

Cost-effectiveness analysis of transarterial chemoembolization combined with stereotactic body radiation therapy versus transarterial chemoembolization for inoperable hepatocellular carcinoma: A markov modelling study

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Research

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Abstract

Background

Transarterial chemoembolization (TACE) and Stereotactic body radiation therapy (SBRT) might both provide survival benefits for inoperable hepatocellular carcinoma (HCC). Adopting combined therapy as a solution carries major cost and resource implications. We aimed to estimate the cost-effectiveness of TACE plus SBRT and TACE alone in inoperable HCC.

Methods

A Markov model was constructed in a hypothetical cohort of patients aged 60 years with inoperable HCC and Child-Pugh A/B cirrhosis over a lifetime frame. Two strategies (TACE plus SBRT and TACE) were compared. Transition probabilities, utility and costs were extracted from published literature. Incremental cost-effectiveness ratios (ICER) were measured. Deterministic and probabilistic sensitivity analyses were conducted to assess the robustness of the findings.

Results

TACE plus SBRT and TACE respectively produced 12.26 and 9.67 quality-adjusted life years (QALYs). The ICER of TACE plus SBRT versus TACE was \$3,133/QALY. One-way sensitivity analysis revealed that the utility of TACE combined with SBRT progress survival, probability of death from progress survival in TACE, and the initial cost of TACE combined with SBRT were the most sensitive parameters. The Monte-Carlo simulation demonstrated that the probability of cost-effectiveness at a willingness to pay threshold of US\$ 29,440 per QALY was 95% and 5% for TACE plus SBRT and TACE.

Conclusions

This study indicated that TACE plus SBRT is cost-effective compared to TACE for inoperable HCC patients at a willingness to pay threshold as defined by WHO guidelines in China.

Background

Liver cancer is one of the most common cancers worldwide. It was estimated of 8 41,080 new liver cancer cases and nearly 781,631 deaths in 2018[1]. The highest incidence of liver cancer happens in Eastern Asia and South-eastern Asia, especially China, which accounts for over 50% of new cases and deaths worldwide[2]. Hepatocellular carcinoma (HCC) is comprising 75%-85% of case of liver cancer and is a severe public health problem.

Lots of clinical guidelines published including surveillance, diagnostic, treatment and follow-up for HCC[3–6]. Staging of liver cancer is crucial for proper treatment plan. There are a number of staging systems, such as the BCLC, TNM, JSH, APASL and CSCO. They include tumours size and number, general state of health, vessel invasion and metastases, and liver function as important factors.

Because most HCC patients are diagnosed late and not candidates for resection or transplantation, nonsurgical local and regional interventions are always used for treatment[7]. Transarterial Chemoembolization (TACE) has been playing an important role in the treatment who are not eligible for curative treatment[8], there were two randomized controlled trials (RCTs) and one meta-analysis demonstrated TACE has better survival benefits over best supportive care (BSC) for intermediate staged HCC[9–11]. Stereotactic body radiation therapy (SBRT) has been increasingly accepted as a treatment option for patients that unable surgery. By giving larger doses to tumour, SBRT provides excellent control rate while minimizing damage to adjacent liver and other normal tissue[12, 13]. Recently, several studies have reported better outcomes using TACE with SBRT for HCC than TACE only. 1-year, 2-year, and 3-year survival rates were apparently higher for TACE with SBRT[14–16]. However, SBRT is expensive and this combined therapy needs more health resources than TACE only, there still has no cost-effectiveness analysis been performed for that.

The aim of the present study was to perform a cost-effectiveness analysis comparing TACE with SBRT versus TACE only in patients of inoperable hepatocellular carcinoma. TACE and SBRT are well-established procedures used in China for the treatment of intermediate and advanced HCC. The unmet clinical needs for this patient group are substantial, and this study may help decision-makers in China regionally and nationally in due course.

Methods

Target Population and Interventions

The study focused on patients with inoperable HCC with conditions listed as follows: (i) histologically or clinically confirmed HCC; (ii) categorized as CSCO stage IIIa or IIIb (according to the China CSCO staging system); (iii) no main portal vein thrombosis or extrahepatic metastasis; (iv) Child-Pugh class A or B liver function; (v) aged at least 60 years old, and Eastern Cooperative Oncology Group (ECOG) performance status: 0–2.

Interventions are TACE followed by SBRT, which alongside the procedure includes a bundle of inpatient procedures including diagnostic tests. TACE was performed through the femoral artery under local anesthesia. A coaxial microcatheter was selectively inserted into the hepatic feeding artery of a segment or sub-segments containing the target tumour. Anticancer chemotherapies include 5-fluorouracil, hydroxycamptothecine, lipiodol, epirubicin, cisplatin, mitomycin et al. SBRT was conducted within 1 to 2 months after TACE. The total dosage was 40–60 Gy in 4–8 fractions individualized according to the normal tissue constraints.

Markov Model

A Markov model was constructed using Excel to evaluate the costs, health outcomes, and cost-effectiveness of TACE combined with SBRT versus SBRT in the treatment of inoperable HCC. In the base case analyses, the model simulated a hypothetical cohort of 10,000 patients. The time horizon of the

model was a lifetime. As the experts' opinion and referred to the published literature, we hypothesized three health states: progression-free survival (PFS), progression survival (PS) and death in the model (Fig. 1). A hypothetical cohort of patients with HCC starts the Markov process in the PFS state. Patients may stay in the PFS state or, may move to the PS state. Progressive patients may remain in the PS state or may die from the disease. They received either TACE combined with SBRT or SBRT initially. In the model, we did not include deaths from natural causes that occurred in any health state. Death from cancer was assumed to occur after disease progression. The model perspective was based on the healthcare in China, with a 1-month cycle length adjusted to half-cycle in each health state process. The willingness-to-pay (WTP) threshold was defined by the World Health Organization (WHO) as 3-times the per capita gross domestic product (GDP) [13, 14]. China per capita GDP in 2018 was US\$9780[15](<http://data.stats.gov.cn/easyquery.htm?cn=C01>); therefore, the WTP threshold was considered to be \$29440/QALY.

Base case data

The base case data (e.g. median survival rate, median OS, median TTP) were derived from the hypothesis patients with inoperable HCC based on some literature. When data can derive from more than one study, we chose the higher level evidence study. For the survival rate, we chose one meta-analysis as the parameter, there were only half-year, 1-year, 2-year and 3-year survival rate reported[17], we assumed that during these intervals and after the monthly survival rate stay the same. The median TTP was only reported in one relevant study[18], we chose the BCLC stage B according to the population criteria. We calculated the median time of progression to death using the median OS minus the median TTP from it. For the TACE group, the median TTP was derived from one meta-analysis using the max values of 6.7 months [19]. The transition probabilities of the health states were estimated using the equation published previously: $P(t) = 1 - \exp(-\mu t)$, $P(1 \text{ month}) = 1 - (0.5)^{(1/\text{median time to event})}$ [20–22](Table 1).

Table 1
Model Input Parameters, Distribution

Parameters	Base case value	α	β	Reference and/or Note
Transition probability (monthly, β distribution)				
Prob die PFS_tace + sbrt				[17],Time dependent
Prob die progress_tace + sbrt	0.04	3	68	[18]
Prob to progress_tace + sbrt	0.07	5	66	[18]
Prob die PFS_tace				[17],Time dependent
Prob die progress_tace	0.06	108	1746	[19]
Prob to progress_tace	0.10	182	1672	[19]
utility (β distribution)				
Utility pfs_ts	0.68	2072	957	[27–33]
Utility ps_ts	0.61	1854	1175	[27–33]
Utility pfs	0.76	2302	727	[27–33]
Utility ps	0.68	2060	969	[27–33]
Direct medical costs(γ distributed,adjusted to 2018 U.S. \$)				
Cost treatment tace + sbrt	8413	101	83	[23, 25]
Cost treatment tace	3473	17	202	[23]
Cost treatment month pfs_ts	801	5	170	[14, 16, 17, 25, 26]
Cost treatment month ps_ts	278	20	14	[14, 16, 17, 25, 26]
Cost treatment month pfs_ta	728	4	187	[24]
Cost treatment month ps_ta	253	17	15	[24]
Parameters	Base case value	α	β	Reference and/or Note
Transition probability (monthly, β distribution)				
Prob die progress_tace + sbrt	0.04	3	68	
Prob to progress_tace + sbrt	0.07	5	66	

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Cost treatment month ps_ta	253	17	15	

Health Care Resource Consumption and Costs

This study was based on the perspective of a healthcare system; therefore, only direct medical costs were included. The direct medical costs included treatments for HCC, cirrhosis and adverse events derived from associated drugs and procedures, inpatient and outpatient visits, laboratory testing and imaging examination. Monthly costs were estimated with the frequency and unit cost of drugs and procedures and all were converted to U.S. dollars in 2019. The costs data of TACE was derived from a previously published study, which extracted from the South China(<http://hcc.dedidata.cn/>). The median cost of one session of TACE was \$3347.97(2016)[23], monthly TACE PFS was calculated by a weighted mean of compensated cirrhosis and decompensated cirrhosis[24]. Monthly TACE progression survival was the same with progressive HCC in the data. The cost data of SBRT was derived from another study [25], we assume SBRT session cost is equivalent to other diseases. We set the TACE combined with SBRT cost as the sum of cost of SBRT and TACE, and as the initial onset cost before the Markov model. Some studies show there were Grade 3 or 4 toxicity and complications for TACE combined with SBRT [14, 16, 17, 26], including gastrointestinal reactions (nausea/vomiting), liver function damage and hematologic toxicity (leukopenia) et al. therefore, we assumed the cost of TACE plus SBRT was 10 percent higher than TACE

only. The cost was adjusted to 2019 dollars with CPI index in China. A discount rate was set at 3% yearly for costs (Table 1).

Quality-of-life Estimates

Health-related quality-of-life measures were not available and a literature search was conducted. The utility coefficients for patients with HCC were obtained from the Cost-Effectiveness Analysis Registry. Utility coefficients were retrieved and an average value was derived for each health state in the model[27–33]. For the toxicity and complications that are transient, we assumed that there was a lower utility for TACE plus SBRT with a multiplier 0.9. A summary of the retrieved utilities and related median values is presented in Appendix Table 1. A discount rate was set at 3% yearly for utilities (Table 1).

Cost-effectiveness Analyses

Indices including LYG and QALY and ICER were estimated. The ICER was calculated using the difference in costs divided by the difference in QALY. The relative cost-effectiveness among the two strategies were compared. After that, one-way sensitivity analysis was performed. The result was presented as a tornado diagram. We hypothesized that the parameters varied over a range of $\pm 30\%$ in relation to its base-case value. Furthermore, the probabilistic sensitivity analysis using a Monte Carlo simulation was conducted to assess the impact of the uncertainty around the key parameters of the model on the ICER. The probabilistic sensitivity analysis was based on 1,000 samples, and the results were presented as a cost-effectiveness acceptability curve. A gamma distribution was employed for cost estimates and a beta distribution for efficacy estimates. An external CE threshold, that is, the largest sum of money you are willing to pay for gaining one QALY was utilized to compare with ICER to decide whether one strategy is cost-effective. For China, we adopted the threshold of \$29440/QALY according to the WHO guidelines for CE analysis.

Results

Base case analysis

In the base case analyses. TACE plus SBRT and TACE accrued 12.26QALYS/\$17295 and 9.67QALYS/\$9173, respectively. The ICER of TACE plus SBRT over TACE was \$3133/QALY. Based on the WTP threshold of \$29,440/QALY, the TACE plus SBRT is cost-effective in this analysis (Table 2).

Table 2
Incremental Cost-Effectiveness Ratios comparing TACE + SBRT
versus TACE at the base case

Variables	TACE + SBRT	TACE
Costs(US\$)	17,295	9,173
Δ Cost(US\$)	8,121	-
QALYs	12.26	9.67
ΔQALYs	2.59	-
ICER(US\$)	3,133	
cost effectiveness threshold(US\$)	29,440	
is TACE + SBRT cost-effective	YES	

One-way sensitivity analysis

As shown in Fig. 2, the utility of TACE combined with SBRT progress survival, probability of death from progress survival in TACE, and the initial cost of TACE combined with SBRT lay in the top three sensitive parameters, reflecting that the utility and transition probability was a vital factor when considering the combined strategy. The ICER of TACE combined with SBRT over TACE was below \$29440/QALY during all the parameters. With the notable change for the utility of TACE combined with SBRT, the ICER is still lower than the ICER threshold (Fig. 2).

Monte Carlo analysis

Based on the probabilistic sensitivity analysis, a scatterplot (Fig. 3) and cost-effectiveness acceptability curve (CEAC) for the population (Fig. 4) showed that a nearly 95% probability of cost-effectiveness at an acceptable ICER of \$29440 (three times the GDP per capita of China in 2018), and that a nearly 84% probability of cost-effectiveness at an acceptable ICER of \$9813(one times the GDP per capita of China in 2018).

Discussion

TACE is the treatment of choice for inoperable tumours that are too large or multifocal for other percutaneous ablation techniques such as radiofrequency ablation (RFA). Some studies show TACE combined with sorafenib or apatinib get a longer TTP, OS and tumour-response rate[28, 34]. Recently, SBRT has emerged as a safe and effective solution for properly selected patients with HCC having excellent rates of local control rate[12], one review study demonstrated that SBRT is an adjunct to TACE and sorafenib, a substitute for RFA[35]. One meta-analysis showed TACE combined with SBRT was more effective than TACE alone[17]. However, due to China imbalanced financing in different area, the high

cost of SBRT used for treating patients of inoperable HCC have become one of the biggest issues, the decision-maker is probably willing to pay for the cost-effective solutions. To the best of our knowledge, this is the first study to compare the cost-effectiveness of TACE plus SBRT versus TACE. The result will provide evidence in determining a reasonable reimbursement decision and price.

In our study, TACE plus SBRT is cost-effective compared to TACE for inoperable based on the base case analysis, sensitivity analysis and WTP analysis. Previous CE studies have confined the comparison of TACE with sorafenib, TACE alone is a more cost-effective strategy from Chinese perspective. And SBRT with other solutions such as sorafenib, RFA, proton beam therapy[32, 36–39], SBRT is cost-effective comparing sorafenib and RFA in early and late-stage HCC, respectively. One other outcome research studies compared the SBRT plus TACE with SBRT[40], which also showed that the combination of TACE plus SBRT achieved higher objective response and local control rate. Our study chose a different comparator TACE, which is widely referenced in clinical guidelines and practiced. This study demonstrated that TACE plus SBRT is a wise choice for the patients at stage IIIa or IIIb and not suitable for surgery.

We tested the stability of the results with various sensitivity analyses, which showed that the results were robust. Several key parameters are impacted on the cost-effectiveness results. One is the utility of progression survival for TACE plus SBRT, it is well known for adverse events of SBRT including fatigue, damage to the liver, gastrointestinal tract, and biliary duct, cytopenia, dermatitis, and rib fractures. We found that there is a higher rate for TACE plus SBRT, therefore, we assumed the utility of patients in each state was lower. Another parameter is the probability of death from progress survival in TACE. When the reduction by 30% of TACE, the ICER is enhanced by 75%. Finally, the cost of TACE plus SBRT is also a parameter that affects the results. In China, different regions can decide their price of health service, so there is a lot of variances. Because SBRT is technology-based, the cost is basically the same according the price system. So we subtract the cost data from Chinese research and set the range for it.

Data constraints inevitably lead to several limitations within our model. First, there were no multi-centered RCT studies that specifically reported TACE plus SBRT outcomes for inoperable HCC. Such a limitation was unfortunately unavoidable in this analysis. This limitation obliged us to use the best available data in the literature review. The resulting uncertainties were not significant, which was confirmed by the unchanged results in the probabilistic sensitivity analysis. Second, the utility estimates were extracted from the CEA registry. This adoption may not be the most rational because utilities might vary between populations. The third limitation concerns the paucity of data on cost estimates for each health state. There were no cost data for TACE plus SBRT, so we collected it separately and combined it, this may be different from the real world. Moreover, we have considered the uncertainties of costs in sensitivity analyses by inputting a wide range of cost values (-30–30% of base-case value). Fourth, we assumed that the utility estimations such as PFS and progression survival were different between two groups and set a lower value for TACE plus SBRT, however, there might be the same or higher. Thus, more specific data are required to obtain more accurate results for it. Fifth, most of the included studies were retrospective and the analyses based on these retrospective data would inevitably result in selection bias.

Conclusion

In conclusion, patients with inoperable hepatocellular carcinoma with the patient's criteria in our study, TACE with SBRT is more cost-effective than TACE in China. Our findings will require further high-quality studies to validate.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analyzed during this study are included in published article as referenced

Competing interests: I declare that I have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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Authors' contributions: Vijay Gc, and Sheng Zhang made substantial contributions to the analysis and interpretation of data and was involved in revising the manuscript critically. Professor Chunlin Jin participated in revising it critically.

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Figures

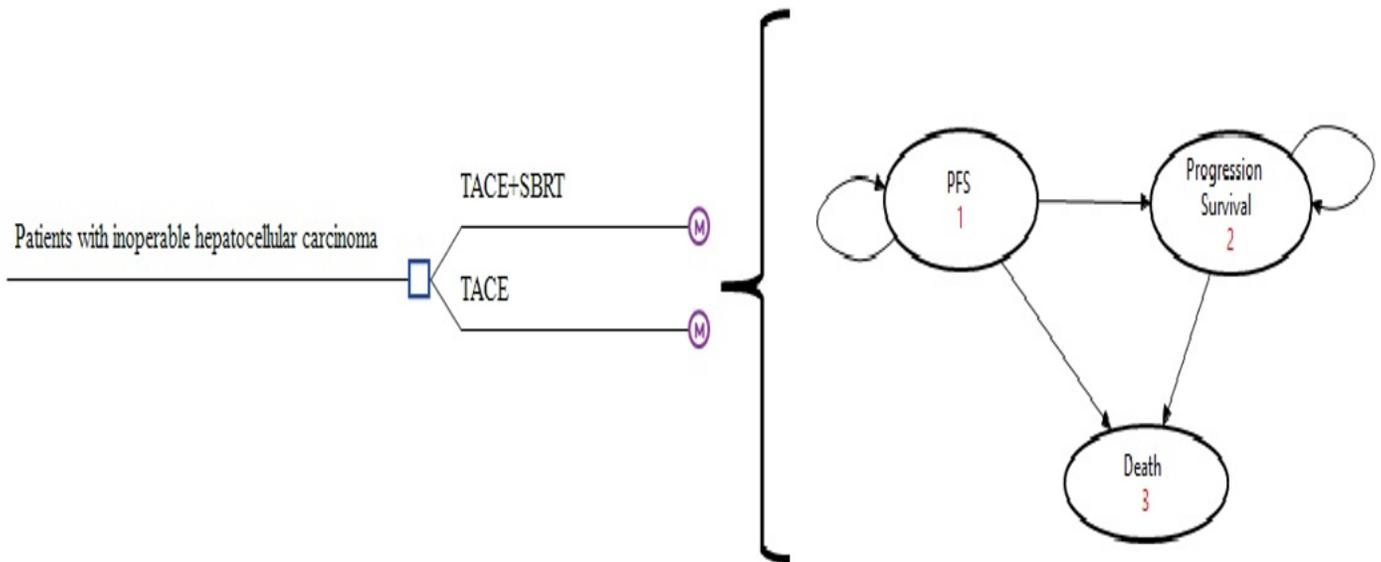


Figure 1

The decision-analytic, Markov model schema. Note: PFS, progression-free survival.

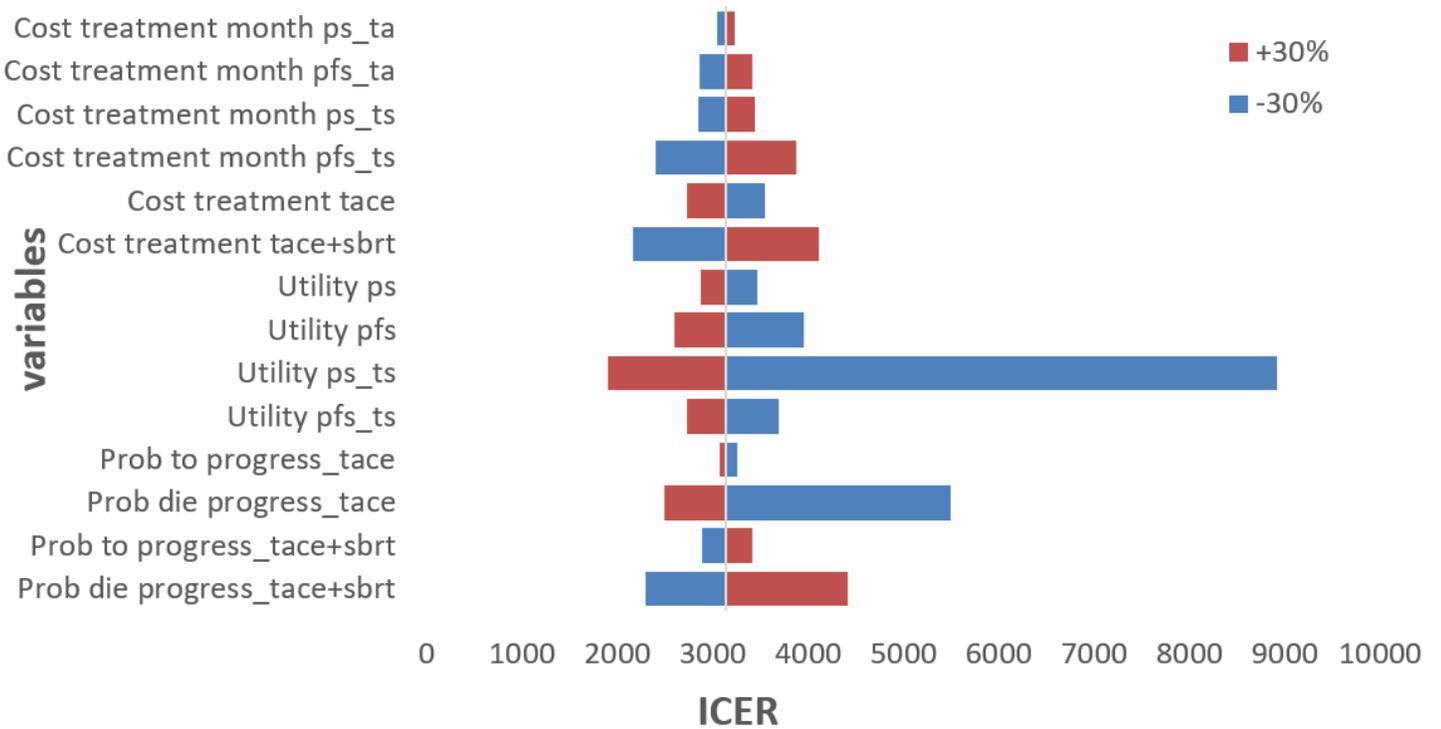


Figure 2

Tornado analysis (ICER) for TACE+SBRT vs TACE

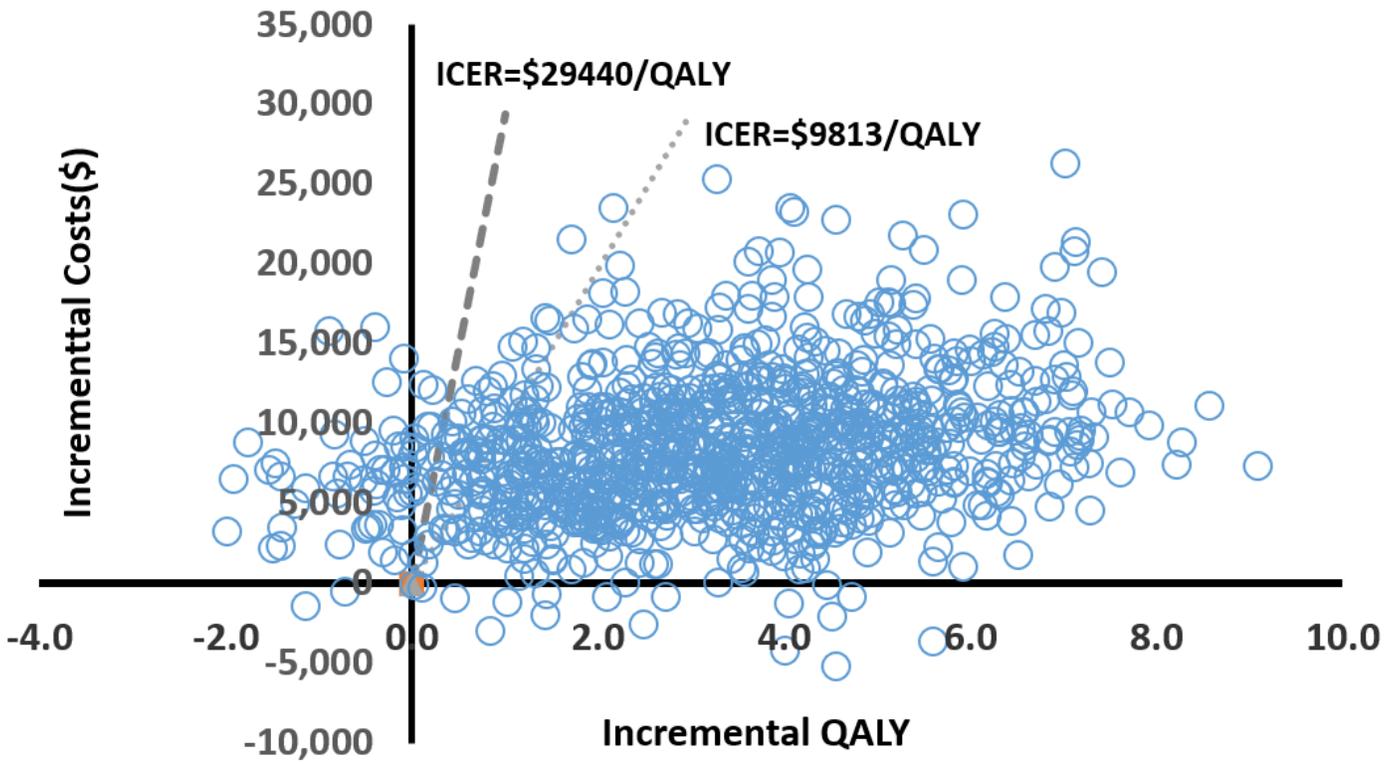


Figure 3

Incremental costs vs. incremental QALYS for TACE+SBRT vs TACE; QALY, quality-adjusted life years

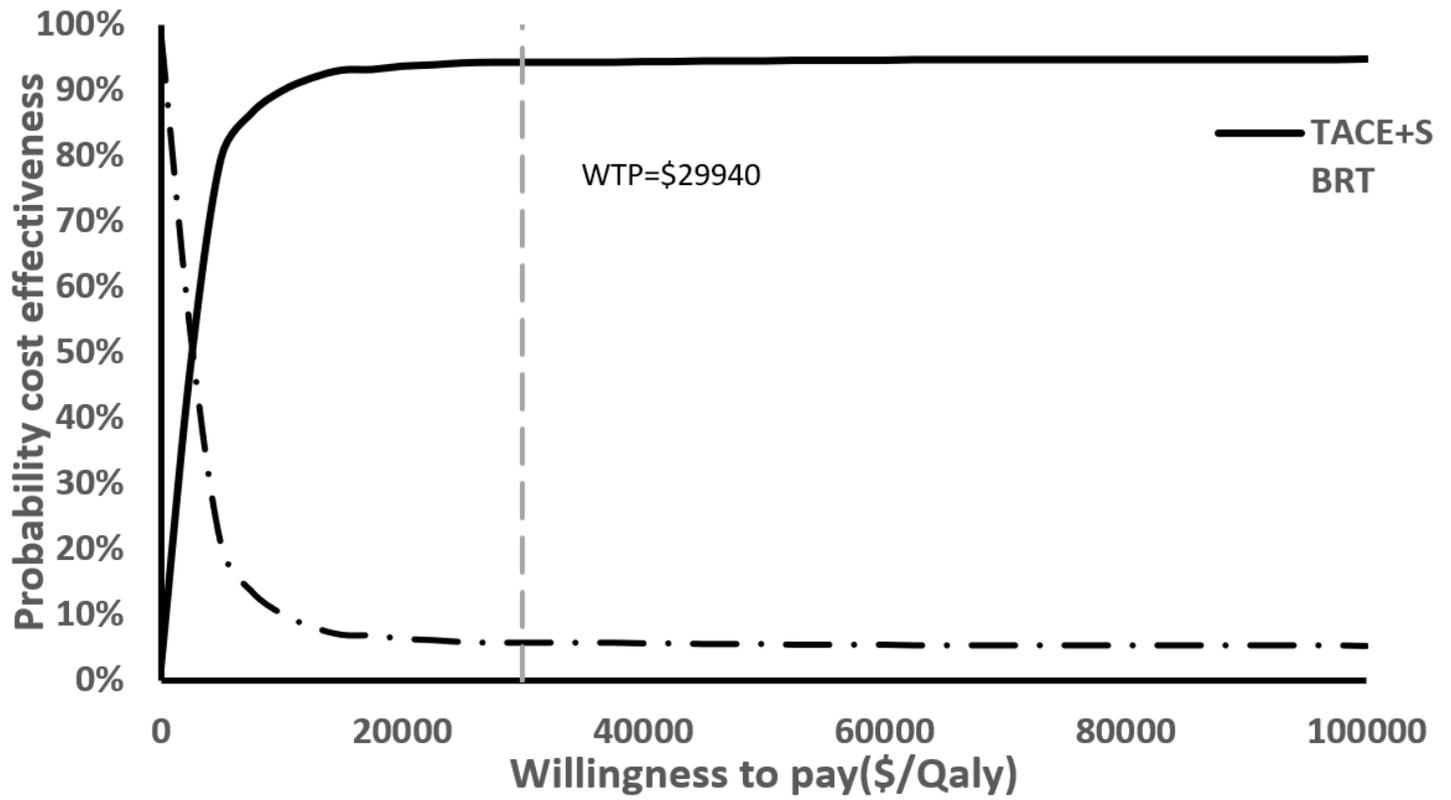


Figure 4

Cost-effectiveness acceptability curve (CEAC) of TACE+SBRT and TACE; CEAC represented the uncertainty in cost-effectiveness analysis and provided the reference to the WTP thresholds