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Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis

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ABSTRACT

Objective/aim: Hepatocellular carcinoma (HCC) surveillance is a common practice for patients with liver cirrhosis. The aims of the study were to assess impacts of surveillance and therapeutic options on survival of patients with HCC.

Methods: A total of 1436 cirrhotic patients with newly diagnosed HCC were enrolled between January 2002 and December 2004. Patients with HCC detected within periodic surveillance were the surveillance group ($n = 318$, 22.1%). The other patients with HCC incidentally detected were the non-surveillance group ($n = 1118$, 77.95%). Initial treatment options were recorded and overall survival was analysed.

Results: Compared with patients in the non-surveillance group, larger proportions of patients in the surveillance group possessed small tumours, at an early stage without vascular invasion or metastases, and afforded more curative treatment options including surgical resection, radiofrequency ablation and percutaneous ethanol injection. The overall survival was better for patients in surveillance (3-year survival rate: 59.1% versus 29.3%, $p < 0.001$), early stages by Barcelona Clinic Liver Cancer (BCLC) staging or curative treatment options. Multivariate analysis demonstrated surveillance, hepatitis aetiology, alpha-fetoprotein, tumour gross type, tumour stage and treatment options were associated factors for patients' survival. Moreover, surveillance patients in curative BCLC stage following the treatment guideline for HCC proposed by the American association for the study of liver disease (AASLD) had a significantly better 3-year survival rate (77.1% versus 55.2%, $p < 0.001$).

Conclusions: HCC surveillance for cirrhotic patients could detect HCC at early and curative stages. However, appropriate treatment options following AASLD guideline further improve the survival for patients in early stage.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours in the world,[1] and has been the leading cause of cancer death in Taiwan, claiming an approximate 7800 lives annually.[2] More than 80% of HCCs arise in cirrhotic patients, suggesting that patients with cirrhosis form the main risk group of HCC.[3] The prognoses of patients with HCC are determined by tumour status, liver function reserve, general health status, treatment modalities and therapeutic effect.[4,5] The screening programmes in high-risk populations such as cirrhotic patients have led to an early detection of small tumours eligible for curative therapies, which might bring about a better outcome.[6] Consequently, Western and Eastern guidelines for HCC management recommend offering surveillance to patients with cirrhosis or chronic liver disease.[4,7,8]

Several cohort studies have demonstrated that cirrhotic patients might benefit from HCC surveillance with serum alpha-fetoprotein (AFP) and ultrasonography (US),[9–11] however, there is considerable controversy about the role of surveillance in its management.[12] Small HCC could afford more effective treatment,[13] however, even those patients in early stages had a variant prognosis due to different treatment options available.[14,15] The aims of this study were to determine the impact of surveillance on survival and to assess the effectiveness of treatment options after HCC diagnosis.

2. Materials and methods

2.1. Patients

The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital. We reviewed the clinical records of patients with HCC evaluated and treated at our institute – Chang Gung Memorial Hospital-Kaohsiung Medical Center between January 2002 and December 2004. A total of 1436 HCC patients with liver cirrhosis were enrolled in this study, and their data including age, gender, aetiologies of HCC, Child-Pugh classification, biochemical variables, serum AFP level, performance status, tumour stage and initial treatment options were recorded. The patients were divided into two groups according to the clinical scenario in detection of HCC, i.e. surveillance and non-surveillance groups. In the surveillance group, HCC was detected by a surveillance programme based on AFP determinations and abdominal US repeated within 1 year. Those who were diagnosed HCC as a result of symptoms or due to a diagnostic workup for other diseases were the non-surveillance group.

2.2. HCC diagnosis, staging, and comparative variables

The diagnosis of HCC was based on the American Association for the Study of Liver Disease (AASLD) practice guidelines.[7] The gross type of HCC was classified according to imaging findings of both US- and triphasic-computed tomography (CT) scan. The macroscopic types of HCC were classified as: solitary, paucifocal ($\leqslant$3 nodules), multifocal (>3 nodules), infiltrating and massive.[16] The patients were staged according to the modified 6th version of the tumour nodes metastases (TNM) system[17] and the Barcelona Clinic Liver Cancer (BCLC) system.[18]

2.3. Initial treatment options for HCC

Initial treatment options for HCC were recorded. Individual decisions regarding treatment were determined by clinical physicians and patients' wishes. Patients who received liver transplantation were not analysed due to the small number of patients (six patients). Hepatic resection and local ablation therapy, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), were assessed as curative treatment.[7] Indocyanine green retention rates at 15 min was used by surgeons to confirm the best candidates for HCC resection. Either hepatic lobectomy or segmentectomy was performed for HCC resection. To ablate the tumour, US-guided PEI was performed with multiple sessions of 99.5% ethanol injection. As for percutaneous RFA, it was performed with Cool-tip needle (Radionics, Burlington, MA) for one or two sessions. Non-curative treatment included transcatheter arterial embolisation (TAE), systemic chemotherapy or conformal radiotherapy (RT).[7] TAE was performed using digital subtraction angiography techniques via the femoral artery approach. After identifying the feeding artery, a mixture of 99.5% ethanol and Lipiodol was injected.[19] Then, gelatin sponge was used to embolise the feeding artery. Systemic chemotherapy was performed using various combinations of Cisplatin, Doxorubicin, Fluorouracil, Etoposide and Tamoxifen. Three-dimensional conformal RT was performed using computed tomography-simulation to acquire the images, and three-dimensional computerised treatment planning to design the treatment fields and dose calculation. A 10 MV linear accelerator was used to deliver a total dose of 55–64 Gy in 22–32 fractions.

2.4. Survival analysis

Survival was defined as the interval between the diagnosis and either the death of the patient or the end of 2006. The identification of overall mortality was according to national mortality datasets up to the end of 2006, established by the Statistics Office, Department of Health, Taiwan. The Student *t*-test or the χ^2 test was used to compare continuous variables or discrete variables, respectively. Kendall's τ_c method was used to compute a coefficient representing strength and direction of a trend for equally spaced data. Cumulative survival rates were analysed by the Kaplan–Meier method, and the difference in survival rates was compared between the groups by the log-rank test. The Kaplan–Meier method was used for univariate analysis, while the Cox proportional hazards model was used for multivariate analysis. Statistical analyses were performed with the Statistical Package for the Social Sciences 15.0 (SPSS Inc., Chicago, IL). The statistical significance was defined as $p < 0.05$.

3. Results

3.1. Patients

There were 318 (22.1%) patients in the surveillance group, including 122 patients regularly followed at other hospitals, and 1118 (77.9%) in the non-surveillance group. The mean

Table 1 – Demographic, clinical, laboratory, tumour characteristics and initial treatment options of the study patient (*n* = 1436) at the time of HCC diagnosis.

	Surveillance group (*n* = 318, 22.1%)	Non-surveillance group (*n* = 1118, 77.9%)	*P* value
Age (years, means ± SD)	59.7 ± 11.2	59.4 ± 12.8	0.655[b]
Sex, *n* (%)			0.002[b]
Male	215 (67.6%)	854 (76.4%)	
Female	103 (32.4%)	264 (23.6%)	
Aetiology, *n* (%)			<0.001[b]
HBV	155 (48.7%)	527 (47.1%)	
HCV	121 (38.1%)	373 (33.4%)	
HBV + HCV	29 (9.1%)	87 (7.8%)	
Non-B/Non-C	13 (4.1%)	131 (11.7%)	
Child-Pugh Class, n (%)			<0.001[c]
A	233 (73.3%)	698 (62.4%)	
B	76 (23.9%)	340 (30.4%)	
C	9 (2.8%)	80 (7.2%)	
Serum AFP (ng/ml), *n* (%)			<0.001[b]
<200	185 (58.2%)	464 (41.5%)	
⩾200	133 (41.8%)	654 (58.5%)	
Gross type, *n* (%)			<0.001[c]
Solitary			
<2 cm	32 (10.1%)	53 (4.7%)	
⩾2 cm	184 (57.9%)	521 (46.6%)	
Paucifocal	56 (17.6%)	185 (16.5%)	
Multifocal	41 (12.9%)	315 (28.2%)	
Infiltrative or massive	5 (1.6%)	44 (3.9%)	
Tumour size (cm), *n* (%)			<0.001[c]
<2	55 (17.3%)	94 (8.4%)	
2–5	224 (70.4%)	421 (37.7%)	
>5	39 (12.3%)	603 (53.9%)	
Vascular invasion, *n* (%)			<0.001[b]
Negative	300 (94.3%)	776 (69.4%)	
Positive	18 (5.7%)	342 (30.6%)	
Distant metastases, *n* (%)			<0.001[b]
Negative	313 (98.4%)	1033 (92.4%)	
Positive	5 (1.6%)	85 (7.6%)	
Modified TNM stage, *n* (%)			<0.001[c]
I	51 (16.0%)	73 (6.5%)	
II	237 (74.5%)	530 (47.4%)	
III	25 (7.9%)	430 (38.5%)	
IV	5 (1.6%)	85 (7.6%)	
BCLC stage, *n* (%)			<0.001[c]
Very early	26 (8.2%)	41 (3.7%)	
Early	192 (60.4%)	258 (23.1%)	
Intermediate	69 (21.7%)	393 (35.2%)	
Advanced	22 (6.9%)	346 (30.9%)	
Terminal	9 (2.8%)	80 (7.1%)	
BCLC stage (1)[a], *n* (%)			<0.001[c]
Curative	218 (68.6%)	299 (26.8%)	
Intermediate	69 (21.7%)	393 (35.2%)	
Advanced/terminal	31 (9.7%)	426 (38.0%)	
Treatment, *n* (%)			<0.001[c]
Resection	76 (23.9%)	190 (17.0%)	
RFA	40 (12.6%)	36 (3.2%)	
PEI	29 (9.1%)	28 (2.5%)	
TAE	150 (47.2%)	427 (38.2%)	
C/T or R/T	5 (1.6%)	138 (12.3%)	
Supportive care	18 (5.6%)	299 (26.7%)	

(*continued on next page*)

Table 1 – continued

	Surveillance group (n = 318, 22.1%)	Non-surveillance group (n = 1118, 77.9%)	P value
Treatment (1)[a], n (%)			<0.001[c]
Curative	145 (45.6%)	254 (22.7%)	
TAE	150 (47.2%)	427 (38.2%)	
Others	23 (7.2%)	437 (39.1%)	

Abbreviation: HBV: hepatitis B virus; HCV: hepatitis C virus; Non-B/Non-C: etiology outside from HBV or HCV; AFP: alpha-fetoprotein; TNM: tumour–nodes–metastases system; BCLC stage: Barcelona Clinic Liver Cancer stage; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TAE: transcatheter arterial embolisation; C/T: systemic chemotherapy; R/T: conformal radiotherapy.

[a] BCLC stage(1): Very early stage, and early stage were combined as curative stage; Treatment(1): Resection, RFA and PEI were combined as curative treatment; C/T or R/T and supportive treatment were combined as other treatment.

[b] Student t-test, or χ^2 test to compare continuous or discrete variables.

[c] Kendall's τ_c method to represent the strength and direction of a trend for equally spaced data.

interval of surveillance was 5.2 ± 3.1 months (range: 2.1–11.8 months) in the surveillance group. The demographic, clinical, laboratory, tumour characteristics and treatment options at the time of initial HCC diagnosis are summarised in Table 1. In the surveillance group, there were 73.3% patients with liver function reserve in Child-Pugh class A, 85.5% with solitary or paucifocal tumour, 5.7% with vascular invasion, 16% in modified TNM stage I, and 69.5% in BCLC curative stage (very early and early stage), compared to that of 62.4%, 67.9%, 30.6%, 6.5% and 28.0% in the non-surveillance group, respectively. Higher proportion (45.6%) of patients in the surveillance group could receive curative treatment options, including hepatic tumour resection and local ablative therapy, than those (22.7%) in the non-surveillance group. Patients with HCC in the surveillance group tended to have well-preserved liver function reserve, small tumour(s), solitary or paucifocal lesions, were in earlier tumour stages and afforded more curative treatment options.

3.2. *Patients' survival*

The median survival time of all patients was 18.2 months. For surveillance and non-surveillance groups, the median survival time was 48.1 months and 12.7 months, respectively. The 3-year survival rate of the surveillance group was significantly superior to that of the non-surveillance group (59.1% versus 29.3%, $p < 0.001$) (Fig. 1a). Fig. 1b illustrates the Kaplan–Meier survival curves of HCC patients stratified according to the BCLC classification. There were statistically significant differences in survival rates among each group, and a decreasing linear trend from the very early stage to the terminal stage was noted ($p < 0.001$). Fig. 1c shows that hepatic resection obtained the best survival, but it was not different from RFA significantly. Among patients underwent local ablation, RFA had a better median survival time than PEI, however, it was not significantly different (median: 31.7 ± 13.7 months versus 28.8 ± 14.7 months, p-value = 0.34). To evaluate the therapeutic effect, we further divided surveillance patients in curative stage into two subgroups according to receiving curative therapy or not (Fig. 2). Patients receiving curative therapy as recommended by AASLD guideline had a significantly better survival than those not (77.1% versus 55.2%; $p < 0.001$).

3.3. *Associated factors of patients' survival*

Univariate analysis showed the factors associated with better survival for HCC patients were surveillance, female gender, HCV-related, Child-Pugh classification A, low serum AFP level and curative treatment options, small tumour, solitary or paucifocal lesion, no vascular invasion or distant metastases, low modified TNM stage, and earlier BCLC stage. Multivariate analysis showed that the factors associated with better survival were surveillance, HCV aetiology, AFP level less than 200 ng/ml, solitary tumour, negative portal vein thrombosis, TNM stage I, very early BCLC stage and surgical resection (Table 2).

4. Discussion

Surveillance in cirrhotic patients with combined US and/or serum AFP in six-monthly intervals has been recommended for early detection of HCC.[4,7,8] Trevisani and colleagues suggested that abdominal imaging at 6- or 12-monthly intervals resulted in early diagnosis.[20] In this study, patients in the surveillance group were prone to have earlier tumour and disease stages according to modified TNM or BCLC classification. Although the interval of surveillance in this study was defined as repeated US and/or combined serum AFP within one year, patients in surveillance were still diagnosed HCC in earlier tumour stages and preserved liver function reserve. Patients in curative stages (BCLC very early and early stages) could be offered more effective therapies than patients in intermediate and advanced stages. Hepatic resection and local ablation treatment were offered as potentially curative therapy in our study, which was performed more frequently in patients in surveillance group than in non-surveillance group, and yielded a better outcome.

Although surveillance has been identified to detect HCC in early stages in previous studies and the present study,[9–12] the prognosis was still different among patients in early stages. In the randomised controlled trial reported by Zhang and colleagues, screening by combined serum AFP and US every 6 months leads to a reduction of 37% in HCC mortality.[21] In another randomised controlled trial of liver tumour screening, Chen and colleagues reported that screening with AFP on a 6-monthly basis resulted in early diagnosis of liver can-

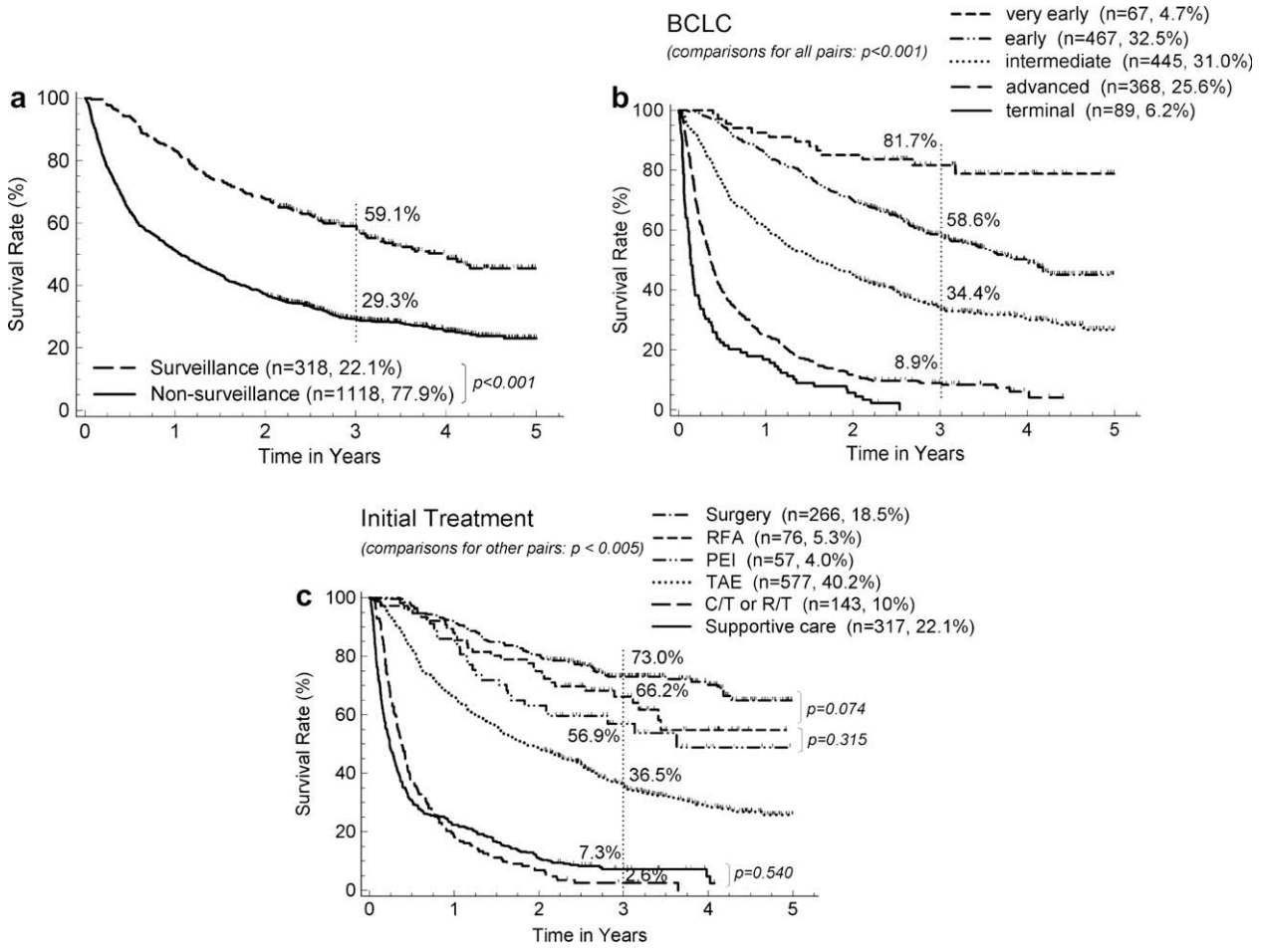

Fig. 1 – (a) Kaplan–Meier survival curves of 1436 hepatocellular carcinoma (HCC) patients stratified according to follow-up status. The survival in the surveillance group is significantly better than that in the non-surveillance group. (b) Kaplan–Meier survival curves of 1436 HCC patients stratified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. There are statistically significant differences in survival rates among each group with a decreasing linear trend from the very early stage to the terminal stage. (c) Kaplan–Meier survival curves of 1436 HCC patients stratified according to initial treatment options. There is decreasing linear trend in survival from curative treatment options (surgery, radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI)) to supportive care. Surgical resection obtained the best survival. However, it was not significantly superior to RFA. There was no statistical difference in survival for patients receiving systemic chemotherapy(C/T)/radiotherapy(R/T) or supportive care.

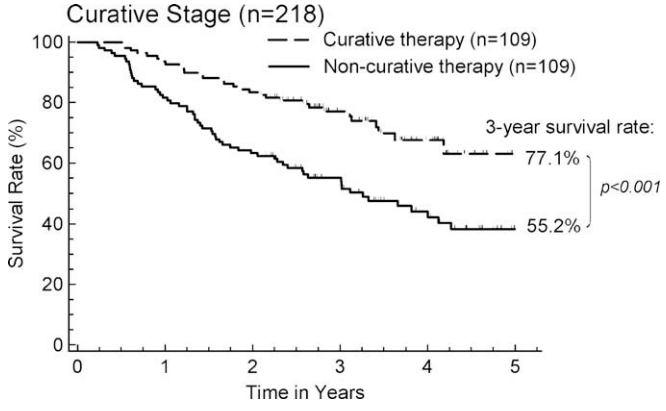

Fig. 2 – For surveillance group, 218 patients in the BCLC very early or early stages were stratified according to curative and non-curative therapies as recommended by AASLD guideline for the management of hepatocellular carcinoma. The cumulative survival of patients with curative therapy was significantly better than that of patients with non-curative therapy (77.1% versus 55.2%, $p < 0.001$).

Table 2 – Variables associated with survival among newly diagnosed HCC patients in a Medical Center.

Variables	No. (%)	Univariate[a]		Multivariate[a]	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)		1.0 (0.99–1.00)	0.575		
Gender					
Female	367 (25.6%)	1			
Male	1069(74.4%)	1.2 (1.0–1.4)	0.017		
Child-Pugh class					
A	931 (64.8%)	1			
B	416 (28.9%)	2.7 (2.4–3.1)	<0.001		
C	89 (6.3%)	6.9 (5.5–8.7)	<0.001		
Distant metastasis					
Negative	1346 (93.7%)	1			
Positive	90 (6.3%)	3.4 (2.7–4.3)	<0.001		
Group					
Surveillance	318 (22.1%)	1	<0.001	1	
Non-surveillance	1118(77.9%)	2.3 (1.9–2.7)		1.2 (1.0–1.5)	0.027
Aetiology					
HCV	494 (34.4%)	1		1	
HBV	682 (47.5%)	1.2 (1.1–1.4)	0.004	1.2 (1.1–1.5)	0.004
HBV + HCV	116 (8.1%)	1.2 (0.9–1.5)	0.190	1.3 (1.0–1.7)	0.044
Non-B/Non-C	114 (10%)	1.3 (1.0–1.6)	0.026	1.3 (1.1–1.7)	0.014
AFP					
<20	472 (32.9%)	1		1	
20–200	250 (17.4%)	1.4 (1.1–1.7)	0.002	1.2 (1.0–1.5)	0.121
⩾200	714 (49.7%)	3.0 (2.5–3.5)	<0.001	1.8 (1.6–2.2)	<0.001
Gross type					
Solitary	790 (55%)	1		1	
Paucifocal	241 (16.8%)	1.2 (1.0–1.4)	0.057	1.2 (0.9–1.5)	0.256
Multifocal	356 (24.8%)	2.6 (2.2–3.0)	<0.001	1.4 (1.1–1.8)	0.004
Infiltrative	25 (1.7%)	7.1 (4.7–10.7)	<0.001	2.4 (1.5–3.7)	<0.001
Massive	24 (1.7%)	5.7 (3.7–8.6)	<0.001	1.5 (1.0–2.4)	0.059
PV thrombosis					
Negative	1087(75.7%)	1		1	
Positive	349 (24.3%)	4.5 (3.9–5.1)	<0.001	1.5 (1.2–2.0)	0.003
TNM stage					
I	634 (44.2%)	1		1	
II	258 (17.9%)	1.2 (0.98–1.4)	0.083	0.6 (0.4–0.8)	0.002
III	454 (31.6%)	4.5 (3.8–5.2)	<0.001	1.2 (0.9–1.7)	0.201
IV	90 (6.3%)	6.1 (4.8–7.8)	<0.001	2.2 (1.5–3.2)	<0.001
BCLC stage					
Very early		1		1	
Early		2.7 (1.5–4.7)	0.001	3.0 (1.7–5.2)	<0.001
Intermediate		5.1 (2.9–8.8)	<0.001	4.5 (2.5–8.0)	<0.001
Advanced		14.8 (8.5–25.9)	<0.001	4.0 (2.1–7.7)	<0.001
Terminal		27.4 (15.3–49.2)	<0.001	10.8 (5.8–20.0)	<0.001
Treatment					
Surgery	266 (18.5%)	1		1	
RFA	76 (5.3%)	1.4 (0.9–2.2)	0.091	2.5 (1.6–3.9)	<0.001
PEI	57 (4%)	1.9 (1.2–2.9)	0.006	3.6 (2.3–5.7)	<0.001
TAE	577 (40.2%)	3.3 (2.5–4.2)	<0.001	3.1 (2.4–4.0)	<0.001
C/T or R/T	143 (10%)	11.9 (8.9–15.8)	<0.001	4.5 (3.3–6.2)	<0.001
Supportive care	317 (22.1%)	11.9 (9.2–15.4)	<0.001	8.6 (6.5-11.3)	<0.001

Abbreviation: HBV: hepatitis virus B; HCV: hepatitis virus C; Non-B/Non-C: etiology outside from HBV or HCV; AFP: Alpha-fetoprotein; PV: portal vein; TNM: tumour–nodes–metastases system; BCLC stage: Barcelona Clinic Liver Cancer stage; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TAE: transcatheter arterial embolisation; C/T: systemic chemotherapy; R/T: conformal radiotherapy.

a Based on Cox's proportional hazard model.

cer but not in mortality reduction, because therapy was ineffective.[22] Therefore, the surveillance programme must be accompanied with appropriate treatment options for patients with newly diagnosed HCC to improve their survival and jus-

tify the expense.[8,13] In the countries with high HCC incidence, surveillance has been considered cost-effective[23]; moreover, the adoption of effective treatment might further achieve the greatest gain in life expectancy economically.[24,25]

In this study, patients receiving surgical resection at initial HCC diagnosis had the best survival. For those patients who were not fit for resection, the survival rate declined from local ablation, TAE, supportive care to conformal RT or systemic chemotherapy. Although surgical resection yielded the best outcome, it was not significantly superior to RFA in this study. Livraghi and colleagues demonstrated that RFA was as effective as hepatic resection in terms of recurrence and long-term survival, especially for patients in very early BCLC stage.[26] Recent systemic review of RFA for HCC supports the thinking that it can be used as an alternative treatment to surgery for resectable HCC sized less than or equal to 3 cm.[27] Therefore, for HCC patients in curative stages with comorbid disease, RFA seemed to be a good substitute for resection. The survival of patients with RFA was better than those with PEI, however, there was no significant difference statistically in this study. Recent randomised control trials comparing RFA with PEI supported RFA for early stage patients.[28–30] Poon and colleagues demonstrated there is a significant learning curve in RFA for liver tumour; a low complication rate and a high complete ablation rate could be achieved with the accumulated experience from the first 50 cases of RFA in a tertiary institution.[31] We started RFA for HCC treatment from 2002; most of our patients were within the learning curve period and might have an unsatisfactory outcome. This might explain why there was no survival benefit for RFA, in comparison with PEI in our study. Longer follow-up of patients with RFA and PEI might show superior survival benefit for RFA. Conformal radiotherapy or systemic chemotherapy did not have significant survival benefit with supportive care for HCC patients in the present study. However, for patients in BCLC advanced and terminal stages, the survival rates at 1 year, 2 years and 3 years for patients with conformal radiotherapy or systemic therapy was superior to those with supportive care (16.1%, 7.3% and 3.2% versus 8.1%, 3.2% and 2.7%, $p < 0.001$). This result was compatible with our previous study in a different cohort, which demonstrated conformal radiotherapy might be beneficial for survival for select patients with HCC in advanced or terminal stages.[15]

Liver transplantation was recognised as the best curative treatment. Strvitz and colleagues reported that long-term survival after HCC diagnosis during surveillance is dependent on receiving an effective treatment such as liver transplantation.[32] However, liver transplantation is not usually the first choice for HCC treatment in an area where liver transplantation was not feasible due to shortage of donors. Potentially curative treatment in this study was defined as hepatic resection and local ablation therapy, and the survival rates were comparable with other reports from Japan and Hong Kong.[33,34] To assess the therapeutic impact in survival, we subgrouped our surveillance patients in curative stage into curative-therapy and non-curative-therapy groups according to AASLD guideline recommendation.[7] The 3-year survival rate in the curative-therapy group was better than that in non-curative-therapy group (77.1% versus 55.2%, $p < 0.001$). Therefore, not only early detection of HCC is associated with better survival but also appropriate treatment option further improves survival for patients in curative stage under HCC surveillance.

As expected, surveillance was able to detect most HCCs at an early stage, which curative treatment might be able to perform. It explained the survival benefit for patients in surveillance programme. Therefore, the effect of surveillance on survival usually was not significant in multivariate analysis after adjusting with these factors in most studies.[32–34] However, surveillance is still an independent factor associated with patients' survival at multivariate analysis in our study. This finding was compatible with that reported from Kemp and colleagues.[35] Patients in the surveillance group might be in better performance status and have higher motivation to receive HCC surveillance and better understanding of HCC. These might explain that surveillance is independently associated with better survival in our study.

This is a retrospective study, which might have some limitations. First, the better survival of patients with HCC detected under surveillance could be simply attributed to the lead-time bias.[35] Patients in the surveillance group were identified as having tumours in an earlier stage than those in the non-surveillance group, and the improved survival might be associated with an earlier diagnosis. Trevisani and colleagues corrected the lead-time bias by adjusting the time of diagnosis based on a literature-derived tumour growth rate and the median tumour size in study.[17] They showed that the survival in the surveillance group with or without adjustment was better than that in the non-surveillance group. However, the adaption of lead-time bias was controversial due to the information of real HCC doubling time still being insufficient. The second point is the length bias resulting from differences in the intrinsic growth rates of tumours. Surveillance might possibly tend to identify slow-growing tumours rather than aggressive tumours. A selection bias is that among those patients in surveillance who could be offered hepatic resection, about two-thirds (51/76) were referred from other hospitals. These select patients with better liver function reserve were simply referred for surgical intervention and this might contribute to a better prognosis.

In conclusion, this study demonstrates that surveillance programme for HCC with US and AFP determination in cirrhotic patients could detect small HCC at a stage eligible for curative treatment and improve long-term survival. In addition, appropriate treatment options following AASLD guidelines further improve the survival for patients in early BCLC stage.

Conflict of interest statement

None declared.

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