Effectiveness and Cost of Radiofrequency Ablation and Stereotactic Body Radiotherapy for Treatment of Early Stage Hepatocellular Carcinoma: An Analysis of SEER-Medicare

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Running Title: SEER-Medicare SBRT RFA

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ABSTRACT

Introduction: For early stage hepatocellular carcinoma (HCC) patients, ablative strategies are potentially curative treatment options. Stereotactic body radiotherapy (SBRT) has emerged as a promising ablative therapy, although its comparison with radiofrequency ablation (RFA) remains confined to a single institution retrospective review. We sought to characterize the comparative outcomes and cost between the two treatment strategies.

Methods: We conducted a secondary analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (2004-2011) and identified adult patients with stage I or II HCC and treated with RFA or SBRT as the initial treatment within 6 months of diagnosis. Survival analysis was conducted using Kaplan-Meier curves and multivariate Cox proportional hazard analysis. Factors associated with overall survival and 90-day hospital admission post-treatment were identified using propensity score

(PS) adjusted multivariate analysis. We performed costs analysis and calculated incremental cost-effectiveness ratios (ICER).

Results: 440 patients were identified, 408 treated with RFA and 32 SBRT. In the overall cohort, 90-day hospitalization and 1-year mortality were similar between groups but RFA patients had better overall survival (p<0.001). Multivariate analysis showed advanced age, higher stage, decompensated cirrhosis, and treatment with SBRT (HR 1.80; 95%CI: 1.15-2.82) were associated with worse survival, but in the PS adjusted analysis, survival and costs were similar between the two groups.

Conclusion: In a national cohort of early stage HCC patients, treatment with RFA vs SBRT resulted in no significant difference in survival, 90-day hospitalization, or costs. These data highlight the need for a randomized clinical trial comparing these two modalities.

Key word: ICER, HCC, RFA, SBRT, comparative

Introduction

Hepatocellular carcinoma (HCC) is an increasingly common and highly morbid malignancy both in the United States and worldwide.(1, 2) Mortality related to HCC is rising in the US due to the peak in the hepatitis C epidemic and recent rise in non-alcohol fatty liver disease.(3-5) Treatment allocation depends on several factors, including tumor burden, liver function, and overall functional status.(6) Early stage disease is best treated by surgical resection, liver transplantation, or local ablative therapies. Surgical resection is commonly contraindicated due to presence of portal hypertension or other medical comorbidities and liver transplantation can be limited by organ availability and strict candidate selection criteria.(7) Thus in a large proportion of early stage patients, local ablative therapies are the mainstay of treatment for early stage HCC. Results from numerous studies show that the most commonly applied local ablative therapy, thermal (radiofrequency or microwave) ablation, provides local control rates of up to 80-90% for small HCCs (< 4 cm in size).(8-12) Thus local ablative therapies can provide an effective primary therapy.

Stereotactic body radiation (SBRT) has been pioneered by several centers worldwide as an alternative local ablative therapy for early HCC.(13-15) SBRT is often used as an alternative to RFA for patients with tumors near anatomical structures or

major vessels due to the heat-sink effect that can occur with RFA. SBRT provides extremely focused high dose radiation to the hepatocellular carcinoma with minimal radiation damage to the surrounding liver parenchyma.(16, 17) Although initially the literature was restricted to retrospective studies, there are now several prospective trials supporting safety and efficacy of SBRT for HCC.(17, 18) We lack multicenter data on SBRT efficacy and an understanding of how demographic or health system characteristics impact treatment effectiveness and survival. The population of patients with HCC is shifting to a more elderly demographic(19), thus, the impact of age and accumulated comorbidities on treatment tolerability and efficacy is an important consideration when making treatment decisions. Finally, we lack understanding on real world resource requirement (e.g. costs, hospitalization) differences between the local ablative therapies, as prior analyses have relied on Markov modeling based on data from a single institution.(20) Thus, the aim of this study was to assess differences in outcomes and resource requirements between local ablation and SBRT using the US Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Methods

Data Source

We performed a secondary analysis of the SEER-Medicare dataset for new diagnoses of HCC (International Classification of Diseases for Oncology, Third Edition, histology codes 8170, 8172, 8173, 8174, and 8175 for HCC and site code C22.0 for liver) from 2004-2011. The details of SEER-Medicare data are described elsewhere.(21) Per SEER-Medicare data use agreement, any reporting of patient numbers <11 were suppressed and not displayed in this study.

Patient Selection

We included patients with American Joint Committee on Cancer (AJCC) Stage I or II HCC who had been treated with RFA or SBRT as their first treatment within 6 months of diagnosis. Patients with another treatment within 30 days of RFA or SBRT were excluded, so that we could accurately capture utilization and survival for patients related to their treatment. Patients with missing data on tumor stage were excluded. Patients with another malignant primary tumor diagnosed prior to HCC diagnosis were excluded. Patients who had HCC diagnosed upon death were also excluded. Those with dates of birth that differed between CMS and SEER by more than a year were removed

from the analysis, as were any people with autopsy or death certificate-only records. Patients were followed until death or the end of the study period.

Covariates

Covariates of interest included patient-level factors (age, gender, race, comorbidities, and presence of hepatic decompensation) and system-level factors, (region of US, residence in an urban vs. rural area [as defined by residence in a metropolitan statistical area,] and association with liver transplant center.) We calculated Charlson comorbidity index using data from 12 months prior to HCC diagnosis, excluding codes for liver disease, as previously described.(22) We excluded liver disease codes from the comorbidity index as nearly all patients had underlying chronic liver disease, if not cirrhosis; further, we were interested in exploring the prognostic significance of hepatic decompensation independent of other comorbidities. We developed a composite variable for liver decompensation that included administrative codes for: 1) ascites (ICD-9 789.5x) and procedural coding for paracentesis (HCPCS 49080 - 49084); 2) hepatic encephalopathy (ICD-9 572.2, 070.4x, 070.6x) and medication codes from Part D for neomycin, lactulose and rifaximin; or 3) esophageal varices (ICD-9 456.0, 456.1, 456.2) and procedural coding for esophagogastroduodenoscopy (EGD) with variceal banding (HCPCS 43205, 43244, 43251, 43999, 46934).(22) We performed a sensitivity analysis excluding esophageal varices from the definition of decompensation, as its inclusion without overt variceal bleeding is controversial.

We also captured all other treatments received during the follow-up period, including surgical resection, repeat local ablative procedures, transarterial chemoembolization, transarterial radioembolization, liver transplantation, or sorafenib.

Statistical Analysis

The primary study outcome was overall survival of the SBRT-treated group versus the RFA-treated group both in the overall and propensity matched analysis. Secondary outcomes included 90-day hospitalization rates and overall costs associated with each treatment strategy.

Patient characteristics were compared between treated and control patients. The survival distributions were reported by median and interquartile range (Q1, Q3).

Continuous variables were compared using Wilcoxon Signed Rank test and dichotomous variables were compared using odds ratios.

We conducted Kaplan-Meier survival analysis with log rank tests to compare survival from the time of HCC treatment between treatment groups. Propensity score adjustment was used to balance the cohorts using 1:1 nearest neighbor matching accounting for differences between the RFA-treated and SBRT-treated cohorts. The propensity score algorithm selected the other predictor variables by predicting the treatment variable in a logistic regression. From that predicted outcome, we comprised a combination of the predictor variables with the slopes and created a propensity score, and this was used to match the treatment group subjects and discard the remainder. We used the Hansen-Bowers measure of global balance post-propensity score matching and standardized differences of individual predictors to affirm the balance. We constructed a multivariate Cox model to identify predictors of overall survival and a logistic regression to characterize predictors of 90-day post-procedural hospitalization. Multivariate survival analysis was calculated using the Cox proportional hazards model. Statistical significance was defined as $p< 0.05$.

We used variance inflation factors to test for collinearity in the model variables with the intention of sequentially removing variables where significant collinearity was present. However, no collinearity was found in any of our multivariate analyses, as all VIF values were less than 5. We also tested for the interaction between relevant variables (i.e. treatment and decompensation) to determine if a stratified analysis was warranted, however no significant interactions were seen. Deviance residuals were examined for both Cox models to ensure model assumptions were met. All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC) and R version 3.2.2. The R package “MatchIt” was used for the propensity scores, the package “survival” was used for Cox Proportional Hazards regression, the package “RItools” was used for evaluation of propensity scores balance and “rms” was used to create the Kaplan Meier survival curves.(23-29)

Cost Analysis

Total costs from the Medicare perspective were compiled using Medicare Part A, B, and D data files from diagnosis to the end of follow-up. We compared costs for SBRT-treated patient and RFA-treated patients and calculated incremental cost-effectiveness ratios (ICERs) per life year gained. ICER is defined as the difference in costs divided by

year of life gained, and compared to the accepted threshold of $100,000 per life-year for cost-effective treatments.(30-33) We used life-year gained instead of quality life-year gained, as there are no available validated quality of life utility adjustments for patients undergoing SBRT for hepatocellular carcinoma. All costs were inflated to 2016 US dollars.

To examine the cost effectiveness ratio, we used a sensitivity analysis where our empirical distribution was resampled using replacement, giving us a total of 1000 bootstrap permutations of the data. We modeled the ICER statistic value for each of the 1000 sets of data and plotted its cumulative density function, producing a cost-effectiveness acceptability curve.(34, 35) To assess the variation of the sample we considered the 2.5% and 97.5% nonparametric percentiles along with its median value. We reported the percent of bootstrap ICER values under $100,000. A cost-effectiveness plane was plotted for both samples, showing where the numerator and denominator for the ICER lay. We conducted traditional two-way sensitivity analyses by varying survival of the SBRT and RFA treatment groups by 10% and 40% to test the robustness of our sample ICER estimates.

Results

Cohort characteristics

We identified 32 SBRT-treated patients and 408 RFA-treated patients. The characteristics of the two treatment cohorts are shown in Table 1. The cohorts had similar gender and stage of HCC as well as similar geographic and treating hospital characteristics. SBRT-treated patients were significantly older and had higher comorbidity but a lower proportion of hepatic decompensation. The median follow-up was 487 days (IQR: 403-808) for SBRT-treated patients and 761 days (IQR: 443-1446) for RFA-treated patients. The SBRT group received significantly less subsequent treatments (median 1 [IQR: 1-1]) during follow-up compared to the RFA group (median 1 [IQR: 1-2]) ($p=0.007$). Specifically, patients in the RFA group were more likely to undergo subsequent liver transplantation ($p<0.001$).

Survival Analysis in Overall Cohort

In Kaplan-Meier survival analysis, SBRT patients had worse survival than RFA-treated patients (log-rank $p<0.001$) (Figure 1). The 1-year survival for SBRT-treated patients was similar 78.1% respectively, compared to 79.4% for RFA-treated patients.

However, 3-year survival was significantly longer in the RFA treated cohort. In the multivariate Cox regression model, receipt of SBRT, age, stage II disease (vs stage I), and presence of hepatic decompensation were associated with worse survival, while number of subsequent treatments was associated with improved survival. (Table 2)

Survival Analysis in Propensity-Adjusted Cohort

After matching patients who underwent SBRT with those who underwent RFA, all covariates were balanced individually and globally, removing baseline differences between the groups (p=0.779). The characteristics of the propensity score matched cohorts is shown in Supplemental Table 1. The median follow-up time for SBRT-treated patients was 487 days (IQR: 403 days – 808 days) and 594 days (IQR: 434 days – 1006 days) for RFA-treated patients.

In the propensity-matched sample, there was no significant difference in survival between SBRT-treated and RFA-treated patients (p=0.30; Figure 2). In the multivariate Cox regression model, treatment in an urban setting was associated with worse survival, while number of treatments during follow-up was associated with improved survival (Supplemental Table 2).

90-Day Hospitalization

To approximate safety and resource utilization of SBRT and RFA, we calculated 90-day post-procedural hospitalization. The proportion of hospitalization (27.2% SD 9.0) was higher in the RFA group than the SBRT groups; however, this difference did not meet statistical significance (p=0.06). In multivariate logistic regression, predictors associated with 90-day hospitalization included region of the country treated (northeast; Reference: midwest), treatment at a transplant center, stage II disease (reference: Stage I), and higher comorbidity index (Supplemental Table 3.) Treatment in an urban setting was associated with lower risk of 90-day hospitalization.

Cost Analysis

We analyzed overall and short-term (90-day) costs for patients treated with SBRT versus RFA in both the overall cohort and the propensity matched cohorts. In the overall cohort, patients treated with RFA had significantly higher overall costs (p=0.002) stemming from higher inpatient costs (Table 3). When examining 90-day costs specifically, overall costs were similar, with SBRT patient having a higher outpatient cost

component. The median cost per median life year gained was similar between the cohorts ($38,810 and $40,777). In the propensity score adjusted sample, overall and the 90-day costs did not differ between treatment groups. The median cost per life year gained was approximately 19% higher in RFA patients ($38,810 vs $46,253) (Supplemental Table 4). Median outpatient costs were higher in the SBRT group, however, this did not translate into significant differences in overall costs.

Both ICER point estimates show that SBRT treatment is cost effective compared with RFA, as they are both lower than $100,000 per life year gained. The full sample (n=440) has an ICER estimate of $56,301 per life year gained, and the propensity score sample (n=64) had an estimate of $1,412 per life year gained. In the two-way sensitivity analysis, varying the estimate of SBRT survival by 10%, we saw a range of ICER values from $47,817 to $68,443. Varying by 40% gave a range of ICER values from $32,931 to $193,908.

The full sample bootstrap median ICER was $61,164 (95% CI: -$420,299, $367,960). Since the upper confidence limit was >$100,000, SBRT was not cost effective compared with RFA in the overall population, although 85.5% of the bootstrap ICER estimates were lower than $100,000 (Figure 3A). The cost-effectiveness plane (Figure 3B) showed the bootstrap ICER estimates mostly in the third quadrant, which signifies that costs were lower in the SBRT group although survival was higher in the RFA group. In the propensity matched sample, the median ICER estimate was $12,592 (95%CI: -$251,874, $390,198). As in the overall cohort, the upper bound of the 95% confidence interval exceeded $100,000 so SBRT was not cost-effective compared to RFA; however, 92% of the bootstrap ICER estimates were lower than $100,000. (Figure 3C). The cost-effectiveness plane (Figure 3D) shows that the ICER bootstrap estimates were centered around no difference between treatments.

Discussion

There are several local ablative therapies available for treatment early stage HCC patients but the literature on comparative effectiveness and cost of the modalities is sparse. In this analysis of elderly Medicare beneficiaries with early stage HCC, patients who received RFA acheived better survival compared to patients who underwent SBRT; however, in propensity matched analysis, overall survival was similar between patients, after adjustment for the higher age and higher comorbidities in patients treated with SBRT. Post-procedural hospitalization was numerically higher in the RFA group in the overall sample of patients but simlar in propensity-matched analysis. Overall, our data suggest these two treatment modalities can result in similar overall survival and comparable costs.

Multivariate predictors of survival in the overall cohort, including age, stage, hepatic decompensation and ability to receive additional treatments, are consistent with prior analyses.(36) The propensity matched multivariate survival analysis was limited by low numbers of patients; however treatment in an urban setting and ability to receive subsequent treatment remained predictors of survival. Predictors of 90-day hospitalization included being treated in the northwest region and being treated at a transplant center which could reflect referral bias of more complex patients.

The effectiveness of SBRT and RFA for early stage HCC has been described in several studies. The largest retrospective single center cohort of 224 patients showed equivalent tumor control between the two modalities for tumors less than 2 cm in size, however SBRT was superior in achieving local tumor control for larger tumors.(37) One and two-year survival was similar between the two groups, which is consistent with the findings of our analysis.(37) A more recent study using the National Cancer Database of nearly 4000 patients who received RFA and SBRT for HCC showed that RFA patients had a superior 5 year survival in a propensity matched cohort.(38) While the conclusions of this study differ from our findings, there are several reasons this may be the case. The large number of patients is a strength of this study, however the lack of granular patient level data unmeasured confounders limited the level of propensity matching that could be conducted with this data set.(38) Most importantly the authors failed to account for hepatic function or decompensation, which we accounted for using diagnosis coding for hepatic decompensation and Part D data for medications associated with hepatic decompensation.(38) Finally, the authors failed to account for subsequent locoregional

treatments after completion of RFA or SBRT, which we were able to adjust for in our propensity matched analysis. These important limitations may explain the difference in the findings of our analysis and the results using the National Cancer Database.(38)

There have been limited analysis of cost-effectiveness of local ablative therapes for HCC. One recent Markov model was published comparing RFA and SBRT for treatment of HCC concluded that SBRT was not a cost-effective strategy for initial HCC treatment compared to RFA (cost per QALY $558,679), however SBRT was cost-effective as a salvage therapy in post-RFA progression.(20) Our study adds valuable real data that supports the use of SBRT as an equivalantly cost-effective initial treatment when compared to RFA for treatment of HCC. While overall costs were higher in the overall RFA cohort, related to higher inpatient costs, this could be in part explained by the prolonged survival seen in the RFA patients and thus added time to accumlate costs. The costs per life year gained were numercially similar between the two groups in the overall cohort, however costs were 19% higher in the RFA group on the PS matched cohort.. Costs were similar in the 90-day post-proedure period. Further, the propensity matched cohort had similar costs between the SBRT and RFA treatment groups. In our cost-effectiveness analysis SBRT had an ICER below $100,000 compared to RFA in our base case analysis. These results were consistent with our two-way senitivity analysis varying survival seen in the SBRT cohort by 10%. A 40% decrease in SBRT-treated patient survival resulted in an ICER>$100,000.

Our study has several strengths and weaknesses that warrant attention. Our data are limited by the use of administrative Medicare coding, which can be subject to omission or misclassification. There were also a relatively small number of patients in our SBRT cohort, reflecting the still emerging use of this technology, which limits the power of our analyses and our ability to draw strong conclusions on SBRT effectiveness and costs. The low number of SBRT patients are due to the strict inclusion criteria for tumor stage and treatment within 6 months of diagnosis we applied to conduct this analysis. The confidence intervals for SBRT effectiveness and costs were relatively narrow and thus we believe this well selected cohort is representative of patients receiving SBRT. Additionally, there is likely selection bias for treatment with SBRT that we could not fully account for in our propensity based analysis. Our hepatic decompensation variable relied on ICD-9 coding, so not all patients with decompensation in both groups were likely captured. SEER-Medicare data has limited

data for HCC tumor stage; the AJCC staging system is not widely endorsed for HCC due to lack of important prognostic information including Child-Pugh classification, alpha-fetoprotein levels, and performance status. It is possible that some patients in our analysis had Child-Pugh class C or ECOG status 3-4, resulting in BCLC stage D disease for whom treatment is not recommended. We lacked data on quality of life, which did not allow us to quality adjust our results for the cost-effectiveness analysis. Although radiation therapy has minimal impact quality of life (37), comparison studies have not yet been performed. Our SEER-Medicare dataset only included data through 2011, however SBRT has become more widely used in more recent years, thus our data may not reflect more contemporary experience with the use of SBRT. Finally, these data are in elderly Medicare beneficiaries, so the data may not be applicable to younger patients with HCC. Nonetheless this study examines the real world impact and value of treatment with SBRT and RFA.

In conclusion, our results suggest SBRT and RFA Medicare beneficiaries have equivalent survival and costs when matched for baseline characteristics. A prospective randomized clinical trial is warranted comparing these modalities head-to-head.

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Figure Legend:

Figure 1: Kaplan Meier Survival Analysis in Overall Cohort

Figure 2: Kaplan Meier Survival Analysis in Propensity Matched Cohort

Figure 3: A: Bootstrap incremental cost-effectiveness ratio distribution for the overall sample. B: Cost effectiveness plane for the overall sample. C: Bootstrap incremental cost-effectiveness ratio distribution for the propensity matched sample. D: Cost effectiveness plane for the propensity matched sample

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Table 1: Patient Characteristics in Overall Cohort

	SBRT **N=32**	**RFA** **N=408**	***p* value**
Socio-demographics			
Age, yrs, median (IQR)	77 (72,71)	73 (70, 78)	**0.004**
Race			
White	24 (75)	236 (57.8)	0.057
Black	NR	32 (7.8)	0.37
Other	NR	140 (34.3)	**0.008**
Sex			
Male	20 (62.5)	254 (62.3)	0.99
Location			
Northeast	NR	70 (17.2)	0.86
Midwest	NR	23 (5.6)	0.054
Southern	NR	61 (15)	0.55
Western	16 (50)	254 (62.3)	0.18
Urban	11 (34.4)	88 (21.6)	0.11
Care Characteristics			
Treated at Transplant Center	NR	45 (11)	0.15
Treated at Teaching Hospital	NR	49 (12)	0.54
Tumor Characteristics			
Stage I	NR	296 (72.5)	0.51

Stage II	NR	112 (27.5)	0.51
Comorbidity			
Charlson Comorbidity, median (IQR)	1 (1,2)	1 (0,1)	0.005
Decompensation	NR	152 (37.3)	<0.001
Additional treatments after initial SBRT or RFA			
Treatment count, median (IQR)	1 (1,1)	1(1,2)	0.007
Liver Transplantation	NR	21 (5.1)	<0.001
Transarterial chemoembolization	NR	111 (27.2)	0.06
SBRT	NR	NR	0.78
Outcomes			
1 year mortality	NR	84 (20.6)	0.84
90-day hospitalization	NR	111(27.2)	0.06

NR – Not reportable per SEER-Medicare data use agreement if cell <11. SBRT – stereotactic body radiation therapy; RFA – radiofrequency ablation; IQR – interquartile range

Table 2. Multivariate Survival Analysis for the Overall Cohort

	Hazard ratio	**95% Confidence interval**	**P value**
SBRT (ref: RFA)	1.80	1.15-2.82	0.01
Age (years)	1.03	1.01-1.05	0.008
Male Sex (ref: Female)	0.86	0.67-1.09	0.21
Race			
White	0.82	0.54-1.26	0.37

Black	REF	REF	REF
Other	0.80	0.50-1.28	0.35
Stage II (ref: Stage I)	1.70	1.32-2.19	<0.001
Charlson Comorbidity Index	0.98	0.89-1.08	0.71
Presence of decompensated cirrhosis	2.34	1.82-3.02	<0.001
Treating Center Midwest	REF	REF	
Treating Center in Northeast	1.11	0.67-1.85	0.68
Treating Center in South	0.96	0.57-1.61	0.88
Treating Center in West	0.72	0.45-1.16	0.18
Treating center in an urban setting	1.3	0.87-1.94	0.20
Treating center a teaching hospital	1.04	0.57-1.91	0.89
Treatment at a transplant center	0.96	0.53-1.73	0.89
Number of treatments during follow-up	0.59	0.48-0.74	<0.001

SBRT – stereotactic body radiation therapy; RFA – radiofrequency ablation

Table 3 Median Costs Per Patient in US Dollars (2016)

	SBRT (median, IQR) (n=32)	**RFA (median, IQR) (n=408)**	**p-value**
Total Costs	$51,746 ($27,199, $95,534)	$85,016 ($46,805, $147,196)	0.002
Inpatient Costs	$23,360 ($9,357, $59,624)	$54,053 ($27,135, $91,653)	0.002
Outpatient Costs	$30,467 ($18,073, $51,171)	$27,294 ($16,737, $47,686)	0.49
Part D Medication Costs	$4,400 ($1,133, $8,916)	$8,201 ($2,407, $26,010)	0.07
90 Day Overall Costs	$16,606 ($11,955, $22,766)	$20,978 ($7,609, $41,798)	0.59

90 Day Inpatient Costs	$21,201 ($17,713, $27,852)	$29,126 ($16,571, $43,175)	0.44
90 Day Outpatient Costs	$15,478 ($10,523, $20,469)	$5,760 ($3,809, $9,167)	<0.001
90 Day Part D Medication Costs	$1,179 ($284, $2,717)	$768 ($230, $1,853)	0.52
Median cost per median lifer year gained	$38,810	$40,777	

SBRT – stereotactic body radiation therapy; RFA – radiofrequency ablation; IQR – interquartile range

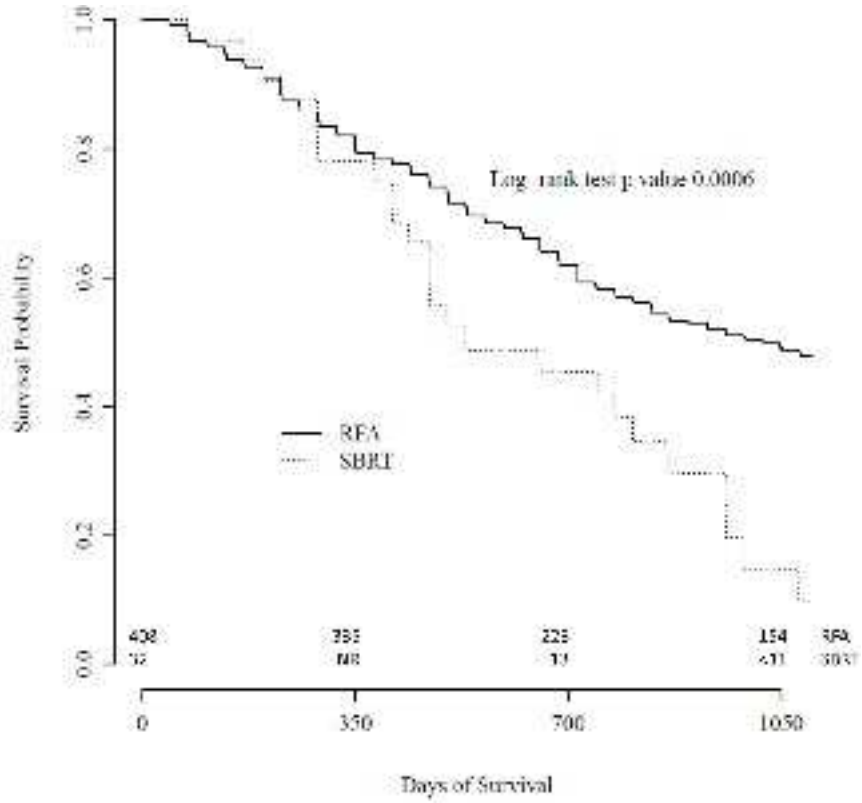

Figure 1

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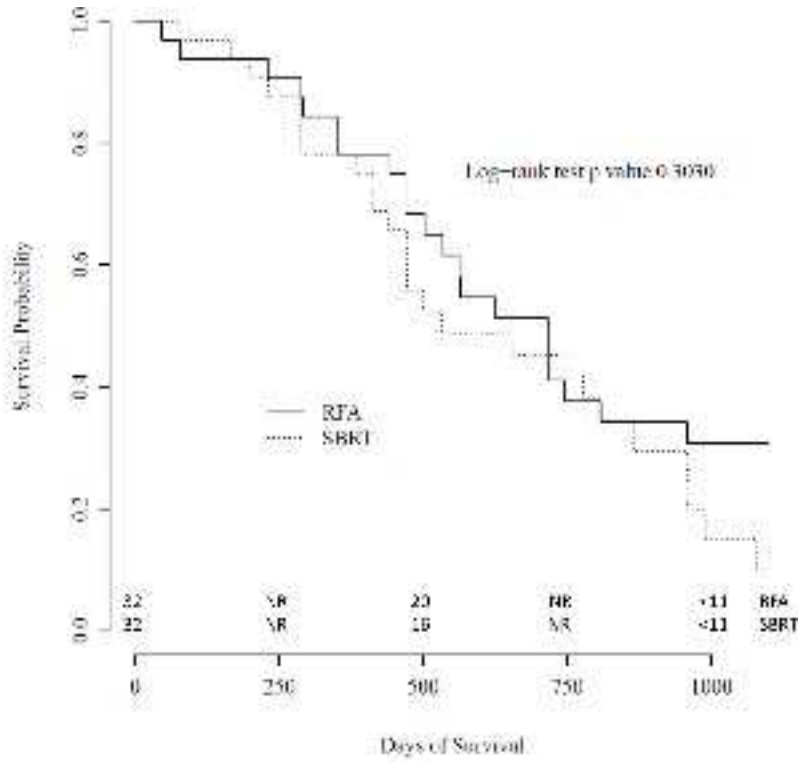

Figure 2

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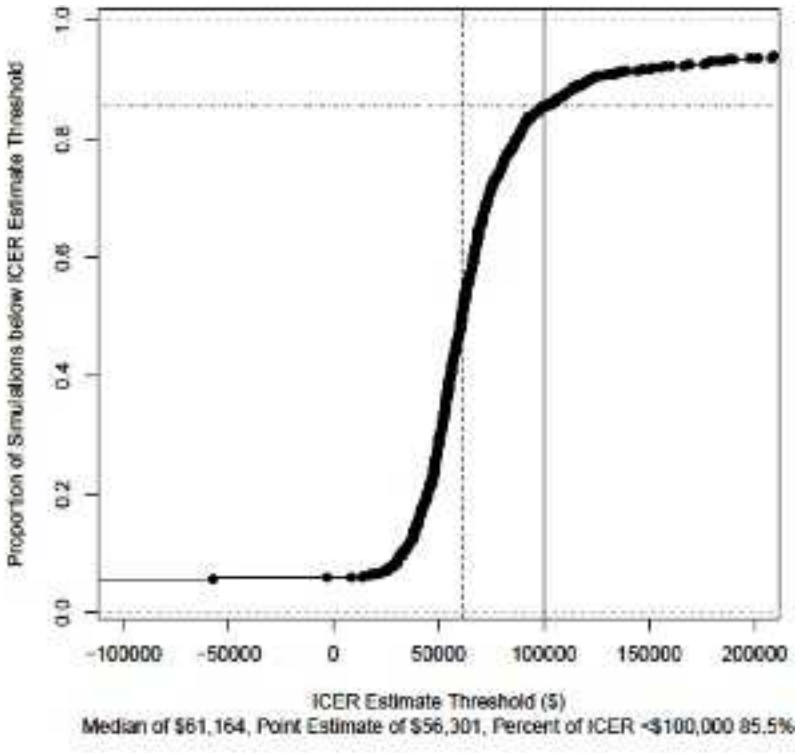

Figure 3A

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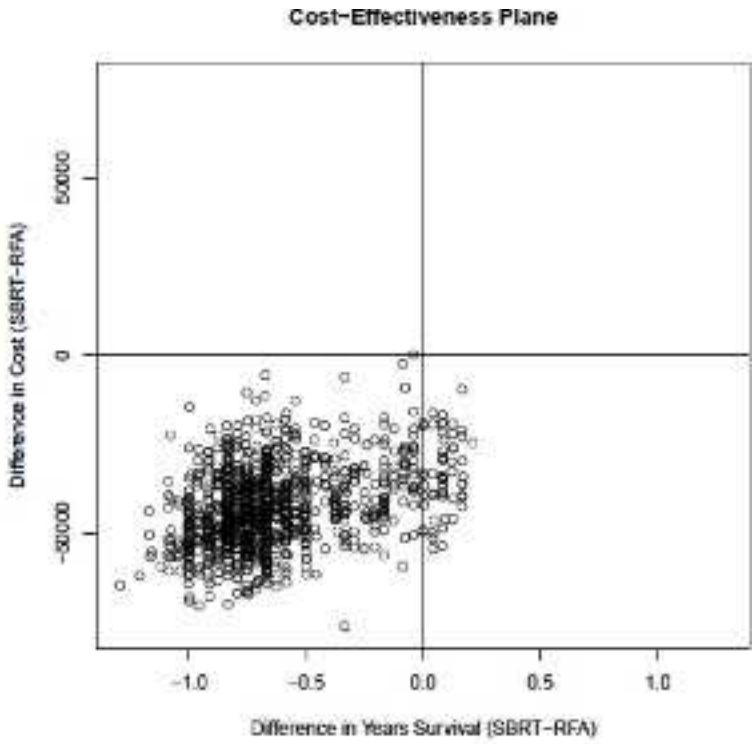

Figure 3B

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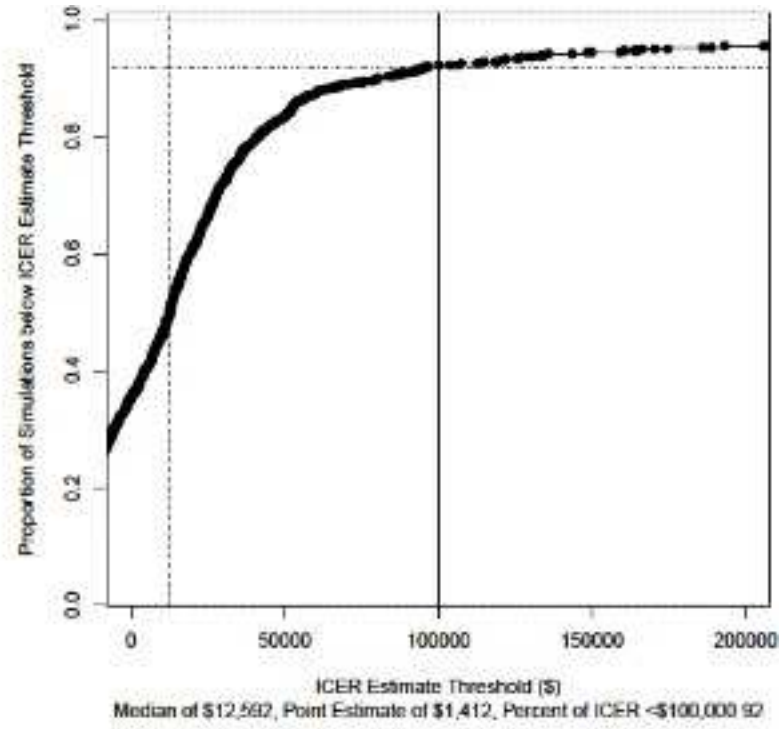

Figure 3C

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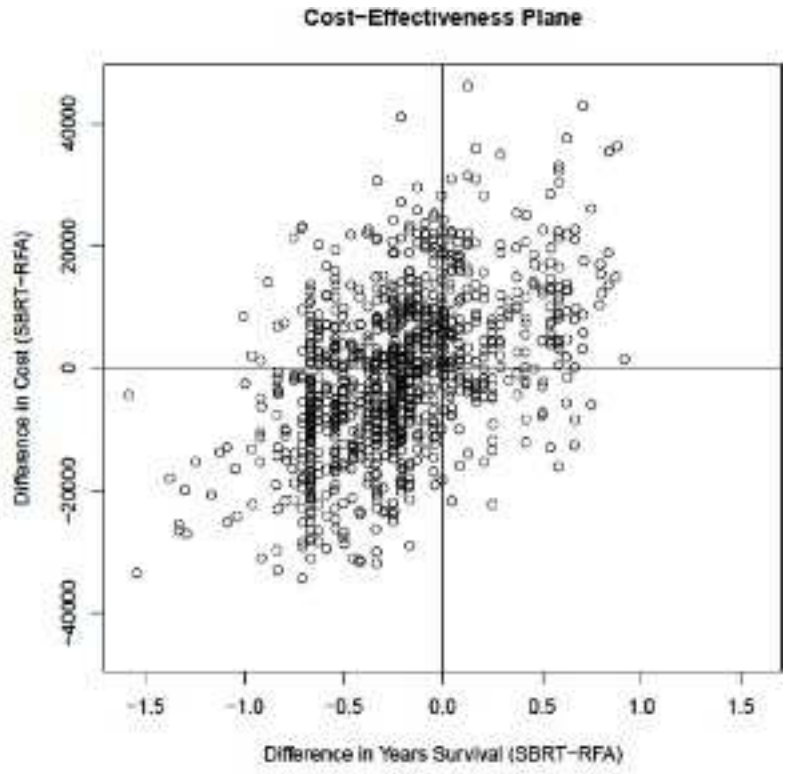

Figure 3D

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