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Screening for Lymphangioleiomyomatosis with High-Resolution CT in Young, Nonsmoking Women Presenting With Spontaneous Pneumothorax is Cost-Effective

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At a glance commentary: The diagnosis of lymphangioleiomyomatosis (LAM) is often delayed for several years into the disease course. By screening young and middle aged, nonsmoking women who present with spontaneous pneumothorax with HRCT, an earlier diagnosis of LAM can be made. We have shown such a strategy in the appropriately selected patient population is "cost-effective".

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Rationale: Women with pulmonary lymphangioleiomyomatosis (LAM) who present with a sentinel spontaneous pneumothorax (SPTX) will experience an average of 2.5 additional pneumothoraces. The diagnosis of LAM is typically delayed until after the second pneumothorax. Our hypothesis is that targeted screening of a LAM enriched population of nonsmoking women between the ages of 25-54 who present with a sentinel pneumothorax with high resolution CT (HRCT) will facilitate early identification, definitive therapy and improved quality of life for patients with LAM.

Methods: We constructed a Markov state-transition model to assess the cost-effectiveness of screening. Rates of SPTX and prevalence of LAM in populations stratified by age, gender and smoking status were derived from the literature. Costs of testing and treatment were extracted from 2007 Medicare data. We compared a strategy utilizing HRCT screening followed by pleurodesis for patients with LAM, versus no HRCT screening.

Results: The prevalence of LAM in nonsmoking women between the ages of 25-54 with SPTX is estimated at 5% based on available literature. In our base case analysis, screening for LAM with HRCT is the most cost-effective strategy with a marginal cost-effectiveness ratio of $32,980 per quality adjusted life year gained. Sensitivity analysis showed that HRCT screening remains cost-effective for groups in which the prevalence of LAM in the population subset screened is greater than 2.5%.

Conclusion: Screening for LAM with HRCT in non-smoking women age 25-54 that present with SPTX is cost-effective. Physicians are advised to screen for LAM with HRCT in this population.

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease which classically affects women of reproductive age (1, 2). LAM occurs in 30% of patients with tuberous sclerosis (TSC) (3-5), and also sporadically (s-LAM) in women without TSC. Smooth muscle infiltration and cystic destruction of the lung lead to progressive dyspnea and respiratory failure (6, 7). Owing to the uncommon nature of the disease (approximately 1-3 cases per million) (7) and the nonspecific nature of symptoms, the diagnosis of LAM is often delayed for several years into the disease process (8). The typical high-resolution chest CT (HRCT) findings associated with LAM, are reticular parechymal opacities and thin walled, 2-5mm cysts, often in a diffuse distribution. Pleural effusion and retrocural lymphadenopathy are also often reported (9). Although the gold standard for diagnosis is thoracoscopic lung biopsy, in the appropriate clinical setting and with characteristic imaging features, the diagnosis can be made with high-resolution CT (HRCT) alone(7, 10, 11).

Spontaneous pneumothorax is a major cause of morbidity in patients with LAM (12). Indeed, 70% of patients with LAM have a pneumothorax at some point in their disease course, and pneumothorax is the presenting manifestation in 55% (13). Those with spontaneous pneumothorax are likely to experience one or more recurrences; the average number of lifetime pneumothoraces in a woman presenting with a sentinel pneumothorax is 3.5 (13). The morbidity and added cost from hospitalizations and complications associated with pneumothorax, in addition to the psychological effects from fear of recurrent pneumothorax and/or sudden respiratory death, can be debilitating for LAM patients (14). Surgical and

chemical pleurodesis has been shown to be effective in reducing the occurrence of recurrent pneumothorax (13). Identification of LAM in women who present with spontaneous pneumothorax might allow for earlier diagnosis and interventions to reduce the likelihood of recurrent pneumothorax. The LAM Foundation, a patient advocacy foundation, recommends HRCT screening for all non-smoking women presenting with spontaneous pneumothorax (15). However, spontaneous pneumothorax is a relatively common occurrence in the population at large. In order for screening for LAM to be cost-effective, screening must be restricted to a smaller LAM-enriched population, such as non-smoking women of an appropriate age range presenting with spontaneous pneumothorax. Data to support this position are lacking, however, and primary care providers and emergency medicine physicians in the United States are more likely to treat spontaneous pneumothorax conservatively, without HRCT, pleurodesis or biopsy (16). Information regarding the cost-effectiveness of screening might encourage appropriately aggressive screening and thereby improve outcomes. In addition to early identification of LAM, other cystic lung disorders could be identified early in the disease course allowing for intervention.

Our hypothesis was that for non-smoking women between the ages if 25-54 years who present with spontaneous pneumothorax, screening for LAM with HRCT is cost-effective. Some of the results of this study have been previously reported in the form of an abstract at the American Thoracic Society annual meeting, in May 2009(17).

Methods

Model

We constructed a Markov state-transition simulation model, using data from the literature and a standard software program (Decision Maker; Boston, Massachusetts) to analyze decision trees and perform sensitivity analyses. In our base case analysis, we assumed a 30 year old, non-smoking female presented to an emergency department or primary care clinic with a spontaneous pneumothorax. We evaluated two strategies following presentation and management with simple pleural drainage or observation. The first strategy utilized no further diagnostic or therapeutic intervention following initial management. The second strategy employed HRCT scanning to screen for LAM. Findings on HRCT were categorized in three ways: pathognomonic findings of LAM leading to final diagnosis; indeterminate findings requiring further evaluation; and findings leading to an alternative diagnosis. Those model subjects with CT and clinical findings which were pathognomonic for LAM proceeded to pleurodesis so as to reduce the risk of recurrent pneumothorax. Those with indeterminate findings underwent open lung biopsy to establish a diagnosis. If patients were found to have a histopathologic diagnosis of LAM on open lung biopsy, pleurodesis was performed. If an alternate diagnosis was found after biopsy, and for those with an alternate diagnosis on CT, no further intervention was performed. In companion analyses, we also evaluated a strategy in which chest CT was performed only after the first recurrence of pneumothorax. When patients underwent lung biopsy or pleurodesis, we applied a short-term reduction in quality of life (QOL) associated with the procedure, and also modeled potential procedural complications and costs.

After these initial management decisions, we modeled the risk of recurrent pneumothorax. Based on previously published data, we assumed the risk of pneumothorax was maximal in the months immediately following the initial event, and tapered to 0 over 24

months. Following an initial recurrent pneumothorax, a loss in QOL was applied over the next 12 months, maximal over the first few months and tapering to baseline QOL by one year. We made similar assumptions following all subsequent recurrent pneumothoraces. The model was designed so that any number of recurrences could occur, but the rates were structured in such a fashion so that very few patients would have greater than 4 recurrences (consistent with clinical observation).

Given that the prevalence of angiomyolipoma in LAM is approximately 30-50% (reference), abdominal imaging can often aid in the diagnosis of LAM. In order to explore the impact of adjunctive abdominal imaging, we constructed a model with an additional arm in which patients with cystic lung changes suggestive of, but non-diagnostic, for LAM on chest CT, underwent subsequent abdominal CT to evaluate for angiomyolipoma. In the presence of cystic lung changes and angiomyolipomata, we assumed that patients with LAM could be diagnosed and then pleurodesed without antecedent open lung biopsy. This strategy was then compared to the others for cost-effectiveness.

We utilized a 3 month cycle length in which patients were exposed not only to recurrent pneumothorax, but also age and gender related death. We applied a discount rate of 3% per year by convention (18). All analyses of cost-effectiveness were conducted from the societal perspective.

Simplifying Assumptions

We made several simplifying assumptions in our model. First, we assumed that lung biopsy and pleurodesis, if indicated, would occur in the 3 months following initial presentation.

Next, we treated all patients with any diagnosis other than LAM as having a clinical course subsequent to their sentinel event as being equivalent to those with primary spontaneous pneumothorax. Finally, we assumed that all patients diagnosed with LAM, either on HRCT alone or following lung biopsy, would choose to proceed with pleurodesis.

Summary of Data

LAM

LAM has an estimated prevalence in the general population of between 0.6 and 3 per million (19-22). We were specifically interested in the prevalence of LAM in women who present for medical evaluation with spontaneous pneumothorax, a population enriched for LAM (Table 1). The incidence of spontaneous pneumothorax in women is 1.2-9.8 per 100,000 per year (23-25). Based upon the US census in July of 2007 (26), this equates to between 1,800 and 14,700 pneumothoraces in women per year in the US. Sixty eight percent of these cases are in the age range that is typical for LAM presentation (25-54 years). The most common etiology of pneumothorax in this group is primary spontaneous pneumothorax, which occurs mostly (80%) in smokers (23). Based upon these figures, between 245 – 2000 spontaneous pneumothoraces occur in non-smoking women aged 25-54 years each year in the US. Over a 30 year period, the expected number of spontaneous pneumothoraces in this demographic would be between 7,350 and 60,000. Of the 850 US patients that have been registered in the LAM Foundation Registry since 1995, the number of pneumothoraces estimated to have occurred during a three decade period would be 2550 (3 pneumothoraces per patient x 850 patients).

We therefore predict that between 5 – 30% of all pneumothoraces in the selected demographic (nonsmoking women, age 25-54 years) occurred in patients with LAM.

The gold-standard for the diagnosis of LAM is histopathologic confirmation, usually through thoracoscopic lung biopsy (27, 28). In many cases, however, the diagnosis can be made from HRCT in the appropriate clinical context (such as a history of tuberous sclerosis, chylothorax or angiomyolipoma (7, 10, 11). Koyama and colleagues reported that a blinded review of HRCT scans by expert radiologists in 92 patients with unknown cystic lung disease yielded a diagnostic accuracy of 72% when compared to thoracoscopic lung biopsy. Another study found that 2 expert radiologist were "confident" of the diagnosis of LAM in 79% of cases, with a sensitivity of 100% and specificity of 95% . Therefore, in our base case, we estimated that 80% of patients with LAM could be diagnosed with HRCT alone, and could be managed with pleurodesis without antecedent biopsy. Fifteen percent would be diagnosed after a suggestive HRCT led to biopsy, and 5% would be false negatives (an alternative diagnosis made). Lesur and colleagues performed CT on patients presenting with spontaneous pneumothorax finding that over half had findings of centrilobular emphysema, or cystic changes (29). Based on these findings, we assumed LAM would be excluded in 80% of patients with diseases other than LAM. Of the remaining 20%, we estimated that three quarters would go to lung biopsy and found to have an alternate diagnosis, and the rest would be false positives (those without LAM undergoing pleurodesis based on HRCT alone).

LAM often progresses to respiratory failure and/or respiratory related death. Different groups that have examined series of LAM patients have shown variation in survival between

histological types and symptoms at presentation (30, 31). Johnson and colleagues studied a cohort of patients with LAM in the UK, and found a 10 year survival of 91% (30). Hayashida reported that Japanese women with LAM have 5, 10 and 15 year survival rates of 91%, 76%, and 65% respectively (20). As this Japanese study had the largest dataset, and provided the longest period of follow up, we used these figures to determine annual rates of mortality.

Pneumothorax and Risk of Recurrence

For patients with primary spontaneous pneumothorax, rates of recurrence have been shown to be as high as 30% if no preventative procedure is performed (e.g. pleurodesis), although rates are higher in women and smokers (32-34). The vast majority of recurrences occur within the first 6 months to 2 years following the initial event. After 2 years, rates of recurrence return to baseline risk. For those with at least one recurrence, little data is available on subsequent recurrences. We assumed the rate of second recurrence to be 15%, most occurring in the first 6 months to 2 years, followed by return to baseline risk (32). Pleurodesis after the initial pneumothorax in PSP reduces rates of recurrence to 1.5% (32). We assumed the rate of second recurrence following pleurodesis was 0%.

In patients with LAM and pneumothorax, 70% will have an ipsilateral recurrence (13). Unlike primary spontaneous pneumothorax, risk of recurrence for patients with LAM does not decrease with time (12, 13). Of these patients with recurrence, 60% will have a third recurrence and many will have additional episodes beyond that. Pleurodesis in LAM patients reduces rate of recurrent pneumothorax to 32% (13).

Quality of Life and Life Expectancy

Death is rare with primary spontaneous pneumothorax, occurring in less than 1% of patients (24, 33, 35). It is, however, associated with significant morbidity. Morimoto and colleagues have evaluated pneumothorax, and its impact on quality adjusted life measures (36). Quality of life estimates vary from 1 (perfect health) to 0 (death) (37). After a pneumothorax, life quality is reduced by a factor of 0.37, so the quality adjustment factor is 0.63. After the second and all subsequent pneumothoraces, QOL is reduced by 0.5. This loss of QOL persists for 1 year following each event, and returns to baseline thereafter. In our model, we structured the quality adjustment so that QOL was lowest in the period immediately following pneumothorax and gradually returns to normal over the course of 1 year.

LAM is associated with a progressive decline in respiratory function. Based upon reports from the NHLBI LAM registry and others, we estimated LAM to be associated with a reduction in QOL equal to 0.02 per year (8, 30). Lung biopsy and pleurodesis are also associated with a short-term reduction in QOL. In their study of spontaneous pneumothorax, Morimoto reported QOL to be reduced by a factor of 0.65 with these procedures (36). We assumed this reduction persisted over 14 days following the procedure.

Costs

All costs are expressed in 2007 U.S. dollars. Details of the costing models are described in Table 2. The costs of adverse events included both institutional and professional services. For procedures, office visits, and hospitalizations, average Medicare reimbursement for the corresponding *Current Procedural Terminology* or *Diagnosis-Related Group* codes was used as a proxy for cost. We did not formally include indirect costs, such as lost income due to absence

from work during hospital stays. Costs were subjected to sensitivity analyses to determine how changes in baseline values would affect results.

Alternative Strategies

We also explored the impact of several alternative but plausible strategies upon the cost-effectiveness of screening: performing HRCT only after the first recurrence of pneumothorax, performing adjunctive abdominal CT after HRCT screening, and performance of open-lung biopsy and subsequent pleurodesis in tandem (at a contemporaneous time).

Results

The results of the base case analysis are shown in Table 3. The strategy which employed the HRCT screening strategy was both more costly and more effective. The marginal cost-effectiveness ratio (mCER) of HRCT screening was $32,980 per quality-adjusted life year (QALY) gained. By convention, treatment strategies costing less than $50,000 per QALY gained are deemed to be "cost-effective" (38). We also performed the analysis on female populations with variable smoking status presenting with spontaneous pneumothorax (Figure 2). HRCT screening in these populations was more expensive owing in part to the lower prevalence of LAM. For example, 18-25 year old smokers have a far greater incidence of primary spontaneous pneumothorax than does our base case population (25-54 year old non-smokers). Therefore, the prevalence of LAM in this population is lower, and the costs of screening greater. For older populations, emphysema is responsible for a greater number of pneumothoraces, not only leading to a lower prevalence of LAM, but also to a higher "false positive rate" on HRCT.

This will result in more “unnecessary” lung biopsies which diminishes the cost-effectiveness of screening.

Our initial strategy of HRCT screening after the initial pneumothorax remained the most cost-effective strategy when compared to the alternative strategies of HRCT only after the first recurrence or performing abdominal CT after HRCT. HRCT screening after the initial pneumothorax cost only an additional $8661/QALY gained compared to waiting until after the first recurrence, and just $36,819/QALY gained compared to the abdominal CT arm.

Results of important sensitivity analyses are shown in Figure 3. The results of our model were most affected by changes in the probability of diagnosing LAM based on HRCT findings alone, and the prevalence of LAM in the population tested. If LAM could be diagnosed with HRCT alone and biopsy avoided in 100% of cases, HRCT screening costs as little as $15,679 per QALY gained. Conversely, when we assumed biopsy could be avoided in just 50% of cases, HRCT screening is considerably more expensive ($178,101 per QALY). Likewise the prevalence of LAM in the population tested had a profound effect on our results. At the lowest prevalence rates tested (0.08%) screening is very costly ($85,291 per QALY), whereas at higher prevalence rates (8.4%), screening cost falls well below the “cost-effectiveness” threshold ($26,570 per QALY). This further emphasizes the importance of selecting the appropriate population for screening. There is considerable variability in clinical practice regarding the timing of the performance of open-lung biopsy and subsequent pleurodesis. In our base case analysis, we considered these procedures to be done successively in different settings. We also considered another scenario in which the procedures were done in tandem (one setting). This scenario

would further enhance the cost-effectiveness of the HRCT screening versus the no CT arm ($17,179/QALY gained). As seen in Figure 3, other variables tested had a less profound impact on our results. All other variables and costs used in the model were tested in sensitivity analyses, and did not significantly impact the results of the model over a clinically plausible range (data not shown).

Discussion

We have demonstrated that screening for LAM with HRCT in women presenting with spontaneous pneumothorax can be "cost-effective" in an appropriately selected patient population (non-smokers, age 25-54 years). Based on our assumption of a prevalence of 5% in this population, 20 patients would need to be screened to identify one patient with LAM. Our data indicate that the benefits of early diagnosis, outweigh the costs of screening these unaffected individuals. As is true for all screening tests, our results also indicate that in other populations with a lower prevalence of LAM, HRCT screening is less "cost-effective". Additionally, our results indicate that HRCT screening after the first pneumothorax is more "cost-effective" than waiting until after the first recurrence.

In our model, all benefits from early diagnosis of LAM were derived from pleurodesis, and prevention of additional spontaneous pneumothoraces. In reality, early diagnosis provides many other less tangible benefits that we did not account for in our analysis. For example, novel therapies for LAM are currently being developed and tested. The Cincinnati Angiomyolipoma Sirolimus Trial (NCT00457808) suggested that sirolimus may have a role in the treatment of LAM (39), and provided the basis for The MILES trial (NCT NCT00414648) - an NIH

funded, multi-center, multinational, randomized, placebo-controlled trial of sirolimus in LAM. Other therapies for LAM are also being studied (40, 41). Early diagnosis would provide greater access to such clinical trials, and add to the benefits incurred with testing. Early diagnosis will also allow LAM patients to make informed decisions regarding air travel (42), smoking cessation and oral contraceptive use (43). Family planning and counseling can also be provided as pregnancy can have potentially devastating effects on the health of LAM patients (44). As many patients with LAM progress to respiratory failure and require lung transplantation (45-48), selection of agents for pleurodesis can be of great importance. An early diagnosis of LAM informs the choice of approaches to pleurodesis (such as mechanical abrasion or chemical pleurodesis rather than pleurectomy or talc pleurodesis) that have the lowest risks of perioperative bleeding at the time of transplant (13). Given that renal angiomyolipomas are found in up to half of patients with LAM, earlier diagnosis might also aid in earlier identification of this manifestation of the disease process and related complications such as catastrophic abdominal bleeding(49, 50). Finally, support networks such as the LAM Foundation are available, and provide LAM patients with education, support and a mechanism to facilitate research. While difficult to incorporate in this type of "cost-effectiveness" analysis, these less tangible benefits should be considered.

Our study has several limitations. As with all analyses of this type, our model relies on previously published data. Efforts to account for potential imprecision in parameter estimates are made through sensitivity analysis. Our reliance on epidemiologic data for spontaneous pneumothorax is one such example as inaccuracies in this data could impact the validity of our estimates for the prevalence of LAM in given populations. The studies cited here, although

well-conducted epidemiologic evaluations, are somewhat older and involve disparate populations (23, 24, 51). Absent the availability of direct data, this limitation can not eliminated. Another example of a particularly influential model assumption is the diagnostic accuracy of HRCT (combined with clinical features) for LAM. We had to rely on imperfect, but best available estimates from the literature(10,11).An additional potential limitation of our analysis is that we assume all spontaneous pneumothorax patients who are found to have LAM will go on to pleurodesis. This is not always congruent with the wishes of patients with LAM (14). Patients are biased toward conservative management of first pneumothoraces, and many will choose to manage the initial pneumothorax conservatively, deferring pleurodesis until after the subsequent pneumothoraces. This would certainly impact the cost-effectiveness of testing, but we believe the non-tangible benefits of early diagnosis noted above may balance this effect. Lastly, as we used Medicare reimbursement data as a proxy for costs, our conclusions should be tempered for international readers, as differences in costs in different health systems may lead to different outcomes of the model.

In conclusion, through the use of decision modeling techniques, we have shown that HRCT screening for LAM in non-smoking women age 25-54 who present with spontaneous pneumothorax is cost-effective. As a result, primary care providers and emergency medicine physicians treating this population are advised to consider obtaining a HRCT in this patient population.

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Figure Legends:

Figure 1. Simplified schematic of model. The darkened, square box represents the decision node where the initial decision is made by the practicing clinician (to obtain HRCT or not). Each darkened circle represents a chance node where the likelihood of a given outcome is defined by a probability entered into the model. Each arm of the tree ultimately ends in the Markov node (∞ symbol). In the Markov node, patients progress through different health states dictated by probabilities entered into the model. These probabilities are different, depending on how the individual entered the Markov node (for example, a patient with LAM who gets pleurodesis has a lower probability of recurrent pneumothorax than a patient with LAM that did not). In each cycle (arbitrarily defined as 3 months), patients are subjected to risk of recurrent pneumothorax or age-sex related death. In each state, costs and quality-adjustment factors are applied and tabulated. These cycles repeat until all patients are dead. Outcomes can then be compared for each strategy tested (HRCT versus no HRCT).

Figure 2. Marginal cost-effectiveness ratio (mCER) of HRCT screening for LAM in different populations of women who present with spontaneous pneumothorax. This analysis illustrates the importance of selecting the appropriate patient population for screening with HRCT. In populations with a lower prevalence of LAM, the marginal cost-effectiveness ratio increases dramatically. By convention, treatment strategies with a mCER of less than $50,000 per QALY gained are considered to be "cost-effective". The * denotes the base case.

Figure 3. Tornado plot demonstrating results of important sensitivity analyses. The purpose of sensitivity analyses are to explore the effects of variations in data input on the results of the model. Data input is varied from the lowest clinically reasonable value to the highest (or 95% confidence interval) , illustrating the change in results if the "base case" assumptions are invalid. The marginal cost-effectiveness ratio in dollars per QALY is shown on the x-axis and ranges from $15,000 to $194,000 per QALY. The analyses with arrows at the right end of the band indicate that the results have been truncated because we only plotted marginal cost-effectiveness ratios up to $60,000 per QALY. Values at the top of the figure, such as the probability of diagnosing LAM based on HRCT alone, show a larger effect on cost-effectiveness across their confidence intervals; thus, resolving uncertainty in these measurements would improve predictions of cost-effectiveness. Uncertainty in the value of measurements at the base of the figure has a smaller effect on the results of the analysis.

LAM, lymphangioleiomyomatosis; HRCT, high-resolution computed tomography; QALY, quality-adjusted life-year; mCER, marginal cost-effectiveness ratio.

Table 1. Prevalence estimates of LAM in patients presenting with spontaneous pneumothorax.

Population	Number of Pneumothoraces in Population Per Year	Proportion of Pneumothoraces Secondary to LAM
Women in the United States[1]	1800 to 14,700	0.5 – 4.8%
Women Aged 25-54 years (68%)	1224 to 12,036	0.7 – 6.9%
Non-smoking Women Aged 25-54 years (20%)[2]	979 to 9629	0.8 – 8.4%

1: based on 1.2 to 9.8 spontaneous pneumothorax per 100,000 women per year (23-25),2: estimates that 85 ptx per year are secondary to LAM, and 83 of those are in non-smokers(23)

Table 2. Data Used in Model.

	Base Case	Values Tested in Sensitivity Analysis	Reference
Prevalence of LAM in population tested	5%	0.8% - 8.4%	
Probability of LAM diagnosis on HRCT alone (no biopsy required)	80%	50% - 100%	(10, 11)
Probability of LAM diagnosis after HRCT and biopsy	15%	10% - 40%	"
Probability of negative HRCT in patients with LAM (false negative rate)	5%	1% - 10%	"
Proportion of patients without LAM who undergo lung biopsy	15%	10% - 30%	"
Proportion of patients without LAM who are given LAM diagnosis on HRCT alone (false positive rate)	1%	0% - 5%	"

Proportion of patients without LAM in which LAM is ruled out on basis of HRCT alone (true negatives)	94%	90% - 100%	"
Probability of recurrent pneumothorax in:			
Patient with diagnosis other than LAM and no pleurodesis	20%	16-52%	(32)
Patient with diagnosis other than LAM after undergoing pleurodesis	1.5%	0% - 5%	"
Patient with LAM and no pleurodesis	66%	42% - 90%	(13)
Patient with LAM after undergoing pleurodesis	32%	20% - 52%	"
Probability of a second recurrent pneumothorax in:			
Patient with diagnosis other than LAM and no pleurodesis	15%	10% - 20%	(32)
Patient with diagnosis other than LAM after undergoing pleurodesis	0%	0% - 2%	"
Patient with LAM and no pleurodesis	60%	40% - 80%	(13)
Patient with LAM after undergoing pleurodesis	6.4%	4% - 8%	"
Quality of Life:			
First pneumothorax (short-term)	0.63	N/A	(36)
Recurrent pneumothorax (short-term)	0.45	N/A	
Pleurodesis (short-term)	0.35	N/A	"
Thoracoscopic lung biopsy (short-term)	0.35	N/A	"
LAM (QOL to diminish annually over 20 year period)	0.60	N/A	(8)
Costs			

Pneumothorax[1]	$10,098	$5,000 - $15,000	
Pleurodesis[2]	$20,054	$15,000 - $25,000	
Thoracoscopic lung biopsy[3]	$20,488	$15,000 - $25,000	

1: DRG 95, CPT 99223, 99232 x 2, 33020 x 1, 71015 x 3; 2: DRG 76, CPT 99222, 99232 x 3, 32005, 71015 x 3; 3: DRG 76, CPT 99222, 99232 x 3, 32402, 71015 x 3

Table 3. Results of the base case analysis (30 year old, non-smoking female, presenting with spontaneous pneumothorax).

	Cost	**Effectiveness**	**Marginal Cost**	**Marginal Effectiveness**	**mCER**
	$	QALY	$	QALY	$/QALY
No Screening	$9,467	15.932			
HRCT Screening	$11,642	15.998	$2,176	0.066	**$32,980**

QALY quality-adjusted life years, HRCT high-resolution computed tomography, mCER marginal cost-effectiveness ratio

Figure 1

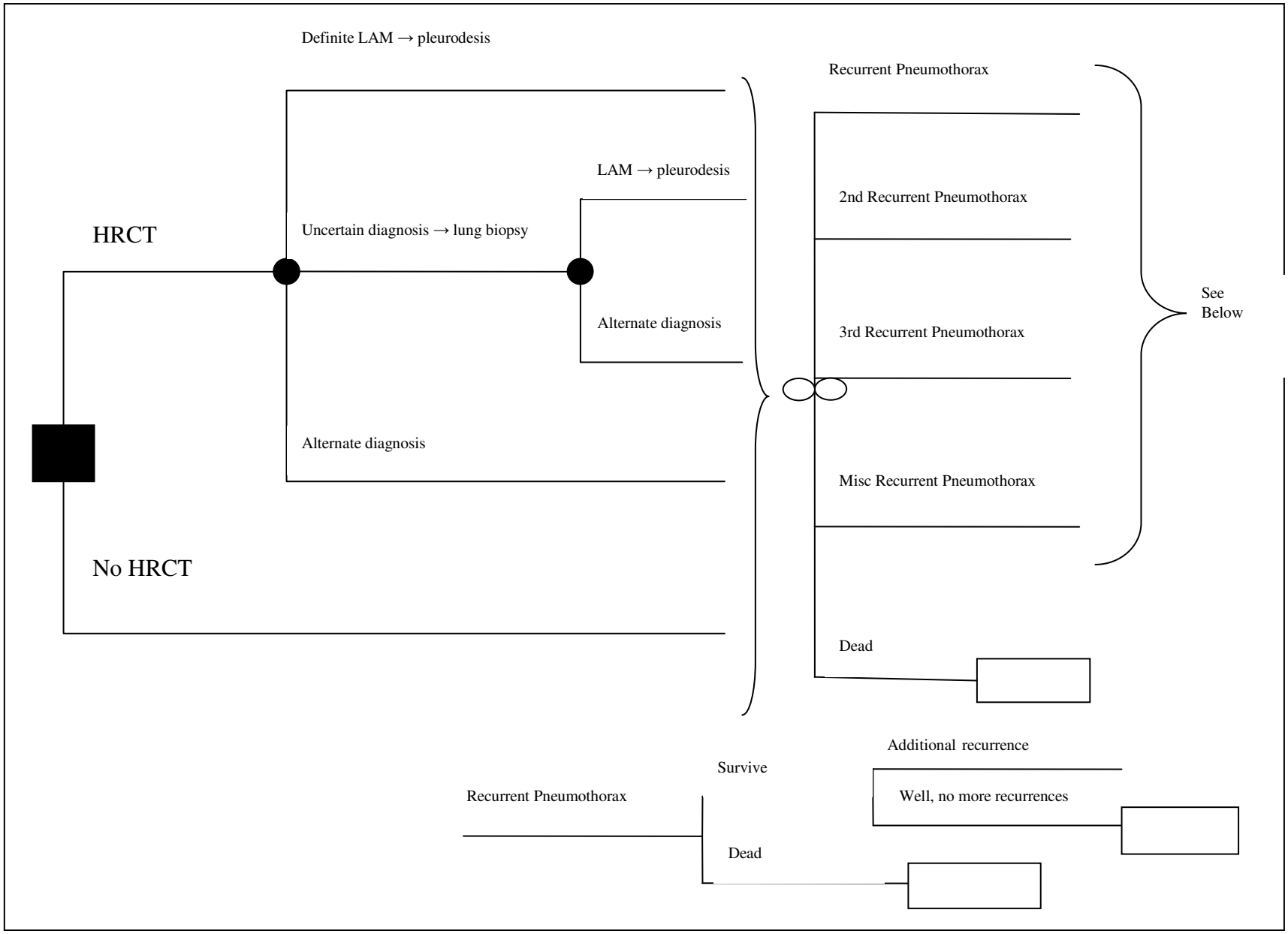

Definite LAM → pleurodesis
Recurrent Pneumothorax
LAM → pleurodesis
2nd Recurrent Pneumothorax
HRCT
Uncertain diagnosis → lung biopsy
See
Below
Alternate diagnosis
3rd Recurrent Pneumothorax
Alternate diagnosis
Misc Recurrent Pneumothorax
No HRCT
Dead
Additional recurrence
Survive
Recurrent Pneumothorax
Well, no more recurrences
Dead

Figure 2

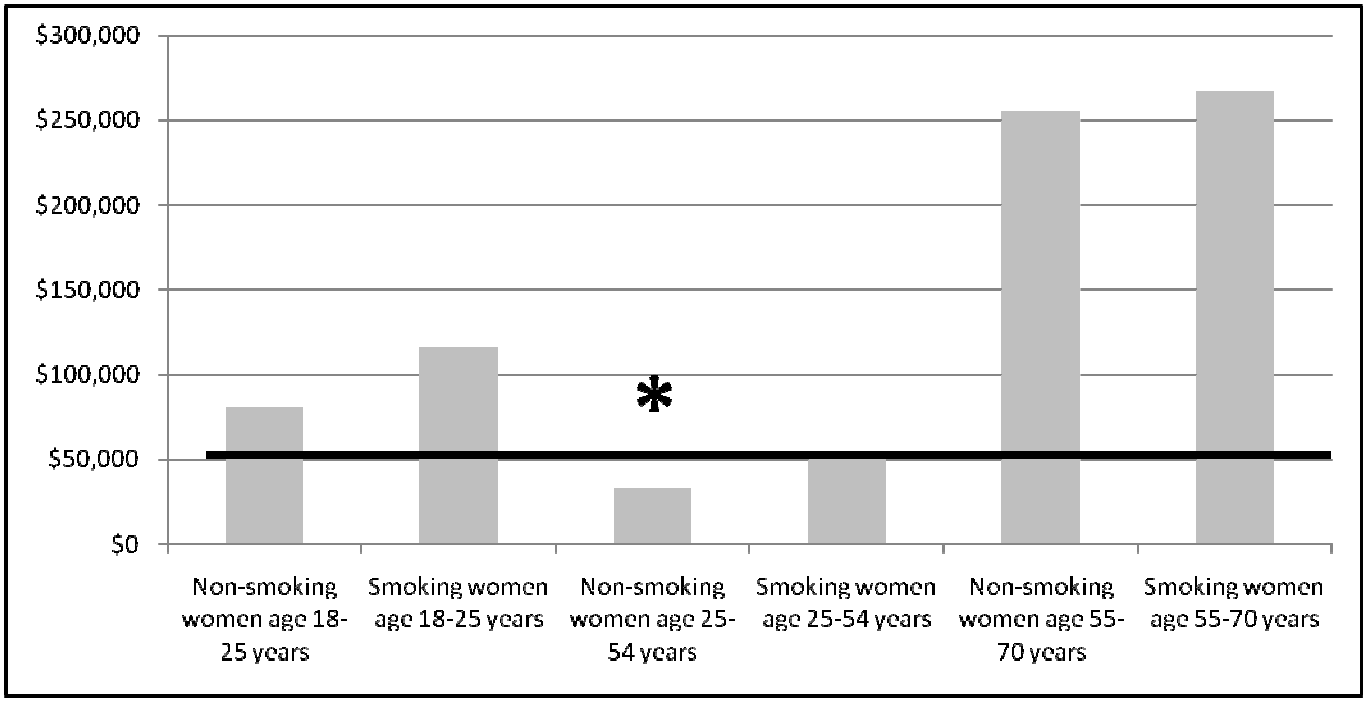
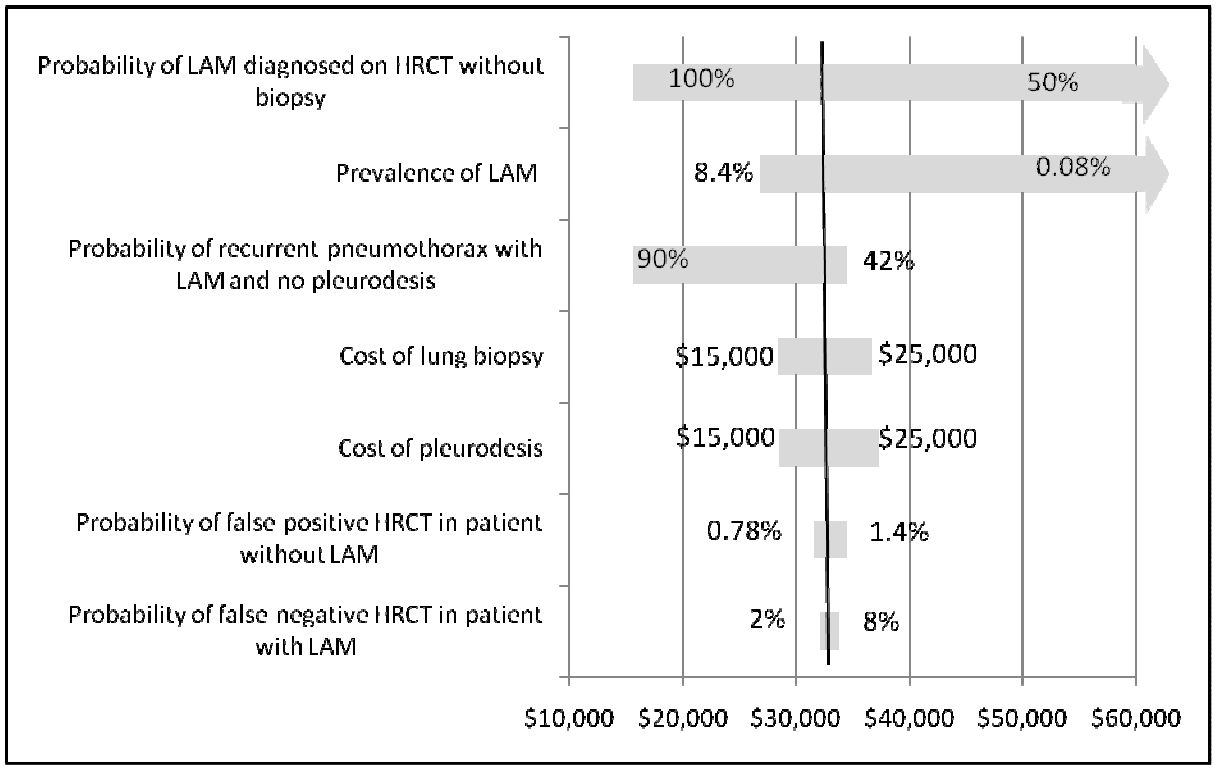

$300,000
$250,000
$200,000
$150,000
$100,000
$50,000
$0
*
Non-smoking women age 18-25 years
Smoking women age 18-25 years
Non-smoking women age 25-54 years
Smoking women age 25-54 years
Non-smoking women age 55-70 years
Smoking women age 55-70 years

Figure 3


Probability of LAM diagnosed on HRCT without biopsy
100%
50%
Prevalence of LAM
8.4%
0.08%
Probability of recurrent pneumothorax with LAM and no pleurodesis
90%
42%
Cost of lung biopsy
$15,000
$25,000
Cost of pleurodesis
$15,000
$25,000
Probability of false positive HRCT in patient without LAM
0.78%
1.4%
Probability of false negative HRCT in patient with LAM
2%
8%
$10,000
$20,000
$30,000
$40,000
$50,000
$60,000