

Hepatocellular Carcinoma at a Tertiary Referral Center-experience with Surveillance in Patients at Risk Over 8 Years

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survival benefit for HCC patients. Strict adherence to regular observation intervals seems warranted in order to prove an impact of surveillance on long-term survival.

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Key words: Hepatocellular Carcinoma; Surveillance; Survival After Liver Transplantation and Liver Cirrhosis

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ABSTRACT

AIM: HCC surveillance is recommended for patients with liver cirrhosis. This study aimed to assess the impact of surveillance on the clinical course and survival in HCC patients.

METHODS: Clinical data of 336 patients with liver cirrhosis were evaluated retrospectively. Patients were divided into 2 groups: group 1 included patients who did not suffer from HCC at initial contact and had at least 2 ultrasound examinations for surveillance purposes (n=161). Group 2 included patients with HCC at first presentation and without any foregoing HCC-surveillance (n=76). Groups were compared regarding patient and disease characteristics, liver transplantation and survival time.

RESULTS: Men were significantly more often affected by HCC ($p=0.005$). The number needed to screen for one incident HCC was 7, and 81% of HCC cases were detected by ultrasound. There was no significant difference between groups 1 and 2 in the number of patients fulfilling Milan or UCSF criteria (45.8% in group 1 vs. 34.2% in group 2, and 50.0% in group 1 vs. 46.1% in group 2, respectively). Mean survival time of patients with incident HCC (group 1: 51.8 +/- 7.7 months) was not significantly different from patients with HCC at first presentation (group 2: 50.4 +/- 5.6 months).

CONCLUSION: Our surveillance program proved to be efficient in terms of number needed to screen but did not result in a proven

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer mortality^[1-4]. Approximately 560 000 cases are diagnosed each year, and 550 000 deaths occur due to liver cancer^[5-7]. There is a wide geographic variation in HCC incidence from 5.5 to 14.9/100 000 inhabitants/year. The great majority occurs in either sub-Saharan Africa or in Eastern Asia due to high rates of chronic hepatitis B and C infection with and without aflatoxin exposure. However, a trend of rising rates of HCC has been reported from several developed countries in Europe and North America. These trends are associated with "new" risk factors such as hepatitis C virus infection (HCV) and, possibly, diabetes^[8-10]. 80-90% of HCC cases are associated with cirrhosis, suggesting that patients with cirrhosis form the main risk group for HCC (11-13). The median survival time of HCC without therapy in symptomatic cases is only about 2-4 months, in asymptomatic patients however, it may reach approximately 24 months^[14]. Liver transplantation (LTx) is the only therapeutic option offering cure in patients with liver cirrhosis and HCC. With the introduction of the Milan criteria, the 5-year survival rate after LTx due to HCC rose from 25.3% in 1987-1991 to 61.1% in 1996-2001^[15]. While the latest update of the European Liver Transplant Registry reports a 5-year survival rate of 58%^[16], more than 70% can be achieved in highly selected patients with HCC^[17]. However, the risk of recurrence after LTx is increased as a result of a life-long immunosuppression^[18, 19].

Table 1 Etiology of liver cirrhosis in the study population.

Risk factor	n (%)	male n (%)	female n (%)
HCV	121 (36.0)	72 (59.5)	49 (40.5)
Alcohol abuse	84 (25.0)	55 (65.5)	29 (34.5)
HBV	44 (13.1)	36 (81.8)	8 (18.2)
HBV and alcohol abuse	9 (2.7)	8 (88.9)	1 (11.1)
HBV and HDV	5 (1.5)	4 (80.0)	1 (20.0)
HCV and alcohol abuse	7 (2.1)	5 (71.4)	2 (28.6)
AIH	14 (4.2)	4 (28.6)	10 (71.4)
AIH and PSC	1 (0.3)	1 (100)	--
PBC	6 (1.8)	1 (16.7)	5 (83.3)
PSC	3 (0.9)	1 (33.3)	2 (66.7)
Hereditary hemochromatosis	3 (0.9)	2 (66.7)	1 (33.3)
Secondary biliary cirrhosis	1 (0.3)	1 (100)	--
Wilson's disease	1 (0.3)	1 (100)	--
Cryptogenic cirrhosis	37 (11.0)	23 (62.2)	14 (37.8)
total	336 (100)	214 (63.7)	122 (36.3)

Table 2 Age, observation time, and outcome in the study population.

	Group 1a	Group 1b	Group 2
total n	24	137	76
male/female	20/4	79/58	55/21
median age at first contact (years)	62.0	55.6	65.5
median age at HCC diagnosis (years)	63.0	not applicable	65.5
median observation time (months)	43.3 (2.4-95.3)	27.6 (2.0-95.0)	5.0 (0-71.0)
lost to follow-up	2 (8.3%)	43 (31.4%)	43 (56.6%)
died	6 (25.0%)	6 (4.4%)	11 (14.5%)
still living	16 (66.7%)	88 (64.2%)	22 (28.9%)

Table 3 LTx and preoperative Milan or UCSF criteria, respectively, in group 1a and 2.

	Group 1a	Group 2
total n of HCC	24	76
Milan criteria	11 (45.8%)	26 (34.2%)
UCSF criteria	12 (50.0%)	35 (46.1%)
total n of LTx	11	12
LTx due to HCC	11	12
LTx within Milan criteria	5 (45.5%)	6 (50.0%)
LTx within UCSF criteria	6 (54.5%)	7 (58.3%)

Several cohort studies have demonstrated that cirrhotic patients might benefit from HCC surveillance with serum alpha-fetoprotein (AFP) measurements and abdominal ultrasound^[20-23]. There is still considerable controversy about the role of surveillance for patients at risk^[24,25]. However, several guidelines for HCC management recommend to offer surveillance to patients with cirrhosis or chronic liver disease^[26-32]. In 2008, we initiated a data base in order to elucidate the incidence, prevalence, and underlying risk factors of HCC in patients who presented to the Clinic for Gastroenterology and Hepatology at the University Hospital of Cologne. Further, the effectiveness of abdominal ultrasound and additional AFP measurements for early detection of potentially curable patients with regard to differences in survival following LTx should be explored. Here we report our findings for the first 100 consecutive patients with HCC.

METHODS

We retrospectively evaluated the medical records of 336 patients with confirmed cirrhosis of different etiologies (Table 1) who presented to the Clinic of Gastroenterology and Hepatology at the University Hospital of Cologne between July 1997 and April 2005. Data concerning patient history, abdominal ultrasound, CT and MRI findings, AFP levels, and histological findings of liver biopsies were collected. At first contact with our institution, the median age of all patients was 57.3 years (range: 19-83 years), 57.8 years for women and 57.0 years for men. The patient population was divided into 3 groups: group 1 - the surveillance group - includes data of 161 patients (47.9% of all patients) who participated in at least 2 ultrasound examinations for surveillance purposes \geq 6 months apart, and were free of HCC at initial presentation to our

institution. Patients who newly developed HCC during our surveillance program were labeled as "patients with incident HCC" (group 1a) while those who did not develop an HCC during the surveillance period were named as "patients without HCC" (group 1b). 76 of 336 (22.6%) patients presented with an HCC already at first contact with our clinic and represent group 2 described as "patients with HCC at initial contact". These patients were referred for further treatment of newly detected HCC by their treating physicians, but had not undergone a formal surveillance program. 99 of 336 (29.5%) patients (60 men, 39 women, median age 56.3 years, range 23-79 years) were seen only once and did not return for scheduled follow-up visits. Thus, due to the lack of outcome data, this group is not further described hereafter.

Patients at risk as well as their treating physicians were informed about our surveillance program that included clinical, laboratory, and abdominal ultrasound examinations as well as the determination of AFP at 6-12 months intervals according to international recommendations^[23,24]. However, we did not routinely arrange for follow-up visits within this time frame when patients were seen at our clinic. AFP values were measured by the ELECSYS-AFP-Test (Roche Diagnostics GmbH, Mannheim, Germany) with a reference value of \leq 7.25 ng/mL (5.8 kU/L). When HCC was suspected, additional imaging procedures such as CT and/or MRI were performed, since contrast enhanced abdominal ultrasound was unavailable during the study period. With typical imaging patterns HCC diagnosis was made according to a published algorithm^[28], and liver biopsies were carried out only when diagnosis remained uncertain. The tumor size was classified as follows: \leq 3 cm (small HCC), $>$ 3 cm and \leq 5 cm (intermediate HCC), $>$ 5 cm (large HCC). The morphology of HCC was classified as solitary, paucifocal ($<$ 3 nodules), and multifocal ($>$ 3 nodules). In case of HCC, possible candidates for LTx were analyzed according to the Milan and UCSF criteria^[29,34-36].

Control of local tumor growth was tried using radiofrequency ablation, transarterial chemoembolization, and percutaneous ethanol injections alone or in combination in suitable cases, e.g. without extra hepatic tumor spread or while on the LTx waiting list. In palliative cases, the decision to prescribe pravastatin^[30] was left to the discretion of the treating physician. During the study period none of the patients received chemotherapy or sorafenib.

Data were analyzed using SPSS (Statistical Package for Social Sciences, Munich) version 18.0 for Windows. The results were expressed as median and range. Categorical variables were explored using the chi²-test (Pearson or Fisher's exact test). The Mann-Whitney U-test was used for continuous variables. For all calculations a $p < 0.05$ was considered as significant. The survival times were calculated using the Kaplan-Meier method and the log-rank test. Here the mean survival with standard error was reported.

RESULTS

HCC developed during a median follow up of 30 months (range: 2-95 months) in 24 (20 men and 4 women; group 1a) of 161 patients. Thus, 7 patients from the surveillance group had to be screened during 2.5 years to detect one new case of HCC. 76 patients (55 men and 21 women; group 2) presented with HCC at initial contact with our clinic. There was no difference in the distribution of HCC risk factors between both groups. Considering all 100 HCC patients there was a male predominance (75 vs. 25, $p=0.005$), and chronic HCV infection was the leading cause (50%). Patients who remained free of HCC (group 1b) were significantly younger at first contact ($p=0.03$) than those who developed HCC during surveillance (Table 2) which in turn did not differ from patients with HCC already at first presentation. In group 1b, 30 of 137 patients without HCC had

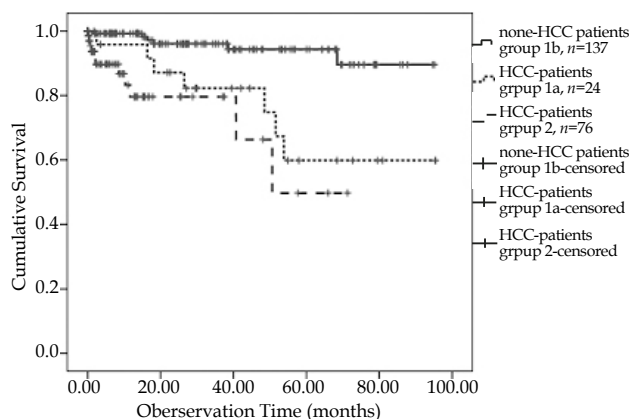


Figure 1 Survival of patients in group 1 and 2 ($n=237$). Observation time from initial contact to event.

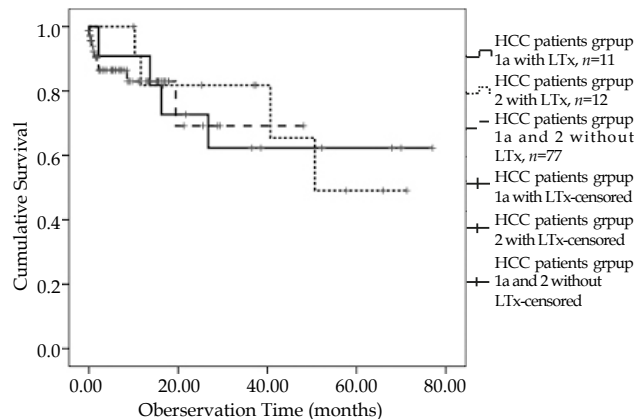


Figure 3 Survival of patients with HCC with or without LTx. Observation time from diagnosis (group 1a) or initial contact (group 2) to event.

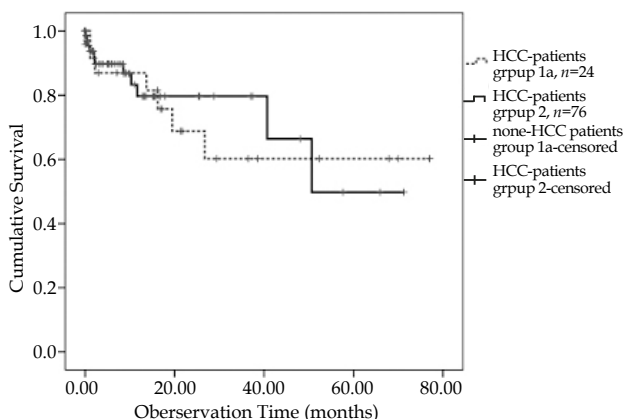


Figure 2 Survival of all patients with HCC ($n=100$). Observation time from diagnosis (group 1a) or initial contact (group 2) to event.

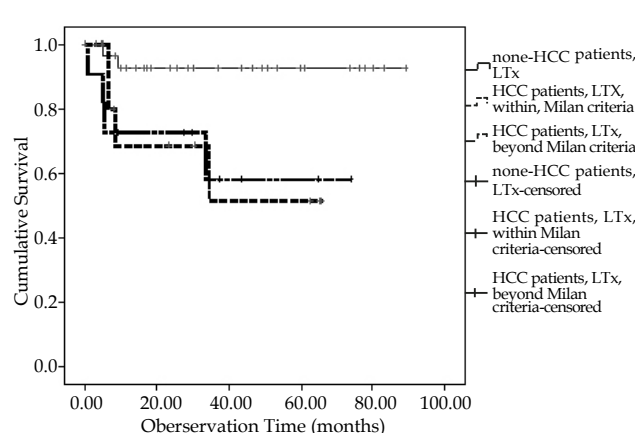


Figure 4 Survival of all patients with LTx: without HCC ($n=30$), with HCC within Milan criteria ($n=11$), and with HCC beyond Milan criteria ($n=12$). Observation time from LTx to event.

undergone LTx. In these patients, alcoholic liver cirrhosis was the most common cause for LTx, followed by chronic HCV infection.

In group 1a the median size of HCC on abdominal ultrasound was 3.1 cm (range: 0.9-7.8 cm, 37.5% ≤ 3 cm) compared to 4.4 cm (range: 1.5-13 cm, 28.9% ≤ 3 cm) in group 2. Neither the size nor the number of HCC nodules differed significantly between both groups. Also, there was no statistically significant difference in the number of patients who preoperatively fulfilled Milan or UCSF criteria or received LTx within these criteria (Table 3).

AFP measurements were available for 82 of 100 patients with HCC and 88 of 137 patients in group 1b. AFP plasma levels were normal in 10 patients and >7.25 ng/mL (>5.8 kU/L) at the time of HCC diagnosis in 72 of the 100 HCC patients. The AFP levels at initial diagnosis of HCC in group 1a were not significantly different from those in group 2. For a cut-off level of 200 ng/ml ($n=31$ patients) as recommended by the previous AASLD guideline (31) sensitivity was 37.8%, specificity 97.7%, the PPV 93.9%, and the NPV 62.8%. When a cut-off level of 400 ng/mL ($n=28$ patients) was applied as recommended by the previous EASL guideline (32), sensitivity and NPV dropped (34.1% and 61.7%, respectively), however specificity (98.9%) and PPV (96.6%) increased.

In group 1b, i.e. patients without HCC, the 1- and 5-year survival rates were 99.3%, and 96%, respectively, and mean cumulative survival time was significantly longer than in patients with incident HCC: 89.6 \pm 2.2 months vs. 71.5 \pm 7.3 months ($p=0.002$, see figure 1). When the time of HCC diagnosis was considered in patients of group 1a, the 1- and 5-year survival rates were 86.9% and 60.2%, respectively, and mean cumulative survival time was 51.8 \pm 7.7 months. In group 2, i.e. patients with HCC already at initial

contact, the 1- and 5-year survival rates were 79.6% and 49.8%, respectively, and mean cumulative survival time was 50.4 \pm 5.6 months. However, there was no significant difference in survival rates or cumulative survival time compared to patients of group 1a after adjusting for the time of HCC diagnosis (Figure 2). The mean cumulative survival time of all 100 patients with HCC was 52.4 \pm 5.0 months. Patients who received LTx had a mean cumulative survival time of 54.3 \pm 6.4 months (group 1a : 53.7 \pm 9.4 months, group 2: 51.9 \pm 7.5 months) with 1-, 2-, and 5-year survival rates of 86.5%, 77.4%, and 55.9%, respectively. In patients who did not receive LTx, the mean cumulative survival time was 36.4 \pm 4.2 months. Here, the 1- and 2-year survival rates were 83.0% and 69.2%, respectively (Figure 3). However, according to log-rank test there was no significant difference in survival between HCC patients with and without LTx. Also, while the same was true for patients who received LTx within or beyond the Milan criteria (49.0 \pm 9.9 months vs. 42.1 \pm 9.0 months) mean cumulative survival time following LTx was significantly longer for patients without HCC (83.2 \pm 4.1 months, $p < 0.02$, see figure 4).

DISCUSSION

Our surveillance program proved to be highly efficient for participants in terms of the number needed to screen ($n=7$) to detect one incident case of HCC. However, there was no significant difference regarding cumulative survival time between patients who developed HCC during surveillance compared to those with HCC already at initial presentation outside a formal surveillance program.

In contrast, a significantly better 3-year survival rate for HCC patients under surveillance was observed in a study by Kuo *et al*^[8]: 59.1% vs. 29.3% in the non-surveillance group. As expected, patients without HCC of group 1 had a significant longer survival than patients with HCC of the same group. Our disappointing results concerning transplantation may be due to the fact, that only about half of the patients in both groups were transplanted within Milan or UCSF criteria. The fact, that LTx was more often used as a therapeutic option in incident cases of HCC probably only reflects the younger median age in these patients but not a truly earlier detection with smaller sized HCCs. Similar observations were made by Bolondi *et al*^[15] who found a lower mean patient age in incident HCC cases (61.8 vs. 63.8 years) with significantly different transplantation rates (26% vs. 13%) despite only slightly smaller tumor sizes (2.73 vs. 3.34 cm; data only given for solitary HCCs).

LTx in patients with HCC resulted in a non significant extension of survival time. The mean cumulative survival time of all 100 patients with HCC was 52.4 +/- 5.0 months. HCC-Patients who received LTx had a mean cumulative survival time of 54.3 +/- 6.4 months (group 1a : 53.7 +/-9.4 months, group 2: 51.9 +/-7.5 months) with 1-, 2-, and 5-year survival rates of 86.5%, 77.4%, and 55.9%, respectively. In Patients with HCC who did not receive LTx, the mean cumulative survival time was 36.4 +/- 4.2 months, with no significant difference in survival compared to those with LTx. Other authors report similar results, with 1-year survival rates of 70%-87% and 5-year survival rates of 49%-75%^[33-36], which is comparable to our 1- and 5-year survival rates for LTx of 86.5% and 55.9%. Earlier studies had shown 3-year survival rates of 21%-47% and recurrence rates of 29%-54% in transplanted patients with advanced HCC^[37-40]. Keeping LTx within the Milan criteria, however, can offer 5-year survival rates of >70% in highly selected patients with HCC and concomitant liver cirrhosis^[5]. Again, our disappointing results may be due to the fact, that only 50% of our analyzed HCC patients were transplanted within Milan or UCSF criteria, which could have negatively influenced the overall survival rates.

The observation that there was no significant difference in survival between patients treated with LTx within Milan criteria or within UCSF criteria could be caused by a dilution effect. The majority of the patients meeting the UCSF criteria also met the Milan criteria (5 of 6 in group 1a, and 6 of 7 in group 2, respectively) and were not evaluated separately, because of a too small sample size to produce clinically useful results.

Currently, the selection criteria for LTx in HCC patients in most centers is tumor size and number according to Milan and/or UCSF criteria. Hoffmann *et al* reported in a recently published study, 1-, 2-, and 5-year overall survival rates of 82%, 74%, and 59%, respectively, for patients fulfilling Milan and 72%, 67%, and 57%, respectively, in patients exceeding the Milan criteria. The authors found that tumor size and number did not influence the post-transplant outcome and suggested, that tumor biology may be more important than tumor size or number for outcome and survival after LTx^[41]. Piardi *et al* found that among patients who met the UCSF criteria, the only significant prognostic factors were tumor size (8 cm) and vascular invasion (VI). VI correlated with AFP levels and histologic grading. The number of nodules was not an independent pathologic variable associated with long-term outcomes in patients who underwent LTx for HCC^[42]. Considering these studies, tumor size and number alone may be insufficient prognostic factors for the outcome and survival after LTx. Assuming this could possibly explain the lack of significant survival benefit for HCC patients in our study who underwent LTx within Milan or UCSF criteria compared to those beyond.

Although the prevalence of HBV and HCV infection in Germany is low, viral hepatitis plays a major role in the development of HCC^[43]. In our study chronic HCV infection was the leading etiology (50%) of all HCC cases. Also, HCC with chronic HCV infection was the most common indication for LTx in both groups. Patients with viral hepatitis associated cirrhosis have significantly lower overall survival compared to those of other causes of cirrhosis^[44,45]. The high rate of patients with viral hepatitis associated HCC might have influenced the outcome and survival in our study.

In both groups, roughly 1/3 of HCC were ≤ 3 cm in size at initial diagnosis. These results are close to the observations of other authors^[17,20,46-49]. Additionally, Colombo *et al.* found that significantly more consecutive patients with HCC were operable (wedge resection, segmentectomy, and subsegmentectomy) than patients who developed HCC within a surveillance program. Thus, they concluded that at least their program did not contribute to the detection of potentially curable tumors^[16]. In our study, the percentage of patients fulfilling Milan or UCSF criteria was slightly higher in group 1a, although there was no statistically significant difference concerning size and cumulative survival in both HCC groups. If tumor size and number are relevant prognostic factors for HCC and following LTx, precise estimation of tumor burden is essential. However, underestimation is still a major concern. Freeman *et al* evaluated the results from UNOS database on 789 LTx recipients to determine the accuracy of pre-LTx imaging compared with explant features. They found that, radiology underestimated tumor staging in 26.6% of cases and showed a risk of overestimation in almost 30%. The overall preoperative accuracy was around 50%, regardless of the radiological technique used^[50]. Another study by Sotiropoulos *et al* reported incorrectly diagnosed number and size of tumors in 66 % and 71% of cases, respectively, in preoperative imaging^[51]. Assuming that tumor size and number are relevant factors concerning outcome and survival in HCC patients (with or without LTx), underestimation of tumor size and number with imaging techniques could probably explain that in our study patients of group 1a did not show a benefit in survival, although they were diagnosed with slightly smaller tumor sizes.

Overall, 81 of a total of 100 HCC in our study were detected by ultrasound, 66.7% of patients with HCC in group 1a and 85.5% in group 2. Abdominal ultrasound is currently the screening method of choice for patients at risk and plays a crucial role in the diagnosis of liver lesions^[21]. It has a sensitivity of 65-80% and a specificity >90%^[52]. If ultrasound findings are suspicious, a second imaging test should be performed. Either dynamic CT or dynamic MRI with the presence of arterial enhancement followed by washout on portal venous or delayed imaging is the best non-invasive test to make a diagnosis in cirrhotic patients suspected of having HCC and for preoperative staging. Currently, there is no data showing the superiority of either MRI or CT^[53].

In approximately 70% of patients with HCC, AFP is expressed in tumor tissue and can be found in the serum^[54]. With an increase of AFP ≥ 400 ng/mL, the existence of an HCC can be expected in 95% of cases^[29]. However, in the present study only 28% of HCC patients showed AFP values above this threshold while more than 50% of values were lower than 200 ng/mL. AFP and ultrasound in combination were recommended for HCC surveillance while our study was performed^[21]. However, an update of this recommendation conclude that AFP is not adequate because of its limited sensitivity and its lower detection capacity as compared to ultrasound. The combination of AFP with ultrasound does not increase sensitivity, while it increases the costs and the false-positive rates^[55,56]. On the other hand another recently published recommendation by experts

conclude that AFP concentrations add prognostic information in HCC patients and may be used for making decisions regarding transplantation in combination with imaging criteria^[53]. Considering this, in our opinion AFP measurement combined with ultrasound should still be a part of HCC surveillance.

We found a male predominance in patients with liver cirrhosis or HCC in our study, a phenomenon that is well known in the literature^[57-59]. In addition to cirrhosis itself^[60] male gender can be considered as a risk factor for the development of HCC, even so the reason is still not fully understood^[61,62]. At initial diagnosis or first contact, respectively, the median age of patients with HCC in groups 1a and 2 was 63.0 and 65.5 years, a non significant difference. However, patients who developed HCC in group 1 were significantly older at first contact than those without HCC during follow-up. Several authors described an age above 50 years as one of the most important risk factors for the development of HCC in patients with liver cirrhosis^[15,20,47]. In our study, 22 patients (13.7%) were older than 65 years when surveillance began. With more stringent indications, these patients had no need for surveillance because they would not have been able to opt for LTx. In fact, no patient in this age group received LTx.

Our study has several limitations. Due to its retrospective design there are incomplete follow-up data, especially for patients who presented with HCC from the beginning. However, data are complete for all patients who had undergone LTx. Our surveillance program was rather limited in controlling time intervals of follow-up visits as well as securing patient participation. While this would have no effect on the number of patients needed to screen it may explain our disappointing results concerning survival time. Around 40% of all patients with confirmed liver cirrhosis were seen only once at our institution. We cannot exclude that patients returning for the proposed control visits probably were more health conscious. We did not adjust our data for treatment modalities other than LTx. However, a selection bias seems unlikely since the decision to use different therapeutic options in order to control local tumor growth followed published guidelines (AASLD, EASL). The date of first cancer diagnosis preceded the date of first contact for patients in group 2. We could only partially account for this possible lead time bias by adjusting survival times to the date of HCC diagnosis in patients of group 1a. A total of 23 patients had undergone LTx, therefore our conclusion of ineffective surveillance in terms of a survival benefit bears a high risk of a beta error.

In conclusion, we were unable to demonstrate a significant improvement in survival time for patients with incident HCC within our surveillance program. Surveillance using abdominal ultrasound followed by AFP measurements in cirrhotic patients was efficient with regard to the number needed to screen. Assuming that detection of HCC in the context of surveillance may provide a chance of detecting tumors in a more favorable stage regarding possible curative options, earlier detection has to translate into prolonged survival to be clinically useful. In order to prove increased survival times for patients at risk it seems mandatory to keep to more stringent surveillance criteria with respect to examination intervals, e.g. 6 months, as well as effective recall systems.

REFERENCES

- 1 Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004; **127**: S5-S16
- 2 Bruix J, Llovet JM. HCC surveillance: who is the target population? *Hepatology* 2003; **37**: 507-509
- 3 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917
- 4 Montalto G, Cervello M, Giannitrapani L, Dantona F, Terranova A, Castagnetta LA. Epidemiology, risk factors, and natural history of hepatocellular carcinoma. *Ann N Y Acad Sci* 2002; **963**: 13-20
- 5 Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology* 2002; **122**: 1609-1619
- 6 Sarbah SA, Gramlich T, Younoszai A, Osmack P, Goormastic M, Grosso L, Cooper JN, Di Bisceglie A, Seneca R, Younossi ZM. Risk factors for hepatocellular carcinoma in patients with cirrhosis. *Dig Dis Sci* 2004; **49**: 850-853
- 7 Patel D, Terrault NA, Yao FY, Bass NM, Ladabaum U. Cost-effectiveness of hepatocellular carcinoma surveillance in patients with hepatitis C virus-related cirrhosis. *Clin Gastroenterol Hepatol* 2005; **3**: 75-84
- 8 Kuo YH, Lu SN, Chen CL, Cheng YF, Lin CY, Hung CH, Chen CH, Changchien CS, Hsu HC, Hu TH, Lee CM, Wang JH. Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis. *Eur J Cancer* 2010; **46**: 744-751
- 9 Ando E, Kuromatsu R, Tanaka M, Takada A, Fukushima N, Sumie S, Nagaoka S, Akiyoshi J, Inoue K, Torimura T, Kumashiro R, Ueno T, Sata M. Surveillance program for early detection of hepatocellular carcinoma in Japan: results of specialized department of liver disease. *J Clin Gastroenterol* ; **40**: 942-948
- 10 El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. *J Clin Gastroenterol* 2002; **35**: S72-S78
- 11 Yoo HY, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. *J Clin Oncol* 2003; **21**: 4329-4335
- 12 European Liver Transplant Register, last accessed 23-07-2011, www.eltr.org
- 13 Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 2005; **25**: 181-200
- 14 Murray KF, Carithers RL. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* 2005; **41**: 1407-1432
- 15 Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 2001; **48**: 251-259
- 16 Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, Donato MF, Piva A, Di Carlo V, Dioguardi N. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991; **325**: 675-680
- 17 Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, Mizoguchi Y, Kobayashi K. Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. *Hepatology* 1990; **12**: 680-687
- 18 Pateron D, Ganne N, Trinchet JC, Aourousseau MH, Mal F, Meicler C, Coderc E, Reboullet P, Beaugrand M. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. *J Hepatol* 1994; **20**: 65-71
- 19 Di Bisceglie AM. Issues in screening and surveillance for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S104-S107
- 20 Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, Romeo R, Morabito A, De Franchis R, Colombo M. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology* 2004; **126**: 1005-1014
- 21 Bruix J, Sherman M. Management of hepatocellular carcinoma.

- noma. *Hepatology* 2005; **42**: 1208-1236
- 22 Bruix J, Hessheimer AJ, Forner A, Boix L, Vilana R, Llovet JM. New aspects of diagnosis and therapy of hepatocellular carcinoma. *Oncogene* 2006; **25**: 3848-3856
 - 23 Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003; **52** Suppl 3: iii1-iii8
 - 24 Santagostino E, Colombo M, Rivi M, Rumi MG, Rocino A, Linari S, Mannucci PM. A 6-month versus a 12-month surveillance for hepatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus. *Blood* 2003; **102**: 78-82
 - 25 Sherman M, Klein A. AASLD single-topic research conference on hepatocellular carcinoma: Conference proceedings. *Hepatology* 2004; **40**: 1465-1473
 - 26 Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430
 - 27 Kudo M, Okanoue T. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. *Oncology* 2007; **72** Suppl 1: 2-15
 - 28 Marrero JA. Hepatocellular carcinoma. *Curr Opin Gastroenterol* 2003; **19**: 243-249
 - 29 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699
 - 30 Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, Inada M, Tamura S, Noda S, Imai Y, Matsuzawa Y. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. *Br J Cancer* 2001; **84**: 886-891
 - 31 Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236
 - 32 Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Juan Rodés J, for the EASL Panel of Experts on HCC. Clinical Management of Hepatocellular Carcinoma. Conclusions of the Barcelona-2000 EASL Conference. *J Hepatol* 2001; **35**: 5421-5430
 - 33 Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999; **19**: 311-322
 - 34 Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, Tzakis AG, Van Thiel DH, Carr B, Selby R. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991; **214**: 221-228
 - 35 Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434-1440
 - 36 Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403
 - 37 Iwatsuki S, Starzl TE. Role of liver transplantation in the treatment of hepatocellular carcinoma. *Semin Surg Oncol* 1993; **9**: 337-340
 - 38 Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993; **218**: 145-151
 - 39 Pichlmayr R, Weimann A, Steinhoff G, Ringe B. Liver transplantation for hepatocellular carcinoma: clinical results and future aspects. *Cancer Chemother Pharmacol* 1992; **31** Suppl: S157-S161
 - 40 Ismail T, Angrisani L, Gunson BK, Hübscher SG, Buckels JA, Neuberger JM, Elias E, McMaster P. Primary hepatic malignancy: the role of liver transplantation. *Br J Surg* 1990; **77**: 983-987
 - 41 Hoffmann K, Hinz U, Hillebrand N, Radeleff BA, Ganten TM, Schirmacher P, Schmidt J, Büchler MW, Schemmer P. Risk factors of survival after liver transplantation for HCC: a multivariate single-center analysis. *Clin Transplant* 2011; **25**: E541-E551
 - 42 Piardi T, Gheza F, Ellero B, Woehl-Jaegle ML, Ntourakis D, Cantu M, Marzano E, Audet M, Wolf P, Pessaux P. Number and tumor size are not sufficient criteria to select patients for liver transplantation for hepatocellular carcinoma. *Ann Surg Oncol* 2012; **19**: 2020-2026
 - 43 Kubicka S, Rudolph KL, Hanke M, Tietze MK, Tillmann HL, Trautwein C, Manns M. Hepatocellular carcinoma in Germany: a retrospective epidemiological study from a low-endemic area. *Liver* 2000; **20**: 312-318
 - 44 Verna EC, De Martin E, Burra P, Neri D, Gaglio PJ, Emond JC, Brown RS. The impact of hepatitis C and biliary complications on patient and graft survival following liver transplantation. *Am J Transplant* 2009; **9**: 1398-1405
 - 45 Aguilera V, Berenguer M, Rubín A, San-Juan F, Rayón JM, Prieto M, Mir J. Cirrhosis of mixed etiology (hepatitis C virus and alcohol): Posttransplantation outcome-Comparison with hepatitis C virus-related cirrhosis and alcoholic-related cirrhosis. *Liver Transpl* 2009; **15**: 79-87
 - 46 Rabe C, Pilz T, Klostermann C, Berna M, Schild HH, Sauerbruch T, Caselmann WH. Clinical characteristics and outcome of a cohort of 101 patients with hepatocellular carcinoma. *World J Gastroenterol* 2001; **7**: 208-215
 - 47 Velázquez RF, Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorriós NG, Martínez I, Rodrigo L. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003; **37**: 520-527
 - 48 Ren FY, Piao XX, Jin AL. Efficacy of ultrasonography and alpha-fetoprotein on early detection of hepatocellular carcinoma. *World J Gastroenterol* 2006; **12**: 4656-4659
 - 49 Trevisani F, D'Intino PE, Caraceni P, Pizzo M, Stefanini GF, Mazziotti A, Grazi GL, Gozzetti G, Gasbarrini G, Bernardi M. Etiologic factors and clinical presentation of hepatocellular carcinoma. Differences between cirrhotic and noncirrhotic Italian patients. *Cancer* 1995; **75**: 2220-2232
 - 50 Freeman RB, Mithoefer A, Ruthazer R, Nguyen K, Schore A, Harper A, Edwards E. Optimizing staging for hepatocellular carcinoma before liver transplantation: A retrospective analysis of the UNOS/OPTN database. *Liver Transpl* 2006; **12**: 1504-1511
 - 51 Sotiropoulos GC, Malagó M, Molmenti E, Paul A, Nadalin S, Brokalaki E, Kühl H, Dirsch O, Lang H, Broelsch CE. Liver transplantation for hepatocellular carcinoma in cirrhosis: is clinical tumor classification before transplantation realistic? *Transplantation* 2005; **79**: 483-487
 - 52 Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther* 2009; **30**: 37-47
 - 53 Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22
 - 54 Zhou L, Liu J, Luo F. Serum tumor markers for detection of hepatocellular carcinoma. *World J Gastroenterol* 2006; **12**: 1175-1181
 - 55 de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. *J Hepatol* 2012; **56** Suppl 1: S75-S87

- 56 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022
- 57 del Olmo JA, Serra MA, Rodríguez F, Escudero A, Gilabert S, Rodrigo JM. Incidence and risk factors for hepatocellular carcinoma in 967 patients with cirrhosis. *J Cancer Res Clin Oncol* 1998; **124**: 560-564
- 58 A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998; **28**: 751-755
- 59 Fasani P, Sangiovanni A, De Fazio C, Borzio M, Bruno S, Ronchi G, Del Ninno E, Colombo M. High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. *Hepatology* 1999; **29**: 1704-1707
- 60 Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008; **371**: 838-851
- 61 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50
- 62 El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004; **127**: S27-S34
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