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ORIGINAL SCIENTIFIC REPORT

Liver Resection for Solitary Transplantable Hepatocellular Carcinoma: The Role of AFP-Score

Benjamin Menahem[1,2] · Christophe Duvoux[3,8] · Nathalie Ganne[5] · Ariane Mallat[3] · Olivier Seror[6] · Julien Calderaro[7,8] · Guy Launoy[2] · Arnaud Alves[1,2] · Daniel Cherqui[9] · Alain Luciani[8,10] · Alexis Laurent[4,8]

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Abstract

Background In 2012, the Liver Transplant French Study Group built the alpha-*fetoprotein*-score (AFP-score), which improved significantly the prediction of tumor recurrence in case of liver transplantation for HCC when compared to Milan criteria. The aim of the study was to test the AFP score in case of liver resection (LR) for HCC.

Methods From 1990 to 2012, 347 patients underwent a liver resection for HCC developed on chronic liver disease (CLD). All patients with solitary HCC <60 mm were included. The primary end point was to investigate if the AFP-score at the first LR was predictive of recurrence and if recurrence occurred within the AFP-score. The secondary end points were overall survival (OS) and disease-free survival.

Results One hundred and eight patients fulfilled the inclusions criteria. After a median follow-up of 65.4_{IQR} [13–114] months, recurrence occurred in 64.8% (70/108) patients. Among the study population, 96 were "in AFP-score" (i.e., ≤2) of whom 60.4% (58/96) developed a recurrence that was cured in curative intent. In contrast, all patients "out AFP-score" experienced recurrence, and 25% were eligible for curative treatment. At the end of the follow-up, 26 patients were listed for liver transplantation (LT). Among them, 21 were finally transplanted. The 5-year OS after salvage LT was $68.5\%_{95\%CI}$ [50.2–93.0].

Conclusion AFP-score is a useful tool for patients selection after LR for solitary HCC developed on CLD. For patients "in AFP-score," up-front LR provides good survival and allows to avoid up-front LT in case of recurrence.

✉ Alexis Laurent
alexis.laurent@aphp.fr

[1] Department of Digestive Surgery, CHU de Caen, Avenue de la côte de Nacre, 14032 Caen Cedex, France

[2] UNICAEN, CEA, CNRS, CHU Caen, INSERM UMR1086, Centre François Baclesse, Normandie University, 3 Avenue du Général Harris, 14045 Caen Cedex, France

[3] Department of Hepatology, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France

[4] Department of Digestive, Hepatobiliary, Pancreatic Surgery and Liver Transplantation, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France

[5] Department of Hepatogastroenterology, Hôpital Jean Verdier, Assistance Publique-Hôpitaux de Paris, Bondy, France

[6] Department of Radiology, Hôpital Jean Verdier Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France

[7] Department of Histopathology, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France

[8] INSERM, UMR 955, Créteil, France

[9] Department of Digestive Surgery, Hôpital Paul Brousse, Assistance Publique-Hôpitaux de Paris, Villejuif, France

[10] Department of Radiology, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France

Introduction

Hepatocellular carcinoma (HCC) is the first cause of primary liver cancer and arises in more than 90% of case on chronic liver disease (CLD). The most frequent etiology of CLD in Europe is viral hepatitis, chronic alcoholism and non-alcoholic steatohepatitis [1–3]. Liver transplantation (LT), that treats the tumor and the underlying chronic liver disease [4], is considered as the best treatment for HCC [4]. However, as a result of organ shortage, LT for HCC is recommended for patients with an expected 5-year post-transplantation survival greater than 50% [5] and an expected 5-year post-transplantation survival similar to the one after liver transplantation for benign liver diseases (i.e., 70%) [6]. In this setting, the Milan criteria [7] were worldwide adopted as a prioritization tool with a 5-year survival rates ranging from 65 to 80%.

Recently, the Liver Transplant French Study Group developed a score that is a predictive model of HCC recurrence after LT. This score, named the "AFP-score," that includes three variables (tumor number, tumor size and AFP serum level), was shown to significantly improve prediction of tumor recurrence when compared to the Milan criteria [8, 9]. In France, in patients suffering from HCC on CLD, the AFP-score has been officially adopted for patients before LT since January 2013 (http://www.agence-biomedecine.fr). Thus, LT for HCC is now contraindicated if the AFP-score is >2, due to a recurrence rate around 50%, irrespective of Milan Criteria.

Graft shortage remains the major problem in LT. For this reason, for patients with solitary HCC, primary liver resection is mandatory and salvage LT is performed in case of tumor recurrence [10–12]. Salvage LT has been largely reported, but salvage studies have been performed in the era of Milan's criteria [13–18]. This two-step strategy was never been evaluated in the AFP-score era.

The aims of this study were therefore to assess if the AFP-score at the first LR was predictive of recurrence in order to determine whether AFP-score can be a useful tool to consider or not a salvage LT in patients suffering from solitary HCC developed on CLD.

Methods

Patients

Between 1990 and 2012, 347 consecutive patients underwent a liver resection (LR) for a HCC developed on CLD (METAVIR F3-F4 [19]) at Henri Mondor Hospital.

Inclusion criteria were: patients with a primary HCC under 6-cm diameter on preoperative CT scan or MRI according to AFP-score criteria. Exclusion criteria were: patients who had a LR as a bridge to LT and patients who had a second resection for recurrence of an initial HCC. We also excluded patients with multiple nodules, based on preoperative imaging CT scan, and patients with macrovascular tumor invasion based on surgical specimen. The remaining 108 patients have formed the study population.

Preoperative management and surgery

Protocol of initial management and surgery was previously described [16]. All patients were discussed at a weekly multidisciplinary meeting including hepatologists, radiologists, pathologists and surgeons. Diagnosis of HCC was based on EASL (European Association for the Study of the Liver) criteria. Selection criteria for resection in patients with HCC on CLD were: CHILD–PUGH class A cirrhosis [20], no esophageal varices, platelet count $>100 \times 10^9$/L for major resection and varices grades ≤ 2 for minor resections and remnant liver volume >50%. Since 2002, portal vein embolization was routinely performed before major hepatectomy on cirrhosis. Laparoscopic approach was introduced in 1998 for selected patients [21–23].

Postoperative cares included fast-track mobilization, proton pump inhibitors, limited intravenous fluid administration and perioperative antibioprophylaxis.

Follow-up and postoperative management

Follow-up including liver function tests, AFP and CT scan or MRI if necessary were performed every 4 months after surgery for 3 years and twice a year after 3 years. Patients with chronic viral hepatitis B or C were treated appropriately before or after surgery.

All recurrences were discussed in the multidisciplinary meeting. Patients were also included in a repeat curative treatment adapted to their recurrence: salvage LT, repeat LR or radiofrequency (RFA). Palliative treatments, TACE or sorafenib, were considered if any of these curative treatments were possible [24].

Method analysis

Data collection

Data were blindly collected retrospectively by a SQL request from our prospective liver database. Demographic criteria, underlying liver disease, surgical results of initial LR (postoperative morbidity according to Dindo-Clavien classification [25]), AFP serum level at diagnosis and recurrence and follow-up care were collected. Brisbane classification was used for LR [26]. AFP-score was

calculated as described previously [6]: tumor diameter <3 cm, between 3 and 6 cm and upper than 6 cm scored 0, 1, 4 points, respectively. Number of nodules from 1 to 3 scored 0 and upper than 4 scored 2 points. AFP level <100, between 100–1000 and upper than 1000 ng/mL scored 0, 2, 3 points, respectively.

End points

To determine, whether or not, the AFP-score could be a useful tool to enroll them in a salvage LT program, a binary variable (VAR_REC) was created. VAR_REC was coded "1" in case of no-recurrence or recurrence "in AFP-score" and coded "0" in case of recurrence "out AFP-score" (i.e., AFP-score >2) or in case of extrahepatic recurrence.

Secondary end points were postoperative overall survival (OS), postoperative disease-free survival (DFS) and postoperative results of the first LR.

In order to establish if a potential biological background may exist, the relationship between the AFP-score and anatomopathological examination was investigated. Tumor differentiation was based on Edmondson classification [27].

Statistical analysis

Results of descriptive continuous variables are presented as mean ±1 standard deviation, median with range for quantitative data and numbers with percentage for qualitative data. Missing data of the database were managed with the multiple imputation by chained equation (MICE) procedure.

Dichotomous variables were tested with the Chi square test or the exact test of Fisher when necessary. The VAR_REC variable was analyzed by a logistic regression. The 10% significative variables in the univariate analysis were included in a logistic multivariate analysis. Stepwise procedure was used to select 5% significative variables, which were considered as independent prognosis factors of recurrence.

Patient's survival was estimated with the Kaplan–Meier's method and compared with the log-rank test when appropriate. Prognosis factor of overall survival and disease-free survival was determined with the Cox model including variable with $p < 0.2$ in the univariate analysis of survival.

All statistical analyses were performed using R software, 3.2.1 version (https://cran.r-project.org/).

Results

Population characteristics

At the first LR, among the 108 patients, 96 were "in AFP-score" (i.e., ≤2) and 12 were "out AFP-score" (i.e., >2). Both groups were comparable for age, sex, body mass index, etiology of liver disease and size of nodule before LR (Table 1).

On pathological examination, patients "out AFP-score" had higher Edmondson grade HCC ($p = 0.04$), higher rate of microvascular invasion ($p = 0.03$) and higher rate of satellites nodes ($p = 0.01$) (Table 1).

Primary end point

After a median follow-up of 65.4_{IQR} [13–114] months, 64.8% (70/108) patients experienced recurrence. Recurrence and modalities of treatment after recurrence are detailed in Table 2.

Univariate analysis showed that before LR, patients "in AFP-score" and tumors size were statistically associated with recurrence in AFP-score. Multivariate analysis failed to determine prognostic factor to predict recurrence (Table 3).

The incidence of recurrence in patients "in AFP-score" was 60.4% (58/96) versus 100% (12/12) in patients "out AFP-score" ($p < 0.01$).

In case of recurrence, it was within the "AFP-score" in 96.5% (45/52) of patients in "AFP-score" before initial LR versus 25% (3/12) for patients out the AFP-score.

Secondary end point

Overall survival (OS)

The median OS was 62.3_{IQR} [11–113] months for the whole population. OS was $86.61\%_{95\%CI}$ [80.32–93.40] at 1 year, $76.66\%_{95\%CI}$ [68.66–85.58] at 3 years and $67.15\%_{95\%CI}$ [57.62–78.26] at 5 years after initial LR.

Three (2.8%) patients died during the postoperative course. In the remaining population, 19 patients were older than 70 years. Among them, 13 died because of HCC recurrence and 6 were alive 5 years after LR.

An age >65 years, male sex and being "in AFP-score" were statistically significant prognostic factors of overall survival in univariate analysis. Edmondson score, histological size of HCC and the presence of microvascular invasion were forced in the multivariate analysis. Multivariate analysis showed that being "in AFP-score" and the presence of microvascular invasion were independent

Table 1 Population characteristics

	Whole population $N = 108$ (%)	In score AFP group $N = 96$ (%)	Out score AFP group $N = 12$ (%)	P value
Age				
(median, range)	65.6 (32–79)	64.2 (32–79)	66.8 (45–78)	0.52
Gender				1
Female	24 (22.2)	21 (22.3)	3 (25.0)	
Male	84 (77.8)	75 (77.7)	9 (75.0)	
BMI				
(median, range)	25.9 (18.7–42.7)	25.8 (18.7–42.7)	25.6 (19.8–31.6)	0.85
Etiology of liver disease[a]				0.65
Alcohol	25 (23.1)	23 (24.5)	1 (8.3)	
HBV	26 (24.1)	23 (24.5)	3 (25.0)	
HCV	41 (38.0)	35 (37.2)	6 (50.0)	
NASH	10 (9.3)	8 (8.5)	1 (8.3)	
Other	6 (5.6)	5 (5.3)	1 (8.3)	
Size of nodule before hepatectomy (mm)				**0.002**
(median, range)	32.8 (10–59)	31.1 (10–59)	47.2 (30–58)	**0.01**
AFP serum level				
Mean (median, range)	2512 (1–26,000)	87 (1–1000)	8321 (30–26,000)	
0–100	87	87	0	
100–1000	14	9	5	
>1000	7	0	7	
Surgical approach				**0.03**
Laparotomy	46 (42.6)	35 (37.2)	9 (75.0)	
Laparoscopy	62 (57.4)	59 (62.8)	3 (25.0)	
Anatomopathological examination				
Nodule size (median, range)	34.5 (10–63)	35.7 (10–63)	39.5 (12–59)	0.06
METAVIR score[a]				0.16
3	22 (20.5)	17 (18.1)	5 (41.7)	
4	86 (79.5)	79 (81.9)	7 (58.3)	
Edmondson score[a]				**0.003**
Grade I–II	53 (55.7)	51 (57.8)	2 (16.6)	
Grade III–IV	42 (44.3)	32 (42.4)	10 (83.4)	
Microvascular invasion[a]				**0.03**
Yes	33 (36.7)	26 (33.3)	7 (63.6)	
No	57 (63.3)	52 (66.7)	4 (36.4)	
Satellites nodes[a]				**0.01**
Yes	22 (22.9)	16 (19.0)	5 (45.5)	
No	74 (77.1)	68 (81.0)	6 (54.5)	

Statistically significative results are given in bold

[a]missing data before MICE procedure, *BMI* body mass index, *AFP* alpha-fetoprotein

prognostic factors of overall survival in the study (Table 4).

Disease-free survival (DFS)

The median DFS was 30.4_{IQR} [15–52] months in the whole population. DFS was $77.15\%_{95\%CI}$ [69.33–85.32] at 1 year, $48.95\%_{95\%CI}$ [39.65–60.43] at 3 years and $39.41\%_{95\%CI}$ [29.92–51.93] at 5 years. An age >65 years and METAVIR score were statistically significant prognostic factors of DFS in univariate analysis ($p = 0.03$ and $p = 0.05$, respectively). Male sex, the AFP-score, the presence of microvascular invasion and mean histological size of HCC were closed to be statistically significant ($p = 0.12$) and therefore forced in the multivariate analysis. Multivariate analysis showed that the presence of microvascular

invasion was an independent prognostic factor of DFS ($p = 0.003$) (Table 5).

Outcome of salvage transplantation in patients resected with "in AFP-score"

At the end of the follow-up, 26 patients were listed for LT. Among them, 21 were finally transplanted. Five were still on the waiting list, and no patient experienced dropout. Two patients died after LT. The first one died, on post-operative day 32, secondary to peritonitis (duodenal fistula), and the other died on postoperative day 58, secondary to a ventilator-associated pneumonia.

The overall survival after the first LR was $95.8\%_{95\%CI}$ [57.62–78.26], $92.1\%_{95\%CI}$ [57.62–78.26] and $81.1\%_{95\%CI}$ [57.62–78.26] at 1, 3 and 5 years, respectively.

The overall survival after LT was $90.9\%_{95\%CI}$ [79.7–100], $85.6\%_{95\%CI}$ [71.6–100] and $68.5\%_{95\%CI}$ [50.2–93.0] at 1, 3 and 5 years, respectively.

The disease-free survival after LT was $94.7\%_{95\%CI}$ [85.2–100], $82.9\%_{95\%CI}$ [90.2–100] and $82.9\%_{95\%CI}$ [90.2–100] at 1, 3 and 5 years, respectively. Three patients recurred after LT at 11.1, 22.6 and 34.4 months and died from recurrence at 41.4, 49.3 and 35.9 months, respectively.

Discussion

This study suggests that the AFP-score select patients for salvage LT after LR for solitary HCC developed on CLD.

Thus, in our study, patients in "AFP-score" at initial LR were either free of recurrence after surgery or, in case of recurrence, were still within LT criteria based on the AFP score in 84% of cases (38/45) and allow to avoid 6% (6/96) of LT for patients who had extrahepatic recurrence.

In patients "in AFP-score," up-front LR was associated with 67.2% 5-year OS. This result is similar to the one after LT within the AFP model [6] and Milan criteria [28–32]. This survival result is in accordance with previous series in patients with solitary HCC <5 cm [33–35]. In the largest series published study [35], reporting 243 LR for patients with solitary HCC <5 cm, the 5-year OS was 76.2%, compared to 81% in 39 LT. This OS, similar to our OS after LT, could be explained by the three principal results of the present study: (1) the low postoperative mortality rate, (2) the type of recurrence (i.e., the primary end point of the study) and (3) the treatment of recurrences.

Patients resected in "out AFP-score" developed extrahepatic recurrence in 50% of the cases, compared to none in "in AFP-score" group. We think that this result emphasizes the ability of the AFP-score to predict LT contraindication, since recurrence after LT is secondary to synchronous extrahepatic disease at the time of transplantation. Graft shortage forces to minimize unnecessary liver transplantation and led to propose valid alternative to up-front LT. The AFP-score was developed and implemented in France for this reason [6]. Nowadays, in France, patients "out AFP-score" are no more eligible for LT and patients "in AFP-score" with solitary HCC <3 cm are no more prioritized. In addition, this strategy allows, in patients "out AFP-score," to avoid 6 unnecessary transplantation, in patients who experience isolated or synchronous extrahepatic recurrence.

The present study is based on a highly selected population that is patients suitable for salvage LT and refers to the concept of "LR as a selection tool" first described by Scatton et al. [36]. Indeed, salvage LT was mainly described for solitary HCC and is sometimes used for multifocal HCC [37]. The inclusion was also based on the presence or not of macrovascular tumor invasion on the final pathological examination because LR anatomopathological examination is by definition a pre-LT

Table 2 Management of recurrence

	AFP-score ≤2 $N = 96$ (%)	AFP-score >2 $N = 12$ (%)
No recurrence	38 (39.6)	0
Hepatic	52 (54.2)	6 (50)
Recurrence with AFP-score ≤2	45 (46.9)	3 (25)
Curative treatment	38 (84.4)	3 (100)
Liver transplantation	21	2
Planed LT-patient on waiting list	5	0
Repeat hepatectomy	6	–
RFx	6	1
Palliative care	7 (15.6)	0 (0)
TACE	6	–
CI to LT ≥chemotherapy	1	–
Recurrence with AFP score >2		
Curative treatment	7 (15.6)	3 (100)
Liver transplantation	1	1
Planed LT-patient on waiting list	1	0
Repeat hepatectomy	1	0
RFx	4	2
Extrahepatic	1 (1.0)	0 (0)
Lung resection	1	–
Hepatic and extrahepatic	5 (5.2)	6 (50)
Palliative care		
TACE + chemotherapy	3	4
Chemotherapy	2	2

LT liver transplantation, *RF* radiofrequence, *TACE* trans-arterial chemoembolization, *CI* contraindication

Table 3 Prognosis factors of no-recurrence or recurrence "in AFP-score"

Factor	Univariate analysis (SHR[a], [95% CI], *P*)	Multivariate analysis (HR[a], [95% CI], *P*)
Population criteria		
Age per 1 year increase	1.1, [0.5–33.3], 0.18	
Gender		
Men	1.3, [0.41–4.16], 0.87	
BMI >25	5.1, [2.5–10.1], 0.14	
Underlying Liver disease		
Alcohol	0.18, [0.11–2.17], 0.23	
HBV and HCV Viruses	0.04, [0.21–3.45], 0.78	
NASH	0.15, [0.52–4.54], 0.55	
Other	0.18, [0.28–1.61], 0.47	
AFP score ≤2	1.21, [1.01–1.48], **0.05**	1.11, [0.69–1.21], 0.54
Preoperative size of HCC	1.1, [0.10–5.21], 0.16	
Anatomopathological examination		
METAVIR score		
F3	2.08, [0.22–5.57], 0.81	
F4	3.21, [0.54–8.79], 0.37	
R0 resection	0.19, [0.08–3.56], 0.56	
Necrosis >50%	0.51, [0.12–0.73], 0.29	
Surgical margin >20 mm	0.40, [0.18–2.43], 0.49	
Histopathological size of HCC	7.72, [0.26–11.7], 0.51	
The presence of satellites nodes	7.11, [0.36–10.1], 0.25	
The presence of microvascular invasion	3.24, [0.32–6.61], 0.15	0.64, [0.18–1.49], 0.18
Differentiation degree undifferentiated versus others	0.32, [0.08–0.59], 0.32	
Edmondson grade: IV versus I–II–III	0.38, [0.12–0.76], 0.12	0.65, [0.34–2.21], 0.39

Statistically significative results are given in bold

SHR sub-hazard ratio, *HR* hazard ratio, *BMI* body mass index; hepatitis B virus, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *HCC* hepatocellular carcinoma

[a]HR adjusted on AFP score (forced in the model), BMI, necrosis >50%, Edmondson grade, differentiation degree

examination, and since macrovascular invasion is a contraindication to LT, we exclude these patients.

Salvage LT as the "resect and wait" concept [3] is based on the AFP-score criteria. This strategy is relevant because it provides the lowest recurrence rate while ensuring that a possible recurrence is still within LT criteria. In the present study, patients "in AFP-score" experienced recurrence in 60% (58/96) and were eligible for LT in 86% (45/52) of cases. In addition, in patients resected "in AFP-score," 26 patients were listed for LT without dropout, 21 were finally transplanted and 5 are still on the waiting list. The 5-year overall survival after the first LR, the 5-year overall survival after LT and 5-year disease-free survival after LT were 81.1, 68.5 and 82.9%, respectively. These results are similar with the one obtained after LT in this stating [6, 28–32].

Postoperative mortality is a major concern. After LT, in CHILD A cirrhosis, postoperative mortality rate is 5% [36]. In our study, postoperative mortality was 2.8% after LR and 9% after salvage LT. This result justifies this surgical strategy of up-front LR. In our recent practice, high selected patients are included in this "resect and wait" concept [38–41].

In the present study, patients in the AFP score whose HCC recurred were not proposed to salvage LT because of age or patients' choice. However, they were treated in curative intent. Six of them underwent a repeat LR and 8 underwent a radiofrequence. Repeat LR was first reported in 1986 [42], and several studies have reported 5-year overall survival that reach 72% to 83% [43–45] with better results if the disease-free interval is >1 year [46]. Moreover, radiofrequency ablation (RFA) is advocated for recurrence treatment with similar results on overall survival [47, 48].

This study showed that the AFP-score is useful to select patients for salvage LT after LR for solitary HCC. For patients "in AFP-score," up-front LR provides good survival and allows to avoid up-front LT in case of recurrence. Future studies are advocated to confirm this result.

Table 4 Prognosis factors of overall survival

Factor	Univariate analysis (SHR[a], [95% CI], *P*)	Multivariate analysis (HR[a], [95% CI], *P*)
Population criteria		
Age >65 years	1.85, [1.03–3.35], **0.04**	
Gender		
Men	1.89, [1.01–3.55], **0.05**	1.69, [0.97–2.41], 0.10
AFP score ≤2	1.41, [0.55–3.60], **0.04**	1.47, [1.04–2.6], **0.006**
Surgical criteria		
Laparoscopy versus laparotomy	1.11, [0.54–1.75], 0.97	
Number of resected hepatic segment (3–4 versus 1–2)	1.20, [0.87–1.62], 0.27	
Length of surgical resection	1.00, [0.97–1.04], 0.64	
Anatomopathological examination		
METAVIR score		
F4 versus F3	2.62, [1.04–6.62], 0.24	
R0 resection	1.69, [0.75–3.82], 0.21	
Necrosis >50%	0.99, [0.96–1.03], 0.82	
Surgical margin >20 mm	1.00, [0.97–1.03], 0.97	
Histopathological size of HCC	1.55, [0.86–2.79], 0.14	
The presence of satellites nodes	1.23, [0.56–2.71], 0.56	
The presence of microvascular invasion	1.72, [0.87–3.41], 0.10	1.10, [1.02–1.86.], **0.004**
Differentiation degree undifferentiated versus others	1.89, [0.73–4.83], 0.19	
Edmondson grade: IV versus I–II–III	1.59, [0.86–3.94], 0.15	

Statistically significative results are given in bold

SHR sub-hazard ratio, *HR* hazard ratio, *BMI* body mass index; hepatitis B virus, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *HCC* hepatocellular carcinoma

[a]HR adjusted on AFP score, gender, histological size of HCC (forced in the model), age >65 year, microvascular invasion (forced in the model), Edmondson score (forced in the model)

Table 5 Prognosis factors of disease-free survival

Factor	Univariate analysis (SHR[a], [95% CI], *P*)	Multivariate analysis (HR[a], [95% CI], *P*)
Population criteria		
Age >65 years	1.93, [1.06–3.53], **0.03**	
Gender		
Men	1.78, [0.63–3.45], 0.07	
AFP score <2	1.44, [0.56–3.70], 0.14	1.65, [1.24–2.61], 0.12
Surgical criteria		
Laparoscopy versus laparotomy	1.01, [0.56–1.85], 0.96	
Number of resected hepatic segment (3–4 versus 1–2)	1.26, [0.91–1.75], 0.16	
Length of surgical resection	1.00, [0.99–1.04], 0.65	
Histopathological criteria		
METAVIR score		
M4 versus M3	2.57, [1.02–6.51], **0.05**	
R0 resection	0.56, [0.43–1.03], 0.26	
Necrosis >50%	0.99, [0.96–1.04], 0.83	
Surgical margin >20 mm	1.03, [0.97–1.05], 0.83	
Histopathological size of HCC	1.63, [0.87–3.04], 0.12	
The presence of satellites nodes	1.12, [0.48–2.56], 0.80	
The presence of microvascular invasion	1.64, [0.82–3.33], 0.12	2.50, [1.42–10.20], **0.003**
Differentiation degree undifferentiated versus others	1.94, [0.75–5.01], 0.17	
Edmondson grade: III–IV versus I–II	1.63, [0.49–5.35], 0.43	

Statistically significative results are given in bold

SHR sub-hazard ratio, *HR* hazard ratio, *BMI* body mass index; hepatitis B virus; *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *HCC* hepatocellular carcinoma

[a]HR adjusted on AFP score (forced in the model), gender (forced in the model), Age >65 years, microvascular invasion (forced in the model), histological size of HCC (forced in the model)

Compliance with ethical standards

Conflict of interest Nothing to disclose.

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