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ORIGINAL ARTICLE

Cost effectiveness of bronchial thermoplasty in patients with severe uncontrolled asthma*

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Abstract

Rationale: Based on its clinical effectiveness, bronchial thermoplasty (BT) was approved by the Food and Drug Administration in 2010 for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonist medicines. **Objective:** Assess the 10 year cost-effectiveness of BT for individuals with severe uncontrolled asthma. **Methods:** Using a Markov decision analytic model, the cost-effectiveness of BT was estimated. The patient population involved a hypothetical cohort of 41-year-old patients comparing BT to usual care over a 10-year time frame. The main outcome measure was cost in 2013 dollars per additional quality adjusted life year (QALY). **Results:** Treatment with BT resulted in 6.40 QALYs and \$7512 in cost compared to 6.21 QALYs and \$2054 for usual care. The incremental cost-effectiveness ratio for BT at 10 years was \$29 821/QALY. At a willingness to pay per QALY of \$50 000, BT continues to be cost effective unless the probability of severe asthma exacerbation drops below 0.63 exacerbation per year or the cost of BT rises above \$10 384 total for all three bronchoscopic procedures needed to perform thermoplasty and to cover the entire bronchial tree (baseline = \$6690). **Conclusions:** BT is a cost-effective treatment for asthmatics at high risk of exacerbations. Continuing to follow asthmatics treated with BT beyond 5 years will help inform longer efficacy and support its cost-effectiveness.

Keywords

Asthma, thermoplasty, cost, effectiveness

History

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Introduction

Asthma is a chronic inflammatory disease affecting more than 34 million people in the USA [1]. Asthma represents a serious public health problem for all ages with more than 3000 deaths reported annually [2]. In addition to the physical toll, asthma imposes a significant economic burden to health systems and society. In 2006, asthma accounted for 1.6 million emergency room (ER) visits and 450 000 hospitalizations in the USA [1]. In 2013, the total cost of asthma exceeded \$20.7 billion in the USA [2].

Bronchial thermoplasty (BT) is a novel outpatient bronchoscopic intervention performed three times in series in order to cover the entire bronchial tree. Each procedure is performed in an outpatient setting and is reimbursed separately by second party payers. Using radiofrequency, BT reduces smooth muscle mass in the walls of conducting

airways, decreasing bronchoconstriction [3]. Studies have shown BT decreases airway hyper-responsiveness [3], improves asthma control [4] and lowers exacerbation rates [5]. To date, three randomized trials have addressed the benefit of BT. The first two trials, Asthma Intervention Research (AIR) and Research in Severe Asthma (RISA) compared BT to usual care, but were subject to placebo effect [4,6]. Subsequently AIR2 was conducted comparing BT to a sham procedure to eliminate this effect [7]. Five years of follow-up has shown that the treatment effect and safety is persistent [8]. A recent study sponsored by Boston Scientific Corporation, the manufacturer of the BT catheters suggested an incremental cost-effectiveness ratio (ICER) at 5 years for BT equal to \$5495. However, the model inputs, particularly costs input and rates of healthcare utilization, may have inflated the benefit of BT, and overestimated the actual cost-effectiveness of BT [9]. This study aims to examine, in a very conservative manner, the cost-effectiveness of BT in improving quality of life (QOL) for patients with severe uncontrolled asthma in order not to overestimate its beneficial effect and to be representative of “real world” practice.

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Methods

Model structure

A cost-effectiveness analysis of BT was performed from a healthcare payer perspective. A state-transition Markov model was developed to assess the predicted costs and outcomes of the interventions; BT and usual care (Figure S1 and S2 in the Supplementary Appendix). A Markov model is a diagrammatic representation of all possible states of a disease, the possible transition paths between those states, and the probability of transition according to time and the health intervention in question. In a cost-effectiveness analysis, the costs and health outcomes for each patient during each time cycle are compiled and compared for the interventions in question. For this study, a two health state model was used; “alive” and “dead”, comparing if patients continued to receive standard care or BT. For each time period, an individual could remain in the alive state or transition to the dead state due to either an asthmatic event or from an unrelated cause. Within an alive state, for each time period, an individual could have no event, or suffer from an exacerbation.

The model accounted for all direct healthcare costs including treatments and complications, cost savings from exacerbation reduction, and the QOL benefits from exacerbation and mortality reductions, allowing the costs and QOL benefits between standard treatment and BT to be compared.

Using TreeAge Pro 2014 Suite (TreeAge Software Inc., Williamstown, MA), the model was constructed with the two health states; dead or alive (Figure S2 in the Supplementary Appendix). The uncertain events of the model included: no health change, change in asthma related QOL or exacerbation. Patients could enter the dead state either because of an exacerbation or background mortality. The model assumed a 1 month time cycle with the costs (\$) and effectiveness (quality adjusted life years – QALYs) calculated for each patient for each cycle according to their health-state transitions. All future costs and benefits were discounted at a rate of 3% [10,11].

Two time frames were considered: 10 and 5 years. As BT is a relatively new procedure, only 5 year outcome data are available from the clinical trials. However, according to expert opinion, the clinical response to BT is from irreversible airway changes, with effects lasting a lifetime. To remain conservative yet account for the longer-term clinical benefits, the primary analysis used a 10-year time frame. To correct any possible bias toward BT, we assumed the effect remained constant for the first 5 years, in line with current trial data, then decreased annually by 20% for the remaining 5 years. To further address any possible debate on the time frame selected, a secondary analysis was conducting using a 5 year time frame. Further time frame uncertainty was addressed using deterministic and probabilistic sensitivity analysis.

Patient population

The model population was based on the patient demographics of the AIR2 trial with the cohort entering the simulation at age 41, the mean age of the AIR2 trial population [7] (Table 1). For each cycle, a patient may have no change in

their health state, or suffer an exacerbation. An exacerbation could be managed at home, at a physician’s office, or in an ER. Depending on the severity of the exacerbation, a hospital admission may be required. Once admitted to the hospital, 0.3% of these patients aged 35–54 will die [12]. For each cycle, a patient may also die due to background mortality.

Within each cycle where a patient suffers an exacerbation or dies, their QOL is adjusted for accordingly. In addition, a patient who remains alive without an exacerbation may have an improvement or decline in their asthma related QOL as measured by the Asthma Quality of Life Questionnaire (AQLQ) [13]. As the clinical trials demonstrated BT had an effect on QOL irrespective of exacerbations, this change was incorporated into the model.

Costs

In accordance with the perspective chosen, only direct costs were included. These costs included the cost of: the BT series; treating any BT related complications; and exacerbation treatment adjusted by location and level of care required. Costs were abstracted from the Healthcare Cost and Utilization Project [14] and from published literature. As BT is a newer procedure, its cost is not well standardized and varies among institutions, average Medicare reimbursement rates [15] were used. Further cost adjustment was also made addressing concerns of the impact of one outlier patient in the AIR2 trial who had nine hospitalizations in a year. The analysis was conducted counting these nine hospitalizations once initially, and results compared for without and without this adjustment.

Costs were adjusted to 2013 US dollars using the medical services component of the consumer price index [16]. For abstracted cost data, the mean was used for the base case analysis with upper and lower values used in the sensitivity analysis. Where an upper and lower value was not available, a 25% two-way variance was applied to the baseline value (Table 2).

Effectiveness

The QALY effectiveness measure was used for this study as it enables quality and quantity of life changes to be assessed and results can be compared in the larger healthcare context. Intervention effectiveness was compared via reduction in exacerbations AQLQ changes. Only the AIR2 trial effectiveness data was used in the baseline analysis as it is the only trial not biased to placebo effect [4,6,7]. Alternate trial results were addressed through sensitivity analysis.

In order to convert the effectiveness measures to a QALY, utility weights abstracted from published literature were applied [17–22]. Utility weights range from 0 to 1 with 0 being death, and 1 being perfect health. As asthmatics eligible for the BT have severe asthma, their baseline utility weight was estimated at 0.77 [18–20]. For each 1 month cycle, patients with no exacerbation and no change in AQLQ, remained in the “alive” state with an unchanged utility of 0.77. For a patient who had an exacerbation and recovered, they would have a decrease in the QOL, adjusted depending on the severity of exacerbation and location of care. As the decrease in QOL was estimated to not last for the entire model

Table 1. Base case and key model input.

Clinical events	BT Value (range)	Usual care value (range)	Distribution in PSA	Reference
Age of the cohort at the start of the model (years)	41	41	NA	[7]
Rate of severe exacerbation (exacerbation/subject/year)	0.48 (0.34–0.61)	0.70 (0.46–0.94)	Gamma	[7]
Rate of outpatient visit (visit/subject/year)	0.28 (0.16–0.40)	0.36 (0.18–0.54)	Gamma	[7]
Rate of ER visit (visit/subject/year)	0.07 (0.03–0.11)	0.43 (0.22–0.62)	Gamma	[7]
Rate of hospitalization (event/subject/year)	0.046 (0.038–0.058)	0.026 (0.02–0.03)	Gamma	[7]
Probability of procedure related hospitalization	0.1 (0.07–0.13)		Beta	[7]
Probability of hospital death due to exacerbations	0.003 (0.002–0.004)	0.003 (0.002–0.004)	Beta	[12]

PSA, probabilistic sensitivity analysis.

Table 2. Utilities and cost.

	Value (range)	Distribution in PSA	References
Utilities			
Utility of severe uncontrolled asthma state	0.77 (0.75–0.84)	Beta	[18–20]
Utility of asthma exacerbation	0.72 (0.70–0.74)	Beta	[19]
Utility of asthma exacerbation requiring office visit	0.66 (0.65–0.67)	Beta	[20,22]
Utility of asthma exacerbation requiring ER visit	0.44 (0.43–0.45)	Beta	[21]
Utility of asthma exacerbation requiring hospitalization	0.326 (0.25–0.41)	Beta	[21]
Cost in 2013 US\$			
Hospitalization cost in asthmatics who die	62 202 (52 000–77 703)	Gamma	[12]
Hospitalization cost in asthmatics who recover	5374 (4554–5893)	Gamma	[12,14,28–35]
Outpatient visit cost	107 (76–161)	Gamma	[28–30,32,33,36]
ER visit cost	573 (281.00–742)	Gamma	[28–33,36]
BT Medicare reimbursement	6690 (5000–15 000)	Gamma	[15]

PSA, probabilistic sensitivity analysis.

cycle of 4 weeks, utilities were averaged for the cycle using the following formula:

$$\frac{\left\{ \begin{array}{l} (\text{Utility of the event} \times \text{duration of the event in weeks}) \\ + ((\text{Baseline utility})(4 - \text{duration of the event in weeks})) \end{array} \right\}}{4 \text{ weeks}}$$

Aside from exacerbations, a change in a patients QOL could be identified through their AQLQ. The AQLQ score ranges from 1 to 7. An increase/decrease by >0.5 units is considered an improvement/decline of clinical significance. An improvement was seen in 79% of the BT group compared to 64% of the usual care group in the AIR2 trial. A decline of 3% was seen in the BT group compared to 7% of the usual care group in the same trial. The AQLQ score was transformed to a QOL weight using the referenced formula: $Q = (A - 1)/6$ [23] where Q represents the preference-based QOL weight, and A represents the overall AQLQ score. Results estimated that for patients with an improvement/decline in their AQLQ had a QALY of 0.85/0.69, respectively.

Mortality is incorporated into the model as a health state with all entering patients receiving a utility weight of 0 for all remaining cycles. Exacerbation related mortality was abstracted from published literature and clinical trials [12]. All-cause mortality was abstracted from an age relevant all-case mortality data set and incorporated into the model [24].

For all effectiveness variables, upper and lower estimates used in the sensitivity analysis were based on published 95% confidence intervals. All variables, their values and distributions are reported in Table 2.

Baseline and sensitivity analysis

BT and usual care were compared using ICERs. The ICER is the difference in cost and effect between interventions, for this study, cost/QALY. Using the baseline values of the model, the baseline ICER was calculated. The results were further put in context based on society's willingness to pay (WTP) for a QALY. A value of \$50 000 was chosen for this analysis [25].

A series of sensitivity analyses were performed to test the robustness of the results to changes within the variable estimates. The variables the model was most sensitive to were identified through one-way sensitivity analysis and summarized in a tornado diagram. To assess the combined effect of all uncertainties on the model and to explore the results within the context of population variability, probabilistic sensitivity analysis (PSA) was conducted by assigning a distribution to each variable. The advantage of PSA is that it incorporates any number of parameter uncertainties into the analysis, drawing values from within each variables distribution. Repeating this numerous times, in this case, 50 000 times, allows the model results to be tested for a wide range of variable value combinations, ultimately estimating the total impact of uncertainty on the model. These results were further explored in the context of WTP/QALY and summarized as a cost-effectiveness analysis acceptability curve (CEAC). This curve indicates the proportion of time an intervention would be deemed cost-effective based on the WTP/QALY value.

Additional outcomes

While cost-effectiveness is the primary analysis of this study, other outcomes of interest to the healthcare system were

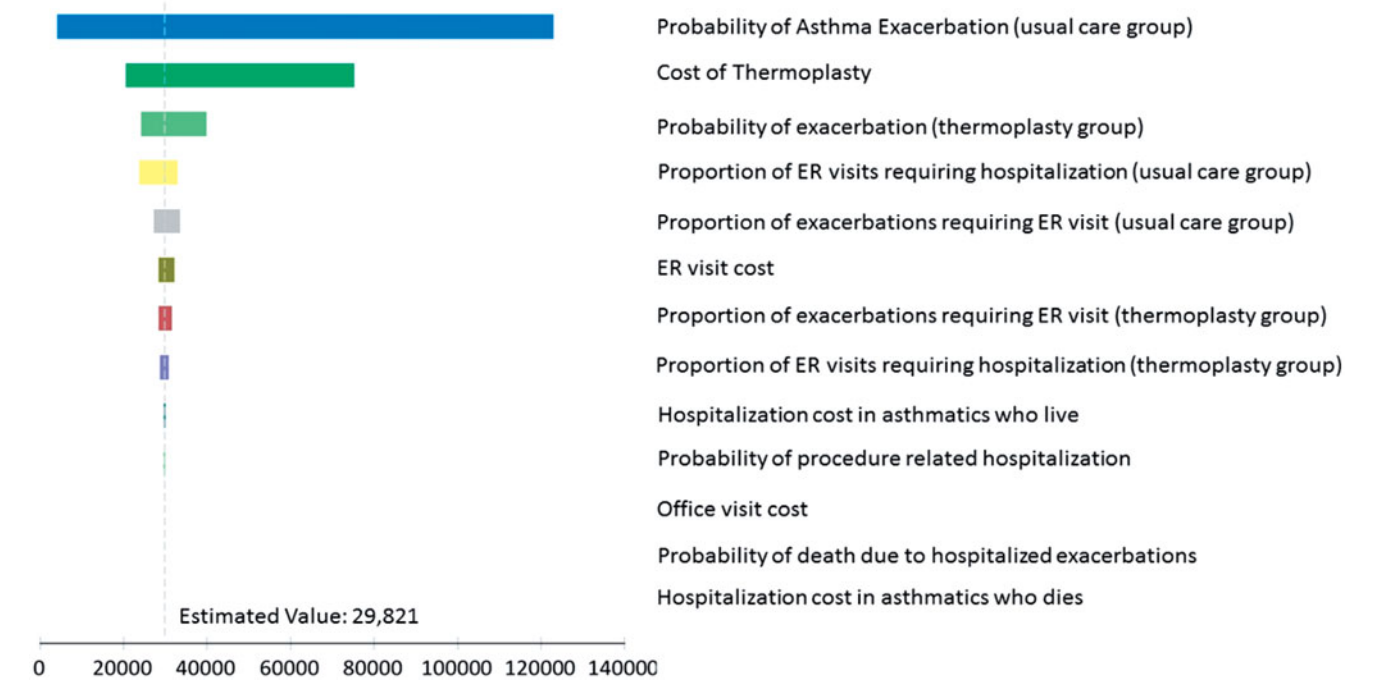


Figure 1. Tornado diagram (ICER) shows that the results are highly sensitive to two variables; probability of asthma exacerbation and by the cost of BT. Severe asthma exacerbation is built as an event in the model, and can result in an office or ER visit, or may result in hospitalization.

abstracted from the model. Tracker variables were used to identify any differences between BT and usual care in terms of number of: (1) exacerbations, (2) ER visits (3) and hospitalizations using a Monte-Carlo simulation. Using the baseline cost of each service, incremental costs between the two groups were estimated. Additionally, potential cost savings from medication reduction were calculated from results reported by Wechsler et al. [8] for patients receiving BT. These results indicated an average ICS dose at 5 years with 12 of subjects being completely of long acting beta agonist (LABA) and 9% weaned off ICS and LABA maintenance medication.

Results

Baseline results

With the model set to baseline values, at 10 years BT was more effective with an incremental QALY gain of 0.18 compared to usual care (6.40 vs. 6.21). However, at baseline, BT also had a higher incremental cost of \$5458 compared to usual care (\$7512 vs. \$2054). The resulting ICER for BT was \$29 821/QALY. At a 5-year time horizon, BT remained cost-effective with an ICER of \$45 170/QALY as compared to usual care.

Sensitivity analysis

The one-way sensitivity analysis and tornado diagram indicated the results were highly sensitive to the cost of BT, and the probability of exacerbations in the BT and usual care group (Figure 1). Threshold analysis identified two thresholds at a WTP of \$50 000 at which BT would no longer be cost effective; if the costs of the BT series exceeded \$10 384; or if the number of exacerbations suffered by the usual care group fell below 0.63/year (Table 3). A two-way analysis of exacerbations and cost of BT as shown in Figure 2

demonstrated that at higher BT cost, a higher probability of exacerbations is required for BT to remain a cost-effective strategy.

The results of the PSA using a hypothetical cohort of 50 000 patients for 10 years produced results similar to the baseline analysis with BT yielding 6.40 QALY's at a cost of \$7514 and usual care yielding 6.22 QALY's at a cost of \$2052. The resultant ICER was \$30 344/QALY. The PSA results were summarized in relation to WTP with a CEAC, with results showing that at a WTP of \$50 000, BT will be cost effective with a 93.3% probability (Figure 3).

Additional outcomes

With 50 000 simulations, at 10 years, the tracker variables indicated the BT group was expected to have \$4633 less in ER and hospitalization costs, and \$2592–\$4244 savings from reduction in medications (Table 4).

Discussion

Asthma is a chronic condition that impacts both the sufferer and society [22,26]. For patients, frequent exacerbations are costly, may require high levels of medical care, may result in death, and have a significant impact on QOL. BT is a potentially cost-effective treatment option.

This study found that for severe asthmatics, at 10 years, BT had an ICER of \$29 821/QALY compared to usual care. At 5 years, BT remained cost-effective with an ICER of \$45 300/QALY. At both time frames, the \$/QALY fell below societies WTP/QALY of \$50 000.

A recent study by Cangelosi et al. found BT to be approximately 10 times more cost-effective [9]. In comparison of model inputs between the two studies, our study included the conservative clinical trial results of the AIR2

Table 3. Uncertainty in model parameters and one-way sensitivity analysis.

	Base case value	Worst case	Best case	ICER \$/QALY		Cost effective At \$50 000
				At parameter worst case (US\$)	At parameter best case (US\$)	
Cost of BT (US\$)	6690	15 000	5000	20 379	74 448	<10 478
Rate of exacerbation in the BT group	0.48	0.34	0.61	24 073	39 381	NA
Rate of exacerbation in usual care group	0.70	0.52	0.88	302 333	8156	> 0.63
Proportion of exacerbations that require ER visit in the BT group	0.15	0.19	0.11	31 233	28 158	NA
Proportion of exacerbations that require ER visit in the usual care group	0.61	0.50	0.70	33 195	26 987	NA
Proportion of ER visits that require hospitalization in the BT group	0.43	0.34	0.58	28 805	30 856	NA
Proportion of ER visits that require hospitalization in the usual care group	0.1	0.05	0.20	33 017	23 824	NA
Cost of office visit (US\$)	107.00	76.00	161.00	29 868	29 797	NA
Cost of ER visit (US\$)	573.00	281.00	742.00	32 240	28 424	NA
Hospitalization cost in asthmatics who recover (US\$)	5374.00	4554.00	5893.000	30 130	29 629	NA
Hospitalization cost in asthmatics who die (US\$)	62 202	52 000	77 703	29 835	29 806	NA

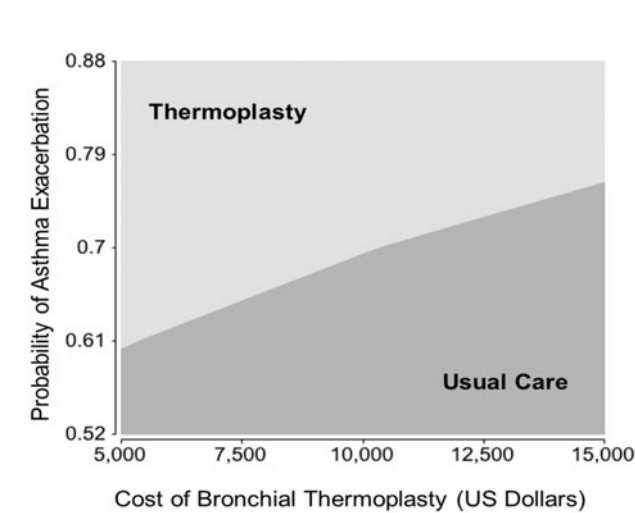


Figure 2. Two-way sensitivity analysis showing the interaction between the yearly probability of exacerbation in the usual care group and the cost of the BT procedure for a WTP threshold of \$50 000 per QALY. As the cost of BT increases, a higher yearly probability of asthma exacerbation is needed for BT to be cost effective and vice versa.

trial. While the clinical benefits of BT of this trial were found to be of a smaller magnitude than other trials, it is deemed by experts to be the closest to real world practice. In further contrast to the Cangelosi study, we chose cost estimates as close as possible to real world costs, and costs that would not bias and artificially inflate the benefit of BT.

The results of this study were robust to changes in variable values as demonstrated by the CEAC results indicating BT will be cost-effective with a 93.3% probability. Further sensitivity analysis found BT would not be cost-effective strategy only under two conditions: if the cost of the BT series exceeded \$10384; or if the probability of severe exacerbations for the usual care group fell below 0.63/year. Regarding its cost, BT is still considered a novel procedure. With time and further standardization, it is reasonable to assume the cost of the BT series would rather fall than rise about the threshold value. Regarding the probability of exacerbations, this value only supports the statement that BT is only cost-effective for

those with severe asthma whose exacerbation frequency is significant enough to be impacted by BT. Furthermore, these thresholds are using the conservative estimate of \$50 000/QALY as the WTP. A less conservative value would find BT to be cost-effective even if the above-stated sensitive thresholds were exceeded.

There are several limitations to this study that warrant further investigation. First, there are only three randomized controlled trials of BT. Due to concerns over the placebo effect of two of the trials (AIR and RISA) [4,6,7], the efficacy used in the baseline analysis was abstracted from the AIR2 trial [7] with the results of the remaining two trials incorporated into the sensitivity analysis. Second, the long-term effects of BT were limited by the long-term follow-up of these clinical trial patients. To date, a follow-up period of only 5 years has been published [8]. The time frame is important as the costs of BT occur only at the beginning of treatment in contrast to usual care where costs continue to accrue. Therefore, the longer the effect of BT persists, the smaller its \$/QALY will become, and therefore strengthening its cost-effectiveness. While an arbitrary time horizon chosen for this analysis, it remained conservative as expert opinion believes BT's effects to be lifelong. To be even more conservative, the model incorporated a declining effect of BT from 5 to 10 years to ensure the beneficial effect of BT was not overestimated given that no clinical data exist for this period. Additionally, we ran the model for the period which clinical data are available. Even at 5 years, BT remained cost-effective with a \$/QALY below \$50 000.

A third limitation of this study included the need to use external data for utility and mortality estimates. Assumptions were made that a utility decline from a BT related asthma exacerbation was similar to an exacerbation not related to the procedure. For inpatient mortality, the study used the hospital fatality rate due to asthma exacerbations of 0.3% sourced from the Nationwide Inpatient Sample for 35–54 years old in the year 2000 [12]. While this estimate ranged between 0.22% and 0.36% between 2001 and 2012 [14], the conservative value was chosen to avoid overestimating deaths from exacerbations in older asthmatics.

Figure 3. Probabilistic sensitivity analysis: cost-effectiveness acceptability curve graphs the probability of cost-effectiveness as a result of 50 000 simulations during which important clinical variables were allowed to vary simultaneously within predefined distributions. The x-axis represents the WTP in US\$ for values ranging from 10 000 to 100 000. The y-axis represents the probability of cost-effectiveness. For a WTP \$50 000, this probability is equal to 93.3%.

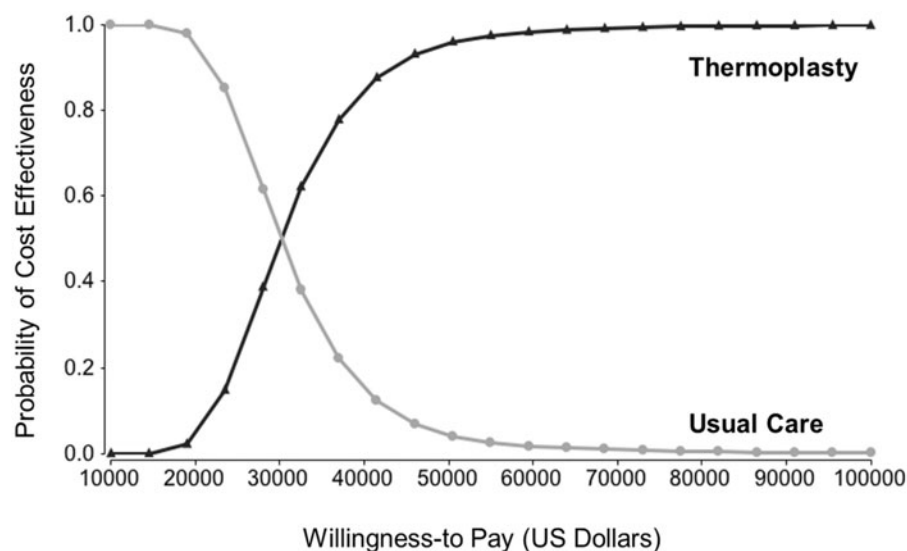


Table 4. Impact on direct medical costs over the 10 year time horizon.

Cost in US\$	BT value (range)	Usual care value (range)
ER visits (<i>n</i>)	0.92	6.1
Hospitalization (<i>n</i>)	0.43	0.62
Estimated total cost from ER visits and hospitalizations ^a	3292	7925
BT procedure cost	6.690	0
Cost of procedure related hospitalization	537	0
Estimated medication cost ^a	28 082 (16 608–59 556)	31 500 (19 200–43 800)

^aCosts are adjusted assuming a 3% yearly inflation rate.

The perspective of this analysis should also be considered when reviewing the results of this study. Using a healthcare perspective, only direct medical costs were included. Had a broader perspective been adopted such as that of society, the inclusion of the opportunity cost of lost time from work and school, or travel time to medical appointments may have made BT even more cost-effective. Another conservative decision was to calculate potential cost savings from medication reductions as an additional outcome, but not include it in the model calculations. The reason for this decision was that medications vary greatly between patients and there is not strong evidence to the degree that BT may reduce medication consumption. Furthermore, our conservative assumptions found BT to be cost-effective. Had medication reductions been included, it may have changed the degree to which BT is cost-effective but would not have changed the overall results.

Finally, all of the results of this study are examined in accordance with the value of the WTP/QALY chosen. The WTP value allows comparison of unrelated interventions and help with healthcare allocation decisions. The value of a QALY remains in debate. The classic value of \$50 000 has become less in favor with a much higher value of 2–3 times a countries GDP gaining acceptance in recent times [25,27]. The US Public Health Service Panel on cost-effectiveness has further debated that although cost-effectiveness should be considered, no threshold should be used to guide healthcare spending decisions [11]. To remain conservative, the lower WTP value of \$50 000/QALY was chosen for this study. While this value continues to be debated, this indecision

should not preclude clinicians from being cost-sensitive in their clinical choices. Furthermore, BT was found to be cost-effective at the lower end of the WTP range. Any increases in the value only strengthen the conclusions of this study.

Conclusion

For patients with severe asthma, BT is a cost-effective treatment option at 5 and 10 years. The cost-effectiveness of BT is highly dependent on suitable patients receiving BT, and that BT costs are controlled. Long-term monitoring of clinical trial patients should be continued to support the belief about BT's long-term efficacy and further support its cost-effectiveness.

Declaration of interest

The authors have no conflicts of interest to disclose.

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Supplementary material available online