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Economic Evaluation of Endoscopic Sinus Surgery versus Continued Medical Therapy for Refractory Chronic Rhinosinusitis

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Abstract

Objective—To evaluate the long-term cost-effectiveness of endoscopic sinus surgery (ESS) compared to continued medical therapy for patients with refractory chronic rhinosinusitis (CRS).

Study Design—Cohort-style Markov decision tree economic evaluation

Methods—The economic perspective was the US third party payer with a 30 year time horizon. The two comparative treatment strategies were: 1) ESS followed by appropriate postoperative medical therapy and 2) continued medical therapy alone. Primary outcome was the incremental cost per quality adjusted life year (QALY). Costs were discounted at a rate of 3.5% in the reference case. Multiple sensitivity analyses were performed including differing time-horizons, discounting scenarios, and a probabilistic sensitivity analysis (PSA).

Results—The reference case demonstrated that the ESS strategy cost a total of $48,838.38 and produced a total of 20.50 QALYs. The medical therapy alone strategy cost a total of $28,948.98 and produced a total of 17.13 QALYs. The incremental cost effectiveness ratio (ICER) for ESS versus medical therapy alone is $5,901.90 per QALY. The cost-effectiveness acceptability curve from the PSA demonstrated that there is 74% certainty that the ESS strategy is the most cost-effective decision for any willingness to pay threshold greater then $25,000. The time horizon

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analysis suggests that ESS becomes the cost-effective intervention within the 3rd year after surgery.

Conclusion—Results from this study suggest that employing an ESS treatment strategy is the most cost-effective intervention compared to continued medical therapy alone for the long-term management of patients with refractory CRS.

Keywords

Chronic rhinosinusitis; sinusitis; endoscopic sinus surgery; medical therapy; Markov; decision tree; economic evaluation; cost effectiveness

Introduction

Chronic rhinosinusitis (CRS) is a common disabling illness affecting approximately 6 to 16% of the population[1,2]. CRS is characterized by diffuse sinonasal inflammation producing symptoms of nasal congestion, facial pain, reduction or complete loss of smell, headache, and fatigue[3]. Furthermore, there are substantial negative impacts on sleep[4] and daily productivity[5]. The economic burden of CRS is substantial with annual direct costs exceeding $8.6 billion, which can be predominantly attributed to, physician office visits, emergency department encounters, and medication use[6].

Following a diagnosis of CRS, the accepted primary management strategy begins with medical therapy to reduce mucosal inflammation and improve sinonasal function. Despite best medical efforts, a subset of patients will have persistent symptoms and are considered refractory. Strong evidence supports the use of endoscopic sinus surgery (ESS) in this cohort of patients with refractory CRS to improve clinical outcomes; however, the costs of surgery have not been justified through a rigorous economic evaluation with a long-term time horizon. Therefore, it is unknown whether ESS or continued medical therapy alone is the most cost-effective option in managing patients with refractory CRS over a life-time.

The purpose of this economic evaluation is to evaluate the cost-effectiveness of an ESS treatment strategy compared to continued medical therapy alone for patients with refractory CRS. A cost-utility analysis (CUA) was performed using a cohort-style Markov decision tree model to determine if the short-term increase in costs associated with performing ESS is justified during the long-term management of refractory CRS.

Methods

The perspective of this economic evaluation was from the United States (US) government payer. All costs are expressed in US dollars (USD) as of June 2013 (published costs prior to 2013 were adjusted to account for inflation). The primary outcome is the cost per quality adjusted life year (QALY). Since refractory CRS is a chronic non-terminal condition, normal life expectancy was assumed based on US population norms and a 30-year time horizon considered for this analysis.

All costs and effects are presented in disaggregated and aggregated form and incremental cost effectiveness ratios (ICERs) are presented for the primary outcome. The ICER is a

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commonly used equation in health economics to provide important information to resource allocation decision makers. It is the ratio of change in costs between two strategies to the change in effectiveness between the two strategies: (Cost strategy A - Cost strategy B)/(Effectiveness strategy A - Effectiveness strategy B)[7]. Therefore, the ICER provides the additional cost associated with the additional benefit of the new intervention being evaluated.

Costs were discounted at a rate of 3.5% for the reference case and multiple forms of sensitivity analysis were performed to account for inherent data uncertainty. The reporting of this economic evaluation followed the 2013 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines[8,9].

I. Economic Model

A cohort-style state transition Markov decision tree model was constructed to simulate the clinical management patients with refractory CRS. Refractory CRS was defined as persistent disease despite a minimum of 3 months topical sinonasal corticosteroid therapy along with a minimum of a 7-day course of systemic corticosteroids +/− 2-week course of broad-spectrum antibiotics[10].

In the model, the two comparative treatment groups for managing refractory CRS included: 1) ESS followed by postoperative medical therapy and 2) continued medical therapy alone. For the ESS group, the first portion of the model involves a decision tree analysis which moves the patient through potential perioperative outcome pathways, including intraoperative and postoperative complications (Figure 1). In this model, a ‘major intraoperative complication’ involved experiencing one of three events: intraoperative CSF leak, intraoperative orbital injury, and major vascular injury. We did not include the probability of having a second CSF leak (in the postoperative period) in patients who sustained an major intraoperative complication to prevent the risk of inappropriately double counting. The risk of death from routine ESS was not included since it was felt to be negligible.

Since refractory CRS is a non-terminal chronic condition, the second portion involves performing a Markov model. The cycle duration was defined as one year. Based on national US life expectancy statistics[11] and using an average age of CRS patients of 45-years old[10], this model used a total Markov model duration of 30 cycles to reach an average age of 75 years old (rounded down from 75.4). Half-cycle corrections were added for all initial and final reward values. The medical therapy alone group entered directly into the Markov model, whereas the ESS group entered into the Markov model after they completed the ESS decision tree. Patients entered the Markov model into one of the following four refractory CRS health states based on their utility score: low, moderate, or high utility state or death. Following each cycle, patients either stayed in their current health state or transitioned into one of the other three states, based on transition probabilities (Figure 2).

II. Effectiveness - Utility Values

Health state utility data for this economic evaluation was obtained using the SF-6D instrument. Health state utility scores (SF-6D) are derived from responses to 6 separate

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items indicated on both the SF-36 and SF-12 using a commercially available weighted algorithm derived by the Department of Health Economics and Decision Science at the University of Sheffield, Sheffield, United Kingdom. This algorithm application was used to calculate standardized health state utility values (range: 0.0= “death” - 1.0= “perfect health”) from follow-up survey responses provided by each study subject. One disadvantage of using the SF-6D utility scoring system is that it is based on standard gamble valuation technique performed in the United Kingdom general population, and therefore may not truly reflect US population preferences.

Utility estimates were obtained from the prospective observational cohort study (Clinicaltrials# NCT00799097; NIH: R01 DC005805) evaluating clinical outcomes following ESS for the management of refractory CRS[10]. Utility scores on 168 patients with a mean follow-up of 1.5 years were obtained. Plotting the distribution of post-ESS utility scores demonstrated three naturally occurring tertiles based on the following utility cut-points: Low: 0.00 to 0.55, Moderate: 0.56 to 0.69, and High: 0.70 and 1.00. These utility cut-points were used to define the three refractory CRS Markov health states. Evaluation of potential confounding variables such as age, gender, allergies, asthma, and other comorbidities, demonstrated that there were no differences between the ESS and medical therapy cohorts[12].

The effect value assigned to each Markov state was determined by calculating the mean utility score of all patients within each of the three health states. The mean utility value per health state was used to assign the effect per cycle. The average utility score for patients in the low state was 0.499, moderate group was 0.619, and high group was 0.786 (Table 1).

III. Probabilities

All ESS perioperative complication probabilities were extracted from the medical literature. The literature search involved querying Ovid MEDLINE (1947-Aug 2012) for studies evaluating complications associated with ESS. The search terms: “endoscop$”, “sinus$”, “surgery”, and “complication$” were combined and produced an initial result of 408 studies. To input the highest level of evidence into the model[13], the search was limited to meta-analyses or systematic reviews and yielded a total of 15 articles. The reference lists of all 15 studies were examined to ensure all relevant studies were captured. Data was extracted from four systematic reviews[14-17] and probabilities are presented in Table 1.

Markov state entrance data was obtained from the prospective observational study (Clinicaltrials# NCT01332136) evaluating clinical outcomes of patients who self-selected management with either ESS or continued medical therapy for refractory CRS. Since it has been demonstrated that patients will self-select into either medical or ESS treatment arms based on their baseline level of QoL impairment[18,19], we had to account for this potential confounding variable to prevent inaccurate health state entrance and transition probabilities. To obtain the baseline health state entrance probabilities, all patients were assumed to receive either ESS or medical therapy alone. Therefore, this removed the selection bias associated with patients self selecting into the medical therapy group with better baseline utility scores. Transition probabilities in the medical therapy group were calculated using

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patients with matched characteristics as those in the ESS group to ensure selection bias did not influence the year-to-year comparisons.

As of March 2013, a total of 442 patients were enrolled into both the ESS and medical therapy treatment arms. Following ESS, the proportion of patients entering into each of the three Markov states were: Low = 3.4%, Moderate = 24.1%, and High = 72.4%. Following continued medical therapy, the proportion of patients entering into each of the three Markov states were: Low = 16.1%, Moderate = 38%, and High = 45.9%.

Using patient level data (Clinicaltrials# NCT00799097)[10], transition probabilities were generated for each of the three Markov states based on year-to-year movements of patients through each state (Table 2 and 3). The transition probabilities are supported by two recent studies which demonstrated that patients with refractory CRS receive stable long-term utility improvements following ESS[20] and patients who have significantly reduced baseline QoL are unlikely to receive further improvements from ongoing medical therapy[21].

IV. Costs

A US-based study by Bhattacharyya et al. reported the mean cost of uncomplicated outpatient ESS to be $7,726 (range $7,554 - $7,898)[22]. Based on a recent study from the perspective of the Canadian government, a cost of $3,510 was included in the sensitivity analysis[23]. The cost of ESS with major complication was obtained from the Healthcare Cost and Utilization Project (HCUP) database produced by the US Agency for Healthcare Research and Quality (AHRQ)[24]. Using the diagnostic-related group (DRG) code for sinus and mastoid procedures with major complication and comorbid conditions (MCC) (DRG #135) the mean charge was $57,449. Following cost-to-charge ratio (CCR) conversion, the mean cost of DRG #135 was $16,877 (Table 1). This cost was applied to all major complications requiring hospital admission such as CSF leak, orbital hematoma, and medial rectus injury.

The three potential postoperative complications included in this economic evaluation were: 1) Epistaxis, 2) Infection, and 3) CSF leak (Table 1). Postoperative complication costs were obtained from the Centers of Medicare and Medicaid Services (CMS) physician Fee Schedule using the corresponding CPT code[25] and the HCUP database[24]. For this model a postoperative sinus infection would receive prednisone 30 mg for 10 days ($6.80) along with a broad spectrum antibiotic for 14 days ($302.45)[26]. The most expensive common oral antibiotic (moxifloxacin) prescribed for CRS was chosen in order to stack the costs against ESS.

Based on the reported annual cost of refractory CRS before and after ESS[22] combined with the mean utility levels before and after ESS[27], the moderate utility health state would cost an average of $2,449 per year and the high utility health state would cost an average of $1,118 per year for patients with refractory CRS. Since CRS-specific health care resource consumption is correlated to the severity of QoL reductions[28], the low utility health state was assumed to cost more than the moderate health state (Table 1).

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V. Discounting

An annual discount rate of 3.5% was applied to all future costs used in the reference case[29] and the sensitivity analysis applied a discount rate of 0 and 6%[30]. The reference case did not discount effectiveness but two scenarios were included in the sensitivity analysis where both costs and effects were discounted at a rate of 3.5% and 6%.

VI. Sensitivity Analysis

Following current recommendations, we have performed several sensitivity analyses to test the influence of inherent data variability on the economic outcomes of this model. First we performed multiple analyses evaluating the change in discounting rates and time horizons[8,29-31]. Lastly, a multivariate probabilistic sensitivity analysis (PSA) using a Monte Carlo simulation with 15,000 scenarios was performed. For each parameter category, the following data distributions were applied: cost = gamma distribution, probabilities = beta distribution, and utilities = beta distribution. Probabilities from a chance node with 3 or more branches were assigned a dirichlet distribution to ensure all values were coherent. Each parameter in the model received a mean point estimate and standard error based on the study sample size[32]. Mean point estimates generated from smaller sample sizes possess high levels of parameter uncertainty and therefore received higher standard errors to test several plausible values in the Monte Carlo simulation. Results are presented in both a cost-effectiveness acceptability curve (CEAC) and ICER scatter plot.

The CEAC is a technique used to graphically represent the uncertainty in an economic evaluation[33]. It is a very important outcome for policy makers since it provides the degree of certainty in an economic conclusion at several different willingness-to-pay (WTP) thresholds. The ICER scatterplot is a technique used to visually demonstrate the cost-effectiveness of all the different ICERs generated from the 15,000 iterations of the PSA. The ICERs are plotted onto the cost-effectiveness plane (CEP) which is divided into four quadrants[34]. Quadrant II ICERs are both cheaper and more effective therefore the dominant intervention. On the other hand, quadrant IV ICERs are more expensive and less effective therefore consider dominated and typically rejected. Decisions to accept the alternative intervention in quadrants I and III depend on the maximum ICER for which policy makers are willing to accept (i.e. willingness-to-pay threshold).

Results

I. Reference Case

The reference case managed a cohort of patients with refractory CRS for 30 years and demonstrated that the ESS strategy cost a total of $48,838.38 and produced a total of 20.50 QALYs. The medical therapy alone strategy cost a total of $28,948.98 and produced a total of 17.13 QALYs. The ICER for ESS versus medical therapy alone is $5,901.90 per QALY (Table 4).

II. Sensitivity Analysis

i). Discounting Sensitivity Analysis—Using both the NICE and WHO guidelines[29,30], an additional four scenarios were considered which discount both costs and effects at

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different rates. The results demonstrate that ESS remains the most cost-effective decision with a maximum ICER of $11,030.24 per QALY when both costs and effects are discounted at 6% per year (Table 4).

ii). Time Horizon Sensitivity Analysis—The reference case assumed treatment duration of 30 years to cover the life span of an average patient cohort with refractory CRS. The time horizon sensitivity analysis from this model demonstrates that ESS becomes the most cost-effective intervention following the 3rd year after ESS with an ICER of $49,238.94 per QALY (Table 5).

iii). Multi-way: Probabilistic Sensitivity Analysis—The CEAC is displayed in figure 3 and demonstrates that there is 74.5% and 77.8% certainty that the ESS strategy is the most cost-effective decision at a WTP threshold of $25,000 and $50,000 per QALY, respectively. When plotting the ICERs from the PSA onto the cost-effectiveness plane, it demonstrates that greater then 74% of individual ICER outcomes (blue dots) are below the $50,000 per QALY threshold (Figure 4).

Discussion

This study evaluated the cost-effectiveness of managing a cohort of patients with refractory CRS with either ESS or continued medical therapy alone. Results from this state transition modeling-based economic evaluation suggest that managing refractory CRS patients with the ESS strategy is the most cost-effective intervention. The probabilistic sensitivity analysis demonstrated that ESS was the most cost-effective management option with greater then 74% certainty for any willingness to pay threshold greater than $25,000 per QALY.

Chronic rhinosinusitis is a highly-prevalent inflammatory disease of the nasal and sinus cavities which often reduces patient QoL and produces a significant financial burden on health systems around the globe[35-38] and is associated with substantial productivity costs[5]. Current accepted practice dictates that CRS is initially treated with medical management, since the majority of patients will improve and require no further interventions[35,36,39]. Initial medical therapy typically includes topical high-volume sinonasal saline irrigations, topical intranasal corticosteroid sprays, short-courses of systemic antibiotics and systemic corticosteroids[40-42]. The challenge remains that despite best initial medical therapy, there is a fraction of patients who will fail to respond and continue to suffer with persistent symptoms and reduced QoL. Options for ongoing management of refractory CRS include either ESS or continued medical therapy. An estimated 240,000 ESS procedures are performed yearly in the US (and the rates appear to be increasing), but a decision to pursue surgery can be difficult given trade-offs in up-front costs and risks of surgery versus potential long-term improvements. Data from this study supporting cost-effectiveness of ESS for refractory CRS helps inform this decision and the robustness of findings applies to both governmental and third-party payer scenarios.

Results from the reference case and all sensitivity analyses suggest that when managing patients with refractory CRS, an ESS strategy was the more cost-effective intervention compared to continued medical therapy alone. However, despite the results from this

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economic evaluation, the outcomes must be taken into context given inherent study limitations. In an ideal situation, all data used in a model would be derived from meta-analyses or the economic evaluation would be performed along-side a large randomized controlled trial (RCT). An RCT evaluating ESS versus continued medical therapy would generate accurate patient level costs and effects; however, the feasibility of this RCT is low for several reasons. Ethical implications aside, it would be difficult to enroll patients and ask them to be randomly allocated to medical therapy in the face of strong effectiveness data supporting surgery. On the contrary, some patients may wish to avoid surgery regardless of the possibility of improved benefit given concerns over complications or perioperative discomfort. Additionally, blinding of patients as to whether surgery was performed or not would be impossible without attempts at a sham procedure. Since CRS is a non-terminal disease, the RCT would also require extensive follow-up (i.e. > 30 years) to accurately define long-term costs and effects without extrapolations. The paucity of published RCTs on CRS speaks to these difficulties and no large trials are currently underway or planned for the future. To overcome the lack of RCT data on this topic, we included the highest level of available evidence and patient-level data from two large NIH funded prospective observational studies[43,44]. For all variables which required an assumption, the highest quality available evidence was used to generate values and uncertainty was accounted for using broad ranges and large standard deviations. The sensitivity analysis failed to demonstrate that any of these parameters fundamentally changed the economic conclusions of this study.

For this model we assumed that refractory CRS was a single disease entity; however, it is likely that CRS represents a heterogeneous group of sinonasal inflammatory disorders whose endotypes are just beginning to be explored. It is likely that distinct subclasses of CRS will be defined in the future whose response to either medical therapy or surgery will differ compared to when the CRS cohort is considered as a single entity. If these subgroups are identified, then future economic evaluations will have to account for these differences to further refine the efficient management of this chronic inflammatory disease. However, despite inherent limitations with any model, this economic evaluation is strengthened by its long-term time horizon (30 years), patient-level data on health state transition probabilities, and robust sensitivity analyses including differing discount rates, time-horizons, and multivariate analysis.

Conclusion

Chronic rhinosinusitis is a common inflammatory disease which produces significant deleterious effects on patients and creates a substantial burden to the health care system. This cohort-style Markov decision tree model evaluated the cost-effectiveness of the ESS strategy compared to continued medical therapy alone for patients with refractory CRS. The purpose was to determine if the short-term increases in cost associated with performing ESS are justified in the long-term management of refractory CRS. When the CRS cohort is considered as one single entity, the results from this initial study suggest that employing an ESS treatment strategy to manage patients with refractory CRS is likely to be the most cost-effective intervention compared to continued medical therapy alone. Future studies will need to evaluate the role of ESS in specific CRS endotypes.

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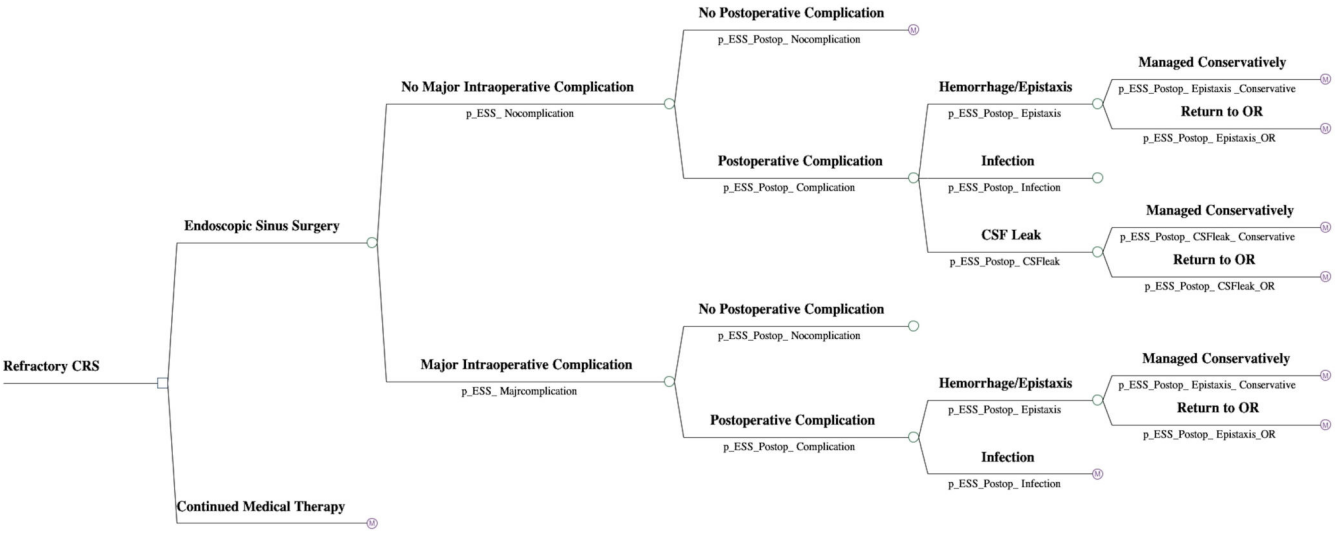

Figure 1.
Economic decision tree for intra- and post-operative outcomes

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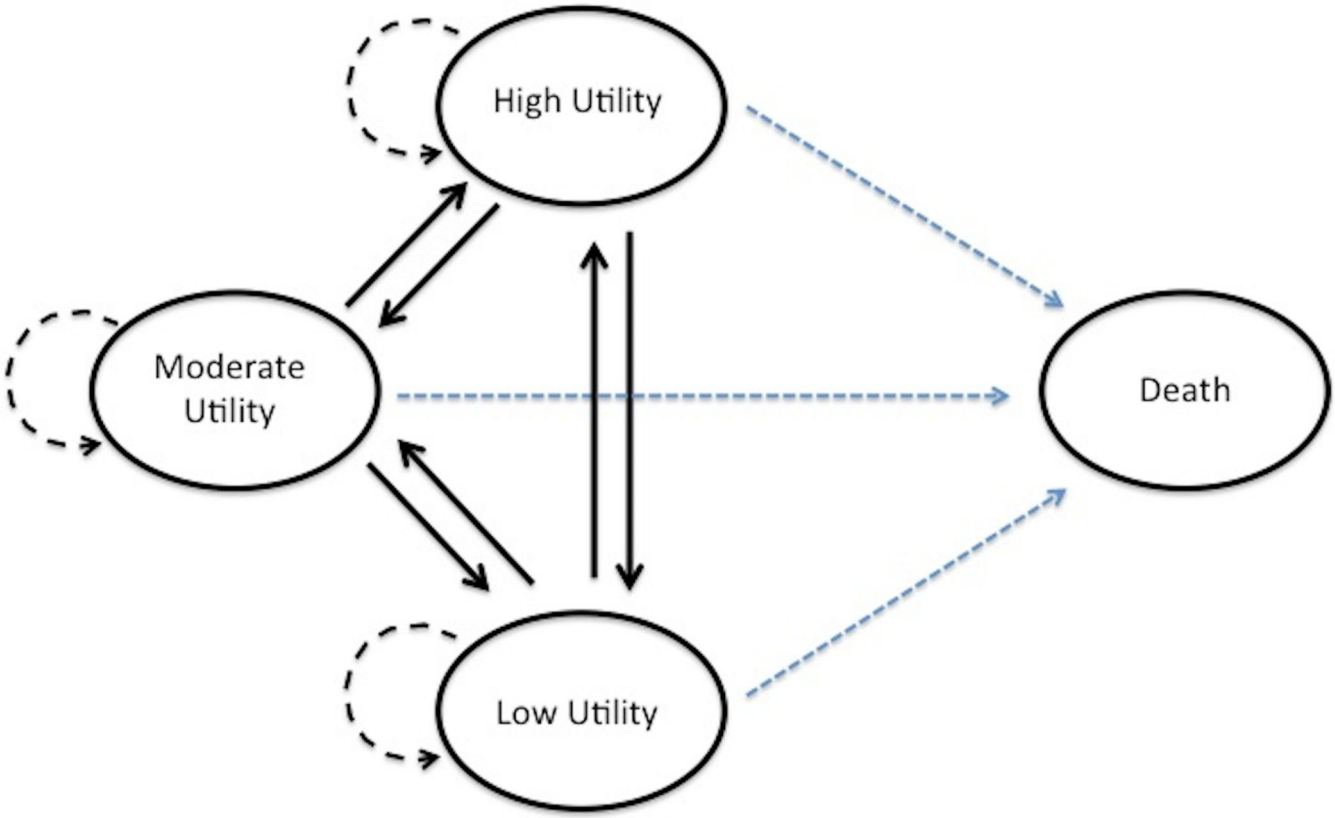

Figure 2.
Markov model bubble diagram for refractory CRS health states

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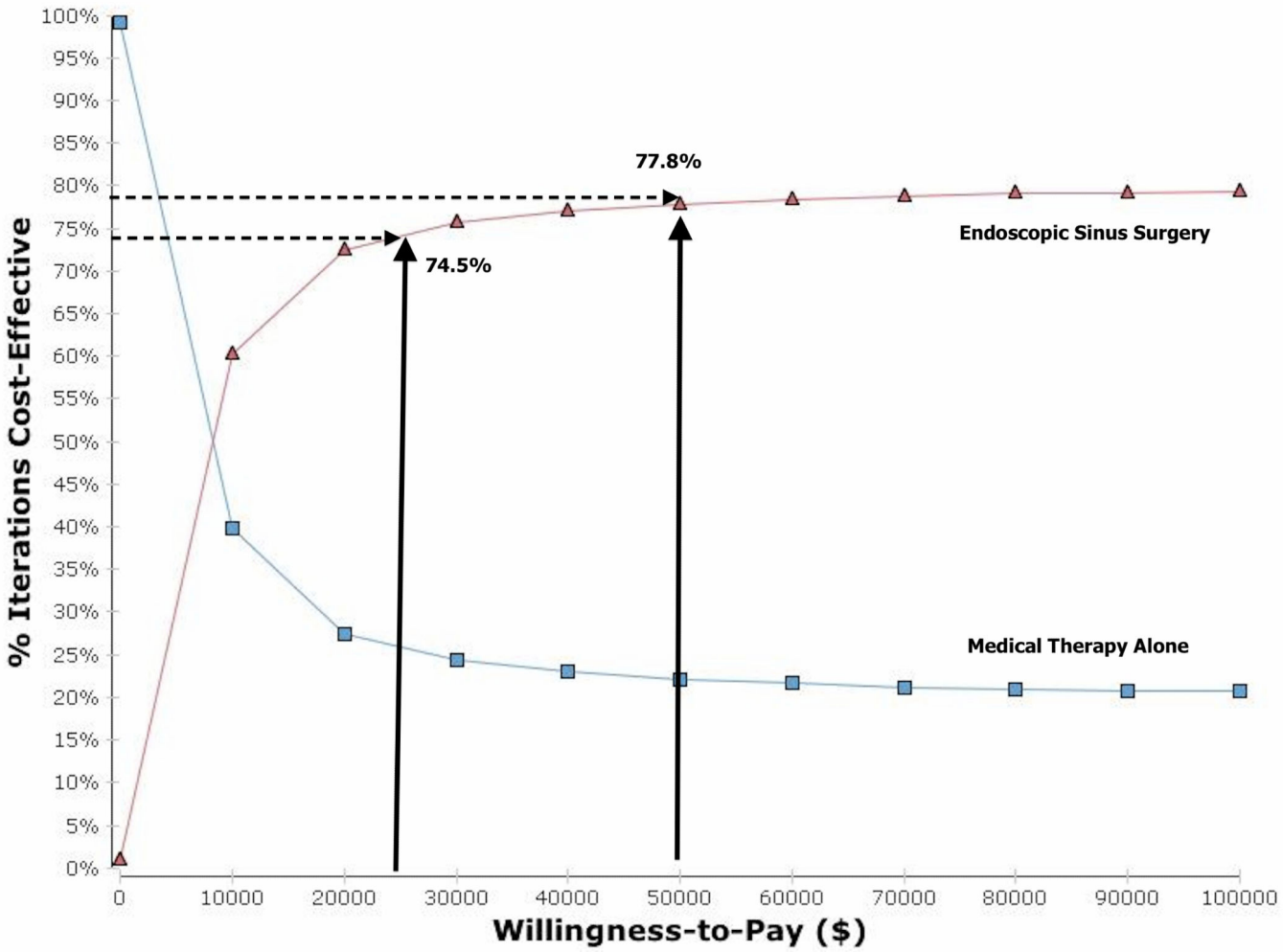

Figure 3.

Cost effectiveness acceptability curve for ESS versus continued medical therapy for refractory CRS

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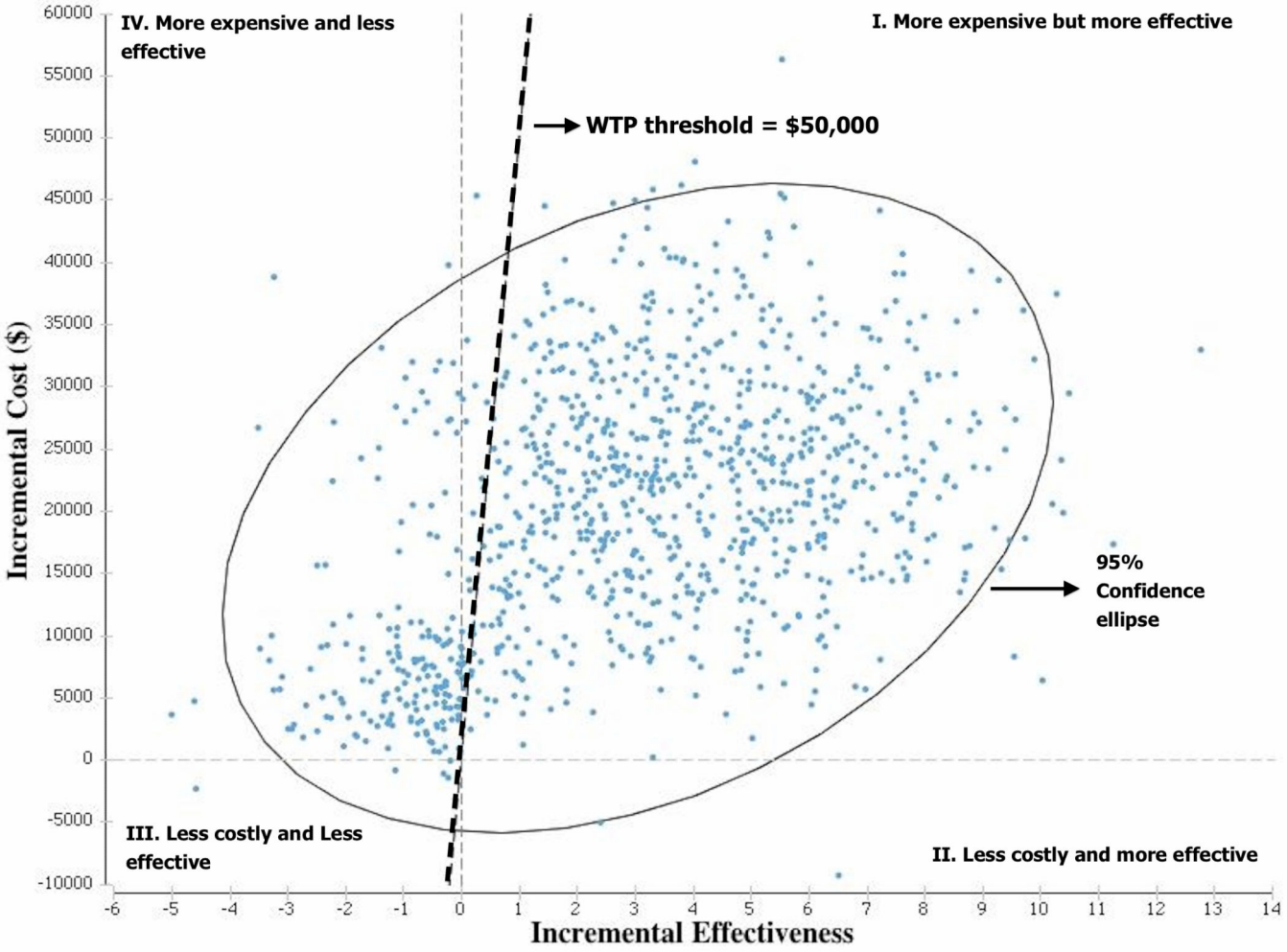

Figure 4.
ICER scatterplot on the cost effectiveness plane

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Table 1

Reference case model data

Parameter	Description	Mean Value	Source
Effect			
u_Healthstate_High	Annual utility value for patients in the High utility Markov state	0.786	Clinicaltrials# NCT00799097; NIH: R01 DC005805
u_Healthstate_Moderate	Annual utility value for patients in the Moderate utility Markov state	0.619	Clinicaltrials# NCT00799097; NIH: R01 DC005805
u_Healthstate_Low	Annual utility value for patients in the Low utility Markov state	0.499	Clinicaltrials# NCT00799097; NIH: R01 DC005805
Probabilities			
p_ESS_Majorcomplication	Probability of major intraoperative complication during ESS	0.01	Ramakrishnan et al.[14]
p_ESS_Postop_Complication	Probability of any postop complication	0.1727	Stankiewicz et al.[15]; Dalziel et al.[16]; Ramakrishnan et al.[14]
p_ESS_Postop_Hemorrhage	Probability that a postop complication is a hemorrhage (ie. Epistaxis)	0.069	Stankiewicz et al.[15]
p_ESS_Postop_Hemorrhage_OR	Probability that postop epistaxis requires OR Tx	0.73	Stankiewicz et al.[15]
p_ESS_Postop_Infection	Probability that a postop complication is an infection	0.93	Dalziel et al.[16]
p_ESS_Postop_CSFleak	Probability that a postop complication is a CSF leak	0.0041	Ramakrishnan et al.[14]
p_ESS_Postop_CSFleak_Conservative	Probability that a postop CSF leak is controlled with conservative Tx	0.19	Lindstrom et al.[17]
Costs			
c_Uncomplicated_ESS	Cost of ESS with no complication	$7,726	Bhattacharyya et al.[22]
c_Complicated_ESS	Cost of ESS with major intraoperative complication	$16,877	HCUPnet DRG #135
c_Postop_Hemorrhage_Conservative	Cost of controlling a postoperative epistaxis with non-operative therapy	$400	(CPT# 99214), (CPT# 31231), (CPT# 30905)
c_Postop_Hemorrhage_OR	Cost of controlling a postoperative epistaxis requiring an OR	$3,500	Assumption based on original cost of ESS
c_Postop_Infection	Cost of a postoperative infection	$559.25	(CPT# 99214), (CPT# 31231), Moxiflaxacin and prednisone
c_Postop_CSFleak_Conservative	Cost of managing a postoperative CSF leak conservatively	$13,594	DRG #52 following CCR conversion
c_Postop_CSFleak_OR	Cost of managing a postoperative CSF leak using operative repair	$16,877	DRG #136 following CCR conversion
c_Highutility	Annual cost for patients in the High utility Markov state	$1,118	Bhattacharyya et al. [15] Soler et al.[20]
c_Moderateutility	Annual costs for patients in the Moderate utility Markov state	$2,449	Bhattacharyya et al. [15] Soler et al.[20]
c_Lowutility	Annual costs for patients in the Low utility Markov state	$3,000	Bhattacharyya et al. 1[5] Soler et al.[20]

NIH, National Institutes of Health; ESS, Endoscopic sinus surgery; Tx, treatment; OR, operating room; CSF, cerebrospinal fluid

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Table 2

Transition probabilities for patients with refractory CRS following ESS

		Time + 1		
		High	**Moderate**	**Low**
Time	**High**	0.809	0.134	0.057
	Moderate	0.857	0.143	0
	Low	0.761	0.239	0

CRS, chronic rhinosinusitis; ESS, endoscopic sinus surgery

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Table 3

Transition probabilities for patients with refractory CRS treated with medical therapy alone

		Time + 1		
		High	**Moderate**	**Low**
Time	**High**	0.882	0.118	0
	Moderate	0	0.889	0.111
	Low	0	0.667	0.334

CRS, chronic rhinosinusitis

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Table 4

Discount rate sensitivity analysis outcomes

Scenario	Cost discount rate	Effect discount rate	Total Cost of ESS	Total ESS QALYs	Total Cost Medical therapy	Total Medical Therapy QALYs	ICER (ESS vs. Medical Therapy Alone)
1 (reference case)	3.5%	0	$48,838.38	20.50	$28,948.98	17.13	$5,901.90/QALY
2	0	0	$71,314.57	20.50	$43,648.29	17.13	$8,209.57/QALY
3	6%	0	$39,579.92	20.50	$22,813.95	17.13	$4,975.07/QALY
4	3.5%	3.5%	$48,838.38	13.23	$28,948.98	11.18	$9,702.15/QALY
5	6%	6%	$39,579.92	10.23	$22,813.95	8.71	$11,030.24/QALY

ESS, endoscopic sinus surgery; QALY, quality adjusted life year, ICER, incremental cost effectiveness ratio

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Table 5

Time horizon sensitivity analysis outcomes

Years from Time = 0	Cost of ESS	Effectiveness of ESS (QALYs)	Cost of Medical Therapy	Effectiveness of Medical Therapy (QALYs)	ICER (ESS vs. Medical Therapy Alone)
1	$10,176.53	0.74	$2,044.19	0.70	$203,308.50/QALY
2	$12,401.17	1.48	$3,931.32	1.38	$84,698.50/QALY
3	$14,542.88	2.22	$5,679.87	2.04	$49,238.94/QALY
4	$16,606.30	2.96	$7,306.79	2.70	$35,767.35/QALY
5	$18,593.60	3.69	$8,826.19	3.34	$27,906.89/QALY

ESS, endoscopic sinus surgery; QALY, quality adjusted life year, ICER, incremental cost effectiveness ratio