J Cancer Res Clin Oncol (2017) 143:2595–2605
DOI 10.1007/s00432-017-2507-2

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Validity of eleven prognostic scores with respect to intra- and extrahepatic recurrence of hepatocellular carcinoma after liver transplantation

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Received: 22 April 2017 / Accepted: 17 August 2017 / Published online: 28 August 2017

Abstract
Introduction Tumor recurrence is the most frequent cause of death after liver transplantation for hepatocellular carcinoma. We selected ten other prognostic classifications to evaluate their potential to predict the risk of recurrence after LT for HCC as compared to the Milan classification. All of the other scores have not been compared with one another in a single cohort.
Methods Data of 147 consecutive patients transplanted at our department between 1996 and 2014 were analyzed and staged for morphological and functional scores of underlying liver disease. For long-term follow-up, we analyzed intrahepatic (within the liver ± distant metastases) and extrahepatic (distant metastases only) recurrence separately.
Results and conclusions The median survival time for all patients was 106 months. The 5- and 10-year observed survival rates were 61 and 43%, respectively. The observed cumulative 5- and 10-year recurrence rates were 37 and 39%, respectively, 10-year intrahepatic and extrahepatic recurrence rates were 12 and 27%, respectively. Median survival time after diagnosis of first recurrence was 7.5 (0–120) months; 2 and 18 months for all, intra- and extrahepatic recurrence, respectively. UCSF-, up to seven-, Shanghai Fudan- or Duvoux classifications can identify patients with a cumulative 10-year recurrence rate below 20%. The pretherapeutic AFP level should be considered in addition to the geometry of the intrahepatic lesions.

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Keywords HCC recurrence · HCC score · Liver transplantation

Introduction and background

Tumor recurrence is the leading cause of death after liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) (Andreou et al. 2015). Early intrahepatic recurrence with poor prognosis can be distinguished from extrahepatic recurrence which develops usually post transplant and has almost always a better prognosis than intrahepatic recurrence (Roayaie et al. 2004). The risk factors and their identification before listing patients for transplantation as well as treatment of recurrence after transplantation are currently debated (Ravaioli et al. 2008; Schwartz et al. 2005; Andreou et al. 2016; Mazzaferro et al. 2009).

After the introduction of the Milan classification in 1996 (Mazzaferro et al. 1996) a group of patients with a long-term survival (and also tumor free) was identified, such as patients with benign diseases as indications for LT. It was also observed that certain patients "outside Milan" survived several years post transplant without recurrence (Duvoux et al. 2012; Chapman et al. 2008; Millonig et al. 2007; Otto et al. 2006; Herrero et al. 2008; Seehofer et al. 2012). There is currently a debate as to whether this scoring system is still appropriate for clinical decision making (Duvoux et al. 2012; Chapman et al. 2008; Millonig et al. 2007; Otto et al. 2006; Herrero et al. 2008; Seehofer et al. 2012).

We selected ten different prognostic classifications/scores to evaluate their potential to predict the risk of recurrence after LT for HCC as compared with the Milan classification (Table 1). All of the other HCC scores together have not been compared with one another in a monocenter cohort of LT patients. We also present the

Table 1 Overview of HCC staging systems

Staging system	Tumor	Liver function
Child–Pugh	–	Bilirubin Albumin Quick Ascites Hepatic encephalopathy
Okuda	</>50% Tumor load	Bilirubin Albumin Ascites
CLIP	</>50% Tumor load Singular single or multiple nodes AFP Portal vein thrombosis	Child–Pugh Score
BCLC[a]	Tumor extent Metastasis Portal vein thrombosis Okuda Score	Child–Pugh Score Portal hypertension Bilirubin
Milan	Solitary tumor <5 cm, or ≤3 tumor ≤2–3 cm no extrahepatic tumor, no macrovascular invasion	–
UCSF	Solitary tumor ≤6.5 cm or ≤3 nodules with largest lesion ≤4.5 cm and total tumor diameter ≤8 cm No macrovascular invasion	–
Shanghai Fudan	Solitary tumor ≤9 cm or ≤3 tumors ≤5 cm and total tumor diameter ≤9 cm	–
Hangzhou	Total tumor diameter ≤8 cm, or total tumor diameter >8 cm, with pathologic grade I or II on biopsy and AFP ≤ 400 ng/mL	–
Asan	≤6 tumors with the maximum diameter ≤5 cm	
Up-to-seven criteria ("new Milan")	Seven as the sum of the size of the largest tumor (in cm) and the number of tumors	–
TNM (UICC 2010)	Number and size of tumor nodes Vascular invasion Lymph node metastasis Distant metastasis	–
Duvoux	Largest tumor diameter Number of nodules AFP	–

Parameters included in the staging systems

[a] In addition performance status

treatment strategies and survival in our patients with HCC recurrence.

Materials and methods

We extracted data of HCC patients who underwent liver transplantation between 1996 and 2014 from our prospectively maintained tumor register. 20 patients who died within 3 months after LT were excluded. All patients were followed up until death, or until July 1st 2016. Eighty percent of patients were followed up by our department. The remaining data were forwarded by other health care providers.

According to the German transplantation law, extrahepatic tumor and macrovascular invasion are considered contraindications of liver transplantation.

In cases of sufficient liver function, bridging procedures, such as liver resection, local ablative procedures (transarterial chemo embolization (TACE), radio frequency ablation (RFA), Yttrium^{90} radio embolization (Y^{90}RE), tomotherapy), accompanied by systemic treatment with tyrosine kinase inhibitors were applied since 2004. All these measures were continued for as long as residual tumor was identified by imaging in 90-days intervals.

Patients with recurrence after LT were treated with curative intent wherever possible, otherwise with palliative intent. We performed surgical resections with curative intent for intra- and extrahepatic recurrence, applied

local therapy (TACE, Y^{90}RE, RFA) in non-resectable intrahepatic recurrences and radiation for bone metastases. Whenever possible, a systemic therapy with a tyrosine kinase inhibitor followed. mTOR-based long-term immunosuppression and sorafenib were administered in patients who had no contraindications.

Follow-up consultations were standardized (monthly during the first year, subsequently four times per year). As long as laboratory tests including AFP were within the normal range, a CT scan was performed every 3 months. If tumor recurrence was suspected or confirmed, therapeutic options were discussed on the interdisciplinary hepatobiliary tumor board.

We analyzed the morphological data of the tumor load in pre-transplant contrast computed tomography (CT) or magnetic resonance imaging (MRI) scans, α-Fetoprotein (AFP) (ng/ml) level, stage of underlying liver disease (Child Stage) (Child and Turcotte 1964), use of locoregional therapy, and type of LT. Patients were classified according to 11 different scores, 8 of which designed to identify patients for LT, Milan classification (Mazzaferro et al. 1996), University of California, San Francisco (UCSF) classification (Yao et al. 2001), the Okuda classification (Okuda et al. 1985), Shanghai Fudan criteria (Fan et al. 2006), Hangzhou criteria (Zheng et al. 2008), Asan criteria (Lee et al. 2008), up-to-seven criteria (Mazzaferro et al. 2009), Duvoux Score (Duvoux et al. 2012), and three established HCC prognostic scores: Barcelona Clinic Liver Cancer (BCLC) Score (Llovet et al. 1999), Cancer of the Liver Italian Program (CLIP) Score (Capuano et al. 1998) and Union for International Cancer Control (UICC) stage 2010 (Sobin et al. 2010). All tumors have been re-classified according to the 7th edition tumor-node-metastases (TNM) staging of 2010 (Sobin et al. 2010).

The univariate analysis was performed with SPSS software version 19. Differences in the distribution of variables have been tested with Fisher's exact test or with χ^2-test for statistically significant differences. Survival rates were calculated with the Kaplan–Meier procedure and significance testing was performed with the log-rank test. Before analysis, the original 3-tier or 4-tier scales of the above-mentioned scores were reduced to a 2-tier system (low risk or high risk of HCC recurrence). The cumulative recurrence rates for HCC were calculated with adjustment for death before HCC recurrence as a competing risk. The competing risk analyses were performed with SPSS using a specially designated macro to calculate the cumulative incidence functions. This macro is freely available at the website http://www.msbi.nl/lecessie (Verduijn et al. 2011).

Results

147 patients underwent LT for HCC between 1996 and 2014. Three patients were diagnosed with incidental carcinoma which had not been detected during the evaluation procedure. In two patients, one positive lymph node metastasis was detected in the resected specimen by the pathologist. There were 120 men and 27 women with a median age of 59 years (35–71 years). The median AFP level before transplantation was 13(1–56,139) ng/ml. The median waiting time was 136 (0–2505) days for all patients. The median waiting time was 170 (0–2505) days for deceased donor transplant and 36 (2–388) days for living donor LT, respectively.

The median follow-up time after LT was 48 (3–238) months for the entire group and 72 (10–238) months for the patients still alive. The cumulative 10-year death rates for death of recurrence, death of other malignancies (three lung cancers, one cancer of the urinary bladder), and death of other causes were 29, 6, and 22%, respectively (Fig. 1).

The median survival time for all patients was 106 months. The 5- and 10-year observed survival rates were 61 and 43%, respectively. Patients treated before 2004 had nearly identical survival rates as compared to patients who underwent transplantation 2004 and later ($p = 0.869$).

Recurrence rates

At the end of the study, 48 patients had developed a recurrence. The median time from transplantation to recurrence was 12.5 (3–62) months. Extrahepatic recurrence was observed in 32 cases and intrahepatic recurrence with or without distant metastases in 16 cases. The median time from transplantation to recurrence was 12.5 (3–62) months for all, 9.5 (3–32) months for intrahepatic recurrence only, and 18 (3–62) months for extrahepatic and combined

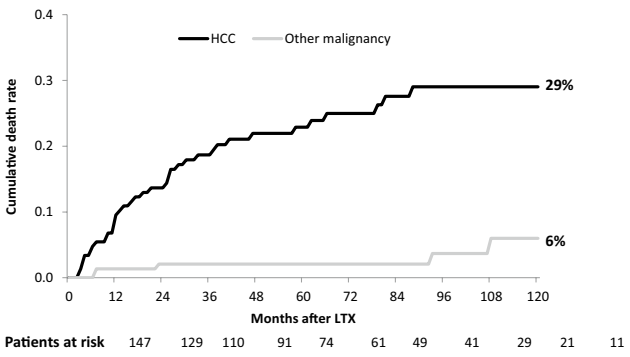

Fig. 1 Cumulative death rates for concurrent causes of death after liver transplantation for HCC

recurrence. The difference is of marginal statistical significance ($p = 0.05$; Mann–Whitney U test). In the univariate analysis, the time to recurrence was related to number of tumors, Milan criteria, CLIP Score, Okuda stage, and UCSF classification, but only the difference between CLIP 0-1 and CLIP > 1 reached statistical significance ($p = 0.014$).

We saw no statistically significant differences in frequencies of recurrence for sex, locoregional therapy, type of LT (LDLT vs DDLT), diameter of lesions (maximum), alpha-fetoprotein level, portal vein thrombosis without tumor invasion in imaging studies pre LT without tumor invasion, child stage, underlying liver disease, and BCLC Score. Details and p values are shown in Table 1.

Prognostic scores

The observed cumulative 5- and 10-year recurrence rates for all patients were 37 and 39%, respectively. The 10-year cumulative recurrence rate corrected for competing risk of death from other causes was 34%.

We analyzed the cumulative 10-year recurrence rate as related to Milan classification, UCSF classification, Up to seven criteria, Shanghai Fudan criteria, Asan criteria, Hangzhou criteria, CLIP Score, Okuda stage, Duvoux Score, UICC stage, and BCLC stage. The first four classifications consider only number and diameter of lesions, the others include gross vascular invasion (Asan criteria), grading (Hangzhou criteria), Underlying Liver Disease Score, laboratory findings (Okuda stage), pre-therapeutic AFP level (Duvoux Score), microvascular invasion (UICC stage), or performance status (BCLC stage). The percentage of patients assigned to the respective low risk groups ranged from 38% (Milan classification) to 91% (Okuda classification). Ten-year cumulative recurrence rates were strongly related to the subgroup under consideration, ranging from 14% in the low risk group of the Duvoux Score to 75% in Okuda A stage III. Only the BCLC Score did not reflect recurrence rates statistically significant. Recurrence rates below 20% in the low risk group were observed only with the up to seven criteria, Shanghai Fudan criteria, Hangzhou criteria, and Duvoux Score. For all groups, the 10-year cumulative recurrence rate corrected for competing risk of death from other causes was slightly lower than the uncorrected rate (Table 2). Two examples for the effect of the different classifications on the 10-year cumulative recurrence rate corrected for competing risk of death from other causes is shown in Fig. 2.

All scores besides BCLC reflected statistically significant differences in intrahepatic recurrence rates. The number of patients with recurrence assigned to the low

Table 2 Number and percentage of recurrences

	Total	Recurrence		p
		Number	%	
Total	147	48	33	–
Number of lesions				
1 lesion	77	13	17	<0.001
2–3 lesions	28	9	32	
≥4 lesions	42	26	62	
Multiplicity				
Solitary	77	14	18	<0.001
Multiple	70	34	49	
Yes	9	5	56	
Extent of hepatic tumor				
Solitary ≤50%	76	13	17	<0.001
Multiple ≤50%	44	16	36	
>50%	27	19	70	
Milan				
Milan in	56	10	18	0.004
Milan out	91	38	42	
UCSF				
UCSF in	72	11	15	<0.001
UCSF out	75	37	49	
Up to seven				
In	76	11	15	<0.001
Out	71	37	52	
Shanghai Fudan				
Low risk	79	12	15	<0.001
High risk	68	36	53	
Asan				
Low risk	76	14	18	<0.001
High risk	71	34	48	
Hangzhou				
Low risk	120	33	28	0.007
High risk	27	15	57	
CLIP score				
CLIP 0–1	84	16	19	<0.001
CLIP > 1	63	32	51	
OKUDA				
OKUDA stage I/II	135	39	29	0.002
OKUDA stage III	12	9	75	
Duvoux score				
Low risk	67	9	13	<0.001
High risk	80	39	49	
UICC stage				
Stage I/II	88	23	26	<0.001
Stage III/IV	42	25	60	
BCLC Score				
Score A/B	89	25	28	0.154
Score C/D	58	23	40	

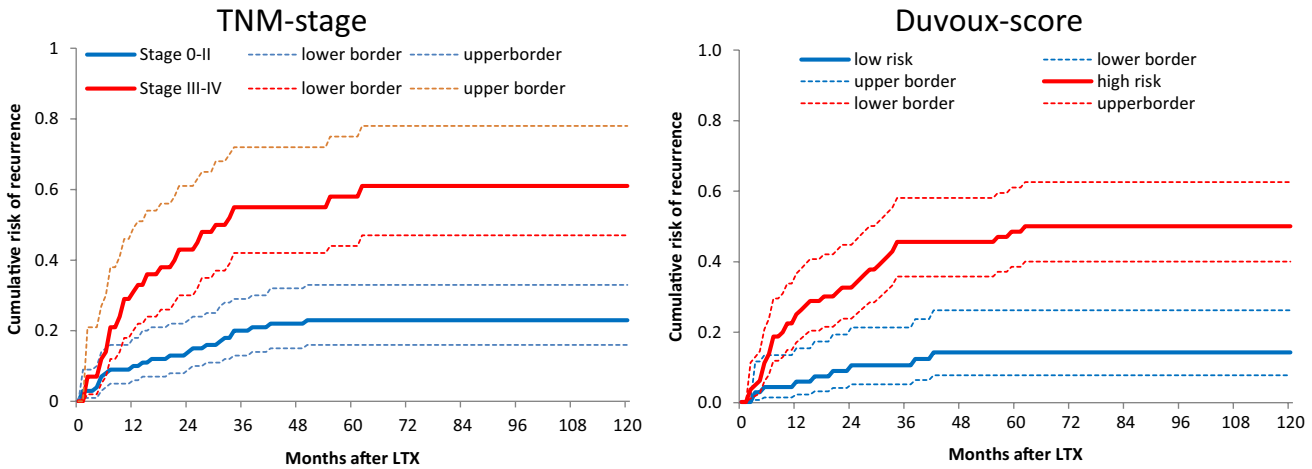

Fig. 2 Cumulative HCC recurrence risk after LTX by the competing risk method. The *dotted lines* show the 95% confidence interval of recurrence rates

risk group ranged from 9/48 (19%, Milan classification) to 33/48 (69%, Hangzhou criteria). Except for the Duvoux Score, scores that combined number and diameter of lesions with other criteria tended to underestimate the risk of intrahepatic recurrence.

Extrahepatic recurrences were not statistically significantly reflected by the Milan classification, Hangzhou criteria, and BCLC Score. Considering the results for total, intrahepatic, and extrahepatic recurrence rates, the Duvoux Score provides the most accurate prediction. The application of the Duvoux Score identified only 9/48 recurrences in the pre-operative low risk group, three of those were intrahepatic and six were extrahepatic (Table 3).

Treatment of recurrences

Fifteen of 48 recurrences (31%) were treated with curative intent. Of 16 patients with intrahepatic recurrence, 14 had diffuse intrahepatic disease which was accompanied by pulmonary or skeletal metastases in nine cases. These patients were given best supportive care only in six cases and systemic therapy in the remaining eight cases. Two patients underwent treatment with curative intent, one partial liver resection followed by TACE, the other radiofrequency ablation followed by RE and percutaneous radiation therapy. One patient died 6 months after the diagnosis of recurrence; the second is still alive with disease 32 months after the diagnosis of recurrence.

Two patients with pulmonary metastases received systemic treatment with a tyrosine kinase inhibitor, five best supportive care only. Seven patients with bone metastases were treated with radiation, one patient received systemic treatment with a tyrosine kinase inhibitor, one best supportive care. In 13 patients the initial extrahepatic recurrence was resected with curative intent (Table 4).

Survival after recurrence

The median survival time after the diagnosis of first recurrence was 7.5- (0–120) month, 2 and 18 months for all, intra- and extrahepatic recurrence, respectively. As yet, none of the patients with intrahepatic recurrence survived 10 years compared with two patients who had developed extrahepatic recurrence. The 10 years survivors are one with eight bilateral lung metastases which were resected 33 months after transplantation and one with metastasis to the adrenal gland which was R0-resected 55 months after transplantation (Fig. 3). The median survival time for patients treated with curative intent was 38 months, compared to 6 months for patients treated with palliative intent. The corresponding 5-year survival rates are 31 and 0%, respectively (Fig. 4).

Discussion

Recurrence is the leading cause of death after curatively intended treatment for patients with solid tumors. We addressed the question as to whether different scoring systems may adequately predict the outcome of LT for HCC. We evaluated the ability of different classifications to predict the risk of recurrence. We choose 10-years recurrence rate to detect late recurrence. Moreover, we checked the ability of the different classifications to predict intra- and extrahepatic recurrences. For patients with intra- or extrahepatic recurrences, we evaluated different therapeutic procedures. We

Table 3 10-year cumulative recurrence rates for different risk groups observed and corrected for the competing risk of death from other causes

	Number of patients	Observed		Corrected for the competing risk of death from other causes	
		10-year cumulative recurrence rate (%)	*p*	10-year cumulative recurrence rate (%)	95% confidence interval (%)
Total	147	37	–	34	27–43
Multiplicity					
Solitary	77	21	0.000	19	12–31
Multiple	70	54		50	39–64
Milan					
Milan in	56	22	0.008	19	11–34
Milan out	91	45		43	34–54
UCSF					
UCSF in	72	19	0.000	17	10–29
UCSF out	75	53		50	40–63
Up to seven					
In	76	17	0.000	16	9–27
Out	71	53		53	42–66
Shanghai Fudan					
Low risk	79	19	0.000	16	10–28
High risk	68	57		54	43–68
Asan					
Low risk	76	22	0.000	20	12–32
High risk	71	52		49	38–62
Hangzhou					
Low risk	120	32	0.003	29	22–39
High risk	27	56		56	40–79
CLIP score					
CLIP 0–1	84	23	0.000	20	13–32
CLIP > 1	63	54		52	41–66
OKUDA stage					
OKUDA stage I/II	135	33	0.000	30	23–39
OKUDA stage III	12	81		75	54–100
Duvoux Score					
Low risk	67	16	0.000	14	8–26
High risk	80	54		50	40–63
UICC stage[a]					
Stage I/II	88	25	0.000	23	16–33
Stage III/IV	42	64		61	47–78
BCLC stage					
Score A/B	89	32	0.134	30	21–41
Score C/D	58	45		41	30–56

[a] UICC stage 2010 (Sobin et al. 2010)

saw the best results after surgical treatment with curative intent and here especially for extrahepatic recurrence.

To our best knowledge, we are the first to investigate the power of predicting the risk of recurrence in a monocenter German study for a variety of classifications. We compared Milan classification, CLIP Score, BCLC Score, UCSF, Shanghai Fudan criteria, Hangzhou criteria, Asan criteria, up-to-seven criteria, UICC stage 2010, and Duvoux Score with respect to their ability to predict cumulative recurrence.

In agreement with other reports, we found different survival with intra- and extrahepatic recurrences and we believe that they are caused by different biological mechanisms. We

Table 4 10-year observed cumulative total, intrahepatic, and extrahepatic recurrence rates for different risk groups

Score	Total	Recurrence		Intrahepatic recurrence		Extrahepatic recurrence	
		N	*p*	*N*	*p*	*N*	*p*
Milan							
In	56	10	0.008	2	0.032	8	0.110
Out	91	38		14		24	
UCSF							
In	72	11	0.000	1	0.000	10	0.013
Out	75	37		15		22	
Up to seven							
In	76	11	0.000	2	0.001	9	0.002
Out	71	37		14		23	
Shanghai Fudan							
Low risk	79	12	0.000	2	0.000	10	0.002
High risk	68	36		14		22	
Asan							
Low risk	76	14	0.000	3	0.006	11	0.019
High risk	71	34		13		21	
Hangzhou							
Low risk	120	33	0.003	10	0.021	23	0.054
High risk	27	15		6		9	
CLIP							
CLIP 0–1	84	16	0.000	3	0.001	13	0.014
CLIP > 1	63	32		13		19	
OKUDA							
Stage I/II	135	39	0.000	12	0.001	27	0.008
Stage III	12	9		4		5	
Duvoux Score							
Low risk	67	9	0.000	3	0.022	6	0.000
High risk	80	39		13		26	
UICC stage							
Stage 0/I/II	105	23	0.000	6	0.001	17	0.004
Stage III/IV	42	25		10		15	
BCLC stage							
Stage A/B	89	25	0.134	4	0.001	21	0.698
Stage C/D	58	23		12		11	

would, therefore, recommend that they should be analyzed individually.

The Milan classification and the Duvoux Score showed the lowest number of false-positive predictions in the respective low risk groups for all recurrences. All classifications considering only number and diameter of intrahepatic lesions, CLIP, and Duvoux Score were able to predict intrahepatic recurrences adequately. On the other hand, all but the Milan classification and Duvoux Score had shortcomings in predicting extrahepatic recurrences. Thus, we assume that the pre-therapeutic AFP level can provide some information about the risk of extrahepatic recurrence after LT. Other authors found that elevated AFP prior to LT is associated with higher recurrence rates (Ravaioli et al. 2008; Hameed et al. 2014; Vibert et al. 2010; Toso et al. 2008).

In our study, one-third of the first recurrences occurred in the liver only. Exactly the same percentage is reported by de'Angelis et al. (2015). Other authors found percentages of intrahepatic recurrences between 14 and 53% (Sotiropoulos et al. 2007; Croome et al. 2015).

There are numerous studies in the literature investigating the prediction of the frequency of recurrence after transplantation for HCC (Table 5). But only five of them (Andreou et al. 2015; Sotiropoulos et al. 2007; Croome et al. 2015; Agopian et al. 2015; Sapisochin et al. 2016) give cumulative predictions of the 5 year recurrence rate and only

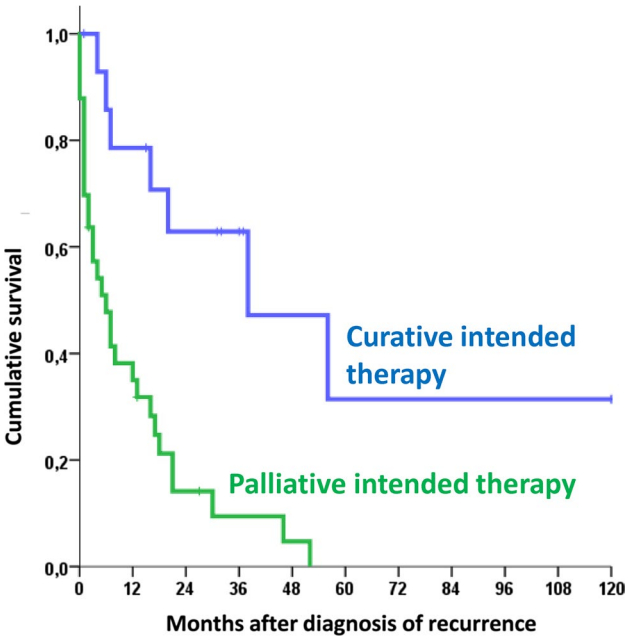

Fig. 3 Observed survival of patients with and without recurrence

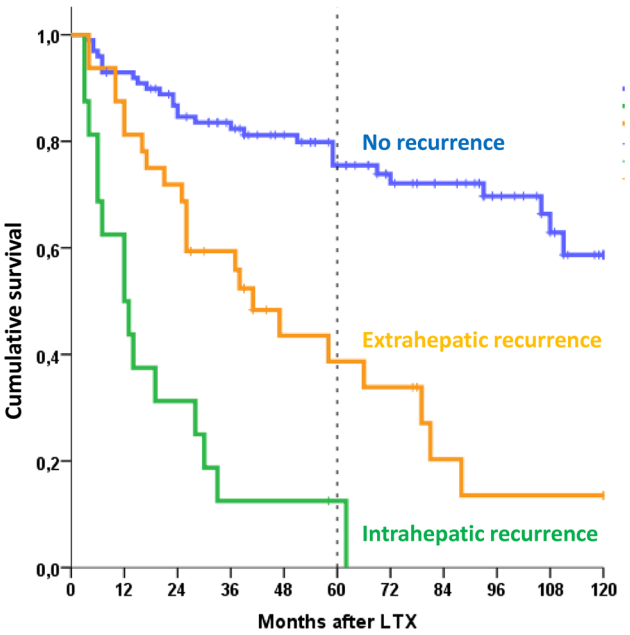

Fig. 4 Observed survival after diagnosis of first recurrence

two (Croome et al. 2015; Agopian et al. 2015) consider the competing risk of death from other causes before the diagnosis of recurrence can be made. Moreover, in some of the studies, patients dying during the first 2 months after transplantation (before recurrence can occur) are included or—more frequently—no information whether these patients are excluded is given. Therefore, not unexpectedly, reported recurrence rates vary from 7.3 to 37.8% (Chaiteerakij et al. 2015; Varona et al. 2015).

In our series, the median time from transplantation to recurrence was 12.5 months. This is in agreement with a recently published review where de' Angelis and colleagues found a median time from LT to HCC recurrence of 13 months (range 2–132 months) (de'Angelis et al. 2015). Some authors distinguish between early recurrence (<2 years after transplantation) and late recurrence (≥2 years after transplantation) (Chok et al. 2011; Pecchi et al. 2015). Others define late recurrence >12 months after transplantation (Escartin et al. 2007; Zhang et al. 2015) or >1000 days after transplantation (Schlitt et al. 1999). In addition, very late recurrences up to 10 years after LT are reported (Decaens et al. 2006).

The median survival time after diagnosis of first recurrence was 7.5 (0–120) months, 2 and 18 months for all, intra- and extrahepatic recurrence, respectively. Bodzin et al. (2016) and Na et al. (2016) report similar findings for recurrences after DDLT and LDLT (10.6 and 6.6 months, respectively). de'Angeilis et al. (2015) found in a multicenter study a median survival of 13 months after the diagnosis of recurrence.

According to the consensus conference, surgical treatment with curative intent should be considered in all cases of recurrence (Clavien et al. 2012). Particularly patients with single intra- or extrahepatic deposit benefit from surgical treatment (Na et al. 2016; Bodzin et al. 2016; Kornberg et al. 2010; Marangoni et al. 2008; Sapisochin et al. 2015; Taketomi et al. 2010; Valdivieso et al. 2010; Hwang et al. 2012).

In summary, tumor recurrence is the leading cause of death for transplanted patients with HCC. With the aim to offer more patients the curative option of LT, UCSF-, up to seven-, Shanghai Fudan- or Duvoux classifications can be applied. All of them can identify a group of patients with a cumulative 10-year recurrence rate below 20%. Most scores are able to estimate the risk of intrahepatic recurrence. In our patients—besides the Milan classification—only the Duvoux classification was able to identify patients with a low risk of extrahepatic recurrence. Therefore, we believe that the pre-therapeutic AFP level should be considered in addition to the geometry of the intrahepatic lesions. Surgical treatment of recurrent tumor can offer 10-year tumor-free survival to patients with resectable recurrence in individual cases. In non-resectable cases, local ablative procedures with or without mTOR-based immunosuppression and systemic therapy with a tyrosine kinase inhibitor may prolong survival.

Table 5 Review of the literature

	Study period	Patients in study	Number of recurrences	% Recurrence	Number of intrahepatic recurrences	% intrahepatic recurrence	Median time to recurrence (months)	Median follow-up (months)
Schraiber et al. (2016)	1997–2010	206	32	15.5	15	46.9	n.a.	44
Andreou et al. (2015)	1989–2010	364	93	25.5	19	20.4	19	78
Croome et al. (2015)	2003–2012	397	48	12.1	24	50	n.a.	47
Chaiteerakij et al. (2015)	2000–2008	127	48	37.8	n.a.	n.a.	n.a.	91
Varona et al. (2015)	1996–2012	109	8	7.3	n.a.	n.a.	23.4	42
Pecchi et al. (2015)	2004–2011	165	24	14.5	7	29.2	12.3 (2–42)	n.a.
Chan et al. (2011)	2000–2009	123	17	13.8	9	52.9	11 (1.2–39)	<35
Valdivieso et al. (2010); Pecchi et al. (2015)	1996–2008	182	23	12.6	7	30.4	n.a.	<60
Escartin et al. (2007)	1988–2005	184	28	15.2	7	25	n.a.	n.a.
Parfitt et al. (2007)	1985–2003	75	20	26.7	4	20	n.a.	~96
Sotiropoulos et al. (2007)	1998–2006	100	14	14	2	14	n.a.	31
Decaens et al. (2006)[a]	1988–1998	412	131	31.8	n.a.	n.a.	12 (1–125)	52
Roayaie et al. (2004)	1988–2002	311	57	18.3	27	47.4	n.a.	~50
Present study	1996–2014	147	48	32.7	16	33.3	12.5 (3–62)	48

[a] Multicenter study

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflictsof interest.

Ethical standard The retrospective study was in accordance with the ethical standards of the Helsinki Declaration.

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

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