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Meer, S. van; Man, R.A. de; Coenraad, M.J.; Sprengers, D.; Nieuwkerk, K.M.J. van; Klumpen, H.J.; ... ; Erpecum, K.J. van

Research Article

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Surveillance for hepatocellular carcinoma is associated with increased survival: Results from a large cohort in the Netherlands

Suzanne van Meer[1], Robert A. de Man[2], Minneke J. Coenraad[3], Dave Sprengers[2], Karin M.J. van Nieuwkerk[4], Heinz-Josef Klümpen[5], Peter L.M. Jansen[6], Jan N.M. IJzermans[7], Martijn G.H. van Oijen[1], Peter D. Siersema[1], Karel J. van Erpecum[1,*]

[1]*Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands;* [2]*Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands;* [3]*Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands;* [4]*Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands;* [5]*Department of Medical Oncology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands;* [6]*Department of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands;* [7]*Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands*

Background & Aims: Effectiveness of surveillance for hepatocellular carcinoma is controversial. We here explore its effects in "real life" clinical practice.

Methods: Patients with hepatocellular carcinoma diagnosed in the period 2005–2012 in five Dutch academic centers were evaluated. Surveillance was defined as $\geqslant$2 screening tests during three preceding years and at least one radiologic imaging test within 18 months before diagnosis.

Results: 295 (27%) of 1074 cases underwent surveillance. Median time interval between last negative radiologic imaging and hepatocellular carcinoma diagnosis was 7.5 months. In the surveillance group, cirrhosis (97% *vs.* 60%, p <0.001) and viral hepatitis were more frequent, and non-alcoholic fatty liver disease or absence of risk factors less frequent.

In case of surveillance, tumor size was significantly smaller (2.7 *vs.* 6.0 cm), with lower alpha–fetoprotein levels (16 *vs.* 44 μg/L), earlier tumor stage (BCLC 0 and A combined: 61% *vs.* 21%) and resection/transplantation (34% *vs.* 25%) or radiofrequency ablation (23% *vs.* 7%) more often applied, with significantly higher 1-, 3-, and 5-year survival rates.

Survival benefit by surveillance remained significant after adjustment for lead-time bias based on assumed tumor doubling time of 90 days, but not with doubling time of $\geqslant$120 days. In multivariate analysis, surveillance was an independent predictor for mortality (for interval $\leqslant$9 respectively >9 months: adjusted HRs 0.51 and 0.50, 95% confidence intervals: 0.39–0.67 and 0.37–0.69).

Conclusions: Surveillance for hepatocellular carcinoma was associated with smaller tumor size, earlier tumor stage, with an impact on therapeutic strategy and was an independent predictor of survival.

Cancer

Introduction

Liver cancer is the sixth most common cancer in the world and the third cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and generally occurs in patients with underlying chronic liver disease. In Western countries with a relatively low incidence rate such as the Netherlands, incidence has increased in the last decade [2,3].

Currently, several international guidelines advise regular surveillance of patients at increased HCC risk [4–6]. The goal is to detect HCC at earlier stages enabling curative therapies with a better outcome and decreased mortality. Nonetheless, surveillance is controversial [7]. One randomized controlled trial from China in chronic hepatitis B (HBV) patients compared surveillance with combined ultrasound (US) and alpha–fetoprotein (AFP) levels at 6-month intervals *vs.* no surveillance, the study found significantly lower HCC-related mortality rates in the surveillance group [8]. Several aspects of this study have been criticized [7,9]. Another randomized controlled study in Chinese HBV patients found no benefit from surveillance with AFP alone at 6-month intervals [10]. Based on lower quality evidence, several cohort studies suggest improved survival with surveillance (studies summarized in references [11,12]).

Keywords: Hepatocellular carcinoma; Surveillance; Survival.
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* Corresponding author. Address: Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Po BOX 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31 88 7557004.
E-mail address: k.j.vanerpecum@umcutrecht.nl (K.J. van Erpecum).
Abbreviations: HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus infection; HCV, Hepatitis C virus infection; US, Ultrasound; AFP, Alpha–fetoprotein; BCLC, Barcelona Clinic Liver Cancer; RFA, Radiofrequency ablation; TACE, Transarterial chemoembolization; TARE, Transarterial radioembolization; HR, Hazard ratio; PS, Performance score.

Conventional US and AFP (alone or combined) are most widely used as surveillance modalities, but their sensitivities and specificities are far from perfect [13,14]. Moreover, the optimal surveillance interval is a matter of debate [15–18].

In the present study we investigate the contribution of surveillance in a large group of HCC patients in "real life" clinical practice in the Netherlands.

Patients and methods

All patients with an HCC diagnosis in the period 2005–2012 in five Dutch academic centers were evaluated. Diagnosis of HCC was based on AASLD 2005 and 2011 guideline criteria [4,19]. Collected data were obtained from (electronic) medical records. Extensive efforts were done to clarify all missing data, e.g. by contacting patients, referring hospitals or general practitioners.

Tumor characteristics, such as number of tumor lesions, maximum diameter of the largest tumor lesion and tumor stage according to Barcelona Clinic Liver Cancer (BCLC) staging system, and laboratory values at time of diagnosis were obtained for each patient. Also, data on ECOG performance status [20], clinical symptoms such as right upper quadrant abdominal pain and weight loss ($\geqslant$3 kg), presence of cirrhosis (based on clinical, laboratory, radiologic, and histologic findings) and cause of underlying liver disease (including HBV and HCV, hemochromatosis, alcohol-related liver disease (defined as $\geqslant$3 alcoholic drinks/-day [21]) and non-alcoholic fatty liver disease ([NAFLD] defined as steatosis or steatohepatitis on liver biopsy or presence of metabolic syndrome in the absence of other risk factors for chronic liver disease such as alcohol abuse) were obtained. Severity of liver disease was estimated by calculating the MELD score [22].

Patients were categorized as receiving surveillance (defined as at least two screening tests (AFP and/or imaging test) during the three years before HCC diagnosis and at least one radiologic imaging test within 18 months before diagnosis) or no surveillance. Additionally, time interval (i.e. time between last negative radiological surveillance imaging and date of HCC diagnosis) for patients in the surveillance group was determined. Patients in the surveillance groups were divided into two subgroups based on this time interval: $\leqslant$9 months and >9 months.

Patients were categorized into treatment groups based on application of surgical therapy (resection or transplantation), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or transarterial radioembolization (TARE), sorafenib or best supportive care. Patients undergoing sequential therapy appertaining to $\geqslant$2 treatment groups were included in the treatment group presumed to have most impact on outcome. In case of RFA and subsequently TACE, with at least a 1-month interval, patients were included in the RFA group. When combined RFA and TACE were performed within a 1-month interval, patients were included in the TACE group.

This study was in agreement with the Declaration of Helsinki and analyses were performed with institutional medical ethical consent, in an anonymized database.

Statistical analysis

Continuous data are expressed as medians and ranges, and discrete variables as absolute and relative frequencies. Mann–Whitney *U* or Kruskal–Wallis tests were applied to compare continuous data in various groups. Categorical variables were compared with Pearson's Chi-square or Fisher's exact tests.

Survival time was calculated from date of diagnosis to date of death or end of follow-up (latest: end of study 1-1-2013). To deal with lead-time bias, which represents the apparently improved survival caused by the earlier diagnosis in the course of the disease, we calculated lead-times for all patients who underwent surveillance prior to HCC diagnosis. Lead-time was calculated by using the parametric model proposed by Duffy *et al.* [23] assuming an exponential distribution of the HCC sojourn time. Calculated lead-time for patients in the surveillance group was subtracted from their survival time.

Kaplan–Meier survival curves and log rank tests were used to compare survival rates between various groups. Apart from HCC surveillance, sex, age, etiology of underlying liver disease, presence of cirrhosis, pain symptoms and weight loss, performance score (PS), year of HCC diagnosis and MELD score were tested as possible predictors for overall mortality by univariate Cox proportional hazard regression analysis. Factors with a p value <0.05 in univariate analyses were included in subsequent multivariate analyses. In a separate uni- and multivariate analysis, BCLC stage and applied treatment were also included. Subgroup analyses were performed in cirrhotic patients and in patients in whom surveillance is recommended according to AASLD guidelines [4]. A two-sided p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (version 20).

Results

Patient characteristics

In the period January 2005–December 2012, 1288 HCC patients were under care in the five participating hospitals (60% of all Dutch HCC patients in this period [3]). After exclusion of 214 patients because of missing data, 1074 (83%) were included in this study (Fig. 1). Of all included patients, 27% (n = 295) underwent HCC surveillance, without change during the study period. Surveillance was performed by radiological investigations (ultrasound, CT, or MR imaging) alone in 17% and in combination with AFP in 83%. Median number of surveillance tests in the three years before HCC diagnosis was 7 (range 2–23: 4 (range 1–9) by radiological investigations and 3 (range 0–15) by AFP). Median time interval between last negative radiologic imaging and HCC diagnosis was 7.5 months (range: 0.2–18 months) ($\leqslant$9 months in 60% of patients and >9 months in 40%).

Patient characteristics of the total group and separately for the surveillance and non-surveillance groups are given in Table 1. Viral hepatitis was the underlying cause for liver disease in 37%, alcohol abuse in 28%, NAFLD in 16%, hemochromatosis in 2%, and other liver diseases in 3%. Fourteen percent had no risk factors for underlying liver disease, despite extensive investigation for potential causes. Viral hepatitis was more common in the surveillance group (61% *vs.* 27%), whereas NAFLD (7% *vs.* 20%) or absence of cause(s) for underlying liver disease (3% *vs.* 18%) were more common in the non-surveillance group. Cirrhosis was present in 97% of the surveillance and in 60% of the non-surveillance groups (p <0.001). In the whole group, 93% of all HCV patients exhibited a cirrhotic liver, which was the case in 75% of HBV patients and in 24% of patients with unknown cause for underlying liver disease. Of the patients without risk factors for underling liver disease (n = 146), 27% had grade $\leqslant$2 fibrosis (based on histology), 4% grade 3 fibrosis (based on

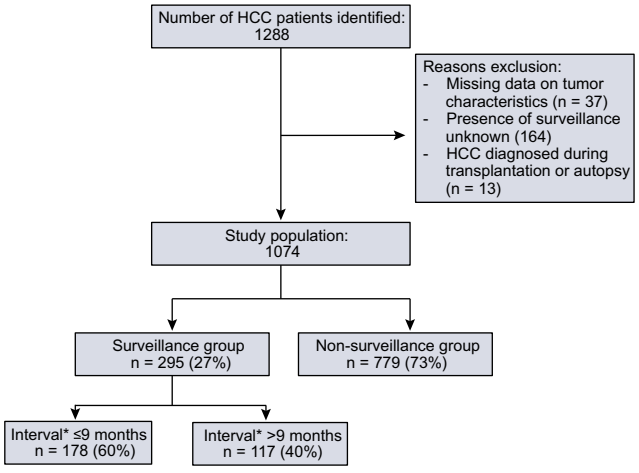

Fig. 1. Flow chart of patient inclusion and details of surveillance. *Time between date of HCC diagnosis and last negative radiologic imaging.

Table 1. Patient characteristics of 1074 patients with hepatocellular carcinoma with or without previous surveillance.

	Total group	Surveillance group	Interval ≤9 months	Interval >9 months	*p* value *	Non-surveillance group	*p* value **
Patient no.	1074 (100)	295 (27)	178 (60)	117 (40)		779 (73)	
Male gender	814 (76)	229 (78)	139 (78)	90 (77)	0.814	585 (75)	0.387
Age at HCC diagnosis (median, range)	63 (8-91)	60 (19-90)	60 (19-90)	61 (29-85)	0.375	64 (8-91)	<0.001
Etiology					0.348		<0.001
Chronic viral hepatitis							
Hepatitis B	171 (16)	58 (20)	29 (16)	29 (25)		113 (14)	
Hepatitis C	206 (19)	113 (38)	76 (43)	37 (32)		93 (12)	
Co-infection	16 (2)	8 (3)	4 (2)	4 (3)		8 (1)	
Hemochromatosis	20 (2)	2 (1)	1 (<1)	1 (1)		18 (2)	
Alcohol	306 (28)	71 (24)	42 (24)	29 (25)		235 (30)	
NAFLD	176 (16)	22 (7)	11 (6)	11 (9)		154 (20)	
Others	33 (3)	13 (4)	10 (6)	3 (3)		20 (3)	
No risk factors known	146 (14)	8 (3)	5 (3)	3 (2)		138 (18)	
Presence of cirrhosis	756 (70)	286 (97)	176 (99)	110 (94)	0.018	470 (60)	<0.001

Results indicate numbers and, between brackets, percentages. *p value applies to differences between the two surveillance interval groups; **p value applies to differences between the surveillance *vs.* non-surveillance groups; HCC, hepatocellular carcinoma; co-infection, hepatitis B+C infection. NAFLD, non-alcoholic fatty liver disease.

histology), 24% cirrhosis (based on histological and/or radiological findings) and 45% no signs of cirrhosis (based on clinical, laboratory and radiological findings in absence of available histology). Furthermore, proportion of patients >75 years old was significantly higher in the non-surveillance group than in the surveillance group (17% *vs.* 8%, p <0.001).

Clinical and tumor characteristics

As indicated in Table 2, most patients had a single tumor (56% and 50% in surveillance and non-surveillance groups, respectively). Nevertheless, patients who did not receive surveillance more often exhibited multifocal or diffuse HCC (35% *vs.* 20%, respectively). In the surveillance group, tumor size was significantly smaller (2.7 *vs.* 6.0 cm; p <0.001) and HCC was detected in an earlier tumor stage (BCLC 0 and A combined: 61% *vs.* 21%) than in the non-surveillance group (Table 2).

Performance scores did not differ between surveillance and non-surveillance groups. In the non-surveillance group, right upper quadrant abdominal pain (36% *vs.* 12%, p <0.001) and weight loss (25% *vs.* 7%, p <0.001) at time of diagnosis were significantly more common than in the surveillance group (Table 2).

In the surveillance group, median AFP (16 μg/L *vs.* 44 μg/L; p <0.001) and ALT levels (44 U/L *vs.* 49 U/L; p = 0.074) were lower than in the non-surveillance group. In contrast, patients who underwent surveillance had higher MELD scores than those in the non-surveillance group (10 *vs.* 9; p <0.001) (Table 2). Tumor size and BCLC stage increased with longer surveillance interval (Table 2).

Treatment

In total, 28% of all patients received surgical treatment (resection/transplantation), 11% RFA, 17% TACE/TARE, 11% sorafenib and 29% best supportive care. Details of treatment were not available in 4%. In the surveillance group, surgical treatment (34% *vs.* 25%) and RFA (23% *vs.* 7%) were more often performed than in patients in the non-surveillance group. In total, 16% and 17% of patients in the surveillance and non-surveillance groups respectively, received TACE/TARE. Proportion of patients who received sorafenib was lower in the surveillance group (3% *vs.* 14%). Applied treatments did not differ between the two interval groups (Table 2).

Survival

Data on vital status were available in 999 patients (93% of all included patients). The median follow-up after HCC diagnosis was 11 months (range 0.1–95) and was significantly longer in the surveillance group (15 months *vs.* 10 months). In total, 58% of all patients (n = 623) died during follow-up. Observed 1-, 3-, and 5-year survival rates were significantly higher in the surveillance group than in the non-surveillance group (68%, 47%, and 39% *vs.* 55%, 29%, and 22%, respectively) (Fig. 2, log rank test p <0.001). When evaluating the survival rates of the two time interval groups separately, both groups had survival benefit compared to the non-surveillance group (hazard ratio (HR) 0.64, 95% CI 0.51–0.81 for interval ⩽9 months and HR 0.55, 95% CI 0.42–0.73 for interval >9 months). However, there was no significant survival benefit in patients >75 years old in the surveillance group compared to the non-surveillance group (HR 0.85, 95% CI 0.48–1.50).

Based on assumed HCC median tumor doubling times of 60 days or 90 days, survival benefit for the surveillance group remained significant after adjustment for lead-time bias based on the approach of Duffy *et al.* [23] (HR 0.74, 95% CI 0.61–0.90 and HR 0.79, 95% CI 0.65–0.95). However when HCC tumor doubling time ⩾120 days was assumed, survival benefit disappeared (HR 0.83, 95% CI 0.69–1.01).

In multivariate analysis, surveillance was an independent predictor for lower overall mortality (adjusted HR 0.51, 95% CI 0.39–0.67 for interval ⩽9 months and adjusted HR 0.50, 95% CI 0.37–0.69 for interval >9 months) after adjusting for age, cause of underlying liver disease, presence of cirrhosis, right upper quadrant abdominal pain symptoms and weight loss, PS and MELD score (Table 3). Nevertheless, when also adjusted for BCLC stage and applied treatment, surveillance was no longer an

Table 2. Clinical and tumor characteristics of 1074 patients with hepatocellular carcinoma subdivided according to presence of surveillance prior to HCC diagnosis.

	Total group	Surveillance group	Interval ≤9 months	Interval >9 months	*p* value *	Non-surveillance group	*p* value **
Patient no.	1074 (100)	295 (27)	178 (60)	117 (40)		779 (73)	
No. of lesions					0.856		<0.001
1	551 (51)	165 (56)	97 (55)	68 (58)		386 (50)	
2	125 (12)	52 (18)	33 (18)	19 (16)		73 (9)	
3	65 (6)	18 (6)	10 (6)	8 (7)		47 (6)	
Multifocal/diffuse	333 (31)	60 (20)	38 (21)	22 (19)		273 (35)	
Tumor size (cm)	5.0 (0.8-26.0)	2.7 (0.8-17.0)	2.5 (0.8-17.0)	3.0 (0.8-12.0)	0.025	6.0 (0.9-26.0)	<0.001
Performance score					0.831		0.277
0	382 (36)	108 (37)	65 (37)	43 (37)		274 (35)	
1	354 (33)	99 (34)	60 (34)	39 (33)		255 (33)	
2	115 (11)	24 (8)	13 (7)	11 (9)		91 (11)	
>2	57 (5)	12 (4)	9 (5)	3 (3)		45 (6)	
Unknown	166 (15)	52 (17)	31 (17)	21 (18)		114 (15)	
Right upper quadrant abdominal pain							
Yes	318 (30)	35 (12)	23 (13)	12 (10)	0.489	283 (36)	<0.001
No	756 (70)	260 (88)	155 (87)	105 (90)		496 (64)	
Weight loss							
Yes	219 (20)	21 (7)	13 (7)	8 (7)	0.879	198 (25)	<0.001
No	885 (80)	274 (93)	165 (93)	109 (93)		581 (75)	
BCLC stage					0.183		<0.001
0	65 (6)	43 (15)	33 (19)	10 (9)		22 (3)	
A	277 (26)	136 (46)	77 (43)	59 (50)		141 (18)	
B	378 (35)	61 (21)	34 (19)	27 (23)		317 (41)	
C	273 (26)	37 (12)	23 (13)	14 (12)		236 (30)	
D	81 (7)	18 (6)	11 (6)	7 (6)		63 (8)	
ALT (U/L)	47 (4-1158)	44 (4-445)	45 (4-282)	44 (14-445)	0.651	49 (7-1158)	0.074
AFP (μg/L)	28 (1-2.7x10^6)	16 (1-2.9x10^5)	19 (1-2.9x10^5)	12 (1-1.9x10^4)	0.092	44 (1-2.7x10^6)	<0.001
MELD score	9 (6-33)	10 (6-28)	10 (6-28)	9 (6-20)	0.087	9 (6-33)	<0.001
Treatments					0.452		<0.001
Surgical therapy	300 (28)	101 (34)	57 (32)	44 (38)		199 (25)	
Resection	191 (18)	31 (10)	13 (7)	18 (15)		160 (20)	
Transplantation	104 (10)	67 (23)	44 (25)	23 (20)		37 (5)	
Both	5 (<1)	3 (1)	0 (0)	3 (3)		2 (<1)	
RFA[$]	120 (11)	66 (23)	37 (21)	29 (25)		54 (7)	
TACE/TARE^	177 (17)	48 (16)	33 (19)	15 (13)		130 (17)	
Sorafenib	115 (11)	10 (3)	8 (4)	2 (2)		105 (14)	
Best supportive care	313 (29)	62 (21)	29 (22)	23 (19)		250 (32)	
Unknown	49 (4)	8 (3)	4 (2)	4 (3)		41 (5)	

Results indicate numbers and, between brackets, percentages; Continuous variables reported as medians and ranges; [$]9 patients received RFA and subsequently TACE with more than 1-month interval; ^in 28 patients combined TACE and RFA within a 1-month interval was performed as initial therapy; *p value applies to differences between the two surveillance interval groups; **p value applies to differences between the surveillance *vs.* non-surveillance groups; BCLC stage, tumor stage according Barcelona Clinic Liver Cancer staging system; ALT, alanine aminotransferase; AFP, alpha–fetoprotein; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

independent predictor for overall mortality (Supplementary Table 1). Analysis in the subgroup of cirrhotic patients (adjusted HR 0.49, 95% CI 0.37–0.65 for interval ⩽9 months and adjusted HR 0.48, 95% CI 0.35–0.67 for interval >9 months) and in the subgroup of patients in whom surveillance is recommended according to AASLD guidelines (adjusted HR 0.49, 95% CI 0.37–0.65 for interval ⩽9 months and adjusted HR 0.49, 95% CI 0.36–0.68 for interval >9 months) yielded similar results. On the other hand, >62 years of age, HCV as cause of underlying liver disease, presence of cirrhosis, a worse PS, right upper quadrant abdominal pain, weight loss and a higher MELD score were independent predictors for higher overall mortality (Table 3).

Discussion

This "real life" study showed that HCC patients who underwent surveillance prior to diagnosis had a smaller tumor size, earlier

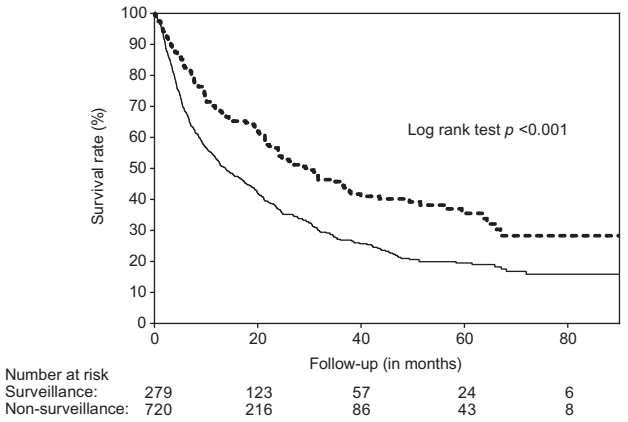

Fig. 2. Observed survival of patients with hepatocellular carcinoma in the surveillance group (dotted line) and non-surveillance group (solid line) (p <0.001).

BCLC tumor stage and lower AFP levels, received more often surgical therapy and had a better overall survival than patients without surveillance. Also, in multivariate analysis, HCC surveillance was found to be an independent predictor of better survival. The findings are in line with previously published retrospective cohort studies, meta-analyses and systematic reviews [11,12]. After additional adjustment for BCLC stage and applied treatment, surveillance was no longer an independent predictor for overall mortality. This interesting finding suggests that surveillance allows better survival through HCC detection in earlier BCLC stage, enabling more effective therapy. Since the two available randomized controlled trials [8,10] on HCC surveillance yielded contradictory results [9,11], lower level of evidence from observational studies could contribute to the advice in current guidelines [11,13,24]. Potential limitations of observational studies are length-time bias (i.e. detection of indolent tumors by surveillance) and/or lead-time bias (i.e. detection of tumors in earlier stage by surveillance). Statistical techniques to adjust for lead-time bias were performed in five earlier observational studies [25–29]: in three studies [26–28] the formula of Schwartz *et al.* [30] was used, whereas the remaining studies [25,29] used the approach of Duffy *et al.* [23]. In three of these, survival advantage of screening disappeared with assumed tumor doubling times of ⩾90 days [25,26,28]. In line with these data, in the current study survival benefit remained when tumor doubling times of 60 or 90 days was assumed, but disappeared with doubling times ⩾120 days. We adjusted lead-time bias according to Duffy *et al.* [23], which may be the most correct method. When we used the formula of Schwartz *et al.* [30] survival benefit remained significant with assumed tumor doubling time of 60 days, but not with doubling times of 90 or 120 days (HR 0.82, 95% CI 0.68–0.99, HR 0.93, 95% CI 0.77–1.12 and HR 1.03, 95% CI 0.86–1.25, respectively).

Based on available data on HCC tumor doubling times, approximately 40% of HCCs could have a tumor doubling time of less than 90 days [29,31–35]. Nevertheless, this is controversial [36] and further research is needed to evaluate HCC tumor doubling time, to identify possible factors associated with slow- and fast-growing tumors and to define the impact of this information on screening strategies. Also, in a recently published study [25] survival benefit of HCC surveillance after correction for lead-time bias became evident after three years follow-up. In the current study, median follow-up time was 11 months.

Interestingly, in most earlier observational studies, patients in the non-surveillance group had more severe liver disease than patients in the surveillance group [11,12]. In contrast, in the current study, liver disease was worse in the surveillance group (cirrhosis in 97% *vs.* 60%; p <0.001 and MELD score higher: 10 *vs.* 9; p <0.001) thus excluding severity of liver disease as a bias explaining observed better survival in our surveillance group. A potential explanation for our relatively low prevalence of cirrhosis in the non-surveillance group could be the relatively large contribution of HCC without risk factors for underlying liver disease (14% of total) in our cohort (especially in the non-surveillance group). This could be related to the low contribution of viral hepatitis to HCC in the Netherlands with low prevalence of HBV and HCV (both estimated 0.2–0.4% of the general population [37–39]).

In previous observational studies 60–100% of patients in the surveillance group and 20–56% of patients in the non-surveillance group exhibited HCC within Milan criteria [11]. In contrast, 61% of our surveillance group and 21% of our non-surveillance group had HCC within Milan criteria. Resection was performed in 10% of our surveillance group *vs.* 20% in our non-surveillance group (3–24% in previously published surveillance groups [11]) and transplantation in 23% of our surveillance group *vs.* 5% of our non-surveillance group (1–30% in previously published surveillance groups [11]). Differences in treatment modalities applied in the current *vs.* previous studies could be due, at least in part, to the high percentage (97%) of cirrhotic patients in our surveillance group and the relatively large contribution of patients without underlying liver disease (favoring resection) in our non-surveillance group.

In the current report, observed 1-, 3-, and 5-year survival rates were 68%, 47% and 39% *vs.* 55%, 29%, and 22% in the surveillance *vs.* non-surveillance group, respectively. Other studies also reported better survival in the surveillance group than in the non-surveillance group. For comparison, previously reported pooled 3-year survival rate of 36 studies was 51% in surveillance groups *vs.* 28% in non-surveillance groups [12]. However, there was no significant survival benefit in our patients >75 years old who underwent surveillance. Probably, older patients are less likely candidates for curative surgical treatment. Therefore the cost benefit for surveillance in elderly patients needs further investigations.

Recall strategy and adherence to follow-up are important factors for success of a surveillance program [40,41]. A large retrospective cohort study in HCC patients with a prior diagnosis of cirrhosis demonstrated that only 17% received regular and 38% inconsistent surveillance [40]. Utilization of surveillance declined with time. In the current study median time interval between previous negative surveillance imaging and HCC diagnosis (7.5 months) was significantly longer than the surveillance interval of 6 months that is advised in the current guidelines [4–6], indicating that surveillance programs can be improved. Furthermore, 62% of patients in the non-surveillance group had an indication for HCC surveillance based on AASLD guideline criteria [4,19]. However, in the majority of these patients presence of liver disease was unknown. In the current study, virtually all patients received surveillance by US, with or without concomitant AFP. Surveillance was associated with survival benefit in subgroups with surveillance interval ⩽9 months as well as

Table 3. Relation between patient/tumor characteristics and mortality in HCC patients in the Netherlands: univariate and multivariate Cox proportional hazard regression analyses.

	Patients	Univariate analysis			Multivariate analysis	
Variables	n = 999	HR	95% CI	*p* value	HR	95% CI
Sex				0.548		
Male	763 (76)	Ref	-			
Female	236 (24)	0.94	0.78-1.14			
Age at HCC diagnosis				0.005		
≤62 years	466 (47)	Ref	-		Ref	-
>62 years	533 (53)	1.26	1.07-1.48		1.26	1.04-1.53
Etiology				0.037		
Hepatitis B	152 (15)	Ref	-		Ref	-
Hepatitis C	190 (19)	1.44	1.09-1.92		1.81	1.32-2.48
Co-infection	15 (2)	0.74	0.34-1.61		0.66	0.28-1.53
Hemochromatosis	20 (2)	1.21	0.66-2.22		1.09	0.58-2.05
Alcohol	292 (29)	1.56	1.20-2.03		1.18	0.88-1.59
NAFLD	168 (17)	1.48	1.10-1.98		1.21	0.86-1.69
Other	30 (3)	1.23	0.72-2.11		1.41	0.79-2.51
No risk factors known	132 (13)	1.40	1.03-1.90		1.04	0.72-1.49
Presence of cirrhosis				0.033		
Yes	709 (71)	Ref	-		Ref	-
No	279 (28)	0.93	0.78-1.11		0.76	0.59-0.97
Unknown	11 (1)	2.05	1.13-3.74		1.31	0.66-2.61
Surveillance				<0.001		
Interval ≤9 months	167 (17)	0.64	0.51-0.81		0.51	0.39-0.67
Interval >9 months	112 (11)	0.55	0.42-0.73		0.50	0.37-0.69
No	720 (72)	Ref	-		Ref	-
Performance status				<0.001		
0	357 (36)	Ref	-		Ref	-
1	337 (34)	1.46	1.19-1.78		1.25	1.00-1.57
2	106 (10)	2.65	2.02-3.46		1.99	1.45-2.71
>2	50 (5)	8.28	5.96-11.50		6.81	4.59-10.11
Unknown	149 (15)	1.84	1.45-2.33		1.61	1.22-2.12
Right upper quadrant abdominal pain				<0.001		
Yes	284 (28)	1.69	1.43-1.99		1.59	1.17-1.80
No	715 (72)	Ref	-		Ref	-
Weight loss				<0.001		
Yes	195 (20)	1.91	1.59-2.30		1.45	1.17-1.80
No	804 (80)	Ref	-		Ref	-
Year of HCC diagnosis				0.060		
2005	66 (7)	1.31	0.86-2.01			
2006	69 (7)	0.90	0.58-1.40			
2007	92 (9)	0.95	0.62-1.45			
2008	126 (13)	1.27	0.86-1.87			
2009	143 (14)	1.32	0.90-1.93			
2010	164 (16)	1.44	0.99-2.10			
2011	180 (18)	1.29	0.88-1.90			
2012	159 (16)	Ref	-			
MELD score	869 (87)	1.09	1.07-1.12	<0.001	1.09	1.06-1.12

Values in parentheses are percentages; Co-infection, hepatitis B+C infection; NAFLD, non-alcoholic fatty liver disease.

surveillance interval >9–18 months, despite significantly larger tumor sizes in the latter group. Potential explanations could be that many tumors in the latter group exceeded limit of ultrasonographic detection only after prolonged time periods after last negative radiological surveillance imaging and/or relatively slow tumor growth. Similar findings were reported in a study from Taiwan comparing 4- and 12-month US screening intervals [17]. We cannot exclude that strict surveillance based on the recommended interval of 6 months could lead to better outcomes, although this is difficult to achieve in clinical practice [40,42].

In the current study, survival was not only determined by tumor features and treatment. Older age, HCV as cause of underlying disease and higher MELD scores were independent predictors for higher overall mortality. One previous study also reported a positive correlation between age and mortality [15], but this was not confirmed in other studies [16,43]. Although Trevisani *et al.* [43] suggested that prognosis is independent of etiology of liver disease, several other studies indicated that cause of underlying liver disease is an independent risk factor for higher mortality in HCC patients in line with our results [44–46].

The strength of our study is that a large cohort of Western HCC patients was included to examine the effect of surveillance in "real life" clinical practice. Also, there appears to be no bias

from overrepresentation of cirrhosis in the group without surveillance (in our study, cirrhosis prevalence was higher in the surveillance group). However, findings of this study are inherently limited by the retrospective study design. Despite correction for lead-time bias, surveillance might still preferentially detect slowly growing indolent tumors (length-time bias). Only patients who were diagnosed or referred to one of the five Dutch academic centers were included. HCC patients with a very poor prognosis could not have been referred.

In conclusion, in this "real life" study, HCC surveillance was associated with a smaller tumor size, earlier BCLC tumor stage, with impact on therapeutic strategy and was an independent predictor of increased survival.

Conflicts of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

Van Meer S, de Man RA, and van Erpecum KJ designed the study, collected patient data and wrote the manuscript; de Man RA, Coenraad MJ, Sprengers D, van Nieuwkerk CMJ, IJzermans JNM., Klümpen HJ, Jansen PLM, and Siersema PD collected patient data, critically revised the manuscript and contributed to the interpretation of the data and manuscript writing; van Meer S and van Oijen MGH performed statistical analyses; van Erpecum KJ and de Man RA supervised the manuscript. All authors approved the final version of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2015.06.012.

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