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Cost-effectiveness analysis of stereotactic body radiotherapy versus transarterial chemoembolization for unresectable hepatocellular carcinoma: An economic evaluation from a payer's perspective

A thesis submitted in partial satisfaction of the requirements for the degree Master of Science in
Statistics

By

Alex David Steiner

2014

ABSTRACT OF THE THESIS

Cost-effectiveness analysis of stereotactic body radiotherapy versus transarterial chemoembolization for unresectable hepatocellular carcinoma: An economic evaluation from a payer's perspective

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Master of Science in Statistics
University of California, Los Angeles, 2014
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Hepatocellular carcinoma is the sixth most common cancer worldwide and the leading cause of death among patients with cirrhosis. The vast majority of these patients have the unresectable, intermediate-stage form of the disease, for which the standard of care is transarterial chemoembolization. With the health care sector rapidly outgrowing the national economy, maximizing value is now a major priority in health policy, especially with regard to cancer. Recent evidence suggests that stereotactic body radiotherapy may be a viable alternative to transarterial chemoembolization among patients of in early or very early stage of carcinoma. This evidence warrants a cost-effectiveness analysis, which not been conducted to date; the results of this study may directly impact practice guidelines for this disease. A Markov decision model was used to model the clinical trajectory of a typical patient with unresectable hepatocellular carcinoma. Costs were derived from a combination of previous studies and economic outcomes data. We hypothesized that stereotactic body radiotherapy achieves significantly greater cost-effectiveness than the current standard of care for hepatocellular carcinoma but we found the opposite may be in fact true and that transarterial chemoembolization may a more efficient management strategy for typical patients with unresectable hepatocellular carcinoma

The thesis of Alex David Steiner is approved.

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Cost-effectiveness analysis of stereotactic body radiotherapy versus transarterial chemoembolization for unresectable hepatocellular carcinoma: An economic evaluation from a payer's perspective

Introduction

The value problem in cancer care. With the health care sector rapidly outgrowing the national economy, maximizing value is now a major priority in health policy.¹ This entails either improving outcomes at the same cost or achieving comparable outcomes at a lower cost. The problem of value is especially pervasive in oncology,^{2,3} as cancer care accounts for over 10% of all health care expenditures, while cancer patients comprise less than 1% of the commercially insured.^{4,5} Although economic impact has not factored into medical decision-making in the US historically, there is growing societal pressure to investigate whether health services are not only clinically effective but also cost-effective.^{6,7} The objective of the proposed study is to improve value in the treatment of unresectable hepatocellular carcinoma (HCC) by evaluating the relative cost-effectiveness of transarterial chemoembolization (TACE), the current standard of care,⁸ and stereotactic body radiotherapy (SBRT). A number of recent studies suggest that SBRT may be a viable alternative to TACE among patients with unresectable HCC.^{9,10}

Background. HCC is the sixth most common cancer in the world, the third most common cause of cancer-related death,¹ and the leading cause of death among patients with cirrhosis.² Typically presenting between the third and fifth decades of life, HCC is almost three times as common among men than among women and disproportionately affects black men over white men. Both the incidence and mortality of HCC have risen significantly worldwide over the last thirty years,³ and in the United States (US), the race-based disparity in outcomes continues to widen. These

changes are attributed to the increased prevalence of cirrhosis, the most common cause of HCC. Worldwide, cirrhosis is predominantly due to chronic viral hepatitis C (HCV) and B (HBV) infections, especially in countries where viral hepatitis remains endemic. In the US, cirrhosis is most often the result of either alcoholic fatty liver disease (AFLD) secondary to chronic alcoholism or non-alcoholic steatohepatitis (NASH) secondary to obesity.⁴ Though HCC has typically presented with a poor prognosis, advances in diagnostic imaging techniques have allowed for greater surveillance and thus much earlier detection, which is thought to be critical for improving outcomes.⁵

Diagnosis and staging. The diagnosis of HCC is established by observation of both arterial hypervascularity and venous- or delayed-phase washout on either ultrasonography (USG), multidetector computed tomography (MDCT), or dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI).^{2,6,7} If necessary, the diagnosis can be confirmed via biopsy and expert pathology.^{8,9} As of 2011, the Barcelona Clinic Liver Cancer (BCLC)¹⁰ system has been the most widely accepted paradigm for staging HCC. This system was adopted over all others because it directly links staging to the most appropriate treatment modality,⁵ and the model has been externally validated.^{11,12} For very early-stage (Child-Pugh class 0) HCC, resection is the preferred treatment strategy, and for early-stage (Child-Pugh class A) disease, either orthotopic liver transplantation (OLT) or radiofrequency ablation (RFA) may be employed. All three of these treatments are curative, while any treatment for more advanced stages HCC, which are considered unresectable, is palliative. Intermediate (Child-Pugh class B) HCC accounts for a great majority of cases and is treated with transarterial chemoembolization (TACE). Advanced

(Child-Pugh class C) HCC is treated with the multi-kinase inhibitor sorafenib, and terminal (Child-Pugh class D) HCC entails supportive care.^{10,13}

Transplantation. Among the available treatment modalities, OLT has the highest five-year survival rate and lowest recurrence rate, but access to OLT is greatly limited by the marked shortage of donor organs. In an effort to maximize the benefit from this scarce resource, Mazzaferro and colleagues developed what are now known as the Milan criteria for establishing candidacy for OLT.¹⁴ A patient with HCC is eligible if she or he has one lesion less than 5 cm or up to three lesions less than 3 cm each, and with no extra-hepatic metastases or macroscopic vascular invasion.¹⁴ Notwithstanding the BCLC guidelines, transplantation has been shown to increase survival for patients with HCC of any Child-Pugh stage, regardless of the size-number restrictions imposed by the Milan criteria.¹⁵ For this reason, the Milan criteria have been criticized for purportedly denying transplantation to many patients on the fringe of the Milan criteria.¹⁶ Though this debate continues to date, the current American Association for the Study of Liver Diseases (AASLD) clinical guidelines for HCC cite weak methodologies in the literature supporting the expansion of the Milan criteria as well as ethical issues surrounding survival that prevent a change in this policy.²

TACE as the current standard of care. HCC undergoes a great deal of neovascularization early in its pathogenesis, and 90% of its blood flow is supplied by the hepatic artery.¹⁷ This provides the basis for radiologic diagnosis as well as interventions such as transarterial embolization (TAE) and TACE. TAE induces hepatic artery obstruction, and TACE does this but with a chemotherapeutic agent.¹⁸ Since the liver itself derives more than two-thirds of its blood flow

from the hepatic vein, TACE has been shown to be quite effective at targeting the tumor without adversely affecting the hepatic parenchyma. Prior to the adoption of the BCLC system, TACE was also indicated for advanced-stage HCC.¹⁹ Nonetheless, the current clinical guidelines state that patients with intermediate-stage HCC are the optimal candidates for TACE.² Hence, TACE is currently the standard of care for unresectable HCC, which comprises the vast majority of cases,²⁰ either as definitive treatment or as a bridge to OLT.²¹

The rise of SBRT. The liver is known to have a low tolerance to radiation, so until recently, radiotherapy (RT) has had little to no applicability in the treatment of liver cancer. This is largely due to the risk of radiation-induced liver disease (RILD) and treatment-induced progression of Child-Pugh class. Over the last three decades, though, the development of stereotactic radiosurgical techniques for delivering RT has led to the increased utilization of stereotactic body RT (SBRT) for treating HCC, as well as a several other radiation-averse tumor histologies.²² In 1991, Blomgren & Goranson were the first to use SBRT in the treatment of primary liver cancer and published their findings in 1998.²³ Since then, the efficacy and safety of SBRT for HCC has been well established by a number of retrospective and phase-I and -II clinical trials.²⁴⁻³¹ A group of researchers in China recently published positive results from a randomized controlled trial (RCT) of SBRT combined with TACE for advanced-stage HCC with portal vein tumor thrombosis,³² and a similar RCT is currently being conducted at Stanford University.³³ However, the present study focuses specifically on the use of SBRT and TACE as alternative options for definitive monotherapy for unresectable HCC.

The need for cost-effectiveness analysis. Within the last three years, SBRT has become widely accepted as a comparable treatment strategy to TACE for patients with unresectable HCC.³⁴⁻³⁶

Due to the strong recommendations from these studies and all the evidence that precedes them, it is possible if not likely that the next version of the AASLD clinical guidelines for HCC, as well as the BCLC system, will incorporate SBRT into the staging and treatment paradigm. However, the question remains as to whether SBRT is able to achieve comparable outcomes to TACE at a lower cost. Given the recently elucidated equipoise between these two treatment modalities, cost-effectiveness analysis (CEA) is now warranted in order to maximize the value of care for patients with unresectable HCC. This study has not been conducted to date, and the results of this investigation could have a direct impact on clinical decision-making, policy decisions in the next revision of AASLD clinical guidelines for HCC, and provider reimbursement rates. Furthermore, we hypothesize that SBRT is significantly more cost-effective than TACE for the treatment of unresectable HCC.

Methods

In accordance with the published guidelines on economic evaluation in health care,³⁷⁻³⁹ a Markov model⁴⁰ will be used to evaluate the clinical trajectory of a typical patient with intermediate-stage. According to the published guidelines on economic evaluation in health care,³⁷⁻³⁹ this is the most appropriate model for the proposed research question, as HCC is a chronic condition occurring over an extended period of time. In the Markov model, we followed 10,000 hypothetical patients as they transition between mutually exclusive health states for a fixed period of time. Transitions occur in fixed time increments that depend on the speed of the disease

progression and at defined transition probabilities. Given the median survival and typical post-treatment follow-up times, the model will had a ten-year time horizon with states transitioning on a three-month cycle. The model was developed and analyzed with TreeAge Pro 2014 (TreeAge Software, Inc., Williamstown, MA). The Markov model simulates a typical patient with unresectable HCC over a 10 year horizon and accumulated costs and life years associated with the states transitioned in and out of over that period. If at any time a patient transitions to the state of death, the simulation for that patient is finished and the life years gained will be the time until death. Average costs and life years gained will be reported in order to determine the typical progression of the disease.

Costs. Costs (Table 1) were obtained from several sources, including local hospital estimates, previous epidemiologic studies. Costs include facility and physician fees as well as drugs and materials used during procedures. Itemized costs were multiplied by the frequency of annual use and divided by the number of cycles per year to obtain the cost per cycle associated with various states. The average number of treatments per year was calculated via the division of the number of treatments per patient by the average length of survival in a given state. Cost estimates for TACE were \$13,400 per procedure, whereas a course of SBRT had a cost of approximately \$11,000.⁴¹ Costs of Liver transplants are estimated to be about \$278,000.⁴²

Transition probabilities. Transition probabilities (Table 2) were derived from retrospective review of outcome studies for HCC. Due to the fact that patients with HCC have a life expectancy between 4 and 6 years,⁴² we chose a time horizon of 10 years with transitions at 3 months for a total of 40 transitions. Transition probabilities are frequently available for various

times periods, but to be used in a Markov Model, they needed to be converted into rates per cycle using actuarial calculation methods.⁴² For some of the probabilities, such as TACE→Progression to Inside the Milan Criteria, we used the stated probability in the model while in others such as TACE→Survival, we needed use the compliment in the model. Two such examples for conversions are given next. First, Naugler et al. estimated that the five year survival rate after receiving TACE is 39% meaning that the five year death rate is 1-39%. In order to find the three month death rate which we will use in the model we use the following actuarial equation⁴²:

$$1 - \exp\left(3 \text{ months} * \frac{\ln(39\%)}{5 \text{ years} * 12 \text{ months}}\right) = 4.6\%$$

This means that 4.6% of patients transition to the death state after three months. Second, Tabrizian et al. estimated that in one year, 20% of patients receiving SBRT progress from outside the Milan Criteria to inside. In order to find the three month probability to use inside the Markov Model, we follow the same process but we do not wish to find the probability of the compliment state like before.

$$1 - \exp\left(3 \text{ months} * \frac{\ln(1 - 20\%)}{1 \text{ years} * 12 \text{ months}}\right) = 5.4\%$$

This means that the three month probability used inside the model for transitioning into the Milan Criteria is 5.4%. In order to estimate the probability of transplantation, the probability is equal to the chance that an individual who is evaluated for transplantation will actually be put on the transplant list (listing rate) multiplied by the transplant rate for patients with HCC. Transplant rates are known to be around 71% for 2 years from the Scientific Registry of Transplant Recipients, listing rates on the other hand, are unknown and estimated to be anywhere from 50% to 80%, we hence used a conservative estimate of 50% giving a 35.5% probability of

transplantation one time meaning that if the patient received a transplant, they would be unable to receive a second.

Decision model. The assumed starting position for an individual in the Markov Model (Figure 1) was that of a patient outside of the Milan criteria. Patients were assumed to be candidates for both SBRT and TACE. The costs during this time period were accumulated for each strategy separately. Future costs were discounted by the standard annual rate of 3% to adjust for the effect of time. A strategy is considered not cost-effective if its implementation is associated with more than \$50,000 spent per life-year gained. A strategy is also considered not cost-effective if it becomes relatively or absolutely dominated by other management strategies. \$50,000 is widely accepted as the societal willingness to pay (WTP).^{43 42} Taking this into account, to determine if SBRT or TACE were not cost-effective, we compared both cost per life saved incremental cost-effectiveness ratios (ICERs). ICERs were computed using the formula:

$$ICER = (Cost_{SBRT} - Cost_{TACE}) / (Years_{SBRT} - Years_{TACE})$$

Discussion

Results Both SBRT and TACE had cost-effectiveness ratios lower than the societal willingness to pay of \$50,000 with CE ratios of \$37,647 and \$38,673 respectively which means they are both cost effective techniques for managing HCC⁴² (Figure 2). Although SBRT is being used a lot in recent years, we found that TACE may be a more cost effective (Table 3). Our analysis showed

that with TACE, a patient may gain an extra 1.11 years of life at a cost of approximately \$46,000 which is very valuable considering that life expectancy with HCC is only about five years.

Further research should be carried out to determine if the extra life year gained is of quality in a Cost-Utility Analysis (CUA). Due to the similarities in the transition probabilities, results are not significantly different between the two strategies for management of HCC. Due to the fact that SBRT is a relatively new procedure, clinical trials of the two treatments may have to be performed in order to determine which of the two strategies is most effective in treating HCC.

Further Research This study focused on a meta-analysis of previous research studies involving SBRT, TACE and HCC. Further research will be done including gaining access to the Medicare SEER database along with other insurance databases. This study also focused on cost per life year gained and hence was a cost effectiveness analysis (CEA). Further research will involve gaining access to a Quality of Life database such as the Health Utilities Inc. Database and perform a Cost Utility Analysis (CUA) to determine the cost per quality adjusted life year. We would also like to split out different stages of HCC to see if there are better decisions that can be made during the progression of HCC.

Tables and Figures

Cost Item	Frequency per year	Cost Per Item	Per Period	Source
TACE	3	\$ 13,400.00	\$ 10,050.00	O'Connor et al.
SBRT	3	\$ 11,000.00	\$ 8,250.00	O'Connor et al.
Liver Transplant	1	\$ 278,000.00	\$ 278,000.00	Naugler et al.
Liver Decomp	1	\$ 43,000.00	\$ 10,750.00	Axelrod et al.
IMC	12	\$ 1,800.00	\$ 5,400.00	Axelrod et al.

	Rate	Period	Rate per cycle	Model Use	Reference
TACE					
Survival	39.00%	5 Years	95.40%	4.60%	Naugler et al.
Progression to Inside Milan Criteria	28.00%	1 Year	7.88%	7.88%	Naugler et al.
Liver Decomp	6.00%	1 year	98.47%	1.53%	Naugler et al.
SBRT					
Survival	41.20%	5 years	95.66%	4.34%	Grutters et al.
Progression to Inside Milan Criteria	20.00%	1 Year	5.43%	5.43%	Tabrizian et al
Liver Decomp	6.00%	1 year	98.47%	1.53%	Naugler et al.
OLT					
Survival	73.00%	5 years	98.44%	1.56%	Tabrizian et al.
Transplant	35.00%	1 time			Naugler et al.
Liver Decompensation					
OLT	25.00%	2 Years	3.53%	3.53%	Naugler et al.
Survival	8.80%	3 Months	8.80%	8.80%	Naugler et al.
Misc					
Cycle Length	1	3 months		3	N/A
Discount Rate	3%	12 Months	0.75%	0.75%	N/A

TABLE 3. Costs and Life-Years Gained					
<u>Strategy</u>	<u>Costs</u>		<u>Years Gained</u>	<u>CE Ratio</u>	<u>ICER</u>
SBRT	\$	126,119.91	3.35	\$ 37,647.73	
TACE	\$	172,484.02	4.46	\$ 38,673.55	41,769.47

Figure 1: Markov Model

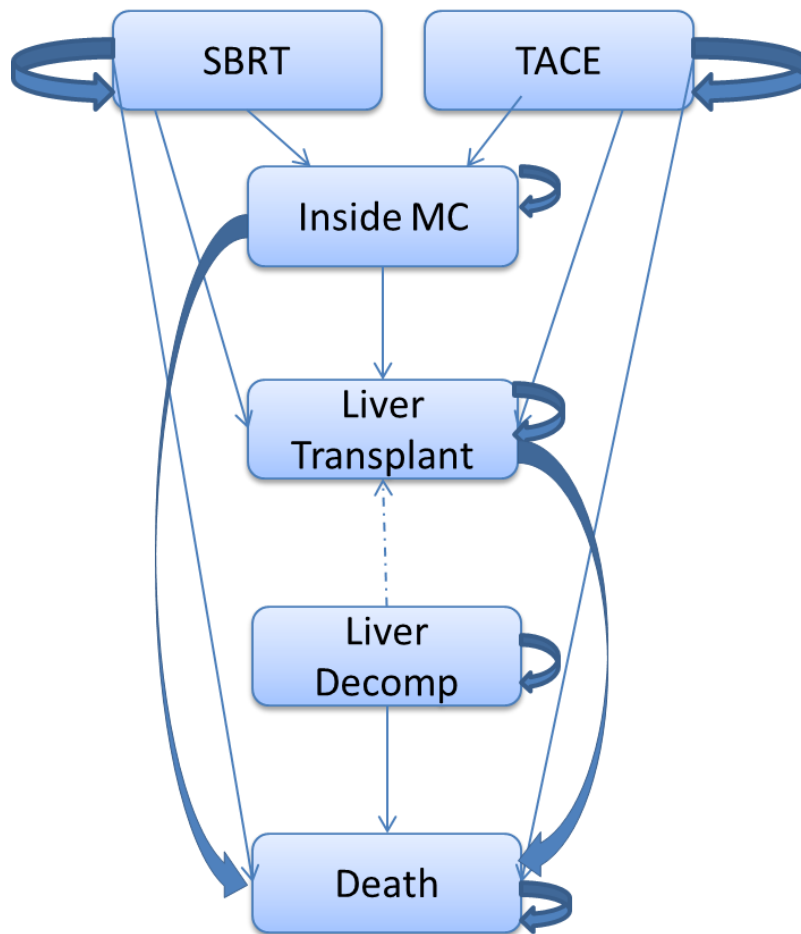
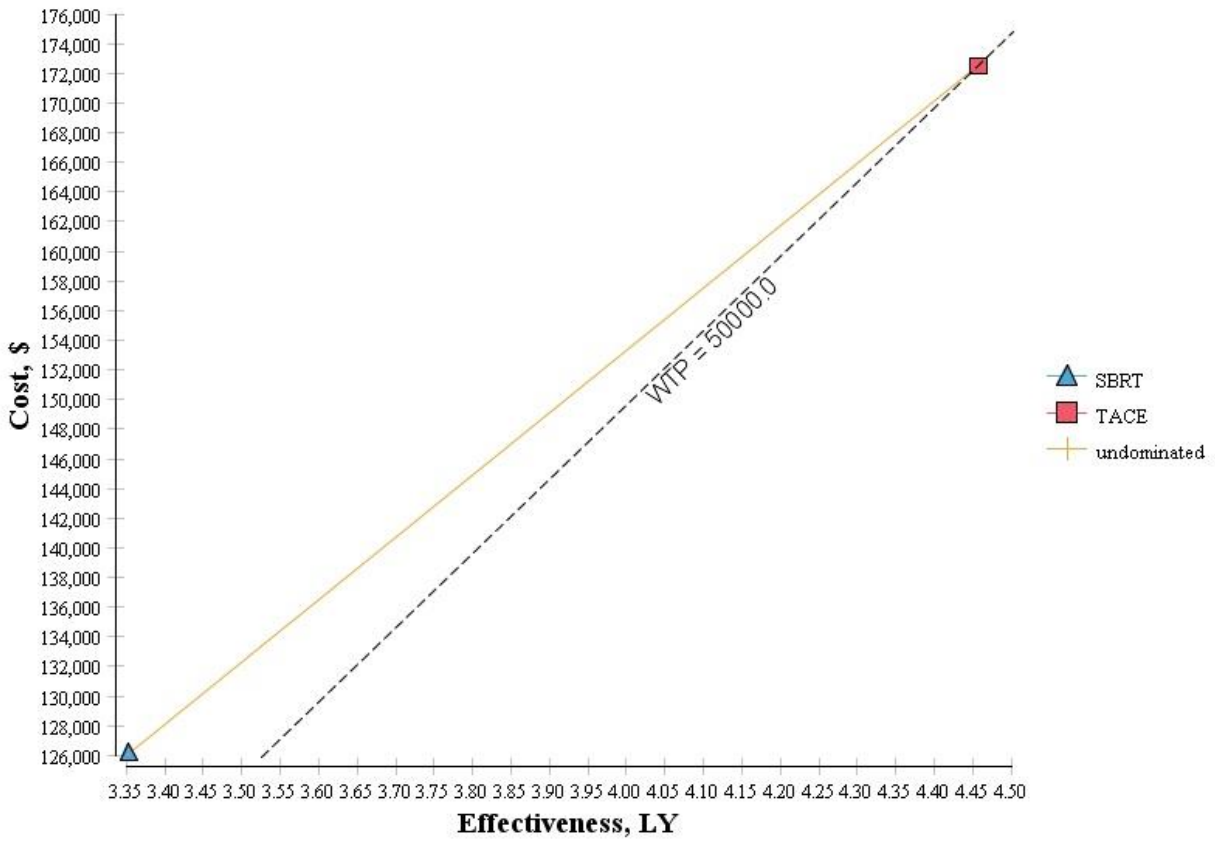


Figure 2: Cost-Effectiveness Analysis



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