

Original Article

Radiofrequency ablation plus nucleotide analogous for hepatitis B virus-related hepatocellular carcinoma: a cost-effectiveness analysis

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Abstract: In the real-world, it is unclear that after the radiofrequency ablation (RFA), whether it is a cost-effective strategy to administer nucleotide analogue (NA) for patients with hepatitis B virus (HBV)-related HCC patients. The aim of this study was to estimate the cost-effectiveness of the RFA plus NA versus RFA alone in patients with HBV-related HCC within the Milan criteria in China and the USA. A Markov model was developed to simulate a cohort of patients with HCC within the Milan criteria and Child-Pugh A/B cirrhosis and underwent RFA with or without NA therapy over their remaining life expectancy. Analysis was performed in two geographical cost settings: China and the USA. The RFA plus NA therapy provided an average of 7.57 years, whereas RFA monotherapy offered 5.83 years. The RFA plus NA therapy produced 5.09 quality-adjusted life years (QALYs), whereas RFA monotherapy achieved 3.89 QALYs. The incremental cost-effectiveness ratio (ICER) of the RFA plus NA therapy versus RFA monotherapy was \$10368.19/QALY in China and \$38805.45/QALY in the USA. These values were below the thresholds of the cost-effectiveness in both countries. Sensitivity analysis revealed that the utility of recurrent HCC was the most sensitive parameter in all cost scenarios in both of the RFA plus NA therapy and RFA monotherapy groups. Our Markov model has shown that for the patients with HBV-related HCC within the Milan criteria and Child-Pugh A/B cirrhosis, RFA plus NA is more cost-effective than RFA monotherapy across the two different cost scenarios namely, China and the USA.

Keywords: Hepatocellular carcinoma, nucleotide analogous, radiofrequency ablation, Markov model

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third cause of cancer-related death worldwide [1], and is responsible for more than 700,000 deaths in the world each year [2]. Among them, at least 80% of HCCs are associated with chronic hepatitis virus infection and, mostly, the hepatitis B virus (HBV) infection accounts for 75-80% of these HCCs [3]. It is clear that there is a close relationship between HCC and HBV infection. Therefore, the concerns are increasingly down about the effects of the antiviral treatment on the tumor.

For HCCs within the Milan criteria, only three types of therapies can be applied as curative treatments, they are surgical resection, liver transplantation and percutaneous ablation therapies such as radiofrequency ablation (RFA). Among them, RFA is widely used as one of the first line treatments, due to its minimal invasion and fewer complications. However, the tumor recurrence rates at up to 70% in 5 years in the liver remnant reduces the therapeutic effect of RFA, and HBV infection appears to add on significant impact on recurrence [4]. Previous studies have revealed that a high HBV virus load was the key prognostic factor for the progression and recurrence of HCC, and it might

RFA plus NA for HBV-related HCC

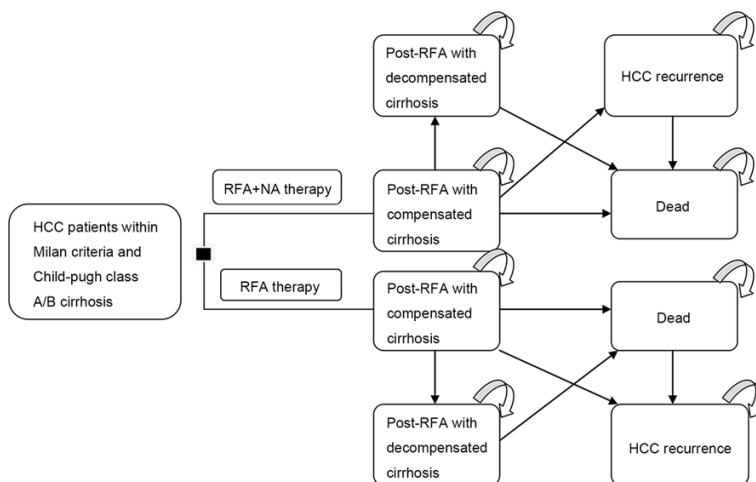


Figure 1. Flow diagram of Markov model. Each pane represents a state of health. Straight lines with arrows indicate transition from one state to another while circular arrows mean that some patients may stay at the same state for more than one cycle.

uld yield a better picture of the characteristics of the individual patient and improve drug's ability, hence to meet the needs of individual patient. This information can be used across a wide spectrum of research, ranging from observational studies to studies that incorporate planned interventions, with or without randomization at the point of care [19]. In this context, it is necessary to incorporate real-world data into a Markov model and to explore the cost-effectiveness in relation of the NA therapy for HBV-related HCC patients after RFA.

influence the survival [5-8]. Moreover, antiviral therapy was associated with a reduced risk of HCC recurrence and an improvement in overall survival (OS) among the patients with HBV-related HCC after RFA [9-11]. However, these studies did not consider the costs of long-term therapy. Although the clinical outcomes of antiviral therapy for HBV-related HCC are substantial, despite the cost of tumor treatments, the cost of antiviral therapy also becomes an economic burden for both of the governments and the patients [12, 13]. Indeed, it remains unclear that whether it is cost-effective strategy to administer antiviral therapy using nucleotide analogue (NA) for HBV-related HCC patients after RFA.

Generally, Markov models are applied in describing stochastic processes, which are random processes that evolve over time [14]. Since its first introduction in determining medical prognosis in 1983, Markov models have been increasingly used in clinical evaluations of the disease screening or the treatments worldwide [15-18]. The model offers advantages such as taking into account of both of the costs and the outcomes over a period of time. Thus, the method is particularly fit to model the progression of chronic diseases. On the other hand, traditional clinical trials are often conducted with specific groups of populations and in special environments where are different from the realities of the clinical or home settings [19]. Real-world evidence (RWE) co-

The aim of this study is to estimate the cost-effectiveness (CE) of RFA plus NA versus RFA alone in patients with HBV-related HCC within the Milan criteria by using a Markov model.

Materials and methods

Model construction

A Markov simulation model [13, 20] was developed to estimate the cost-effectiveness of the NA therapy in a hypothetical cohort of patients aged 55 years with early HBV-related HCC who received RFA as initial treatment, with Child-Pugh class A or B liver function and without anti-HBV treatment before RFA. The hypothetical cohorts were then followed by a 20 series of Markov cycles governing patient transitions between relevant states (**Figure 1**). Among the two alternatives, the baseline comparator was RFA monotherapy. Early HCC was defined as HCC meeting the Milan criteria (solitary nodule not exceeding 5 cm; no more than three nodules, none exceeding 3 cm; no evidence of macrovascular invasion or distant metastasis) [21]. Given that tumor burden and liver function were the two dominant factors related to the survivals and costs, patients with advanced HCC or decompensated cirrhosis were assumed to receive no further active treatments.

In this model, a 1-year cycle time was selected to reflect the clinical cost and quality of life impact of the treatments. During each cycle, a

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Table 1. Base case value and sensitivity range extracted from literature for transition probabilities

Parameter	Base Case Value (Median of Literature Range Unless Separately Referenced) (%)	Literature Range Tested (%)
Background (all-cause) mortality [23]	Age-specific	
Cirrhosis annual decompensation rate: RFA [24-26] ^{†‡}	11.80	3.90-12.50
Cirrhosis annual decompensation rate: RFA+NA [34-36] ^{†‡}	7.30	3.18-13.73
Annual mortality risk of compensated cirrhosis: RFA [27-29] ^{†‡}	9.76	0-9.76
Annual mortality risk of compensated cirrhosis: RFA+NA [34, 35] ^{†‡}	4.90	0-5.07
Annual mortality risk of decompensated cirrhosis: RFA [27, 28, 30] ^{†‡}	18.94	18.94-31.57
Annual mortality risk of decompensated cirrhosis: RFA+NA [28, 31, 32] ^{†‡}	19.00	3.57-27.52
Annual recurrence risk after RFA:RFA [11, 31, 33] ^{†‡}	32.40	13.40-32.40
Annual recurrence risk after RFA:RFA+NA [11, 31, 33] ^{†‡}	23.71	13.5-23.71
Annual mortality risk of recurrent HCC:RFA [11, 32, 33] ^{†‡}	13.40	13.40-50.41
Annual mortality risk of recurrent HCC:RFA+NA [11, 32, 33] ^{†‡}	10.33	10.33-17.59

†, Refers to more detailed reference list and original probabilities. ‡, All probabilities were transited into monthly rate. Detailed methods were listed in supporting material.

Table 2. Base case value and sensitivity range for costs

Parameter	Base case value	Range tested (50%-200%)
Cost in China (\$)		
RFA+NA therapy		
One time cost of RFA [39]	2210	1105-4420
Yearly cost of compensated cirrhosis [41]	2065	1032.5-4130
Yearly cost of decompensated cirrhosis [41]	4290	2145-8580
HCC recurrence [41]	6054	3027-12108
Yearly cost of follow-up [†]	367	183.5-734
Yearly cost of NA [40]	2044	913-3167
RFA		
One time cost of RFA	2210	1105-4420
Yearly cost of compensation cirrhosis [41]	2065	1032.5-4130
Yearly cost of decompensation cirrhosis [41]	4290	2145-8580
HCC recurrence [41]	6054	3027-12108
Yearly cost of follow-up [†]	367	183.5-734
Cost in the USA (\$)		
RFA+NA therapy		
One time cost of RFA [42]	18386	14709-22063
Yearly cost of compensated cirrhosis [43-45]	732	366-1464
Yearly cost of decompensated cirrhosis [43-45]	18228	9114-36456
HCC recurrence [44]	38715	19357.5-77430
Yearly cost of follow-up [44]	2500	1250-5000
Yearly cost of NA [44] [†]	2508	1080-2508
RFA		
One time cost of RFA [42]	18386	14709-22063
Yearly cost of compensated cirrhosis [43-45]	732	366-1464
Yearly cost of decompensated cirrhosis [43-45]	18228	9114-36456
HCC recurrence [44]	38715	19357.5-77430
Yearly cost of follow-up [44]	2500	1250-5000

†, Refers to clinical expert opinions.

Table 3. Base Case Value and sensitivity range extracted from literature for Utilities

Parameter	Base case value	Range tested
Compensated cirrhosis [47-49]	0.76	0.65-0.90
Decompensated cirrhosis [47-49]	0.66	0.37-0.86
HCC recurrence [47-49]	0.63	0.26-0.86

patient in one health state might be transitioned to another or occupied the same state according to transition probabilities (**Figure 1**). Each health state had its associated cost and utilities. The yearly transition probabilities were derived from cumulative probabilities using the declining exponential approximation of life expectancy (DEALE) method [22].

Literature review

Transition probabilities, utilities and costs (**Tables 1-3**) were derived from studies identified through PubMed and Cochrane Library database and the latest search performed on Jun, 2016. We used the Medical Subject Headings (MeSH) “hepatocellular carcinoma”, “antiviral therapy” and “ablation techniques” in the literature search. The following keywords were also used to complete the literature research: “radiofrequency ablation” or “percutaneous ablation” and “HBV infection” and “survival”. Details regarding parameters used to derive transition probabilities are displayed in [Tables S1](#), [S2](#), [S3](#), [S4](#), [S5](#).

Transition probabilities in the RFA monotherapy arm

In the RFA monotherapy arm, which served as the baseline comparator for the analysis, it was assumed that patients did not receive NA therapy after the RFA treatment and were in a compensated cirrhosis state. These patients were exposed to the risks of age-related mortality, decompensated cirrhosis and tumor recurrence. The transition probabilities were obtained from the studies inclusive of the patients with HBV-related cirrhosis. In addition, it was assumed that RFA treatment did not influence the cirrhosis deterioration, given that the impairment effect of RFA in liver was transient and the liver function could gradually be recovered by liver protective drugs. Age-related mortality risks were derived from life tables based on the hypothetical age in this model [23]. The annual decompensation rates were

reported ranging from 3.9% to 12.5% [24-26]. The rate of 11.8% was selected as the base case estimate due to the largest sample size of the relevant study and the remaining data from other studies were used as the range for sensitivity analysis. The 6-year cumulative

survival of compensated cirrhosis was 54%, which served as the base case value derived from a series of studies [27-29]. This value was further converted to an annual mortality risk of compensation cirrhosis using the DEALE method [22]. In addition, a 5-year cumulative decompensated cirrhosis of 35% was used as the base case value [27, 28, 30], and this value was also converted to annual mortality risk of decompensation cirrhosis using the DEALE method [22]. However, RFA is a curative treatment for early HCC. Studies specified whether the patients with recurrent HCC after RFA were undergoing an NA therapy or not were extremely difficult to identify, which made the mortality of recurrent HCC in our model unable to calculate. Thus, to focus on the impact of NA therapy, the mortality risk of recurrent HCC was assumed to be the same as the primary HCC. The 2-year cumulative recurrence rate after RFA was 54.3% and the 2-year mortality risk of recurrent HCC was 25%. The values were derived from studies by Lee et al. [11, 31-33].

Transition probabilities in the RFA plus NA therapy arm

NA therapy was recommended to the patients after RFA treatment. Similarly, these patients started at a state of compensated cirrhosis. These patients were also exposed to the risks of age-related mortality, decompensated cirrhosis and tumor recurrence. The transition probabilities were also obtained from studies involving the patients with HBV-related cirrhosis. The annual decompensation rate was 7.3% with a range from 3.18% to 13.73%, and these values were extracted from Kanwal et al. [34-36]. The annual mortality rate of the compensated cirrhosis was 4.9%, which served as the base case value derived from a series of studies [34, 35]. The annual mortality risk of the decompensated cirrhosis was 19%, which served as the median value derived from a series of studies [34, 37, 38]. The 3-year cumulative recurrence rate of RFA with NA therapy

RFA plus NA for HBV-related HCC

Table 4. Incremental cost-effectiveness ratios comparing three therapy strategies in the two countries at the base case

Various parameters	China		USA	
	RFA+NA	RFA	RFA+NA	RFA
QALYs (years)	5.09	3.89	5.09	3.89
Incremental QALYs gain (years)	1.20	-	1.20	-
Life time cost (\$)	41967.72	29564.96	211007.95	164587.65
Incremental cost (\$)	12402.76	-	46420.30	-
ICER (\$)	10368.19	-	38805.45	-
Avg CE	8250.99	7599.94	41484.82	42308.73
WTP (\$)	24,840		50,000	
Is RFA+NA cost-effective?	Yes		Yes	

was 35.1% and the 2-year mortality risk of recurrent HCC was 19.6%. These were derived from studies by Lee et al. [11, 31-33].

Costs and utilities

This study was conducted from a healthcare system perspective. Therefore, only direct medical costs were included. We obtained cost estimates for cirrhosis and other related health states from published studies of detailed, itemized inpatient and outpatient direct costs incurred by patients with cirrhosis [39-45]. Entecavir (ETV) is a very potent and highly selective inhibitor of HBV that is widely prescribed [46]. The yearly cost of ETV as the base case value, and the ranges of yearly costs of other NAs (Lamivudine: LAM; Adefovir: ADV; Telbivudine: LdT; Tenofovir: TDF) were used for sensitivity analysis. The cost estimates were separately obtained from cost-relative studies specific for China [39-41] and the USA [42-45]. All costs are presented in **Table 2**. The base case estimates and sensitivity ranges of utilities in each health state were extracted from studies [47-49] (**Table 3**). A discount rate was set at 3% yearly for both costs and utilities.

The outcomes used to assess both of the health benefits and costs included life year gain (LYG), quality-adjusted life expectancy (QALY) and incremental cost-effectiveness ratio (ICER). QALYs were determined by the quality and quantity of patient years accrued, with one QALY equal to one year in perfect health. ICERs were calculated to determine the incremental costs of the implementing strategy divided by the incremental QALY gain. A lower ICER indicated a lower cost per unit gain in benefit, and therefore a higher value to society. Willing to pay (WTP) was an addi-

tional cost-effectiveness (CE) threshold, which was the largest amount of money an individual was willing to pay to gain one QALY. This metric was used for comparisons with ICER to decide whether a strategy was cost-effective. For the USA, we adopted the commonly cited CE threshold of \$50,000/

QALY [50]. For China, we adopted the threshold of \$24,840/QALY, which was the 3 times GDP per capital of China according to the WHO guidelines for CE analysis [51].

Sensitivity analysis

TreeAge Pro 11.0 (TreeAge Software, Williamstown, MA) was used for modeling. One-way deterministic sensitivity analysis was performed for all transition probabilities, costs and utilities. Net monetary benefit (NMB), which combined cost, effectiveness and WTP into a single measurement, was introduced to reduce the mathematical uncertainty of ICER. The strategy with the higher NMB was more cost-effective under the given WTP parameter. For transition probabilities and utilities, the sensitivity analysis was performed by varying each parameter over the range of variations among the included studies. For the costs, by considering the lack of reported range data, a wider range of 50%-200% of the base case value was applied as described by Lim et al. [49].

Monte Carlo probabilistic sensitivity analysis was performed to evaluate the total impact of parameter uncertainties on the model results, from which random draws were made during 10,000 simulations. Findings are depicted on a CE acceptability curve (CEAC). A gamma distribution was assumed for cost estimates and a beta distribution was used for efficacy estimates.

Results

Base case analysis

Table 4 summarizes the results of base case analyses. For LYG, the RFA plus NA therapy

RFA plus NA for HBV-related HCC

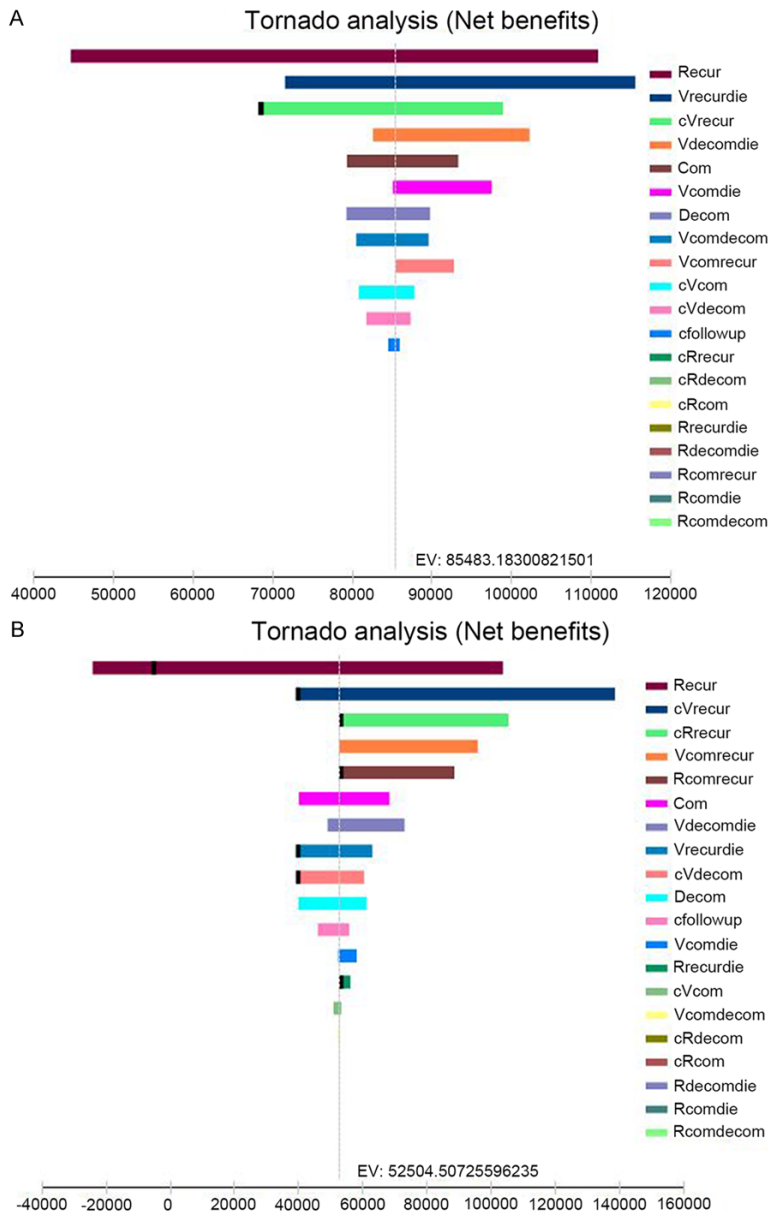


Figure 2. Tornado diagrams of one-way sensitivity analysis for China (A) and the USA (B). All transition probabilities and some cost defined in this model are analyzed. It is displayed that the conditions about recurrent hepatocellular carcinoma (HCC) were important factors affecting the strategy selection. The length of the colored bar for each factor represents the extent of its effect on NMB. A wider bar of the corresponding variable indicates a larger potential effect on the NMB. Ranges are presented in **Tables 1** and **2**. cVcom: the cost of compensation cirrhosis in the radiofrequency ablation (RFA) plus nucleotide analogue (NA) therapy; cVdecom: the cost of decompensation cirrhosis in the RFA plus NA therapy; cVrecurr: the cost of recurrent HCC in the RFA plus NA therapy; cRcom: the cost of compensation cirrhosis in the RFA monotherapy; cRdecom: the cost of decompensation cirrhosis in the RFA monotherapy; cRrecurr: the cost of recurrent HCC in the RFA monotherapy; cfollowup: the cost of the follow-up; Vcomdie: the annual mortality rate of compensation cirrhosis in the RFA plus NA therapy; Rcomdie: the annual mortality rate of compensation cirrhosis in the RFA monotherapy; Vcomdecom: the cirrhosis annual decompensation rate in the RFA plus NA therapy; Rcomdecom: the cirrhosis annual decompensation rate in the RFA monotherapy; Vcomrecur: the recurrent rate after RFA in the RFA plus NA therapy; Rcomrecur: the recurrent rate after RFA in the RFA monotherapy; Vdecom-

die: the annual mortality rate of decompensation cirrhosis in the RFA plus NA therapy; Rdecomdie: the annual mortality rate of decompensation cirrhosis in the RFA monotherapy; Vrecurrdie: the annual mortality rate of recurrent HCC in the RFA plus NA therapy; Rrecurrdie: the annual mortality rate of recurrent HCC in the RFA monotherapy; Com: the utility of compensation cirrhosis; Decom: the utility of decompensation cirrhosis; Recur: the utility of recurrent HCC.

strategy provided an average of 7.57 years, whereas the RFA monotherapy strategy offered 5.83 years. With quality of life adjustments, the RFA plus NA therapy produced 5.09 QALYs, whereas the RFA monotherapy achieved 3.89 QALYs. The ICER of the RFA plus NA therapy was \$10,368.19/QALY in China and \$38,805.45/QALY in the USA. These values were less than the corresponding WTP thresholds in both countries. This finding implied that the RFA plus NA therapy strategy was more cost-effective in both China and the USA.

One-way sensitivity analysis

Figure 2 depicts the tornado diagrams of all the input parameters for China and the USA. The utility of recurrent HCC was the most sensitive parameter in both China and the USA. The next sensitive parameters were the annual mortality rate of recurrent HCC in the RFA plus NA therapy and the cost of recurrent HCC in the RFA plus NA therapy in China, as well as the cost of recurrent HCC in the RFA plus NA therapy and the cost of recurrent HCC in the RFA monotherapy in the USA. It was displayed that the conditions about recurrent HCC

were important factors to affect the strategy selection. In China, if the yearly cost of recurrent HCC patients with NA therapy increased up to \$9,946.10, the corresponding NMB would be reduced compared with RFA monotherapy, which made the RFA monotherapy more cost-effective. Moreover, if the cost was less than \$9,946.10, the RFA plus NA therapy might be recommended. In the USA, more parameters influenced the strategy selection. If the rate of annual recurrent risk of RFA increased to 25.67%, the corresponding NMB would reduce below that of the RFA plus NA therapy, which made the RFA plus NA therapy more cost-effective. Regarding the cost scenario, if the expenditure of recurrent HCC with the RFA plus NA therapy was greater than \$41,725.71, the RFA plus NA therapy would be more cost-effective. Moreover, if the cost of recurrent HCC with the RFA plus NA therapy increased, a cut-off of \$41,725.71 might indicate that the RFA plus NA therapy could be less competitive.

Two-way sensitivity analysis

The top two sensitive parameters were related to the cost of recurrent HCC. These parameters were included in the two-way analysis. In China, the analysis demonstrated that the costs of recurrent HCC for both strategies had different effects on cost-effectiveness. However, we assumed the same base case and range. Assuming that the yearly cost of recurrent HCC patients was \$3,027 in the RFA monotherapy cohort, the NMB was the same as that of the yearly cost of recurrent HCC patients at \$7,567.5 in the RFA plus NA therapy group. Given the influences of liver function on the HCC treatment, this finding suggested that the RFA plus NA therapy might offer greater tolerance to gain cost-effectiveness. In the USA, assuming that the yearly cost of recurrent HCC patients was \$19,375.5 in the RFA monotherapy cohort, the NMB was the same as that when assuming the yearly cost of recurrent HCC patients was \$26,616.5 in the RFA plus NA therapy group.

Monte Carlo probabilistic sensitivity analysis

The median ICERs of the RFA plus NA therapy compared with the RFA monotherapy were \$10,531.73 (10,460.06-10,603.40) in China and \$37,773.2 (37,274.59-38,271.82) in the

USA. For China, the acceptability curve revealed that the RFA plus NA therapy exhibited an increased probability of being more cost-effective compared with the RFA monotherapy considering WTP (\$13,028) (**Figure 3A**). The result was the same for the USA, indicating that if the decision maker was willing to pay \$43,180 or more, the RFA plus NA therapy was more cost-effective with an increased portion of populations attaining CE (**Figure 3B**). Our model demonstrated that considering the WTP, 99.8% and 71.6% of patients in China and the USA, respectively, it would choose the RFA plus NA therapy strategy.

Discussion

Most HCCs are associated with hepatitis B in China and the USA [3], and hepatitis virus infection affects tumor recurrence and liver function. The effect of antiviral treatment on HCC is becoming an increasingly concern. Our model demonstrated that RFA plus NA therapy produced relatively better results (5.09) compared with RFA monotherapy (3.89). The ICER of the RFA plus NA therapy was \$10,368.19/QALY in China and \$38,805.45/QALY in the USA, which was less than the corresponding WTP thresholds in both countries. Thus, NA plus RFA therapy could provide enhanced CE for HBV-related HCC within Milan criteria both in China and the USA compared with RFA alone.

To date, a series of studies have demonstrated that the treatment survivals of HBV-related HCC after RFA were significantly improved with antiviral therapy [31-33]. In 2006, Lee et al. [31] showed that NA therapy was independently associated with a decreased risk of HCC recurrence among patients with HBV-related HCC after RFA. In addition, in the study of Sohn et al. [33], it was declared that oral antiviral treatment not only reduced HCC recurrences but also improved patients' overall survival after curative RFA. The mean overall survival after RFA was 9.4 years in the antiviral treatment group, while it was 6.1 years in the non-antiviral treatment group. However, these prior studies were lacking of health and economic evidence. In the present study, we constructed the Markov model to simulate clinical situations. The results revealed that RFA plus NA therapy produced 5.09 QALYs, whereas RFA monotherapy offered only 3.89 QALYs. The pos-

RFA plus NA for HBV-related HCC

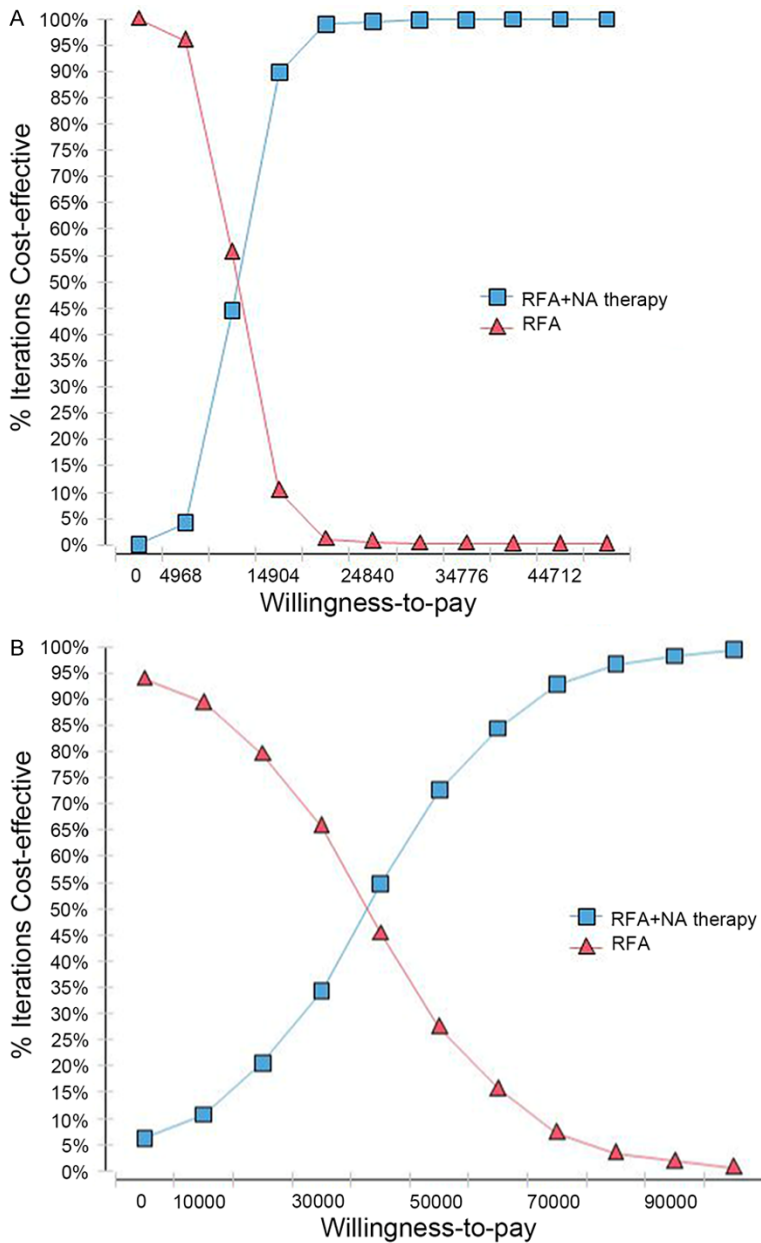


Figure 3. Cost-effectiveness acceptability curve (CEAC) of two treatment strategies for both China and the USA. CEAC presents the uncertainty in cost-effectiveness analysis and provides the reference to the WTP thresholds. For China, the (radiofrequency ablation) RFA plus nucleotide analogue (NA) therapy exhibits an increased probability of being more cost-effective compared with RFA monotherapy considering (willing to pay) WTP (\$13028) (A). For the USA, if the decision maker is willing to pay \$43180 or more, the RFA plus NA therapy was more cost-effective (B).

itive effects of RFA plus NA therapy for HCC may be attributed to the following reasons. Antiviral treatment decreases hepatitis activity, improves liver function and gains better liver function preservation by inhibiting HBV reactivation [52-55]. The recurrence rate after RFA is obviously reduced with the RFA plus NA ther-

apy [11, 31, 33], which relieves patient tumor burden and further leads to increased utilities.

Regarding the CE analysis, our model demonstrated that RFA plus NA therapy strategy was more cost-effective compared with RFA monotherapy for the treatment of HBV-related HCC within Milan criteria both in China and the USA, based on the case analysis, sensitivity analysis and CE acceptability curve analysis. The ICER of the RFA plus NA therapy versus RFA monotherapy was \$10,368.19/QALY in China and \$38,805.45/QALY in the USA, and both values were less than the WTP thresholds of cost-effectiveness, indicating that the RFA plus NA therapy was cost-effective whether in China and the USA. Therefore, we considered that the RFA plus NA therapy should be recommended for better CE in both countries. CE acceptability curves were also performed for both countries. The values of the cross points were \$13,028 in China and \$43,180 in the USA. The same trend is noted in both countries, suggesting that RFA monotherapy may be proper for the populations with rather poor economic conditions (when WTP was less than the cross points). On the other hand, RFA plus NA therapy is likely to be accepted by patients with a relatively high WTP.

According to the tornado diagrams, the top three sensitive factors were all associated with tumor recurrence, and this feature was in common in both countries. These findings were reasonable because tumor recurrence reduces disease-free survivals and overall survivals. In addition, the cost of consecutive treatments in

the next cycle was the highest among all Markov states [39-45], indicating that HCC recurrence indicates a poor prognosis of the CE. In addition to the treatment of primary HCC, the optimal treatment for recurrent HCC after RFA deserves equal attention. Despite its expense, the cost of the NA therapy did not affect the medical decision when its range varied. These results further confirm that it is worthwhile to recommend a NA therapy after RFA, despite of its additional cost.

There are several limitations in our model. First, the cost estimates in our analysis were based on national data and regional differences in outcomes after RFA were not considered. Costs may vary in different regions as well as the treatment plans. Thus, we sought to minimize the uncertainties by using a wide range of cost values (50%-200% of base-case value) in the sensitivity analyses. Therefore, our model could be applied in both countries if cost data lie within the ranges we established. Second, no subgroup analysis was performed for patients who received NA therapy, such as subgroups of different HBV-DNA levels and HBeAg states. This analysis could help elucidate the specific effect of antiviral therapy for HCC patients in different HBV infection states. However, given limited literature focusing on this area, data for subgroup analysis was difficult to obtain. Our article suggests that the RFA plus NA therapy performs better in both LYG and CE, and we are hopeful that more researchers will pay attention to the RFA plus NA therapy in early HCC treatment to validate our conclusions and provide more information for the subgroup analysis.

In conclusion, additional NA therapy after RFA is more cost-effective than RFA monotherapy for HCC patients within Milan criteria in both China and the USA. Our findings should be validated in further high-quality studies.

Disclosure of conflict of interest

None.

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References

- [1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87-108.
- [2] Bray F, Ren JS, Masuyer E and Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer* 2013; 132: 1133-1145.
- [3] McGlynn KA and London WT. The global epidemiology of hepatocellular carcinoma: present and future. *Clin Liver Dis* 2011; 15: 223-243, vii-x.
- [4] Cucchetti A, Piscaglia F, Cescon M, Ercolani G and Pinna AD. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. *World J Gastroenterol* 2013; 19: 4106-4118.
- [5] Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, Asaoka Y, Sato T, Masuzaki R, Kondo Y, Goto T, Yoshida H, Omata M and Koike K. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol* 2012; 107: 569-577; quiz 578.
- [6] Hasegawa K, Kokudo N, Makuuchi M, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O and Matsuyama Y. Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol* 2013; 58: 724-729.
- [7] Kim BK, Park JY, Kim DY, Kim JK, Kim KS, Choi JS, Moon BS, Han KH, Chon CY, Moon YM and Ahn SH. Persistent hepatitis B viral replication affects recurrence of hepatocellular carcinoma after curative resection. *Liver Int* 2008; 28: 393-401.
- [8] Sheng RF, Zeng MS, Ren ZG, Ye SL, Zhang L and Chen CZ. Intrahepatic distant recurrence following complete radiofrequency ablation of small hepatocellular carcinoma: risk factors and early MRI evaluation. *Hepatobiliary Pancreat Dis Int* 2015; 14: 603-612.
- [9] Hann HW, Bergin D, Coben R and DiMarino AJ. Prevention of new hepatocellular carcinoma with concomitant antiviral therapy in chronic hepatitis B patients whose initial tumor was successfully ablated. *Int J Cancer* 2011; 128: 739-742.

- [10] Nishikawa H, Nishijima N, Arimoto A, Inuzuka T, Kita R, Kimura T and Osaki Y. Effect of nucleoside analog use in patients with hepatitis B virus-related hepatocellular carcinoma. *Hepatol Res* 2014; 44: 608-620.
- [11] Lee TY, Lin JT, Zeng YS, Chen YJ, Wu MS and Wu CY. Association between nucleos(t)ide analog and tumor recurrence in hepatitis B virus-related hepatocellular carcinoma after radiofrequency ablation. *Hepatology* 2016; 63: 1517-1527.
- [12] Meropol NJ and Schulman KA. Cost of cancer care: issues and implications. *J Clin Oncol* 2007; 25: 180-186.
- [13] Zhang H, Chao J, Wang S and Liu P. The impact of health insurance on economic burden for hepatitis B inpatients in China. *Iran J Public Health* 2016; 45: 107-108.
- [14] Briggs A and Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics* 1998; 13: 397-409.
- [15] Parsonnet J, Harris RA, Hack HM and Owens DK. Modelling cost-effectiveness of helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials. *Lancet* 1996; 348: 150-154.
- [16] Nayagam S, Conteh L, Sicuri E, Shimakawa Y, Suso P, Tamba S, Njie R, Njai H, Lemoine M, Hallett TB and Thursz M. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. *Lancet Glob Health* 2016; 4: e568-578.
- [17] Hillner BE and Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. A decision-analysis model. *N Engl J Med* 1991; 324: 160-168.
- [18] Sonnenberg FA and Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993; 13: 322-338.
- [19] Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, LaVange L, Marinac-Dabic D, Marks PW, Robb MA, Shuren J, Temple R, Woodcock J, Yue LQ and Califf RM. Real-world evidence-what is it and what can it tell us? *N Engl J Med* 2016; 375: 2293-2297.
- [20] Naimark D, Krahn MD, Naglie G, Redelmeier DA and Detsky AS. Primer on medical decision analysis: part 5—working with markov processes. *Med Decis Making* 1997; 17: 152-159.
- [21] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A and Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334: 693-699.
- [22] Beck JR, Kassirer JP and Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. *Am J Med* 1982; 73: 883-888.
- [23] Arias E. United states life tables, 2010. *Natl Vital Stat Rep* 2014; 63: 1-63.
- [24] Fleming KM, Aithal GP, Card TR and West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. *Aliment Pharmacol Ther* 2010; 32: 1343-1350.
- [25] Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW and Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112: 463-472.
- [26] Hu KQ and Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the united states. *Hepatology* 1999; 29: 1311-1316.
- [27] D'Amico G, Morabito A, Pagliaro L and Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci* 1986; 31: 468-475.
- [28] de Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW and van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology* 1992; 103: 1630-1635.
- [29] Benvegnu L, Gios M, Boccato S and Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004; 53: 744-749.
- [30] Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, Christensen E, Krogsgaard K, Degos F, Carneiro de Moura M and et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EURO-HEP Study Group on Hepatitis B Virus and Cirrhosis. *Hepatology* 1995; 21: 77-82.
- [31] Kuzuya T, Katano Y, Kumada T, Toyoda H, Nakano I, Hirooka Y, Itoh A, Ishigami M, Hayashi K, Honda T and Goto H. Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. *J Gastroenterol Hepatol* 2007; 22: 1929-1935.
- [32] Yoshida H, Yoshida H, Goto E, Sato T, Ohki T, Masuzaki R, Tateishi R, Goto T, Shiina S, Kawabe T and Omata M. Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma. *Hepatol Int* 2008; 2: 89-94.
- [33] Sohn W, Kang TW, Choi SK, Jung SH, Lee MW, Lim HK, Cho JY, Shim SG, Sinn DH, Gwak GY, Choi MS, Lee JH, Koh KC, Paik SW, Rhim H and Paik YH. Effect of oral antiviral treatment on

- long-term outcomes of radiofrequency ablation therapy for hepatitis B virus-related hepatocellular carcinoma. *Oncotarget* 2016; 7: 47794-47807.
- [34] Kanwal F, Gralnek IM, Martin P, Dulai GS, Farid M and Spiegel BM. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. *Ann Intern Med* 2005; 142: 821-831.
- [35] Tsai MC, Yu HC, Hung CH, Lee CM, Chiu KW, Lin MT, Tseng PL, Chang KC, Yen YH, Chen CH and Hu TH. Comparing the efficacy and clinical outcome of telbivudine and entecavir naive patients with hepatitis B virus-related compensated cirrhosis. *J Gastroenterol Hepatol* 2014; 29: 568-575.
- [36] Lampertico P, Invernizzi F, Viganò M, Loglio A, Mangia G, Facchetti F, Primignani M, Jovani M, Iavarone M, Fraquelli M, Casazza G, de Franchis R and Colombo M. The long-term benefits of nucleos(t)ide analogs in compensated HBV cirrhotic patients with no or small esophageal varices: a 12-year prospective cohort study. *J Hepatol* 2015; 63: 1118-1125.
- [37] Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS and Suh DJ. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010; 52: 176-182.
- [38] Das K, Das K, Datta S, Pal S, Hembram JR, Dhali GK, Santra A and Chowdhury A. Course of disease and survival after onset of decompensation in hepatitis B virus-related cirrhosis. *Liver Int* 2010; 30: 1033-1042.
- [39] Lai Y, Li K, Li J and Liu SX. Cost-effectiveness of navigated radiofrequency ablation for hepatocellular carcinoma in China. *Int J Technol Assess Health Care* 2014; 30: 400-408.
- [40] Zhang C, Ke W, Liu L, Gao Y, Yao Z, Ye X, Zhou S and Yang Y. Cost-effectiveness comparison of lamivudine plus adefovir combination treatment and nucleos(t)ide analog monotherapies in Chinese chronic hepatitis B patients. *Drug Des Devel Ther* 2016; 10: 897-910.
- [41] Hu M and Chen W. Assessment of total economic burden of chronic hepatitis B (CHB)-related diseases in Beijing and Guangzhou, China. *Value Health* 2009; 12 Suppl 3: S89-92.
- [42] Naugler WE and Sonnenberg A. Survival and cost-effectiveness analysis of competing strategies in the management of small hepatocellular carcinoma. *Liver Transpl* 2010; 16: 1186-1194.
- [43] Lee TA, Veenstra DL, Iloeje UH and Sullivan SD. Cost of chronic hepatitis B infection in the united states. *J Clin Gastroenterol* 2004; 38: S144-147.
- [44] Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG and Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997; 127: 855-865.
- [45] Lang K, Danchenko N, Gondek K, Shah S and Thompson D. The burden of illness associated with hepatocellular carcinoma in the united states. *J Hepatol* 2009; 50: 89-99.
- [46] Chang TT, Gish RG, de Man R, Gadano A, Solitano J, Chao YC, Lok AS, Han KH, Goodman Z, Zhu J, Cross A, DeHertogh D, Wilber R, Colonna R, Apelian D; BEHoLD A1463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; 354: 1001-1010.
- [47] Levy AR, Kowdley KV, Iloeje U, Tafesse E, Mukherjee J, Gish R, Bzowej N and Briggs AH. The impact of chronic hepatitis B on quality of life: a multinational study of utilities from infected and uninfected persons. *Value Health* 2008; 11: 527-538.
- [48] Lam ET, Lam CL, Lai CL, Yuen MF, Fong DY and So TM. Health-related quality of life of southern Chinese with chronic hepatitis B infection. *Health Qual Life Outcomes* 2009; 7: 52.
- [49] Lim KC, Wang VW, Siddiqui FJ, Shi L, Chan ES, Oh HC, Tan SB and Chow PK. Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria. *Hepatology* 2015; 61: 227-237.
- [50] Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res* 2008; 8: 165-178.
- [51] Murray CJ, Evans DB, Acharya A and Baltussen RM. Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ* 2000; 9: 235-251.
- [52] Kim CH, Um SH, Seo YS, Jung JY, Kim JD, Yim HJ, Keum B, Kim YS, Jeon YT, Lee HS, Chun HJ, Kim CD and Ryu HS. Prognosis of hepatitis B-related liver cirrhosis in the era of oral nucleos(t)ide analog antiviral agents. *J Gastroenterol Hepatol* 2012; 27: 1589-1595.
- [53] Xu Y, Zhang YG, Wang X, Qi WQ, Qin SY, Liu ZH, Jiao J and Wang JB. Long-term antiviral efficacy of entecavir and liver histology improvement in Chinese patients with hepatitis B virus-related cirrhosis. *World J Gastroenterol* 2015; 21: 7869-7876.
- [54] Hou JL, Xu D, Shi G, Wan M, Goodman Z, Tan D, Xie Q, Chen C, Wei L, Niu J, Wang Q, Ren H, Wang Y, Jia J, Bao W, Dong Y, Trylesinski A and Naoumov NV. Long-term telbivudine treatment results in resolution of liver inflammation and fibrosis in patients with chronic hepatitis B. *Adv Ther* 2015; 32: 727-741.
- [55] Lun-Gen L. Antiviral therapy of liver cirrhosis related to hepatitis B virus infection. *J Clin Transl Hepatol* 2014; 2: 197-201.

RFA plus NA for HBV-related HCC

Table S1. References used to derive cirrhosis annual decompensation probabilities

Reference	Author/Publication year	Center	Sample size	Decompensation rate at corresponding years (%)	Annual rate (%) ^ψ
RFA					
24	Fleming KM, 2010	UK	3123	-	11.8 [#]
25	Fattovich G, 1997	Italy	355	18 (5 years)	3.9
26	Hu KQ, 1999	USA	112	22.2 (5 years)	5.0
RFA+NA					
34	Kanwal F, 2005	USA	-	-	7.3 ^{&.#}
35	Tsai MC, 2014	Taiwan	176	6.25 (2 years)	3.18
36	Lampertico P, 2015	Italy	414	83 (12 years)	13.73

#, Selected as base value for its largest sample size. Ψ , Calculated from decompensation rate at corresponding years (time) using the following formula: $1-(1-r)^{1/\text{time}}$, r refers to probability extracted from literatures and time refers to corresponding time horizon. &, Systematic review results.

Table S2. References used to derive annual mortality rate of compensated cirrhosis

Reference	Author/publication year	Center	Sample size	Mortality rate of compensation cirrhosis at corresponding years (%)	Annual rate (%) ^ψ
RFA					
27	D'Amico G, 1986	Italy	1155	-	9.76 [#]
28	De Jongh FE, 1992	Netherlands	98	15 (5 years)	3.2
29	Benvegnù L, 2004	Italy	312	14.4 (5 years)	3.06
RFA+NA					
34	Kanwal F, 2005	USA	-	-	4.9 ^{&.#}
35	Tsai MC, 2014	Taiwan	176	18.8 (4 years)	5.07

#, Selected as base value for its largest sample size. Ψ , Calculated from decompensation rate at corresponding years (time) using the following formula: $1-(1-r)^{1/\text{time}}$, r refers to probability extracted from literatures and time refers to corresponding time horizon. &, Systematic review results.

Table S3. References used to derive annual mortality rate of decompensated cirrhosis

Reference	Author/Publication year	Center	Sample size	Mortality rate of decompensation cirrhosis at corresponding years (%)	Annual rate (%) ^ψ
RFA					
27	D'Amico G, 1986	Italy	1155	-	22.9
28	De Jongh FE, 1992	Netherlands	98	85 (5 years)	31.57
30	Fattovich G, 1995	Italy	349	35 (5 years)	18.94 [#]
RFA+NA					
34	Kanwal F, 2005	USA	-	-	19 ^{&.#}
37	Shim JH, 2010	Korea	70	-	8.6
38	Das K, 2010	India	253	80 (5 years)	27.52

#, Selected as base value for its largest sample size. Ψ , Calculated from decompensation rate at corresponding years (time) using the following formula: $1-(1-r)^{1/\text{time}}$, r refers to probability extracted from literatures and time refers to corresponding time horizon. &, Systematic review results.

RFA plus NA for HBV-related HCC

Table S4. References used to derive recurrence rate after RFA

Reference	Author/Publication year	Center	Sample size	Recurrent risk after RFA at corresponding years (%)	Annual rate (%) ^ψ
RFA					
31	Kuzuya T, 2006	Japan	49	39.2 (2 years)	22.03
11	Lee TY, 2015	Taiwan	399	54.3 (2 years)	32.4 [#]
33	Sohn W, 2016	Korea	228	85.3 (5 years)	31.8
RFA+NA					
31	Kuzuya, 2006	Japan	49	35.1 (2 years)	19.44
11	Lee TY, 2015	Taiwan	399	41.8 (2 years)	23.71 [#]
33	Sohn W, 2016	Korea	228	56.2 (5 years)	15.2

#, Selected as base value for its largest sample size. ^ψ, Calculated from median survival using the DEALE method as described above.

Table S5. References used to derive annual mortality rate of recurrent HCC

Reference	Author/Publication year	Center	Sample size	Mortality rate of recurrent HCC at corresponding years (%)	Annual rate (%) ^ψ
RFA					
11	Lee TY, 2015	Taiwan	399	25 (2 years)	13.4 [#]
32	Yoshida H, 2008	Japan	104	97 (5 years)	50.41
33	Sohn W, 2016	Korea	228	85.3 (5 years)	34.8
RFA+NA					
11	Lee TY, 2015	Taiwan	399	19.6 (2 years)	10.33 [#]
32	Yoshida H, 2008	Japan	104	62 (5 years)	17.59
33	Sohn W, 2016	Korea	228	85.3 (5 years)	15.2

#, Selected as base value for its largest sample size. ^ψ, Calculated from median survival using the DEALE method as described above.