# A Cost-Effectiveness Analysis of Magnetic Resonance Imaging Contrast Agent for Early Diagnosis of Hepatocellular Carcinoma Based on Decision Tree + Partitioned Survival Model

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## Abstract

**Objective** To evaluate the cost-effectiveness of gadopentetate dimeglumine (Gd-DTPA) and gadobenate dimeglumine (Gd-BOPTA) magnetic resonance imaging (MRI) contrast agents for the early diagnosis of hepatocellular carcinoma (HCC) from the perspective of China's healthcare system. **Methods** A decision tree + partitioned survival model was constructed for early diagnosis of HCC based on literature data. Taking quality-adjusted life year (QALY) as the main health outcome measure for incremental cost-effectiveness ratio (ICER) analysis, the sensitivity analysis by Monte Carlo simulation was constructed to generate corresponding tornado diagram, incremental cost-effectiveness scatter plot, and cost-effectiveness acceptability curve. **Results and Conclusion** The basic analysis results showed that the ICER value of Gd-BOPTA diagnostic scheme compared with Gd-DTPA diagnostic scheme was 17 302.46 yuan/QALY, which is less than 1 times of China's gross domestic product (GDP) per capita. The sensitivity analysis results showed that the cost of delayed treatment and timely treatment had a significant impact on the results. When the willingness to pay (WTP) was 1 time of GDP per capita, the probability of cost-effectiveness advantage of Gd-BOPTA diagnostic scheme was 65.30%. When the WTP value is set at 1 times of GDP per capita, Gd-BOPTA MRI has cost-effectiveness advantages for the early diagnosis of HCC.

**Keywords:** early HCC; Gd-DTPA; Gd-BOPTA; cost-effectiveness analysis; sensitivity analysis

Primary liver cancer ranks fourth in morbidity and second in mortality of cancer in China. The latest data released by the National Cancer Center shows that the 5-year relative survival rate of malignant tumors is 40.5% [1], however, the corresponding value of primary liver cancer is only 14.1% [2]. A major factor for the poor survival rate of primary liver cancer is the delayed detection and low incidence of early diagnosis among patients. Research have shown that patients in the early stages exhibit significantly higher survival rate compared to those in mid to late stages [3]. According to China liver cancer staging (CNLC), early detection of primary liver cancer can result in a 5-year survival rate as high as 77.2% and 62.5% for stage Ia and Ib respectively after treatment, while the

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5-year survival rate for stage IIIa or IIIb is only 23.8% even with the opportunity of surgery and systems therapy [4]. Therefore, the promotion of early detection, accurate diagnosis and timely treatment of primary liver cancer is crucial to improving patient survival rate. Hepatocellular carcinoma (HCC) is the most predominant type of primary liver cancer, accounting for about 75%−85% of total liver cancer case [5]. HCC has been extensively researched by scholars due to its high proportion of primary liver cancer and clearly defined treatment pathway. Target population will be the patient of HCC in this paper.

Regular screening of high-risk patients can effectively improve the early detection rate of HCC. China started to focus on screening for cancer after 2005 and gradually incorporated it into major national health services [6]. "Health China 2030 Plan" released in 2016 pointed out that "it is necessary to carry out early diagnosis and treatment of priority cancer in high-incidence areas and promote opportunistic screening for chronic diseases such as cancer, stroke and coronary heart disease". To improve the detection rate of early HCC, in addition to screening potential patients with HCC, accurate diagnosis and timely treatment of patients with abnormal screening is also crucial. Correctly detecting whether a malignant lesion has occurred can help patients to intervene early and improve their survival rate. The diagnostic instruments recommended in the "Guidelines for the Treatment of Primary Liver Cancer (2022)" (hereinafter referred to as "Guidelines") are mainly computed tomography (CT) and magnetic resonance imaging (MRI). MRI outperforms CT in diagnostic performance of early HCC. Gd-DTPA and Gd-BOPTA are recommended MRI contrast agents in the "Guidelines". Contrast agent is chemicals injected (or administered) into human tissue or organs to enhance image observation. It is one of the most commonly used drugs in radiology. The injection of contrast agent can increase the contrast and enhance the lesion appearance of patients, which will help clinicians better determine the abnormal morphological structure of human tissues and organs. So, contrast is usually injected before MRI examinations of suspected patients. Based on this, a cost-effectiveness study was conducted on the MRI contrast agents Gd-DTPA and Gd-BOPTA which are recommended in the "Guidelines" to provide reference for the selection of contrast agents when MRI diagnosis of early HCC and the rational allocation of medical resources.

## 1 Materials and methods

### *1.1 Target population and diagnostic schemes*

Considering that both Gd-DTPA and Gd-BOPTA MRI-enhanced imaging having an advantage in the diagnosis of small HCC, the study population was set to patients with early HCC [7, 8]. Both the Barcelona clinic liver cancer (BCLC) and CNLC recommend hepatectomy as the primary treatment for patients with early HCC [9, 10]. Therefore, patients with clear early HCC are treated using hepatectomy after MRI examination. In summary, the target population in this study is patients with early HCC and subsequent hepatectomy. Two schemes for the diagnosis of early HCC using Gd-DTPA and Gd-BOPTA MRI contrast agents are set up.

### *1.2 Decision tree + partitioned survival model architecture*

The model for this study is a combination of two models. Firstly, it is the decision tree model, which has two decision nodes, i.e., two diagnostic schemes. Both diagnostic schemes are followed by two branching nodes of timely treatment for detection and delayed treatment for undiscovered. After the detected branch nodes, a partitioned survival model simulation for timely treatment is performed. After the undetected branch nodes, a partitioned survival model simulation for delayed treatment is performed. Both timely treatment and delayed treatment partitioned survival models are set up with three states: Relapse, relapse

free, and death. Patients who entered the partitioned survival model from the decision tree model are all post-treatment patients with an initial status of disease relapse free in the partitioned survival model. The specific architecture of the decision tree + partitioned survival model is shown in Fig. 1. According to the average onset age of HCC in China, the entry age of patients in the partitioned survival model is 52 years [11], the model cycle is 1 month, and the simulation duration is 10 years, for a total of 120 cycles.

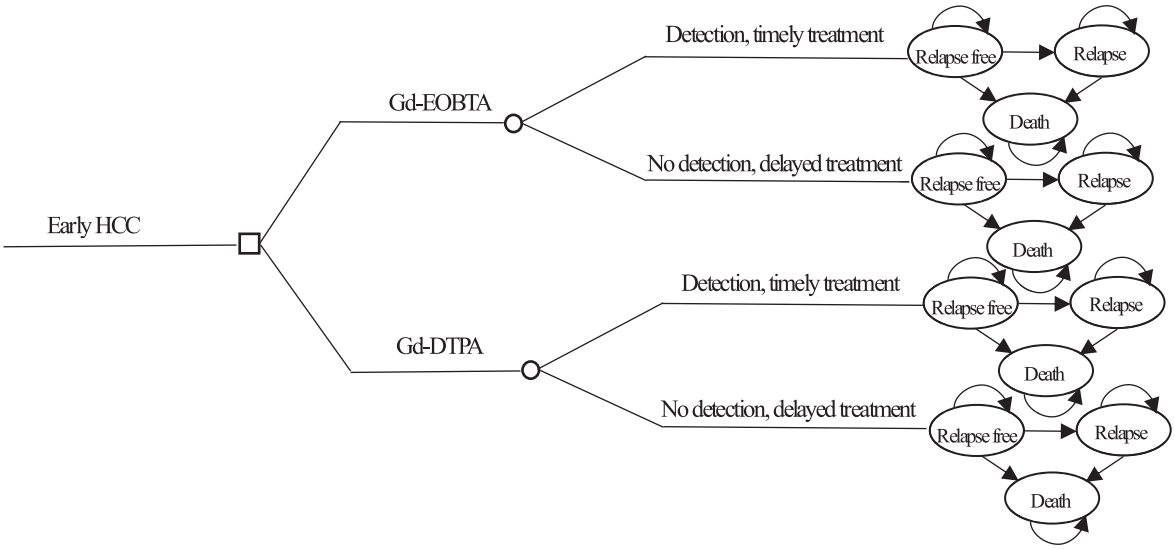


**Fig. 1 Decision tree + partitioned survival mode**

### *1.3 Key assumptions*

Based on the model including diagnosis and treatment, the following assumptions are made: (1) All study subjects entered the partitioned survival model with a disease relapse free state after receiving treatment; (2) When study subjects enter the partitioned survival model with delay treatment, the delay time is negligible, but the effect of delay treatment will be reflected in conversion parameter; (3) According to the average onset age of HCC in China, the patient's entry age is 52 years and the simulated duration is 10 years.

### *1.4 Related parameters*

#### *1.4.1 Conversion parameter*

Sensitivity is the ability of a test to correctly identify those with the disease (true positive rate), which can also be interpreted as the probability of not missing a diagnosis of a disease. In the decision tree model of this study, the probability value of detecting a patient is the sensitivity, and the probability value of not detecting a patient is (1 − sensitivity) × 100%. Sensitivity of Gd-DTPA and Gd-BOPTA are obtained from some papers [12-19] , and the results are shown in Table 1. A weighted average was performed to yield a sensitivity of 92.1% and 87.9% for Gd-DTPA and Gd-BOPTA, respectively.

**Table 1 Gd-DTPA and Gd-BOPTA sensitivity source article statistics**

| References | Contrast agent | Object | Number | Tumor size | Sensitivity (%) |
|---|---|---|---|---|---|
| Besa C, et al. [12] | Gd-DTPA | Patients at risk for HCC from Mount Sinai Hospital, New York, USA, from November 2010 to November 2012 | 12 | Average 2.60 cm, range from 1.00−5.00 cm | Observer 1: 85.70 Observer 2: 78.50 |
| Simon G, et al. [13] | Gd-DTPA | Patients at risk for HCC from a hospital in Germany between June 1999 and November 2002 | 25 | 11 were larger than 5.00 cm, 46 were larger than 1.50 cm, and 29 were smaller than 1.50 cm | 94.20 |
| Youk JH, et al. [14] | Gd-DTPA | Patients at risk of HCC from a hospital in Korea between October 2000 and July 2002 | 46 | (2.20 ± 1.80) cm | 87.50 |
| Becker-Weidman DJ, et al. [15] | Gd-BOPTA | The University of Arizona College of Medicine treated patients who received liver transplants and pre-transplant abdominal magnetic resonance imaging within 90 days between January 2008 and April 2010 | 101 | Average 2.00 cm, range from 0.50−5.00cm | 97.10 |
| Kim YK, et al. [16] | Gd-BOPTA | A suspected hepatocellular carcinoma patient at the National University Hospital of Jeonju University, South Korea, from October 2003 to March 2004 | 31 | Average 1.80 cm, range from 0.60−6.60 cm | 93.70 |
| Park Y, et al. [17] | Gd-BOPTA | Patients with HCC at Shinkyunkwan University College Samsung Medical Center between January 2007 and January 2008 | 18 | 0.50−10.00 cm | 83.30 |
| Choi SH, et al. [18] | Gd-BOPTA | The Seoul National University School of Medicine suspected HCC patients from October 2003 to July 2005 | 47 | Average 2.20 cm, range from 0.30−6.50 cm | 87.00 |
| Ji SW, et al. [19] | Gd-BOPTA | Suspected HCC patients admitted to the Fourth Affiliated Hospital of Anhui Medical University from January 2016 to November 2020 | 58 | (5.12 ± 2.46) cm | 89.19 |

In this study, relapse free survival (RFS) and overall survival (OS) curves for timely and delayed treatment of early HCC though literature review were obtained [20]. And then, GetData software was used to capture the proportion of patients with relapse free and survival of disease at different time points and cleaning the data. Finally, the individual data which fitted with six distributions include Exponential, Weibull, Log-logistic, Log-normal, Gompertz and Generalized Gamma in R was reconstructed. The optimal distribution was selected by the results of the Akaike information criterion (AIC) and Bayesian information criterion (BIC) value, the results are shown in Table 2. The optimal distribution was confirmed through comparing the AIC and BIC values of each survival curve which has been fitted. Among them, Exponential distribution was selected for delayed treatment RFS survival curve, timely treatment OS survival curve and delayed treatment OS survival curve, and Log-normal distribution was selected for timely treatment RFS survival curve.

**Table 2 Summary of six distribution fitting results of Kaplane-Meier curve**

| Distribution | Exponential | | Weibull | | Log-logistic | | Log-normal | | Gompertz | | Generalized Gamma | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC |
| Timely treatment-RFS | 180.4 | 182.3 | 179.5 | 183.3 | 178.2 | 182.0 | 177.9 | 181.7 | 181.7 | 185.5 | 179.8 | 185.6 |
| Delayed treatment-RFS | 170.9 | 172.8 | 169.4 | 173.2 | 169.9 | 173.8 | 170.2 | 174.0 | 170.1 | 173.9 | 171.4 | 177.1 |
| Timely treatment-OS | 59.7 | 61.6 | 58.9 | 62.7 | 58.7 | 62.5 | 58.1 | 62.0 | 60.2 | 64.0 | 59.5 | 65.2 |
| Delayed treatment-OS | 94.0 | 96.0 | 94.5 | 98.4 | 94.1 | 98.0 | 93.2 | 97.0 | 95.7 | 99.6 | 93.3 | 99.0 |

*1.4.2 Cost*

The study takes a Chinese health system perspective and considers only all direct medical costs within the health system based on recommend of "China Guidelines for Pharmacoeconomic Evaluations" (hereinafter referred to as "Guidelines for Evaluation") [21]. In the decision tree model section, the main costs included the cost of each diagnostic schemes, timely treatment, delayed treatment, and treating postoperative complications. In the partitioned survival model section, the main costs included regular follow-up costs for relapsed free patients, treatment costs for relapsed patients, and regular follow-up costs for relapsed patients. The values of each cost are shown in Table 3.

*1.4.3 Utility value*

The utility values involved in this study included the utility values for the relapse free and relapse state. Data were obtained from the utility values of relapse and relapse free in patients after hepatectomy in the cost-utility study of hepatectomy, radiofrequency ablation and liver transplantation for small HCC conducted by Jiao Xueli, et al. [22]. The final utility value for disease relapse free after hepatectomy was 0.70, and the utility value for disease relapse was 0.50.

*1.4.4 Discount rate*

The "China Guidelines for Pharmacoeconomic Evaluation: A Manual" (hereinafter referred to as "A Manual") [23] regulates that when the study timeframe exceeds 1 year, costs and health outputs may be incurred in the future should be discounted. The discounting formula specified in the "A Manual" is: As an example with cost, assuming that both the base period and actual costs occur at the end of the year, the cost $Cn$ in year $n$, discounted at a discount rate $r$ to the present value of money $Cc$ in the current year, is calculated as follows (see Equation 1). Based on the requirements of "A Manual", a discount rate of 5% per year is recommended for discounting. The cost and effectiveness discount rate for this study is 5%.

$$Cc = \frac{Cn}{(1+r)^{(n-1)}} \quad (1)$$

*1.4.5 Other parameters*

Patients with early HCC are prone to postoperative complications after hepatectomy. According to Lim C, et al. [20] in a study of 100 stage 0−A BCLC patients undergoing first-time hepatectomy from January 2006 to June 2016, it was found that a 3-month delay in treatment significantly increased the probability of postoperative complications, with 36% and 16% for delayed and timely treatment, respectively.

***1.5 Cost-effectiveness analysis***

Using QALY as an effect indicator, the "A Manual" recommends 1−3 times GDP per capita as the WTP value. Based on this, the study sets the WTP

value as 1 time of GDP per capita. According to the "2022 National Economic and Social Development Statistical Bulletin", China's GDP per capita in 2022 was 85 698 yuan. The relevant data were entered into the model which already constructed in Excel 2021, and then cost-effectiveness analysis and half-cycle correct of partition survival model were carried out. The ICER is used as an evaluation indicator and compared with the WTP value to determine the economy of diagnostic scheme.

### *1.6 Sensitivity analysis*

In this study, we mainly set up one-way sensitivity analysis and probabilistic sensitivity analysis (PSA), and the variation of each parameter is shown in Table 3. The upper and lower limits of contrast sensitivity are derived from the sensitivity data sorted above, and the range of variation of the discount rate is the recommendation in the "A Manual". The incidence of complications was subjectively set to vary by ± 10% because of lacking reference basis. The upper and lower limits of the other parameters were obtained from the relevant papers. As recommended in "A Manual", Beta distributions were performed for each contrast agent sensitivity, complication rate, discount rate, and utility value, and then, Gamma distributions were performed for cost.

**Table 3 Related parameter values**

| Parameter | Baseline value | Range | | Distribution | References |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| Sensitivity of Gd-DTPA (%) | 87.90 | 78.50 | 94.20 | Beta | [12−14] |
| Sensitivity of Gd-BOPTA (%) | 92.05 | 83.30 | 97.10 | Beta | [15−19] |
| Incidence of Clavien-Dindo complications after timely treatment (%) | 16.00 | 14.40 | 17.60 | Beta | [20] |
| Incidence of Clavien-Dindo complications after delayed treatment (%) | 36.00 | 32.40 | 39.60 | Beta | [20] |
| Diagnostic cost of Gd-DTPA (yuan) | 990.62 | 968.55 | 1 052.87 | Gamma | [24], Yaozhi Data |
| Diagnostic cost of Gd-BOPTA (yuan) | 1 062.60 | 1 056.61 | 1 092.30 | Gamma | [24], Yaozhi Data |
| Cost of timely treatment (yuan) | 51 522.90 | 43 659.70 | 61 219.40 | Gamma | [25] |
| Cost of delayed treatment (yuan) | 53 670.10 | 45 171.10 | 62 159.80 | Gamma | [25] |
| Treatment cost after relapse (yuan) | 81 136.31 | 56 795.41 | 105 477.20 | Gamma | [26] |
| Follow-up cost for relapsed patients per year (yuan) | 12 000.00 | 8 400.00 | 15 600.00 | Gamma | [26] |
| Follow-up cost for relapsed free patients per year (yuan) | 3 750.00 | 2 625.00 | 4 875.00 | Gamma | [26] |
| Cost of postoperative complications treatment (yuan) | 8 066.00 | 3 174.00 | 1 3261.00 | Gamma | [27] |
| Utility value for the relapse free state | 0.773 | 0.656 | 0.886 | Beta | [28] |
| Utility value for the relapse state | 0.656 | 0.554 | 0.756 | Beta | [28] |
| The cost discount rate | 0.05 | 0.00 | 0.08 | Beta | [21] |
| The effectiveness discount rate | 0.05 | 0.00 | 0.08 | Beta | [21] |

## 2 Results

### *2.1 Results of basic analysis*

The basic results of the decision tree + partitioned survival model showed that the total 10-year cost value of Gd-DTPA for diagnosing patients with early HCC was 156 171.87 yuan, and QALY value was 5.261. The total 10-year cost value of Gd-BOPTA for diagnosing patients with early HCC was 156 506.09 yuan, and QALY value was 5.280. The ICER value was 17 302.46 yuan /QALY, which is less than 1 time of GDP per capita. The Gd-BOPTA diagnostic scheme was economical compared to the Gd-DTPA diagnostic scheme. The values of each diagnostic scheme cost and effectiveness are shown in Table 4.

**Table 4 Each diagnostic scheme cost and effectiveness value**

| Diagnostic scheme | Total coat (yuan) | Total effectiveness (QALYs) | ICER (yuan/QALY) |
|---|---|---|---|
| Gd-DTPA diagnostic scheme | 156 171.87 | 5.26 | — |
| Gd-BOPTA diagnostic scheme | 156 506.09 | 5.28 | 17 302.46 |

### *2.2 Results of sensitivity analysis*

#### *2.2.1 One-way sensitivity analysis*

The results of the one-way sensitivity analysis are shown in Fig. 2. The horizontal coordinate represents the ICER after upward or downward adjustment of the parameter, and the middle axis is the ICER of the base analysis. The factors that had a large effect on the outcome in terms of the amount of change from largest to smallest were the cost of timely treatment, the cost of delayed treatment, the cost discount rate, Gd-DTPA sensitivity, Gd-BOPTA sensitivity, the effectiveness discount rate, and the cost of treatment after relapse. After one-way sensitivity analysis of all parameters, the ICER was the largest at 38 135.15 yuan/QALY, less than 1 time of GDP per capita, when the cost of timely treatment was adjusted upward.

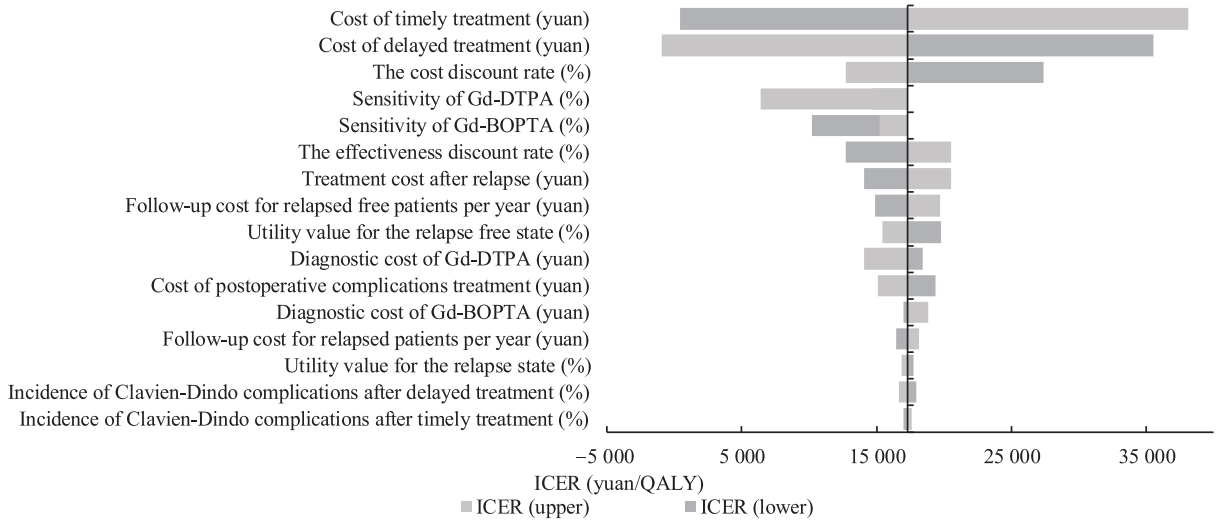


**Fig. 2 Tornado diagram of Gd-BOPTA diagnostic group versus Gd-DTPA diagnostic group**

The tornado diagram shows a decrease in ICER for both up and down of Gd-DTPA and Gd-BOPTA's sensitivity value, which is not empirical, so a the relevant data are analyzed. The results are shown in Table 5. From the results in the table, it can be concluded that when Gd-BOPTA was adjusted downward or Gd-DTPA was adjusted upward, the economic results of ICER value of the Gd-DTPA diagnosis scheme have been reversed compared with hat of the Gd-BOPTA diagnosis scheme.

**Table 5 The results of partial one-way sensitivity analysis**

| Parameter | Changing situation | Incremental cost *(yuan) | Incremental effectiveness * (QALYs) | ICER (yuan/QALY) |
|---|---|---|---|---|
| The sensitivity of Gd-DTPA | Raised to 94.20% | −63.88 | −0.01 | 6 383.13 |
| | Revised down to 78.50% | 928.19 | 0.06 | 14 717.33 |
| The sensitivity of Gd-BOPTA | Raised to 97.10% | 653.32 | 0.04 | 15 256.97 |
| | Revised down to 83.30% | −218.69 | −0.02 | 10 214.13 |

* Incremental cost = Cost of Gd-BOPTA diagnosis scheme − Cost of Gd-DTPA diagnosis scheme; Incremental effectiveness = Effectiveness of Gd-BOPTA diagnosis scheme − Effectiveness of Gd-DTPA diagnosis scheme.

*2.2.2 Probabilistic sensitivity analysis*

After setting up 1 000 Monte Carlo simulations and distributing all parameters except for the probability of transfer in the partitioned survival model, the incremental cost-effectiveness scatter plot and cost-effectiveness acceptability curve are shown in Fig. 3 and Fig. 4. The horizontal coordinate is the incremental effectiveness, and the vertical coordinate is the incremental cost in the incremental cost-effect scatter plot. The threshold is 1 time of GDP per capita. The horizontal coordinate is the WTP value, and the vertical coordinate is the probability of having an economic in the cost-effectiveness acceptability curve.

The scatter points in the incremental cost-effectiveness scatter plot are mainly distributed in the first and third quadrants, partly in fourth quadrant, and a small amount in second quadrant. ICER values were either positive or negative for the Gd-BOPTA diagnostic scheme compared to the Gd-DTPA diagnostic scheme. When the WTP was 1 time of GDP per capita, 65.30% of the points fell below the threshold line, which means when WTP was 1 time of GDP per capita, the Gd-BOPTA diagnostic scheme had an economic probability of 65.30% compared with the Gd-DTPA diagnostic scheme. Cost-effectiveness acceptability curve showed that when the WTP value is greater than 19 426.60 yuan/QALY, the probability of being economic is higher in the Gd-BOPTA diagnostic scheme than the Gd-DTPA diagnostic scheme. As the WTP value increases, the probability of being economic in the Gd-BOPTA diagnostic scheme increases to about 70.00% and then begins to level off.

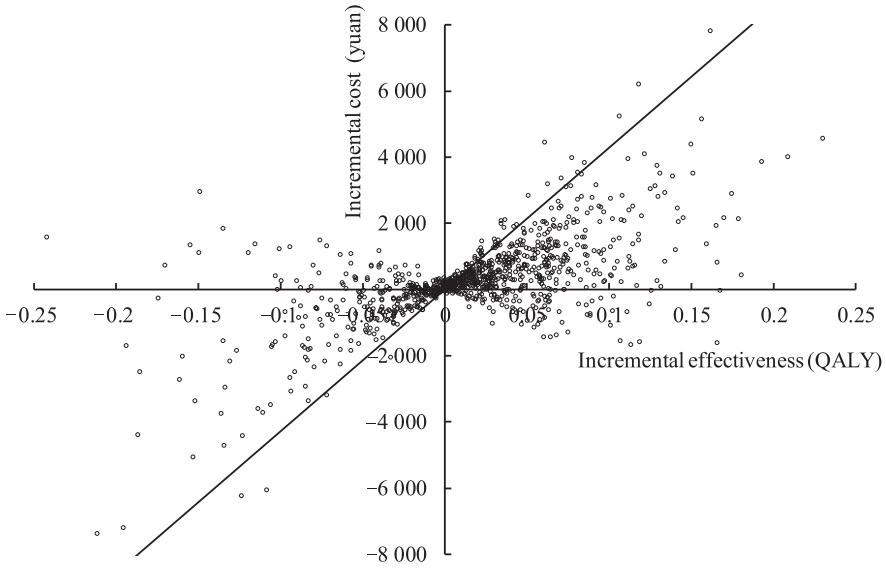


**Fig. 3 Incremental cost-effectiveness ratio scatter plot of Gd-DTPA diagnostic scheme versus Gd-BOPTA diagnostic scheme**

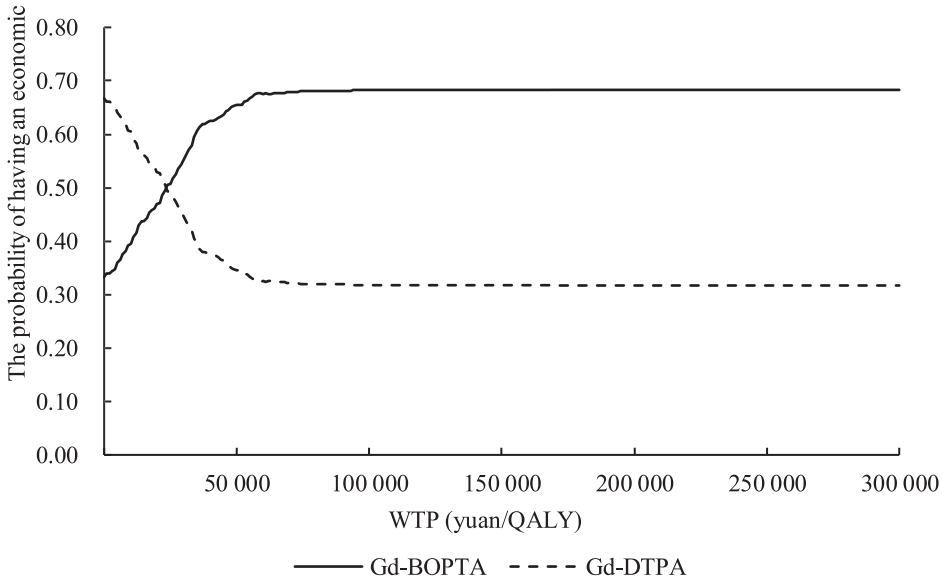


**Fig. 4 Cost-effectiveness acceptability curve of Gd-DTPA diagnostic scheme versus Gd-BOPTA diagnostic scheme**

## 3 Summary and discussion

The results of base analysis showed that the Gd-BOPTA diagnostic scheme had a cost-effectiveness advantage over the Gd-DTPA diagnostic scheme when using 1time of GDP per capita as WTP value. The results of the one-way sensitivity analysis showed that the cost of delayed treatment, timely treatment and contrast agents were the factors that affected more on the model results. The results of the probabilistic sensitivity analysis showed that the Gd-BOPTA diagnostic scheme had an economic advantage when WTP values were greater than 19 426.60 yuan/QALY, with a maximum probability of advantage of about 70%. The incremental cost-effectiveness scatter plot reveals that the scatter is more concentrated at the origin position, indicating that the variability between the study protocol and the control protocol is not significant across the schemes. Comparison with the results of the basic analysis in the previous section shows that the difference in cost and effectiveness values between the Gd-BOPTA diagnostic scheme and the Gd-DTPA diagnostic scheme is slight. The effectiveness difference value is even less than 0.10 QALYs and it is around 0.02 QALYs. Therefore, the model input parameters are likely to have a large impact on the results when small changes are made, making the analysis results unstable. This also explains the fact that the scatter points in the scatter plot are mostly concentrated at the origin and distributed in all quadrants.

The study based on published data presents an economical diagnosis of patients with early HCC in China on the use of different contrast agents. However, there are still shortcomings. First, although the sensitivity of each contrast agent is obtained by weighted averaging, model parameter uncertainty cannot be avoided because of differences in the target population. If the diagnostic performance of both contrast agents in the same target population can be studied, the corresponding results will be much more accurate when used in this model. Secondly, the survival curves for timely and delayed treatment in partitioned survival model for HCC are derived from a prospective study in France due to the lack of clinical trials of timely and delayed treatment of early HCC exclusively for Chinese. This may be somewhat different from the actual survival of the Chinese population. Finally, only patients with HCC who underwent hepatectomy for the first time were studied.

Although hepatectomy is the main treatment method for early HCC, there are still some patients who cannot undergo hepatectomy for objective reasons in clinical. Therefore, these patients could be considered for inclusion in the model in future studies.

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