MRI-Guided Focused Ultrasound Surgery for Uterine Fibroid Treatment: A Cost-Effectiveness Analysis

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OBJECTIVE. The purpose of this article is to evaluate the cost effectiveness of a treatment strategy for symptomatic uterine fibroids that uses MRI-guided focused ultrasound as a first-line therapy relative to uterine artery embolization (UAE) or hysterectomy.

MATERIALS AND METHODS. We developed a decision-analytic model to compare the cost effectiveness of three first-line treatment strategies: MRI-guided focused ultrasound, UAE, and hysterectomy. Treatment-specific short- and long-term utilities, lifetime costs, and quality-adjusted life years (QALYs) were incorporated, allowing us to conduct an incremental cost-effectiveness analysis, using a societal willingness-to-pay (WTP) threshold of $50,000/QALY to designate a strategy as cost effective. Sensitivity analyses were subsequently performed on all key parameters.

RESULTS. In the base-case analysis, UAE as a first-line treatment of symptomatic fibroids was the most effective and expensive strategy (22.75 QALYs; $22,968), followed by MRI-guided focused ultrasound (22.73 QALYs; $20,252) and hysterectomy (22.54 QALYs; $11,253). MRI-guided focused ultrasound was cost effective relative to hysterectomy, with an associated incremental cost-effectiveness ratio (ICER) of $47,891/QALY. The ICER of UAE relative to MRI-guided focused ultrasound was $234,565/QALY, exceeding the WTP threshold of $50,000/QALY, therefore rendering MRI-guided focused ultrasound also cost effective relative to UAE. In sensitivity analyses, results were robust to changes in most parameters but were sensitive to changes in probabilities of recurrence, symptom relief, and quality-of-life measures.

CONCLUSION. First-line treatment of eligible women with MRI-guided focused ultrasound is a cost-effective noninvasive strategy. For those not eligible for MRI-guided focused ultrasound, UAE remains a cost-effective option. These recommendations integrate both the short- and long-term decrements in quality of life associated with the specific treatment modalities.

Keywords: cost effectiveness, hysterectomy, MRI-guided focused ultrasound, uterine fibroids

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Uterine fibroids are the most common benign tumors in women of reproductive age, affecting 70–80% of women at some point in their lives and leading to a significant reduction in their quality of life as a result of pelvic and abdominal pain, heavy menstrual bleeding, and fertility issues [1]. Most women with fibroids undergo pharmacologic therapy before other interventions. Although surgical treatments such as hysterectomy and myomectomy have been shown to improve symptoms for women, uterine fibroids remain a significant source of economic burden for affected women and society [2].

The treatment of uterine fibroids accounts for 30–70% of hysterectomies performed in the United States, with annual health care costs for hysterectomies estimated to be greater than $2 billion [3]. In 2005, over 500,000 hysterectomies were performed in the United States [4]. The distribution of the different hysterectomy approaches were abdominal (24%), transvaginal (44%), and laparoscopic (32%), according to a large prospective hysterectomy study illustrating observed complications from these procedures [5]. The increasing utilization of both laparoscopic and transvaginal hysterectomy has resulted in a marked improvement in both the reduction of postprocedure recovery time and overall cost. However, laparoscopic and transvaginal hysterectomy have slightly more stringent eligibility requirements, resulting in over 10% of all patients not qualifying for the procedure, necessitating an abdominal hysterectomy procedure instead [5]. Today, most studies (both ran-

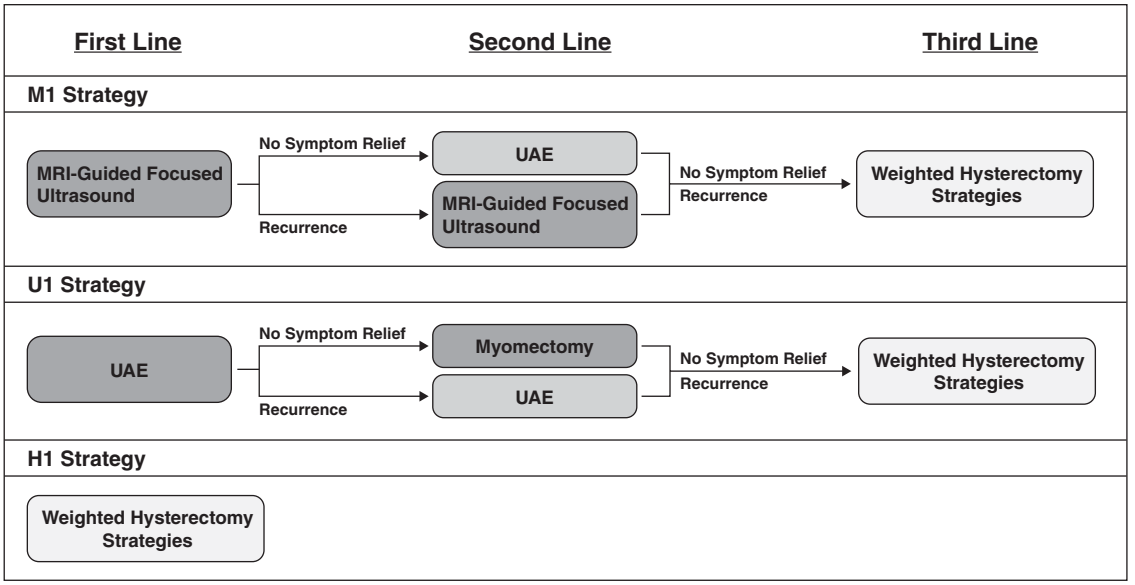

Fig. 1—Overview of treatment strategies. Strategies for symptomatic fibroids are labeled as M1, U1, and H1 to indicate that MRI-guided focused ultrasound, uterine artery embolization (UAE), and hysterectomy are first-line treatments in each strategy, respectively. Secondary to lack of symptom relief, women are retreated with next least invasive strategy. If fibroids recur, previous treatment modality is repeated. In all strategies, maximum treatments are limited to three, with third-line treatment being hysterectomy. Women who are considered for treatment with MRI-guided focused ultrasound or UAE undergo eligibility tests. Ineligible women are treated by next least invasive strategy in following order: MRI-guided focused ultrasound, UAE, myomectomy, and hysterectomy. MRI-guided focused ultrasound and UAE as first-line treatments in diagram represent women who are found eligible to undergo these procedures.

domized and observational) have concluded that transvaginal hysterectomy should be the preferred route of hysterectomy because it is associated with fewer complications, shorter length of hospitalization, and lower hospital charges than abdominal hysterectomy [4].

Added onto the monetary cost of the hysterectomy procedure are both the physical burden of an invasive surgery and the psychologic burden of uterine removal for a benign disease, particularly for younger women who may have wanted to preserve their fertility [6]. This has resulted in the emergence of a spectrum of nonsurgical and less-invasive options for fibroids, including uterine artery embolization (UAE) [4, 7, 8] and, more recently, MRI-guided focused ultrasound surgery [9–11].

UAE is an accepted and important treatment option for uterine fibroids [12]. First introduced in 1995 [4], it has been repeatedly shown to be a safe and effective treatment option [8]. In 2004, MRI-guided focused ultrasound surgery, a novel, minimally invasive, and uterus-sparing option, received clearance by the U.S. Food and Drug Administration for treatment of uterine fibroids [13]. Focused ultrasound surgery is an in situ thermal ablation method that uses highly focused ultrasound waves to heat targeted tissues to a critical level (> 55°C) that results in cell death, leading to thermocoagulation tissue necrosis. The addition of MRI guidance allows excellent target definition, and, very importantly, it can provide real-time "thermometry," with thermal mapping sequences that allow confirmation of thermal dose delivery to the targeted tissue, while also confirming the lack of thermal build-up in nontargeted tissue. MRI-guided focused ultrasound surgery is truly noninvasive, compared with UAE, which is semiinvasive, and hysterectomy, which could be classified as invasive or semiinvasive depending on the hysterectomy type. Previous studies have concluded that MRI-guided focused ultrasound surgery is safe and effective in shrinking fibroids and producing symptom relief [9–11]. Unlike surgical treatments, it is a short outpatient procedure and there are few adverse events or minor complications associated with it [14]. However, MRI-guided focused ultrasound is a new and emerging technology with improving performance. Ablation of the greatest amount of fibroid tissue possible is key to successful and improved MRI-guided focused ultrasound treatment [15], with a recent study showing the impact of technology advancement on fibroid ablation volumes [16]. This study assumes optimal standards of MRI-guided focused ultrasound treatment with ablation volumes of 80% or greater.

Prior cost-effectiveness analyses have compared MRI-guided focused ultrasound with conventional treatments for fibroids [17, 18]. However, the quality-of-life values assigned to women with symptomatic fibroids have often been derived from studies of women with menorrhagia [19], because no utilities specific to uterine fibroids were available for use. Recently, we studied the short- and long-term decrements in health-related quality of life as reported by women with different treatment options specific to uterine fibroids [20]. In the analysis presented here, we used these quality-of-life measurements derived from patient responses to evaluate the true cost-effectiveness of treatment strategies that use MRI-guided focused ultrasound as a first-line treatment (M1) against strategies that use UAE (U1) or hysterectomy (H1) as a first-line treatment (see details in the next section). In addition, we track women as they move through the model to assess the success of treatment, as well as the types of complications that occur during the simulation. The goal of our cost-effectiveness analysis was to determine the optimal treatment strategy for uterine fibroids from a societal perspective, on the basis of contemporary evidence.

Materials and Methods

Institutional review board approval was not necessary because this study was based solely on literature estimates and on publically available de-identified data.

TABLE 1: Model Transition Probabilities

Parameter, Procedure	Base-Case Estimates	Sensitivity Analysis	Source
Treatment eligibility (%)			
Abdominal hysterectomy	100	—	Expert opinion
Transvaginal or laparoscopic hysterectomy	90	—	[40]
Myomectomy	100	—	Expert opinion
Uterine artery embolization	90	88.6–100	[17, 41, 42]
MRI-guided focused ultrasound	35	25–75	[17, 33, 43, 44]
Procedure-related death (%)			
Hysterectomy	0	0–0.03	[5, 43, 45, 46]
Myomectomy	0	0	[42]
Uterine artery embolization	0	0	[46, 47]
MRI-guided focused ultrasound	0	0	[8, 29, 33, 43, 46]
Symptom relief at 0–6 months (%)			
Hysterectomy	100	89–100	[17, 46]
Myomectomy	92	88–93	[8, 47]
Uterine artery embolization	92	80–92	[8, 46, 48, 49]
MRI-guided focused ultrasound	93	70–95	[11, 33, 34]
Fibroid recurrence (%)			
Hysterectomy	0	0	Expert opinion
Myomectomy	3.2	3.2–5.0	[49, 50]
Uterine artery embolization	3.2	2.0–6.9	[47–49]
MRI-guided focused ultrasound	7.4	6.0–7.4	[17, 34]
Major complications (%)			
Abdominal hysterectomy			
Bowel injury	0.2	—	[5]
Bladder injury	0.9	—	[5]
Ureter injury	0.3	—	[5]
Other[a]	5.8	5.8–8.5	[5]
Laparoscopic hysterectomy			
Bowel injury	0.1	—	[5]
Bladder injury	0.6	—	[5]
Ureter injury	0.04	—	[5]
Other[a]	1.6	—	[5]
Myomectomy[a]	6.6	6.6–7.9	[32, 48]
Uterine artery embolization[a]	0.5	0.00–0.66	[17, 31, 46]
MRI-guided focused ultrasound	0	—	[14, 33, 34]
Minor complications (%)			
Abdominal hysterectomy	30	14.8–30.0	[45, 46]
Transvaginal or laparoscopic hysterectomy	20	—	[5]
Myomectomy	11	—	[29]
Uterine artery embolization	6.5	—	[17]
MRI-guided focused ultrasound	0	—	[14, 33, 34]

(Table 1 continues on next page)

Overview of Treatment Strategies

Previous studies report that many women with symptomatic fibroids do not achieve adequate results or durability with a single treatment modality and will undergo repeat treatments [21, 22], except when treated with hysterectomy. Considering this, we modeled three treatment strategies—M1, U1, and H1—in which the first-line treatment was MRI-guided focused ultrasound, UAE, and hysterectomy, respectively. Within the hysterectomy treatment line, we used weighted averages of the true proportions of all three treatment types—transvaginal hysterectomy, laparoscopic hysterectomy, and abdominal hysterectomy—as observed from the large prospective hysterectomy study from which we also draw complications data [5]. We labeled the strategies as M1, U1, and H1 to emphasize that the three treatments highlighted here are first-line treatments, because M1 and U1 may involve second- and third-line treatments that are different from the first-line treatment. Figure 1 summarizes the lines of treatments in each strategy.

The size of the uterus and the number, size, type, and location of fibroids often determines the type of fibroid treatment. Therefore, women who are considered for MRI-guided focused ultrasound or UAE as the first-line treatment undergo imaging tests for eligibility assessment. If they are ineligible because of fibroid size or location, referral is made for the next least invasive treatment. The degree of invasiveness to the patient among treatment modalities is MRI-guided focused ultrasound (least invasive), followed by UAE, myomectomy, and hysterectomy (most invasive). In the case of no symptom relief after treatment, retreatment is with the next least invasive strategy, as shown in Figure 1. In the case of fibroid recurrence, women are retreated by their initial (first-line) treatment modality. We limit the maximum number of treatments to three, with hysterectomy as the third-line treatment. In all three strategies, women are treated either until their symptoms resolve or until menopause. For women at or over 51 years of age (average age of menopause) [23], fibroid symptoms are assumed to resolve of their own accord. Note that myomectomy was included as a second-line treatment strategy only in the U1 treatment arm. All procedural reinterventions are tracked throughout the model so that we can understand the underlying reason behind the reintervention (whether the patient had a fibroid recurrence or a lack of symptom relief). Complications from procedures are also tracked so that the number of major or minor complications attributed to each procedure can be identified.

TABLE 1: Model Transition Probabilities (continued)

Parameter, Procedure	Base-Case Estimates	Sensitivity Analysis	Source
Utility values			
Long-term utilities			
Symptomatic fibroids	0.815	0.528–0.978	[20]
Symptom relief from fibroids	0.944	0.811–0.944	[20]
Postmenopause[b]	1		[20]
Death	0		[20]
Short-term disutilities[c]			
After hysterectomy	0.311		[20]
After myomectomy	0.311		[20]
After uterine artery embolization	0.085		[20]
After MRI-guided focused ultrasound	0.0623		[20]
Costs (US$, 2013)			
Screening costs			
Hysterectomy or myomectomy	375.35	281–469	
Uterine artery embolization or MRI-guided focused ultrasound	1435.16	1076–1794	
Procedure costs			
Hysterectomy (weighted)[d]	6751.91	5064–8440	
Myomectomy	7614.39	5711–9518	
Uterine artery embolization	10,835.32	8126–13,544	
MRI-guided focused ultrasound	6093.90	4570–7617	
Annual follow-up cost[e]	199.78	150–250	
Follow-up cost of uterine artery embolization (first year)	1635.44	1227–2044	
Bowel injury (weighted major complications)	3912.89	2935–4891	
Bladder injury (weighted major complications)	4821.94	3616–6027	
Ureter injury (weighted major complications)	9942.14	7457–12,428	
Cost of other major complications (weighted)	2242.60	1682–2803	
Cost of major complications			
Myomectomy	3579.73	2685–4475	
Uterine artery embolization	6694.92	5021–8369	
MRI-guided focused ultrasound	—	—	
Cost of minor complications			
Hysterectomy or myomectomy[e]	—	—	
Uterine artery embolization	1679.23	1259–2099	
MRI-guided focused ultrasound	—	—	

(Table 1 continues on next page)

Model Overview

We used a microsimulation model with a 6-month cycle length to calculate quality-adjusted life years (QALYs) and lifetime costs. All women enter the model at an age of 40 years. After treatment, women traverse through the health states associated with each strategy. The possible health states include survival or death after the procedure, the presence or absence of postprocedure symptom relief, the recurrence or no recurrence of fibroids, and death from natural causes. Those who reach the no-fibroid-recurrence state remain at risk for fibroid recurrence until menopause. Each health state had a specific cost and utility assigned. The model yielded strategy-specific lifetime costs and quality-adjusted life expectancy values, with total costs broken down into the components of screening, procedure, follow-up, lost productivity, and total complications.

In accordance with standard methods for the calculation of incremental cost-effectiveness ratios (ICERs) [24], strategies were first ranked according to increasing QALYs. If a strategy was more expensive than the next most effective strategy, it was considered dominated. ICERs for all remaining strategies were then calculated. Because there is no single willingness-to-pay (WTP) threshold for medical procedures in the United States, we used a conservative threshold of $50,000/QALY from the widely accepted range of $50,000–$100,000/QALY for the designation of a strategy as cost effective in the United States [25]. Strategies were determined to be cost effective if they had an associated ICER that was less than the designated WTP threshold. Costs and QALYs were discounted at a 3% annual rate. For each strategy, cohorts of 250,000 women were simulated per run, with model outcomes being an average of 5 runs. The microsimulation model was built using TreeAge Pro (version 2012, TreeAge Software).

Model Parameters: Transition Probabilities

Base-case transition probabilities and ranges for sensitivity analysis were obtained through clinical trials, case-controlled studies, and previous cost-effectiveness studies in MEDLINE (Table 1). When deciding which parameters to use in our base-case analysis, multisite randomized clinical trials took priority over single-site clinical trials. The latter took priority over retrospective case-controlled studies and previous cost-effectiveness analyses. Similarly, a higher priority was assigned to more recent studies. In the absence of existing data, model parameters were estimated by one of the radiologist coauthors and a gynecologist coauthor. All-cause mortality probabilities were based on U.S. life tables [26].

Quality-of-Life Measures: Utilities

A utility value is a measure of quality of life and provides a person's relative preferences for different health states compared with death (the worst possible outcome). These values range from 0 (death) to 1 (perfect health). Short- and long-term utility values were obtained from a recent survey on women with uterine fibroids who had undergone MRI-guided focused ultrasound, abdominal hysterectomy, or UAE, whereby quality-of-life measures were determined according to patient responses [20].

An additional 0.015 decrement was applied to women who underwent a final hysterectomy to account for the effect of the loss of fertility (i.e., early menopause) and femininity [6, 17]. Utility values used in our model are outlined in Table 1.

TABLE 1: Model Transition Probabilities (continued)

Parameter, Procedure	Base-Case Estimates	Sensitivity Analysis	Source
No. of missed work days			
Hysterectomy	39.8	—	[17]
Transvaginal or abdominal hysterectomy	22.0	—	[51]
Myomectomy	38.9	—	[17]
Uterine artery embolization	10.0	—	[17]
MRI-guided focused ultrasound	2.0	—	[17]
Daily wage for women ($)	145.64	—	
Discount rate	0.03	—	

Note—Dashes indicate base-case estimates that are single point values or that are unavailable in the literature. Thus, no sensitivity analysis was performed.

[a]Other major complications of hysterectomy include pulmonary embolism, hemorrhage > 1000 mL, and sepsis. Major complications of myomectomy are pulmonary embolism, hemorrhage, sepsis, and laparotomy conversion. The major complication of uterine artery embolization is pulmonary embolism. See the Materials and Methods section for details.

[b]A 0.015 decrement is applied after hysterectomy to account for loss of fertility and femininity [6, 17].

[c]Utility is equal to (1 – disutility).

[d]The hysterectomy procedure costs, utilities, and probabilities were calculated separately for transvaginal hysterectomy, laparoscopic hysterectomy and transvaginal hysterectomy and then converted to a weighted average using observed proportions in a large prospective study of hysterectomy procedures.

[e]See Materials and Methods section for Current Procedural Terminology and diagnosis-related group (DRG) codes used to calculate costs and details of lost productivity calculations. The costs of anesthesia (not shown) were calculated on the basis of age-adjusted weights and were added to procedure costs. Follow-up costs were accrued annually until menopause. Cost of minor complications associated with hysterectomy or myomectomy is accounted for in DRG 742.

Cost Measures

We included all hospital and physician costs incurred, including diagnostic and follow-up imaging and laboratory tests, office visits, procedures, and hospital stays, as well as lost-productivity costs that refer to wages lost by the patient because of missed workdays. Outpatient procedures and physician costs were based on Medicare reimbursements from the American Medical Association designated Common Procedural Terminology (CPT) codes [27]. Hospital costs of inpatient procedures were based on Medicare reimbursements corresponding to specific diagnosis-related groups (DRGs). We use Medicare reimbursements, which are close to true resource utilizations and are standard for use in cost-effectiveness analyses [28]. Table 1 shows the costs associated with different treatments. Detailed justifications for our cost estimates and lost productivity calculations are outlined next.

Screening—All first-line treatment modalities require initial screening, which included two office visits (CPT 99212 and 99213) an ultrasound (CPT 76856) and pertinent laboratory tests (CPT 85025 and 81025). In addition, patients undergoing MRI-guided focused ultrasound and UAE receive an initial MRI scan (CPT 72196).

Procedure—Procedure costs in Table 1 include both hospital and physician costs associated with each procedure based on 2013 reimbursements. Inpatient costs for the transvaginal hysterectomy, abdominal hysterectomy, laparoscopic hysterectomy, and myomectomy procedures were calculated using DRG 742. Physician costs were calculated using CPT 58150 for abdominal hysterectomy, CPT 58260 for transvaginal hysterectomy, CPT 58570 for laparoscopic hysterectomy, and CPT 58140 for abdominal myomectomy. In addition, we have added the cost of anesthesia, based on age-adjusted weight tables, to the procedural cost of transvaginal hysterectomy, abdominal hysterectomy, laparoscopic hysterectomy, and myomectomy. Outpatient hospital and physician costs for UAE were calculated using CPT 37210. Because MRI-guided focused ultrasound is a fairly recent method of treatment of fibroids, the current billing practice for this procedure is to substitute ("crosswalk") a combination of several other CPT codes specific for radiation. We have used the crosswalk codes (CPT 77295, 77334, 77370, 77300, and 77470) provided by the developers of the ExAblate 2000 MRI-guided ultrasound system (Insightec) to calculate the outpatient hospital and physician costs of MRI-guided focused ultrasound.

Inpatient hospital stays after transvaginal hysterectomy, abdominal hysterectomy, laparoscopic hysterectomy, and myomectomy are accounted for in the cost of the procedure as obtained through the DRG. However, because UAE is considered an outpatient procedure, we added the cost of an extra night of hospital stay. The cost of the extra night of hospital stay was obtained from Beinfeld et al. [29] and converted to 2013 U.S. dollars by using the medical care component of the consumer price index.

Lost productivity—To calculate the costs of lost productivity, the daily wage rate for women was obtained from the U.S. Bureau of Labor Statistics [30] and adjusted to 2013 dollars using the 2011 semiannual average consumer price index. The number of days missed per procedure was obtained from O'Sullivan et al. [17].

Follow-up—On the basis of expert opinion, follow-up for transvaginal hysterectomy, abdominal hysterectomy, laparoscopic hysterectomy, myomectomy, and MRI-guided focused ultrasound included one office visit (CPT 99213) 2 weeks after the procedure. Follow-up for UAE included three office visits total, at 2 weeks, 6 months, and 12 months, as well as one MRI (CPT 72196) 6 months after the procedure. Each office visit and MRI appointment also had an additional half-day productivity loss. In the case of fibroid recurrence, women incurred the cost of an office visit (CPT 99213) and a half-day productivity loss.

Complications—Major and minor complications were included if they required significant medical or surgical intervention and cost and had greater than a 0.1% chance of occurrence in multiple studies. Complication costs included hospital, physician, and lost-productivity costs associated with each procedure. Bladder, bowel, and ureter injuries were included among the major complications associated with laparoscopic and abdominal hysterectomy. Because bladder injury can be recognized intraoperatively or postoperatively, costs of these procedures were calculated separately. Intraoperative bowel injury costs included a general surgeon consultation (average of five CPT codes, 99251–99255) and intervention (CPT 51925) in addition to the difference in hospital costs between hysterectomy with major complications (DRG 742) and hysterectomy without major complications (DRG 743). On the basis of the expert opinion of the gynecologist coauthor, postoperative bladder injury costs include readmission to the hospital (DRG 674). To calculate the total cost of hysterectomy-related major complications, intraoperative and postoperative bowel injuries were weighed according to results from a large study in Finland that found 88% of injury was recognized intraoperatively [31]. The costs of bowel and ureter injury were also calculated separately for intra- and postoperative complications and weighted accordingly in the total costs given in Table 1. Other periprocedural major events associated with hysterectomy included hemorrhage requiring transfusion, sepsis, and pulmonary embolism. The costs for these events were assumed to be covered in the hospital cost difference between hysterectomy with major complications (DRG 742) and hyster-

ectomy without major complications (DRG 743). The costs associated with minor complications with transvaginal, laparoscopic, and abdominal hysterectomy included urinary tract and wound infections, hematomas, and febrile events. These were covered in the reimbursement for hysterectomy and did not extend beyond the hospital stay covered by Medicare. Because most major and minor complications occur within 0–30 days after the procedure [31], lost-productivity costs for major and minor complications of hysterectomy were assumed to be included within the lost-productivity costs of the procedure. A weighted average of the three different hysterectomy strategies was used to compute a weighted average of the cost of complications on average for hysterectomy.

We have not included organ-related injuries as a major complication of myomectomy on the basis of a recent clinical trial [32]. Instead, major complications included hemorrhage requiring transfusion, sepsis, ileus, and pulmonary embolism occurring during the hospital stay. The costs of these complications were calculated as the difference in hospital costs between myomectomy with major complications (DRG 742) and without major complications (DRG 743). Minor complications were similar to hysterectomy and covered in the reimbursement for myomectomy.

Pulmonary embolism was the major complication for UAE included in our cost calculation. According to a clinical trial of uterine fibroid treatments, complications after surgical events occur during the hospital stay, whereas medical event complications occur after discharge [5]. The cost of pulmonary embolism after UAE was calculated as a readmission to the hospital using CPT 78588 and DRG 078. Minor complication costs included an office visit and a procedure for dilatation and curettage (CPT 58120). Pulmonary embolism resulted in 5 days of lost productivity, whereas the dilatation and curettage required 1 day of missed work for the outpatient procedure.

For MRI-guided focused ultrasound, we assumed no major or minor complications because these were generally short-term side effects that were treatable with over-the-counter medication.

TABLE 2: Base-Case Results

Strategy	Total Cost ($)	Incremental Cost ($)	Total No. of QALYs	No. of QALYs Gained	ICER (Cost $/ QALY Gained)
H1	11,253	—	22.54	—	—
M1	20,252	8999	22.73	0.188	47,891
U1	22,968	2717	22.75	0.012	234,565

Note—Starting strategies are given in order of increasing quality-adjusted life years (QALYs). Strategies are compared incrementally where each strategy was compared with the next most effective one based on QALYs. Total cost includes lifetime screening, procedural complications, follow-up, and lost-productivity costs. The incremental cost-effectiveness ratio (ICER) is calculated by dividing the cost difference by the QALY difference. Dashes indicate incremental cost and number of QALYs gained are not applicable for the H1 strategy.. H1 = hysterectomy is first-line treatment, M1 = MRI-guided focused ultrasound is first-line treatment, and U1 = uterine artery embolization is first-line treatment.

TABLE 3: Summary of Additional Outcomes, by Treatment Strategy

Outcome	M1	U1	H1
No. of reinterventions/100 women	94	71	0
Due to fibroid recurrence, no. (%)	80 (85)	59 (83)	—
Due to no symptom relief, no. (%)	14 (15)	12 (17)	—
No. of complications/100 women	12	15	29
Total major complications	2 (17)	3 (17)	4 (15)
Total minor complications	10 (83)	12 (83)	25 (85)

Note—The number of reinterventions, percentage likelihood of fibroid recurrence, and lack of symptom relief are listed. Reinterventions after starting treatment strategy may be due to fibroid recurrence or lack of symptom relief. Major and minor complications represent the likelihood of events after procedures. Dashes indicate the H1 strategy would have zero fibroid recurrence and symptom relief for all patients. M1 = MRI-guided focused ultrasound is first-line treatment, U1 = uterine artery embolization is first-line treatment, H1 = hysterectomy is first-line treatment.

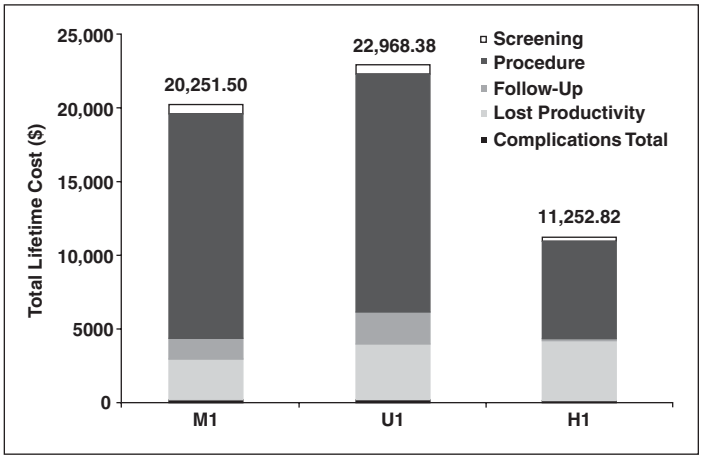

Fig. 2—Total lifetime costs by component. Graph shows breakdown of total lifetime cost associated with each starting treatment strategy. Screening costs include eligibility assessment tests. Procedure costs include starting strategy and any reintervention strategies, and make up largest component of each total. Follow-up costs are laboratory and imaging tests costs incurred after symptom free stage until time of death. Lost productivity costs include wages lost due to absence from work during recovery. Treatment strategies are defined as follows: M1, first-line treatment is MRI-guided focused ultrasound; U1, first-line treatment is uterine artery embolization; and H1, first-line treatment is hysterectomy.

Sensitivity Analysis

We performed a one-way sensitivity analysis and additional threshold analyses to examine the effect of uncertainty regarding input parameter values on model estimates of the ICERs. Table 1 shows the base-case parameter values and ranges evaluated in sensitivity analysis. We use a WTP threshold of $50,000/QALY in our analysis but also evaluate higher WTP thresholds ($75,000 and $100,000), providing extra information for the readers.

Results

Base-Case Analysis

The costs, effectiveness, and ICER output values for M1, U1, and H1 are shown in Table 2. The procedure with the highest cost was U1, followed by M1, and with the cheapest being H1. In order of increasing QALYs, the

ranking was H1, M1, and U1, with U1 being only marginally better than M1. The ICER of M1 relative to H1 was $47,891/QALY gained, and the ICER of U1 relative to M1 was $234,565/QALY gained. Using our set threshold of $50,000/QALY, this results in M1 being cost effective compared with both H1 and U1.

As shown in Figure 2, an analysis of the cost breakdown associated with each strategy showed that procedure costs made up the highest percentage of the total cost incurred for all three strategies. The procedural components of the total costs were greatest for M1 (75%) and U1 (70%) as opposed to H1 (59%). The percentage due to lost productivity was highest for H1 (36%) as compared with M1 (14%) and U1 (16%). The component of total

TABLE 4: Sensitivity Analysis Results

Parameter, High and Low Values	ICER (M1 vs H1)	ICER (U1 vs M1)	Change in Preferred Strategy (WTP $50,000)	Change in Preferred Strategy (WTP $75,000)	Change in Preferred Strategy (WTP $100,000)
Probability of fibroid recurrence (%)					
Uterine artery embolization					
Low, 2.0	34,020.65	60,434.73	—	U1	U1
High, 6.9	127,956.86	Dominated	H1	H1	H1
MRI-guided focused ultrasound					
Low, 6.0	40,573.85	831,370.90	—	—	—
High, 7.4	47,891.19	234,564.74	—	—	—
Treatment eligibility (%)					
Uterine artery embolization					
Low, 88.6	47,139.16	188,868.68	—	—	—
High, 100	41,843.47	90,558.21	—	—	—
MRI-guided focused ultrasound					
Low, 25	48,405.66	243,382.67	—	—	—
High, 75	37,265.70	142,272.84	—	—	—
Utilities					
Symptomatic fibroids					
Low, 0.528	Dominated	41,369.60[a]	H1	H1	H1
High, 0.978	28,226.35	Dominated	—	—	—
Symptom relief					
Low, 0.811	30,527.25	1,521,814.01	—	—	—
High, 0.944	47,891.19	234,564.74	—	—	—
Cost (2013 US$)					
Hysterectomy					
Low, 5063.93 (75%)	55,307.40	125,452.78	H1	—	—
High, 8439.88 (125%)	38,231.31	147,632.45	—	—	—
Myomectomy					
Low, 5710.79 (75%)	45,780.14	119,464.64	—	—	—
High, 9517.98 (125%)	47,806.97	120,330.79	—	—	—
Uterine artery embolization					
Low, 8126.49 (75%)	33,594.51	94,408.93	—	—	U1
High, 13,544.16 (125%)	57,292.00	759,583.17	H1	—	—
MRI-guided focused ultrasound					
Low, 4570.42 (75%)	40,674.07	175,155.15	—	—	—
High, 7617.37 (125%)	52,604.19	116,525.00	H1	—	—

Note—Literature values were tested to determine the robustness of our results. If a parameter was sensitive across the range of literature values, further values were tested to determine the value at which the incremental cost-effectiveness ratio (ICER) crosses the $75,000/quality-adjusted life year (QALY) gained and $100,000/QALY gained threshold. Dashes indicate no change in the preferred strategy. M1 = MRI-guided focused ultrasound is first-line treatment, H1 = hysterectomy is first-line treatment, U1 = uterine artery embolization is first-line treatment, WTP = willingness to pay.

[a]In cases where MRI-guided focused ultrasound was dominated, ICER for uterine artery embolization was calculated by dividing the cost difference between U1 and H1 by the difference in QALYs gained.

costs due to procedure-related complications was lowest for M1 (0.9%) as compared with U1 (1.1%) and H1 (1.2%). Follow-up costs for U1 made up 10% of the total cost, which was higher than all other strategies.

We also tracked the procedural component of the reinterventions and complications to quantify the impact of follow-up procedures and complications on each of the three strategies. As shown in Table 3, on average, 94 and 71 of 100 hypothetical patients required reintervention in the M1 and U1 strategies, respectively. Because all hysterectomy procedures (transvaginal, laparoscopic, and abdominal) are onetime solutions that have a 100% chance of symptom relief and a 0% chance of fibroid recurrence, no reintervention was required on the H1 strategy arm. However, within the H1 strategy, an average of four of 100 women experienced a major complication involving injury to an internal organ, such as the bladder, bowel, or ureters, or a risk of a hemorrhage of greater than 1000 mL, sepsis, or a pulmonary embolism event. In addition, 24 of 100 women had a minor complication, such as a minor hemorrhage or infection. With the M1 strategy, the risks of major and minor complications were considerably lower. Only two of 100 were at risk for a major complication and 10 of 100 were at risk for a minor complication.

Sensitivity Analysis

During sensitivity analysis, we found that as we increased the starting age for women entering the model from 40 to 49 years, the ICER for M1 improved significantly (Fig. 3). U1 was dominated (more expensive and less effective) by M1 at all ages above 41 years. Varying the probability of symptom relief for the M1 strategy showed that, at values below 80% (compared with a base-case value of 93%), U1 became the preferred strategy (Fig. 4).

Table 4 summarizes additional results from our one-way sensitivity analyses. Through testing the maximum and minimum thresholds of 10 key parameters (a total of 20 test scenarios), our recommendations for the cost effectiveness of MRI-guided focused ultrasound only changed in five cases (outlined in Table 4), suggesting the relative robustness of our results. When the probability of fibroid recurrence after UAE was varied to be above 6.9% (compared with a base-case value of 3.2%), the ICER for M1 exceeded the WTP threshold of $50,000/QALY gained, making H1 the preferred strategy. In addition, our results were sensitive to the long-term utility value associated with symptomatic fibroids. At the lowest utility value (0.528), H1 dominated M1, changing the preferred strategy to H1 from M1. Results were also found to be sensitive to changes in the procedural cost of the procedures. At values above 125% of the base-case cost for MRI-guided focused ultrasound and UAE, H1 became the preferred strategy according to our WTP of $50,000/QALY. Subsequently, if the cost of hysterectomy were to decrease to 75% of base-case estimates, H1 would again become the preferred strategy.

If the cost of UAE were to be 50% of our established estimates, the ICER of UAE compared with MRI-guided focused ultrasound would be $29,789/QALY, and the ICER of MRI-guided focused ultrasound compared with hysterectomy would be $22,763/QALY. Given that these two values would both be lower than our established threshold of $50,000/QALY, both treatment types are cost effective for those eligible. On the basis of results of our model, those patients eligible for MRI-guided focused ultrasound should undergo MRI-guided focused ultrasound as a first-line treatment, whereas those not eligible for MRI-guided focused ultrasound should undergo UAE as a first-line treatment. In addition, we found that the point at which the ICER of UAE compared with MRI-guided focused ultrasound exceeds our $50,000/QALY threshold was at a UAE cost of $6173. Therefore, if the cost of

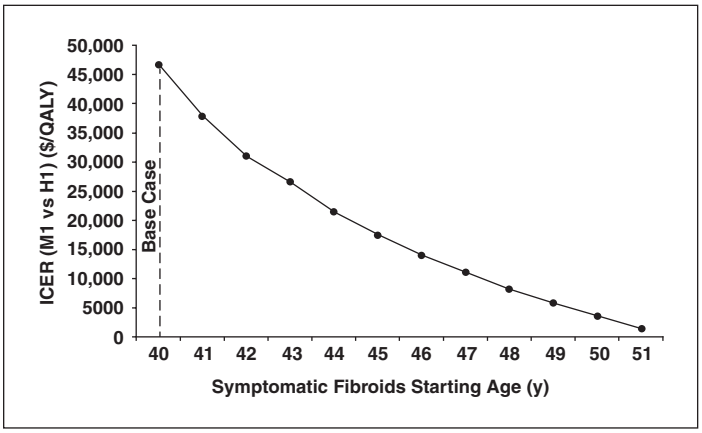

Fig. 3—Sensitivity analysis results for age of starting treatment. Graph shows incremental cost-effectiveness ratio (ICER) for MRI-guided focused ultrasound as first-line treatment strategy (M1) versus hysterectomy as first-line treatment (H1) at different treatment starting ages. Treatment starts at age 40 years in base-case scenario. ICER decreases as treatment start age increases. At age 51 years and over, M1 becomes dominant strategy with lowest cost and highest quality-adjusted life years (QALYs).

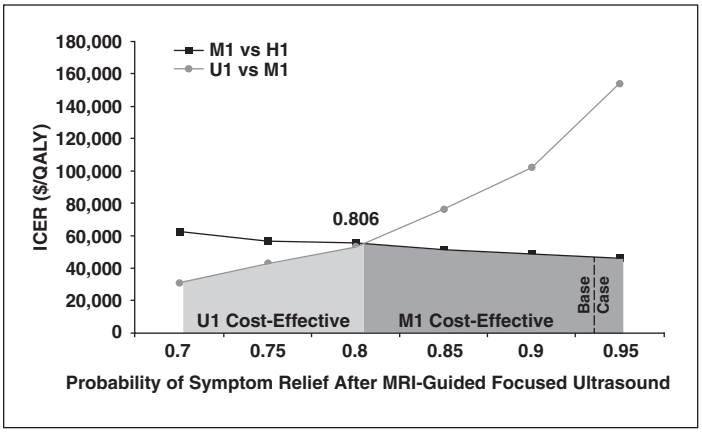

Fig. 4—Sensitivity analysis results for probability of symptom relief. Graph shows change in incremental cost-effectiveness ratio (ICER) for strategy using MRI-guided focused ultrasound as first-line treatment (M1) and uterine artery embolization as first-line treatment (U1) as function of probability of symptom relief after MRI-guided focused ultrasound (base case, 0.93). H1 = hysterectomy as first-line treatment, QALY = quality-adjusted life year.

UAE goes below $6173 (approximately 57% of our base-case cost estimate), both UAE and MRI-guided focused ultrasound would remain cost-effective strategies. We tested these same results against other acceptable WTP thresholds of $75,000/QALY and $100,000/QALY and found that costs were not as sensitive as the probability of fibroid recurrence in UAE and the utility of being affected with symptomatic fibroids.

Discussion

Our analysis shows that, as a first-line treatment of eligible patients with symptomatic uterine fibroids, MRI-guided focused ultrasound is preferred to both UAE and hysterectomy as a cost-effective strategy. MRI-guided focused ultrasound has an associated ICER of $47,891/QALY relative to hysterectomy, which is below the WTP threshold of $50,000/QALY used in our analysis. UAE presented with a much higher ICER of $234,565/QALY, which was far above our WTP threshold, thus rendering it not a cost-effective strategy. Additionally, it is worth noting that the cost effectiveness of MRI-guided focused ultrasound further improves as the starting age for fibroid symptoms increases from 40 to 50 years.

Through sensitivity analyses, our findings were shown to remain stable, provided the probability of symptom relief after MRI-guided focused ultrasound remains above 80%. The lowest reported probability of symptom relief after MRI-guided focused ultrasound in the literature (71%) was from a 2006 study that treated patients under restricted guidelines [33]. A 2007 study with modified less-restrictive selection criteria for MRI-guided focused ultrasound treatment reported 79% symptom relief, sustained for 12 months after MRI-guided focused ultrasound procedure [11]. Although MRI-guided focused ultrasound treatment as a cost-effective first-line treatment strategy is dependent on symptom relief remaining above 80%, technology improvements [16] and more recent clinical outcome studies [16, 34] point toward 80% symptom relief being achievable and the probability of postprocedure symptom relief close to base case of 93% being reasonable. Our results were also shown to be sensitive to the overall cost of MRI-guided focused ultrasound, UAE, and hysterectomy, with the procedure not being as cost effective after reaching 200% of current cost estimates.

Since 2008, there have been two studies published that investigate the cost effectiveness of MRI-guided focused ultrasound. In 2009, O'Sullivan and colleagues [17] concluded that using MRI-guided focused ultrasound and UAE as the first-line treatment of uterine fibroids resulted in similar cost-effectiveness outcomes, with UAE having a slightly higher total cost and QALY value. Although their incremental costs and QALY rankings were similar to those seen in our analysis, their omission of short-term disutility related to treatments resulted in their detection of a much greater gain in effectiveness with UAE relative to MRI-guided focused ultrasound. In addition, the long-term utility associated with symptomatic fibroids in our base-case scenario (0.82) is higher than the value of 0.67 used by O'Sullivan et al. When we decreased the long-term utility value to 0.67 in our sensitivity analyses, we obtained similar results as O'Sullivan et al.; U1 became most cost-effective relative to M1 with an ICER of $58,050/QALY gained. This result suggests that the differences between our conclusions may be largely a result of the differences in the long-term utilities associated with symptomatic fibroids. However, this difference between our estimates is important, because the utility measure of 0.67 was obtained through internal estimates from Insightec, the manufacturers of the ExAblate 2000 system used to perform MRI-guided focused ultrasound [17], whereas our estimate is generated from a comprehensive patient survey [20]. The 0.15 utility difference between both studies is actually greater than the utility difference (0.129) between a woman with symptomatic fibroids (0.815) and a woman with symptom relief from successful treatment (0.944), underscoring the significance of our findings.

The second cost-effectiveness study done most recently was from the United Kingdom, which compared MRI-guided focused ultrasound with the current treatment practice in the United Kingdom. Their conclusion was that including MRI-guided focused ultrasound within current practice is both cost saving and effective [18]. Despite the differences in our health care systems, our results show similar improvements in terms of both cost and outcome.

From a patient's perspective, tradeoffs are involved in each of the first-line treatment strategies. Although a treatment plan in which hysterectomy is the first-line treatment is associated with the lowest lifetime cost and is the only strategy that requires no further intervention after first-line treatment, the invasive nature of a surgical procedure, as well as the definite loss of fertility are points of consideration. Although patients who start their treatment plan with MRI-guided focused ultrasound or UAE are likely to require a second treatment, the breakdown of procedural components in the reintervention methods revealed that 67–79% of these reinterventions would be nonsurgical, such as another round of MRI-guided focused ultrasound or UAE, respectively. In addition, our results suggest that patients choosing hysterectomy as a first-line treatment have substantially higher probabilities of major and minor complications. Only 14% and 16% of the total costs of M1 and U1 are attributable to lost productivity as compared with over 35% of the cost involved in H1. This result is largely due to longer recovery times and time taken off from work related to the surgical hysterectomy procedures.

Furthermore, MRI-guided focused ultrasound surgery is a promising option for women considering future pregnancy. There have been several reports of successful term pregnancies among women who underwent MRI-guided focused ultrasound surgery [35, 36]. The largest data series (which was reported to the U.S. Food and Drug Administration as a part of postapproval medical device monitoring) found a higher rate of successful term delivery, a lower rate of cesarean section, and a lower rate of low birth weight and stillbirth than that previously reported for pregnancy after UAE [37]. Although the starting age of our model is 40, the rate of pregnancy in the United States after the age of 40 has been increasing, according to the latest report from the Centers for Disease Control and Prevention [38]. Therefore, such tradeoffs are often important points of consideration for premenopausal women.

The main limitation of our study is the small population size of MRI-guided focused ultrasound clinical trials, as opposed to hysterectomy and myomectomy studies, which have data on thousands of women. To address this limitation, we used data from more recent and multicenter clinical trials in our base-case scenario and tested the effect of the variability in the literature through extensive sensitivity analyses. We should also caution that not all patients with uterine fibroids are suitable candidates for all therapies, including MRI-guided focused ultrasound [39], and that the results presented here assume patients to be candidates for at least one of the fibroid options. Another limitation of our study is the limited availability

of published data on specific treatment eligibilities and fibroid recurrence, for which we had to rely on expert opinion.

In conclusion, our findings suggest that MRI-guided focused ultrasound is cost effective as a noninvasive first-line therapy relative to both hysterectomy and UAE for patients eligible for treatment. For patients who are not eligible for MRI-guided focused ultrasound, UAE, and hysterectomy remain important treatment options. Because MRI-guided focused ultrasound is an evolving procedure that is constantly being improved, our estimates regarding the number of repeat procedures and quality-of-life values after MRI-guided focused ultrasound may be conservative. To our knowledge, this is the first cost-effectiveness analysis to include short- and long-term fibroid-specific quality-of-life decreases (disutilities) related to MRI-guided focused ultrasound, UAE, and hysterectomy. This approach strengthens our results as we take into account the difference in the quality of life and duration of recovery after each treatment option.

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