.

2.2 Statistical methods

All statistical analyses were performed using SPSS 26.0 software (IBM, Chicago, IL, USA) software. Distributions of variables were tested using the Chi square test, Fisher's exact test or Mann-Whitney-U-Test, as indicated. Cumulative recurrence rates were calculated from the date of liver transplantation to first clinical diagnosis of tumor recurrence. Patient deaths unrelated to HCC recurrence were censored. Cumulative recurrence curves were created using the Kaplan–Meier method. Median follow-up time was calculated using the reverse Kaplan-Meier method. Differences in recurrence rates as well as significant and independent predictors of recurrence were identified by Cox proportional hazard analysis. Statistical significance was defined as a p value < 0.05 for all analyses.

3. Results

From 2009 to 2019 103 patients underwent ^{18}F -FDG-PET/CT in our hospital before liver transplantation for HCC. Patients' age at transplantation was median 62 years (range 23–71 years). Morphological tumor load was inside

Milan in 54 (52%) patients and outside Milan in 49 (48%) patients. 79 (77%) patients received a liver from deceased donors. 24 patients got a split from a living donor (all of them were right lobes). The waiting time was median 9 months (range 0–45 months) for LT from deceased donor and 6 months (range 0–34 months) for the living donations. The median interval between PET/CT scan and liver transplantation was 6 months (range 0-41 months). Further details on patients, tumor load and treatment are shown in Table 1.

Table 1
Patient characteristics

Item	Strata	n	%
Age	under 60	38	37
	60 u and above	65	63
Sex	male	91	88
	female	12	12
Milan	in	54	52
	out	49	48
UTS	in	57	57
	out	46	46
Bridging before PET/CT	No	71	69
	Yes	32	31
AFP	0-399 ng/ml	87	90
	≥400ng/ml	10	10
Grade	grade 1-2	88	85
	grade 3	15	15
Type of transplantation	deceased donor	79	77
	living donor	24	23
pV	V0	82	80
	V1	21	20
Number of lesions	solitary	49	48
	multiple	54	52
Size of lesion	< 5cm	72	72
	5 cm an larger	31	31
Child stage	Milan-Kriterien	92	89
	Child A/B	11	11
pT-category	pT1/2/3	88	85
	pT3/pT4	15	15
Total		103	100
1) 6 missings ???			

Median follow-up time after LT was 79 months (range 0–139 months). During the interval 48 patients died, 9 of them in the postoperative interval, 18 due to HCC recurrence. Three patients died from malignant second tumor (lung

cancer in 1, ENT area in 2), and 18 died from tumor unrelated causes.

SUV_{max} in tumor tissue ranged from 1.1 to 23.6 with a median of 2.6. SUV_{mean} in non-tumor liver tissue ranged from 1.1 to 3.6 with a median of 2.3. Median tumor to liver SUV ratio was 1.0 (range 1.0–8.74).

Tumor to liver SUV ratio (TLR) of the primary tumor was statistically significant higher in Milan out tumors ($p=0.018$), “up-to-seven” out tumors ($p=0.015$), grade 3 ($p=0.023$), patients with AFP level >400 ng/ml ($p<0.001$) and lesions of a diameter of 5 cm and more ($p=0.007$). All other factors (age, sex, bridging therapy before PET/CT, type of transplantation, number of tumors, Child-Pugh- stage, pT-category, necrosis in the tumor) did not show a statistically significant dependence on the Tumor to liver SUV ratio.

A ROC analysis was performed to define the optimal cut-off for the Tumor to liver SUV ratio to predict tumor recurrence. In the present study, we chose a cut-off value of >1.38 , giving a sensitivity of 70.0% and a specificity of 67.6%.

3.1 Analysis of overall survival

Patients who died in the first 3 months were excluded from survival and recurrence analysis resulting in 94 patients for long term analysis. All 94 patients were followed-up until death or until 31st December 2020. To date, 5 patients lived for more than 10 years after transplantation, 34 for more than 5 years. All living patients have been followed up for at least one year. Five patients died from HCC recurrence during the first year after LTX.

Median survival time after transplantation was 106 months, overall 5- and 10-year-survival rates were 66% and 34%, respectively.

Univariate analysis found only four factors with statistically significant influence on 10-year overall survival: Milan ($p=0.018$), “up-to-seven” ($p=0.044$), number of lesions ($p=0.011$) and pT-category ($p=0.047$). Milan, number of lesions and pT-category were included in a multivariate COX regression analysis, which did not show independent statistically significant factors for 10-year overall survival.

3.2 Analysis of cumulative recurrence rate

The majority of the 23 recurrences (70%) occurred in the first two years after transplantation, but there was also a significant number of later recurrences. The median interval to tumor relapse was 15 months (range 2-84 months).

Recurrence was intrahepatic in 6 patients and extrahepatic in 17 patients. Sites of extrahepatic recurrence were lung (6 patients), bones (5 cases), adrenal gland (2 patients), peritoneum (2 patients), abdominal wall (1 patient) and lymph nodes (1 patient). Tumor recurrence was treated with curative intent in 8 patients. Pulmonary metastases were resected in 3 patients, adrenal metastases in 2 patients, and metastases in lymph nodes and

metastases in the abdominal wall and local recurrence in the liver in one patient each.

Five- and 10-year cumulative recurrence rates were 28% and 34%. Age, sex, bridging before PET/CT and Child stage did not influence cumulative 10-year recurrence rates statistically significant but Milan, “up-to-seven” grade, pV, AFP-level, number of lesions, size of lesion, pT-category, Tumor to liver SUV ratio did (Figure 1, Details are shown in Table 3).

Table 3
Studies with univariate COX analysis of recurrence rates

	Present study	Yang [26]) **	Lee [13] * ³⁾	Detry [5]	Kim [11]	Hsu [8]	Hsu [14] ³⁾	Lee [27] ⁴⁾	Kang [10] ^{1) 3)}
Period under study	2009-2019	2000-2004	2005-2011	2006-2011	2008-2012	2006-2014	2005-2013	2006-2013	2005-2013
Patients under study	95	38	191	27	110	147	280	103	239
Patients with "positive" PET	39 (42%)	13 (34%)	55 (29%)	8 (30%)	39 (35%)	30 (20%)	90	78 (76%)	—
Median follow up (months)	79 (3-122)	19 (5-40)	28 (1-79)	26 ²⁾	46 ²⁾	26	n.s.	26 ²⁾	53 (5-131)
Patients with recurrence	20 (21%)	11 (29%)	38 (20%)	5 (19%)	30 (27%)	18 (12%)	n.s.	53 (52%)	74 (31%)
Cutoff value of SUV ratio	1.38	1	1	1.15	1.16	2	1	1	2.8
Milan	p=0,012	—	p<0,001	p=0.21	p=0.004	p=0.830	—	p<0.001	—
Size of lesions	p=0,068	—	p<0,001	p=0.05	p<0.001	p=0.347	p=0.015	—	p<0,001
Number of lesions	p=0,021	—	—	p=0.99	p=0.012	p=0.795	p=0.280	p=0.005	p<0,001
pT-category	p<0.001	—	—	—	—	p=0.032	—	—	—
AFP	p=0,035	—	p=0,001	p=0.47	—	p=0.894	p=0.722	p=0.001	p<0,001
Tumor to liver SUV ratio	p=0,015	p=0.003	p<0,001	p=0.01	p<0.001	p<0.001	p=0.003	p=0.011	p<0,001
n.s. not stated, — not investigated, *3-year rates presented, **2-year rates presented, ¹⁾ multicentric, ²⁾ mean follow-up, ³⁾ only living donor liver transplantation									
⁴⁾ only patients with HBV-related HCC									

To achieve reliable results in multivariate COX analyses for the 23 patients with recurrence, a maximum of three factors should be used [20]. pT-category (because this factor takes number and size of lesions and vascular invasion into account), tumor to liver SUV ratio and grade were chosen. All three factors proved to be independent statistically significant factors for 10-year cumulative recurrence rates (Table 3). For a second multivariate COX analysis we chose pT-category, tumor to liver SUV ratio and pre-transplant AFP-level. In this analysis, pT-category and pre-

transplant AFP-level were independent statistically significant factors for 10-year cumulative recurrence rates but tumor to liver SUV ratio was not (Table 3).

4. Discussion

In our study, tumor to liver SUV ratio (TLR) of the primary tumor was statistically significantly higher in Milan out tumors, “up-to-seven” out tumors, Grade 3 tumors, AFP level >400 ng/ml and lesions of a diameter of 5cm or more.

Like us, many investigators found TLR to be statistically significantly higher in tumors with negative prognostic factors, such as high grade and microvascular invasion [1], high preoperative AFP level, Milan out, University of California, San Francisco (UCSF) out, large tumor size, major vessel invasion, and serosal invasion [13, 27].

Therefore, they presumed ^{18}F -FDG PET/CT could be a noninvasive diagnostic tool to identify HCCs with negative prognostic factors and a high incidence of tumor recurrence.

Like others, we found an independently statistically significant influence of metabolic activity in ^{18}F -FDG PET/CT on cumulative recurrence rate. Therefore, it can add some valuable information to other preoperative findings, such as tumor size, tumor number and AFP value.

Seo et al. were among the first authors who reported a prognostic usefulness of ^{18}F -FDG PET/CT in transplanted patients with HCC [23]. They found that in HCC patients with an uptake of ^{18}F -FDG in a primary HCC lesion equal to the uptake in a normal liver the 2-year recurrence-free survival rate was significantly higher than that of PET patients with an increased uptake of ^{18}F -FDG in the primary HCC lesion.

Since then many studies reporting the influence of metabolic activity on overall survival or recurrence rates were undertaken. They either used a semi-quantitative classification [12, 24] or the TLR [5, 13, 27].

Integrated PET/CT, combining a full-ring-detector clinical PET scanner with a multi-detector-row helical CT scanner has made it possible to acquire both metabolic and morphologic imaging data with a single device in one diagnostic session, and has been demonstrated to show precise anatomic location of suspicious areas of increased FDG uptake.

In our study, factors which had a statistically significant influence on 10-year overall survival in univariate analyses were Milan, up-to-seven”, number of lesions and pT-category. Multivariate COX regression analysis did not show independently statistically significant factors for 10-year overall survival.

In Table 4 several key data from studies about the prognostic value of ^{18}F -FDG PET/CT are compared. Noticeably, some authors report very short follow-up intervals [26], which might miss a significant proportion of recurrences. Another surprising point is that not all studies analyzed the influence of Milan criteria on the cumulative recurrence rate [10, 26] and others did not find a statistically significant influence of Milan on recurrence rates [11, 13, 27] in the univariate analysis.

Table 4
Studies with multivariate COX analyses of recurrence rates

	Present study	Lee [13] 3)4)	Detry [5]	Kim [11]	Lee [14]³⁾	Ye [27]	Kang [10] 1)3)
Patients with recurrence (events)	23	28	5	30	n.s.	53	74
Number of variables in multivariate COX analysis	3	11	3	5	13	9	4
Events per independent variable	7.7	2.5	1.6	6	n.s.	5.9	18.5
Milan	—	n.s.	—	0.029	—	0.004	—
AFP	—	n.s.	—	—	0.991	0.001	<0.001
Number of lesions	—	n.s.	—	—	0.534	0.485	0.046
Size of lesions	—	n.s.	n.s.	—	0.001	—	0.003
Grade	0.044	n.s.	n.s.	—	0.927	0.380	—
pV	—	n.s.	—	—	0.033	<0.001	—
pT-category	<0.001	—	—	—	—	—	—
Tumor to liver SUV ratio	0.031	0.024	0.018	0.009	0.001	0.011	<0.001
— = not included in COX analyses, n.s. not stated, ¹⁾ multicentric, ²⁾ mean follow-up, ³⁾ only living donor liver transplantation ⁴⁾ 3-year rates presented							

Recurrence rates vary between 12% [8] and 52% [27]. The number of patients with recurrence limits the informative value of multivariable analyses, because results of studies having fewer than ten events per variable analyzed should be interpreted with caution [20].

In our study, 5-year and 10-year cumulative recurrence rates are 27% and 34%, respectively. An univariate analysis found that they were statistically significantly influenced by Milan, grade, pV, number of lesions, size of lesions, pT-category, and tumor to liver SUV ratio (Table 4).

After the introduction of the Milan criteria, multiple other classifications were proposed. Most of them are based on the morphologic tumor burden, measured by number and diameter of the lesions, sometimes complemented by variables of liver function or preoperative AFP-value [3].

Two study groups from South Korea proposed scores including the findings in PET/CT in new scores for estimation of the prognosis after living donor liver transplantation for HCC. Both yield results comparable to the Milan criteria [10, 14].

Table 5 lists studies with PET/CT using multivariate Cox regression analysis to identify independently statistically significant factors for cumulative recurrence rates. Only in two cases, the number of events per variable analyzed exceeds 5. Therefore, there is an urgent need for studies with larger sample sizes to overcome the methodical problem of low numbers of recurrences in small sample sizes.

Summary

The sensitivity of ^{18}F -PET/CT for predicting recurrence after liver transplantation is approximately 70%. Like others, we found a statistically independently significant influence of metabolic activity in ^{18}F -FDG PET/CT on cumulative recurrence rate. Therefore, it may add some valuable information to other preoperative findings, such as tumor size, tumor number and AFP value.

Declarations

- * Conflict of interest: no conflict of interest
- * Financial support: no financial support
- * Trial registration number: no trial registration number

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Disclosure: The authors of this manuscript have no conflicts of interest to disclose

The study in humans has been carried out with approval of the local ethics committee (Nr. 4337-02/15), in accordance with national law and the Declaration of Helsinki of 1975 (in the current form).

Informed consent: All patients give their consent for clinical registration. We have only used data from the clinical data registry.

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Tables

Table 2: Univariate and multivariate analyses of cumulative recurrence rates

Figures

All patients, n=93		Univariate		Multivariate Model 1		Multivariate Model 2	
Prognostic factor	Strata	p	Exp(B) (95% CI)	p	Exp(B) (95% CI)		Exp(B) (95% CI)
Age	<60years/≥60 years	0.975	1.013 (0.437 - 2.350)				
Sex	female/male	0.394	0.532 (0.124 - 2.272)				
Milan	in/out	0.001	4.344 (1.780 - 10.602)				
UTS	in/out	0.001	5.056 (1.984 - 12.887)				
Bridging before PET/CT	Yes/no	0.609	0.784 (0.309 - 1.990)				
AFP	0-399 / ≥400 ng/ml	0.008	3.939 (1.426 - 10.878)			0.036	3.165 (1.080 - 9.276)
Grade	grade 1-2/grade 3	0.016	3.179 (1.242 - 8.131)	0.044	2.780 (1.029 - 7.513)		
pV	pV0/pV1	0.008	3.099 (1.340 - 7.166)				
Number of lesions	Solitary/multiple	0.014	3.066 (1.254 - 7.496)				
Size of lesion	<5cm/≥5cm	0.014	2.799 (1.232 - 6.362)				
Child stage	Child A-B/Child C	0.653	1.321 (0.392 - 4.450)				
pT-category	pT0-2/pT3-4	<0.001	5.326 (2.270 - 12.496)	<0.001	5.564 (2.272 - 13.622)	0.001	5.192 (1.951 - 13.818)
Tumor to liver SUV ratio	<1,38/≥1,38	0.005	3.562 (1.463 - 8.672)	0.031	2.783 (1.096 - 7.067)	0.056	2.667 (0.975 - 7.297)

Figure 1

Cumulative Recurrence Rate according to tumor to liver SUV ratio