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ORIGINAL RESEARCH

Comparison of Costs, Re-Intervention Rates, and Length of Hospital Stay for Three Uterus Sparing Interventions for Uterine Fibroids: A 2-Year Retrospective Claims Analysis

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Purpose: To describe two-year post-operative outcomes, and healthcare utilization of three uterus-sparing interventions used to treat women with intramural and/or subserosal uterine fibroids.

Subjects and Methods: This was a post-market, randomized, prospective, multi-center, longitudinal, interventional, and comparative clinical study to evaluate the costs and health outcomes of LAP-RFA vs the standard uterine conserving technologies (myomectomy and UAE) for the treatment of symptomatic uterine fibroids in women who desire uterine conservation. For this RCT study, 54 subjects were randomized on a 1:1 ratio across the three procedures and followed out to two years. Their results were compared to retrospective US insurance claims from the IBM MarketScan® Commercial Database from 2017–2020 for 96,854 women who underwent a uterus-sparing procedure for fibroids.

Results: Mean ambulatory surgical center costs and the mean out-patient hospital costs were lowest for LAP-RFA ($13,134 and $14,428) and highest for UAE ($28,214 and $19,131). The total two-year re-intervention rate of any subsequent procedure (AM, LM, LAP-RFA, or UAE) was lowest in AM group (0%) followed by LM (4.2%), LAP-RFA (11%), and UAE (33%). Mean peri-operative reintervention costs and the mean reintervention total costs were $2429 and $5939 for LAP-RFA, $2122 and $8368 for LM, $4410 and $11,942 for AM, and $8113 and $46,692 for UAE subjects. In the RCT study, the average length of hospital stay was significantly less for the LAP-RFA group subjects (8.2 hours) in contrast to both the laparoscopic myomectomy group subjects (16.0 hours) and the abdominal myomectomy group subjects (33.6 hours). Despite the small numbers, two-year reintervention rates followed a similar pattern as the IBM MarketScan data.

Conclusion: In comparing these three non-invasive approaches, LAP-RFA was associated with the lowest peri-operative cost, and UAE was associated with the highest peri-operative cost. Further studies are needed to assess the cost, effectiveness, and subject satisfaction with each procedure.

Keywords: health economics, leiomyomas, interventional, cost/burden

Introduction

Uterine fibroids are benign masses found in at least 25% of reproductive-age women, with Black women bearing the greatest burden.[1,2] Indeed, 30% of the women between 40 and 60 years of age show the presence of fibroids, though many are discovered incidentally.[3] Fibroids are associated with symptoms of menorrhagia, dysmenorrhea, infertility, pelvic pain, anemia, bloating, urinary issues (retention or pressure), and dyspareunia.[4] In the last quarter century, new less-invasive surgical treatments have become available that allow women greater choices regarding fibroid treatment while maintaining uterine preservation.[5] Multiple studies have described both subject outcomes and overall cost of

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excisional methods such as laparoscopic myomectomy, abdominal myomectomy, hysteroscopic myomectomy, and hysterectomy for symptomatic fibroids.[6] While excisional methods account for the majority of fibroid surgical procedures,[7] less invasive procedures such as hysteroscopic and laparoscopic radiofrequency fibroid ablation (LAP-RFA) and uterine artery embolization (UAE) are being offered in an increasing number of centers across the United States (U.S.) In 2016, we sought to compare the costs and health-related outcomes of three minimally invasive therapies for the treatment of symptomatic fibroids: myomectomy, LAP-RFA, and UAE. The TRUST (Treatment Results of Uterine Sparing Technologies) study, a randomized controlled trial (RCT, ClinicalTrials.gov Identifier: NCT02163525) was initiated in the US following the successful launch of a similar study (Laparoscopic Myomectomy vs LAP-RFA, ClinicalTrials.gov Identifier: NCT015663783) in Canada.[8] The Canadian RCT compared the detailed costs (direct and indirect) of both procedures after three months of follow-up. Our goal in the US RCT was to focus not only on the costs of the three uterine-sparing procedures available at centers in the US but to also evaluate the longer-term health-related outcomes associated with each procedure. Yu et al published the health-related outcomes after one-year of follow up but it was too early to examine the costs of reinterventions.[9] This paper presents the two-year follow-up of the US RCT health-related outcomes in addition to the associated estimated costs of the procedures and reinterventions using the most currently available IBM MarketScan® data of commercial cases.

Materials and Methods

This was a post-market, randomized, prospective, multi-center, longitudinal, interventional, and comparative clinical study to evaluate the costs and health outcomes of LAP-RFA vs the standard uterine conserving technologies (myomectomy and UAE) for the treatment of symptomatic uterine fibroids in women who desire uterine conservation. Subjects were identified and recruited from clinics, hospitals, and each investigator's practice. All subjects were randomized on a 1:1 ratio to one of the two groups. Group 1 subjects were those who were randomized to either myomectomy (laparoscopic or abdominal) or LAP-RFA and Group 2 subjects were those randomized to either uterine artery embolization (UAE) or LAP-RFA. Written informed consent was obtained for all study participants by the Principal Investigator or his/her designee according to Good Clinical Practices (GCP) guidelines established by the US Food and Drug Administration, international standard EN ISO 14155–1:2020 Clinical Investigation of Medical Devices for Human Subjects, and the guidelines delineated in the Declaration of Helsinki. A full listing of the clinical sites with corresponding IRB can be found in Appendix 1.

The LAP-RFA procedures in this study were performed using the Hologic Acessa LAP-RFA System™ with or without the addition of the optional guidance system. The Hologic Acessa LAP-RFA System™ is an electrosurgical radiofrequency generator and accessories that is designed to deliver monopolar radiofrequency (RF) energy to tissue through a handheld disposable electrosurgical RF probe. Although the primary focus of this paper is on the results at 24 months, the following information continues to be collected by mail and phone at 3, 6, 12, 24, 36, 48, and 60 months following the procedure:

- Post procedure quality of life and fibroid symptom severity assessments
- Procedural and post-procedure complications
- Post-procedure Interventions, for the same diagnosis, (ie, medication use change, clinic visit occurrence, surgical treatments, hospitalizations, etc).
- Pregnancy

For this RCT study, results were compared to retrospective US insurance claims analysis from the IBM MarketScan® Commercial Database from 2017–2020 for 96,854 women who underwent a uterus-sparing procedure for fibroids. Of those, 25,086 subjects underwent abdominal myomectomy (AM) only or combination, 18,873 underwent laparoscopic myomectomy (LM) only or combination, 7262 underwent uterine artery embolization (UAE) only, and 270 underwent laparoscopic radiofrequency ablation (LAP-RFA) only or combination. Two-year reintervention data were also available.

Total costs were divided into the categories of procedure, reinterventions, and complications. For example, the procedure category includes costs for operating room and recovery room time, among others, while supply costs include

items such as sterile and non-sterile supplies. All charges were estimated using Retrospective US insurance claims analysis from the IBM MarketScan® Commercial Database from 2017–2020.

The evaluation of treatment effectiveness was based upon the subject's perception of symptom relief.[10] To evaluate subject-reported outcomes, the Uterine-Fibroid Symptom and Health Related Quality of Life questionnaire (UFS-QOL) assessment tool was used to evaluate symptom severity and health-related quality of life pre- and post-treatment. The UFS-QOL is a useful tool for measuring uterine-fibroid-related symptoms and for the evaluation of treatment outcomes. In addition to the UFS-QOL, the EQ-5D, a standardized Instrument, was used as a measure of health outcome, the Menstrual Impact Questionnaire (MIQ),[11] also a validated questionnaire, was utilized to examine the impact of heavy menstrual bleeding on a subject's quality of life, and an Overall Treatment Evaluation (OTE) was used to measure the subject's general health and overall satisfaction with treatment.[12]

When considering the appropriate analytical methods to use, the study sample size is critical. In the situation where the population variance is unknown and the sample size is 30 or more in each group, the population variance can be estimated from the sample variance and the standard normal distribution can be used for inference. However, when the sample size is below 30 in each group, this method does not give reliable probabilities, and a normal distribution cannot be assumed. Therefore, a *t* distribution was assumed. Dowdy and Wearden (1985) emphasized that the *t* distribution is a good estimate of the actual sampling distribution.[13]

For each single group pre- and post-test study design, the significance of the change from baseline was determined using a paired *t*-test (H_0: m*d* = 0). The inference problem is one of testing the null hypothesis that the population mean difference was equal to zero versus the two-sided alternative hypothesis in addition to considering the problem of estimating the mean difference (m_d).

Analysis of variance techniques was used for multiple comparisons. Where it was found that the variances were not homogeneous, and the sampling distributions were not normal, non-parametric alternatives were employed. Those included the Wilcoxon-Mann–Whitney Rank Sum Test for two independent samples and the Wilcoxon test for analysis of variance, which is appropriate for small sample sizes.[14] Mean comparisons of repeated measures over time were performed using Tukey-Kramer HSD with alpha = 0.05.

Binomial and polynomial outcomes were assessed using chi-square statistical tests of the hypothesis that the response rates are the same in each sample category. Correction for continuity, exact probabilities, and 95% confidence intervals were computed where appropriate. Univariate analysis and Fisher's Exact *t*-test were employed to analyze dichotomous outcomes such as the procedural and safety endpoints.

All missing data were assumed to be missing-at-random unless trends were detected. The computer software used for this analysis was JMP Statistical Software, Version 17.0 (SAS Institute, Inc., Raleigh, North Carolina).

Results

Twenty-seven subjects were randomized to the LAP-RFA treatment group, 24 subjects were randomized to the myomectomy treatment group, and three subjects were randomized to the UAE treatment group. These 54 subjects were treated at nine clinical centers between May 13, 2016, and March 15, 2019. The average age was 42.3 ± 6.6 years for the LAP-RFA group, 40.8 ± 6.3 years for the myomectomy group, and 47.0 ± 2.6 years for the UAE group. When comparing the age for the LAP-RFA group and the myomectomy group, the difference was found to not be statistically significant ($p = 0.418$). The average weight was 77.2 ± 15.2 kg for the LAP-RFA group, 72.8 ± 17.9 kg for the myomectomy group, and 101.0 ± 27.9 kg for the UAE group. In addition, the difference in average body weight for the LAP-RFA group and the myomectomy group was not statistically significant ($p = 0.352$). The average height was 150.9 ± 43.9 cm for the LAP-RFA group, 162.0 ± 22.1 cm for the myomectomy group, and 161.7 ± 9.6 cm for the UAE group. For the LAP-RFA group, 22.2% of the subjects were Caucasian and 51.9% were Black. For the myomectomy group, 50.0% of the subjects were Caucasian and 41.7% were Black. For the UAE group, 33.3% of the subjects were Caucasian and 66.7% were Black. At the time of screening, 78% of the LAP-RFA subjects, 83% of the myomectomy subjects, and 100% of the UAE subjects reported having heavy menstrual bleeding. Dysmenorrhea was found at the time of screening in 63%, 67%, and 67% of the LAP-RFA, myomectomy, and UAE subjects, respectively. The average days per month with fibroid symptoms were 23.2 for the LAP-RFA subjects, 19.4 for the myomectomy subjects, and 22.3 for the UAE

subjects. The majority of the subjects went home on the day of the procedure and reported returning to normal activity approximately 3–4 days after surgery.

Following intervention, 26 (96.3%) LAP-RFA subjects were seen at the 3-month follow-up visit and 27 (100%) at the 24-month visit. As seen in Table 1, the percent reduction from baseline to 24 months post-treatment in the number of days per month with fibroid symptoms was 70.7%, 84.0%, and 53.8% for the LAP-RFA group, the myomectomy group, and the UAE group, respectively. The reduction was statistically significant for both the LAP-RFA group ($p = 0.0001$) and the myomectomy group ($p = 0.0002$). The difference in percent change from baseline for the LAP-RFA group and the myomectomy group was not statistically significant ($p = 0.272$).

Upon review of Table 2, it is apparent that the peri-operative parameters of anesthesia time, procedure time, and overall OR time were lower, although not statistically significant, for the LAP-RFA procedure in contrast to the myomectomy procedure and the UAE procedure (Table 2).

Table 3 illustrates the operative equipment used for LAP-RFA, myomectomy, and UAE procedures.

Table 4 illustrates the length of hospital stay (hours) for each procedural group. Both the laparoscopic ($p = 0.010$) and abdominal myomectomy ($p = <0.0001$) procedures had significantly longer hospital stay on average than the LAP-RFA procedure.

Table 5 highlights treatment-associated costs obtained from the MarketScan data with codes from 2017–2020. The costs are grouped by surgical center (ie, Office, Ambulatory Surgery Center (ASC), and Out-Patient Hospital). For the office-based procedures, both the laparoscopic myomectomy costs and abdominal myomectomy costs were significantly greater than the LAP-RFA procedure costs ($p < 0.0001$). For the ambulatory surgery center procedures, the laparoscopic myomectomy costs and UAE costs were significantly greater than the LAP-RFA procedure costs ($p < 0.0001$). However, the average abdominal myomectomy procedure costs were less than the laparoscopic myomectomy costs. For the out-patient hospital-based procedures, the laparoscopic myomectomy costs, the abdominal myomectomy costs, and the UAE costs were significantly greater than the LAP-RFA procedure costs ($p < 0.0001$).

Table 6 depicts the recovery time for all three treatment groups. Following treatment, the average number of days it was recommended the subject remains off work was significantly less for the LAP-RFA group versus the myomectomy group ($p = 0.011$). When comparing the average number of days missed from work and the total days until back to normal activity for the LAP-RFA subjects and the myomectomy subjects, the differences were not found to be

Table 1 Days per Month of Fibroid Symptoms for RCT Subjects

	LAP-RFA	Myomectomy	UAE
Baseline (Mean ± SD)	n = 27 23.2 ± 16.9	n = 23 19.4 ± 18.7	n = 3 22.3 ± 13.3
24 Months (Mean ± SD)	n = 26 6.8 ± 9.6	n = 24 3.1 ± 6.4	n = 3 10.3 ± 4.2
Percent Change from Baseline	70.7%	84.0%	53.8%

Table 2 Operative Room Time in the RCT

	LAP-RFA (N = 27)	Laparoscopic Myomectomy (N = 19)	Abdominal Myomectomy (N = 5)	UAE (N = 3)
Anesthesia Time Mean ± SD (min)	180.4 ± 49.5	212.0 ± 67.5	195.8 ± 78.3	137.7 ± 14.2
Procedure Time Mean ± SD (min)	122.7 ± 44.4	156.3 ± 62.7	152.2 ± 63.3	99.0 ± 27.5
OR Time Mean ± SD (min)	171.6 ± 46.2	205.8 ± 65.4	190.4 ± 77.7	163.0 ± 36.0

Table 3 Operative Equipment Use for the RCT Subjects

	LAP-RFA (N = 27)	Laparoscopic Myomectomy (N = 19)	Abdominal Myomectomy (N = 4)	UAE (N = 3)
Foley Catheter Drainage Bag (Disposable)	27 (1.00)	19 (1.00)	4 (1.00)	3 (1.00)
Veress Needle (Disposable)	22 (0.86)	16 (0.84)	3 (0.75)	0 (0.0)
Hasson Trocar (Disposable)	2 (0.07)	19 (1.00)	4 (1.00)	0 (0.0)
Insufflation Tubing (Disposable)	26 (0.96)	19 (1.00)	3 (0.75)	0 (0.0)
Laparoscopic Tray (Reusable)	27 (1.00)	19 (1.00)	3 (0.75)	0 (0.0)
Trocar 10–12 mm (Disposable)	25 (0.93)	13 (0.68)	2 (0.50)	0 (0.0)
Trocar 10–12 mm (Quantity, Mean)	1.2 ± 0.4	1.5 ± 0.7	1.0 ± 0.0	0
Trocar 5 mm (Disposable)	24 (0.89	18 (0.95)	3 (0.75)	0 (0.0)
Trocar 5 mm (Quantity, Mean)	1.7 ± 0.7	1.7 ± 0.8	1.0 ± 0.0	0
Single Tooth Tenaculum (Reusable)	17 (0.63)	14 (0.74)	3 (0.75)	0 (0.0)
Open Sided Speculum (Reusable)	19 (0.70)	16 (0.84)	3 (0.75)	0 (0.0)
5 mm Suction Irrigator (Disposable)	15 (0.58)	17 (0.89)	2 (0.50)	0 (0.0)
Hand Piece 2000 (Disposable)	11 (0.41)	0 (0.0)	0 (0.0)	0 (0.0)
Dispersive Electrodes (Disposable)	26 (0.96)	0 (0.0)	0 (0.0)	0 (0.0)
Dispersive Electrodes (Quantity)	1.5 ± 0.5	0	0	0
Sutures	27 (1.00)	18 (0.95)	4 (0.95)	0 (0.0)
Other Equipment (LAP-RFA)	Hand Piece (3), Lut Sleeve (3), Endo Pauch Bag (2), Carter Thomasen Device (1), Towel Clamp (1), Silver Nitrate (1), 40 Vicryl Skin (1), Dolphin Nose Ligasure (1), Dermabond (1), Pratt Dilator (1)			
Other Equipment (Abdominal Myomectomy)	Ultrasound Cutting Instrument (3), 5 mm Suction Irrigator (2), Kronner Uterine Manipulator (2), Endo Mini Shears (1)			
Other Equipment (Lap Myomectomy)	Da Vinci Coagulation Device (3), Robi Coagulation Device (3), Harmonic Scapel (4), Ultrasound Cutting Instrument (3), 5 mm Suction Irrigator (17), Kronner Uterine Manipulator (5), Morcellator (4), Endo Mini Shears (7), Lahey Tenaculum Clamp (4), Storz Lap needle Driver (7), Adhesion Barriers (5), Robotic Canula (1)			
Other Equipment (UAE)	UAE Instrument Tray (2), Embospheres (3), Microcatheter (3), Contrast Dye (3), Radiology Specialty Bag (1), 5FR Pigtail Catheter (1), 5FR UAC Catheter (1), Pigtail Flush Angio Catheter (1)			

Table 4 Length of Hospital Stay for the RCT Subjects

	LAP-RFA (n = 26)	Laparoscopic Myomectomy (n = 19)	Abdominal Myomectomy (n = 5)	UAE (n = 3)
Hospitalization Time Mean ± SD (hrs)	8.2 ± 5.8	16.0 ± 13.2	33.6 ± 14.9	21.05 ± 10.2

Table 5 MarketScan Procedure-Based Costs Grouped by Surgery Center

Procedure Type	Codes	Office		ASC		Out-Patient Hospital	
		Count	Mean Cost	Count	Mean Cost	Count	Mean Cost
LAP-RFA	58674, 0336T	2	$10,427.64	70	$13,134.80	137	$14,427.89
LAP Myomectomy	58545, 58546	90	$17,193.25	787	$19,014.49	8331	$18,135.37
Abd Myomectomy	58140, 58146	132	$12,757.79	331	$12,439.56	3338	$15,397.58
UAE	36247, 37204, 52250, 37210, 37243	902	$16,396.12	91	$28,213.90	4875	$19,130.56

Table 6 Recovery Time for RCT Subjects Within 3 Months Post-Procedure

	LAP-RFA	Myomectomy	UAE
Number of days doctor recommended taking time off before returning to work (Mean ± SD)	(n = 19) 9.5 ± 5.4	(n = 19) 14.5 ± 5.9	(n = 3) 11.7 ± 4.0
Days Missed from Work as a Result of Fibroids (Mean ± SD)	(n = 20) 8.9 ± 6.7	(n = 19) 13.1 ± 8.4	(n = 3) 13.0 ± 14.9
Total Days Until Back to Normal Activity from Procedure Date (Mean ± SD)	(n = 24) 17.8 ± 26.0	(n = 23) 25.5 ± 16.6	(n = 3) 21.0 ± 25.1
Proportion of subjects who returned to normal activity within 3 months of procedure n (%)	21/22 (95.5%)	22/23 (95.7%)	0/0 (0.0%)

statistically significant. Over 95% of the subjects in the LAP-RFA group and in the myomectomy group returned to normal activity within 3 months of their procedure. Note: Indirect cost of time off was not calculated.

In the TRUST RCT post-procedure hospitalizations, one LAP-RFA subject was hospitalized due to the complication of inferior epigastric artery injury. The subject was observed overnight, stabilized, and discharged home the following day. In the myomectomy group, four subjects were hospitalized post-treatment. One subject experienced nausea, dysfunctional voiding of urine, and stress urinary incontinence, and was hospitalized for 2.4 days. Another subject experienced excessive vaginal bleeding and anemia which warranted 3.6 days of hospitalization. A third subject experienced anemia and pericardial effusion, which required 4.8 days of hospitalization. The fourth subject had a pericardial effusion and was hospitalized for 4.4 days. None of the three subjects in the UAE group were hospitalized.

The 37-item, self-administered UFS-QOL Symptom Severity (eight items) and HRQoL (29 items) sub-scales were used as the primary assessments of quality of life in the TRUST study. The HRQoL Total scale consists of six subscales: Concern, Activities, Energy/Mood, Control, Self-Consciousness, and Sexual Function. Response options for Symptom Severity scale items are scored from 1 (“Not at all”) to 5 (“A very great deal”); response options for items in the HRQoL subscales range from 1 (“None of the time”) to 5 (“All of the time”). The Symptom Severity scale, HRQoL subscales, and HRQoL Total scale scores are summed and transformed into a 0–100-point scale, with higher Symptom Severity scores indicating greater symptom severity and higher HRQoL scores indicating better HRQoL. The Symptom Severity scale is unidimensional, and the HRQoL subscales can be treated as unidimensional scales of a multidimensional construct (HRQoL); the HRQoL Total scale is a sum of the HRQoL subscales.

As seen in Figure 1 and Table 7, all three procedural groups demonstrated a dramatic improvement from baseline to 3 months post-treatment and from baseline to 24 months in mean transformed Symptom Severity Scores. Comparisons of the differences in proportions across time were all found to be non-significant (Table 7).

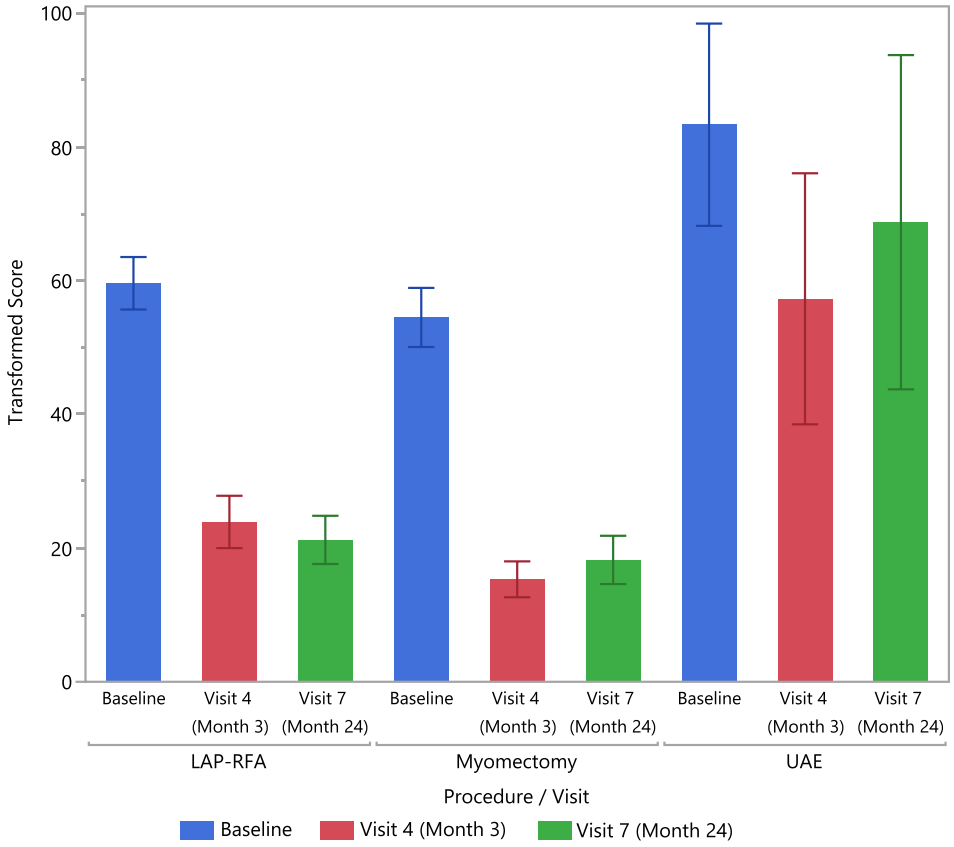

Figure 1 UFS-QOL Symptom Severity Score for the RCT Subjects (Each error bar is constructed using 1 standard error from the mean).

From Figure 2 and Table 8, all three procedural groups demonstrate a dramatic improvement from baseline to 3 months post-treatment and from baseline to 24 months in mean transformed HRQL scores. Comparisons of the differences in proportions across time were all found to be non-significant.

The EQ-5D-3L descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is comprised of three

levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D-3L health state is defined by combining one level from each of the three dimensions. This information can be used in the following ways:

- As an EQ-5D-3L health profile for individuals or groups, either at a single point in time, or over a period of time. Differences in such profiles can be used to describe outcomes.

- Health states defined by the 5-dimensional descriptive system can be converted into a weighted health state index by applying scores from EQ5D "value sets" elicited from general population sample.

Table 7 Mean UFS-QOL Percent Improvement in Mean Transformed Symptom Severity Scores

	LAP-RFA	Myomectomy	UAE
Baseline to 3 Months	(n = 23) 60.0%	(n = 21) 71.9%	(n = 3) 31.2%
Baseline to 24 Months	(n = 24) 64.4%	(n = 24) 66.7%	(n = 2) 17.5%

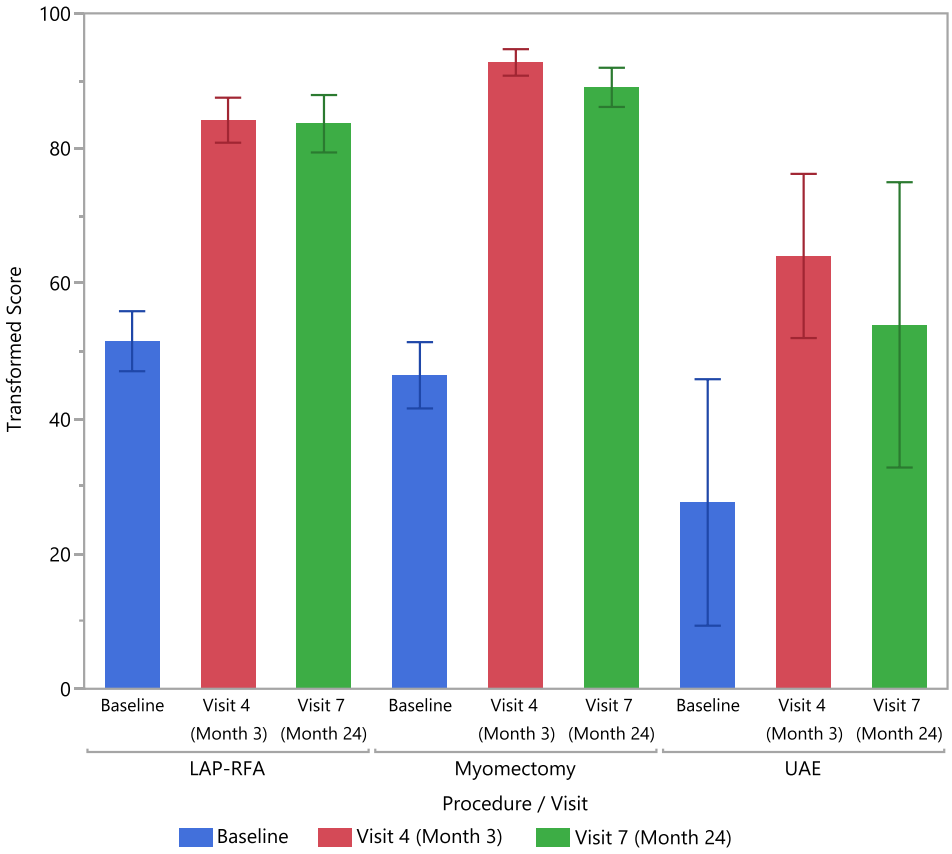

Figure 2 UFS-QOL HRQL Score for the RCT Subjects (Each error bar is constructed using 1 standard error from the mean).

As seen in Figure 3, EQ-5D-3L scores improved over time for all three procedures. However, none of the procedure demonstrated significantly better improvement than another.

The Menstrual Impact Questionnaire (MIQ) is a validated questionnaire that examines the impact of heavy menstrual bleeding on a subject's quality of life. The MIQ is considered to be one instrument that can be used to show the impact of a device or drug on a woman's menstrual cycle and has the potential to detect a clinically relevant outcome. When contrasting the baseline response percentages in Table 9 for the LAP-RFA group and the myomectomy group, the differences were not statistically significant. As reported at baseline, the response percentages for the LAP-RFA group and the myomectomy group were not significantly different.

From Table 10, we can see that one subject required reintervention less than one-year post-treatment. Two more LAP-RFA cases had reinterventions 1–2 years post-treatment. One subject had a hysterectomy due to fibroid symptoms and adenomyosis. The second subject had a subtotal hysterectomy due to unresolved fibroid symptoms. One myomectomy subject and one UAE subject had reinterventions 1–2 years subsequent to their original procedure. The myomectomy

Table 8 Mean UFS-QOL Percent Improvement in Mean Transformed HRQL Scores

	LAP-RFA	Myomectomy	UAE
Baseline to 3 Months	(n = 23) 63.5%	(n = 21) 99.8%	(n = 3) 103.2%
Baseline to 24 Months	(n = 24) 62.5%	(n = 24) 91.8%	(n = 2) 95.3%

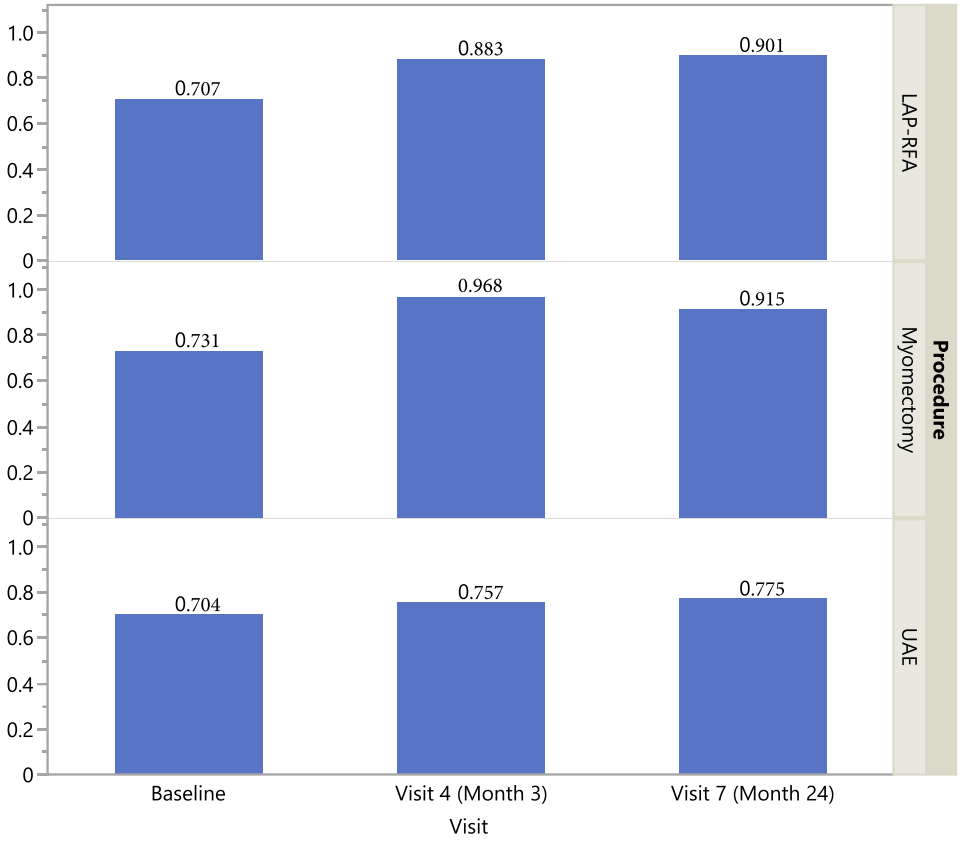

Figure 3 EQ-5D-3L Scores for the RCT Subjects.

case had another myomectomy procedure which did not resolve her fibroid symptoms. The UAE case had a subtotal hysterectomy due to fibroid symptoms.

In Table 11, the Mean Days to Repeat obtained from the MarketScan data was defined as the average number of days from the index procedure to a second procedure of the same approach; it counts both the first and last days. Note that each of the data points (reintervention count, mean days to repeat, etc.) is based upon a repeat procedure of the same type (LAP-RFA repeated with a second LAP-RFA; LAP myomectomy with a second LAP myomectomy, etc.) rather than a repeat of any type. The Mean Peri-operative Costs consisted of the sum of payments for encounters having Procedure 58674 Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency, 0336T Laparoscopy, surgical, ablation of uterine fibroid(s), including intraoperative ultrasound guidance and monitoring, and radiofrequency. The mean peri-operative costs at 1-year post-intervention were comparable for the

Table 9 RCT Subject Response to MIQ by Procedure at Baseline and 24-Months Post-Procedure

Response	Baseline			24 Months		
	LAP-RFA (n= 27)	Myomectomy (n=24)	UAE (n =3)	LAP-RFA (n=23)	Myomectomy (n=24)	UAE (n=2)
Heavy Blood Loss	44.4%	45.8%	0.0%	39.1%	20.8%	0.0%
Very Heavy Blood Loss	40.7%	37.5%	100%	13.0%	4.2%	50.0%
Limitation of Physical Activity	81.5%	83.3%	100%	56.5%	45.8%	0.0%
Limitation of Social or Leisure Activity	85.2%	83.3%	100%	30.4%	16.7%	0.0%

Table 10 Re-Interventions by Treatment Group in the RCT, n (%)

	< 1 Year	1–2 Years
LAP-RFA	1 (3.7)	2 (7.4)
Myomectomy	0 (0.0)	1 (4.2)
UAE	0 (0.0)	1 (33.3)

Table 11 MarketScan Reintervention-Based Costs Grouped by Surgery Center

Time	Procedure	Count	Mean Days to Repeat	Mean Peri-op Costs	Mean Additional Costs
1 Year	**LAP-RFA**	6	66	$2429.12	$5939.31
	LAP Myomectomy	421	20	$2122.03	$8367.71
	Abd Myomectomy	169	29	$4410.10	$11,942.54
	UAE	181	52	$8113.28	$46,691.50

LAP-RFA and the LAP myomectomy groups. However, the mean peri-operative costs for the abdominal myomectomy procedures were twice the costs of the LAP-RFA and LAP myomectomy procedures and the mean peri-operative costs for the UAE procedures were four times the costs of the LAP-RFA and LAP myomectomy procedures. The Mean Additional Costs represented the sum of payments for encounters having emergency settings, specialty office visits, PCP office visits, Lab tests, inpatient admission, non-MD office visits, other outpatient office visits, and pharmacy. The mean additional costs at 1-year for the LAP myomectomy, the abdominal myomectomy, and the UAE procedures were significantly greater than the LAP-RFA mean total costs.

In the RCT, there was one procedural-related serious complication attributable to uterine fibroids. One subject in the RCT was reported to have experienced a serious complication after UAE. The initial ultrasound Doppler findings were of distal radial artery vasospasms. Ultrasound Doppler findings 30 days later were approximately equal to 75% focal stenosis of distal radial artery. Therapeutic interventions consisted of oral medications cilostazol 100 mg bid for 3 months and aspirin 325 mg qd for 3 months.

Within the first 2 years of the study, five serious adverse events (SAEs) were reported among four subjects as illustrated in Table 12. Two subjects were LAP-RFA cases (7.4%), and two subjects were LAP-Myomectomy case (10.5%). All five SAEs were unanticipated except for the repair of posterior fossa pseudo meningocele which was anticipated due to a pre-existing condition. All SAEs were resolved without sequela.

Table 12 Serious Adverse Events in the RCT Group (Not Related to Fibroids or the Fibroid Procedure)

Subject Number	Initial Procedure	Reported Term for Serious Adverse Event
1	**LAP-RFA**	REPAIR OF POSTERIOR FOSSA PSEUDO MENINGOCELE
2	**LAP Myomectomy**	SMALL RIGHT LOWER LOBE BRANCH PULMONARY EMBOLISM
2	**LAP Myomectomy**	RIGHT LOWER EXTREMITY DEEP VEIN THROMBOSIS
3	**LAP Myomectomy**	ANEMIA WITH PERICARDIAL EFFUSION / PERICARDITIS
4	**LAP-RFA**	LEFT RENAL EMBOLIZATION / ANGIOMYOLIPOMA OF LEFT KIDNEY

Discussion

The TRUST study is a prospective, multicenter, randomized comparative trial of uterine-sparing procedures. This report is the second-year update of the secondary outcomes, including metrics of symptomatic improvement, long-term efficacy, and re-interventions. It is also the first report of the primary outcomes of the study, which include cost effectiveness, immediate postoperative recovery, times, and time of return to normal activity.

The updated data on secondary outcomes show laparoscopic RFA compares favorably with myomectomy, as well as prior single cohort data on laparoscopic radio frequency ablation as a uterine sparing option for symptomatic fibroids. While there is a diminution in efficacy over time, with a reintervention rate of 11%, this is not unexpected in light of data on sustainability over time of uterine-sparing treatments[15] and is the same as the single cohort follow-up data.[16,17]

The original study design used length of stay as a proxy outcome for resource utilization. In both the Canadian cohort and the present study, this metric favored LAP-RFA. This was statistically significant in the Rattray et. al[8] study, whereas it is marginally statistically significant in this cohort. Similarly, to Rattray et. al, we also used market data to compare preoperative, perioperative, postoperative, and longer-term costs associated with three interventions. By harnessing the strength of the Canadian system in retrieving specific resource utilization costs, investigators in the Canadian counterpart study were able to retrieve specific cost data for their study subjects, which illustrated detailed areas of cost-savings in the LAP-RFA group compared to the other groups. For this American cohort, we used the best available market data to compare utilization costs. While less specific and detailed than the Canadian cohort, we feel it is a real-world reflection of the nature of cost utilization in the three procedural groups.

Evaluation of new technologies for the treatment of fibroids must take into account cost as well as safety and efficacy, when the upfront costs of innovations such as LAP-RFA will hopefully be offset by savings from decreased length of stay, fewer complications, and reduced future interventions. As doctors and their patients increasingly look for treatment options for fibroids, such data supports counseling as well as potential insurance coverage for care. This is crucial as patients deal both with delays in diagnosis and treatment due to lack of awareness of the prevalence of fibroids, acceptance of fibroid-associated symptoms as "normal",[18] as well as limitations in knowledge surrounding fibroids in general, and specific metrics of abnormality, such as a definition of abnormal uterine bleeding. And yet, the impact of fibroid-associated illness, both physical and mental, is high. Survey studies show significant rates of depression, anxiety, and overall emotional distress in affected patients.[19] Demographic disparities are also relevant, as Black patients present with a higher burden of disease earlier in life, and demonstrate different priorities, such as choosing non-surgical options.[20] In addition, the impact on healthcare resources is undeniable. In 2012, Cardozo et al conducted a study to estimate the total annual societal cost of uterine fibroid tumors in the US based on direct and indirect costs that included associated obstetric complications. The estimated annual direct costs (surgery, hospital admissions, outpatient visits, and medications) were $4.1 to 9.4 billion. Obstetric outcomes that were attributed to fibroid tumors resulted in a cost of $238 million to $7.76 billion annually. Uterine fibroid tumors were estimated to cost the US $5.9 to 34.4 billion annually.[6]

The introduction of robotic assisted laparoscopic surgery to facilitate minimally invasive myomectomy consistently showed greater procedure-related costs due to investment in platform and instrumentation,[21,22] but benefited both the patient and the medical system with the reduction in the cost of associated with laparotomy (ie length of hospital stay and rate of complications).[18] The second-year data of the TRUST study concurs with this principle, with instrument-related costs already comparing favorably to laparoscopic myomectomy, while peri-operative and post-operative costs are contained via shortened hospitalizations and limited follow-up care costs. This is also consistent with the earlier data reports on TRUST: doctor-recommended time off of work (10 vs 14 days) and time to normal activity (16 vs 26 days) for LAP-RFA vs myomectomy in the 12-month TRUST report.[9]

Our data are the latest of three decades of studies assessing innovation in fibroid management. In the multicenter randomized EMMY (EMbolization versus hysterectoMY) trial designed to investigate whether uterine artery embolization (UAE) was a cost-effective alternative to hysterectomy for patients with symptomatic uterine fibroids, the investigators performed an economic evaluation and found that between 2002 and 2004 that the mean total costs per patient for the UAE treatment group were significantly lower than those in the hysterectomy group ($11,626 vs $18,563; mean difference, -$6936 [−37%]. The 24-month cumulative cost of UAE is lower than that of hysterectomy. From a societal

economic perspective, the investigators concluded that UAE was the superior treatment strategy for women with symptomatic uterine fibroids.[23]

A retrospective observational cohort study used healthcare claims for several million individuals with healthcare coverage from employers in the MarketScan Database for the period 2003–2010. The sample comprised 14,426 patients (MRgFUS = 14; UAE = 4092; myomectomy = 10,320) with a higher percent of older patients in MRgFUS cohort (71% vs 50% vs 12% in age-group 45–54, $P < 0.001$). Adjusted all-cause mean cost was lowest for MRgFUS ($19,763; 95% CI: $10,425-$38,694) followed by myomectomy ($20,407; 95% CI: $19,483-$21,381) and UAE ($25,019; 95% CI: $23,738-$26,376) but without statistical significance. Adjusted UF-related costs were also not significantly different between the three procedures. Adjusted all-cause and UF-related costs at one year were not significantly different between patients undergoing MRgFUS, myomectomy, and UAE.[24]

A multi-center, open, randomized trial with a parallel economic evaluation was conducted to examine the clinical effectiveness and cost-effectiveness of uterine artery embolization (UAE) compared with myomectomy in the treatment of symptomatic fibroids where the primary outcome was the Uterine Fibroid Symptom Quality of Life questionnaire. Over a 2-year follow-up period, uterine artery embolization was associated with higher costs than myomectomy (mean cost £7958, 95% confidence interval £6304 to £9612, vs mean cost £7314, 95% confidence interval £5854 to £8773), but with fewer quality-adjusted life-years gained (0.74, 95% confidence interval 0.70 to 0.78, vs 0.83, 95% confidence interval 0.79 to 0.87). The differences in costs (difference £645, 95% confidence interval -£1381 to £2580) and quality-adjusted life-years (difference −0.09, 95% confidence interval −0.11 to −0.04) were small. Similar results were observed over the 4-year time follow-up period. The authors concluded that among women with symptomatic uterine fibroids, myomectomy resulted in greater improvement in quality of life than did uterine artery embolization. The differences in costs and quality-adjusted life-years were very small. Future research was recommended for women who desired pregnancy.[25]

In 2009, You et al[26] found that hysterectomy appeared to be more cost-effective than myomectomy and UAE for management of symptomatic uterine fibroids over a 5-year period among patients who did not have a preference for uterus-conserving interventions. However, our paper is focused on women who are interested in conserving their uterus and preserving their ability to bear children.

The strengths of this study are its randomized design, standardized inclusion criteria (ie, uterine size ≤16 gestational weeks as determined by pelvic exam, all fibroids less than 10 cm in any diameter, and the desire uterine conservation) which yielded treatment groups with statistically similar baseline characteristics, and an ongoing appraisal of fibroid status which informs the study of the sustainability of treatment effects.

Limitations of the study focus on sample size. The original sample size estimates generated in 2012 were based on the cost of hospital stay and nursing costs for the three different treatment groups. However, when making multiple comparisons, the conservative approach for setting the overall alpha level at 0.05 was to recalculate the sample size using a one-tailed alpha level of 0.025/3 or 0.00833 when making three comparisons or a one-tailed alpha level of 0.025/2 = 0.0125 when making two comparisons. Therefore, using an alpha level of 0.0125 yielded a total sample size of 64 subjects for each comparison or 128 subjects for both comparisons. Using an alpha level of 0.00833 yields a total sample size of 70 subjects for each comparison or 210 subjects for all three comparisons. Consequently, the sample size and power estimates for the number of subjects less than 30 as seen with each group comparison for this study yields a power less than 0.80 for most comparisons.

Conclusion

The three minimally invasive approaches had similar clinical outcome rates and re-intervention rates at 2 years. LAP-RFA was associated with the lowest peri-operative cost, and UAE was associated with the highest peri-operative cost. Moreover, LAP-RFA provides sustainable relief of fibroids symptoms over two years and is cost-effective compared to other uterine-sparring- treatments. Further studies are needed to assess the cost, effectiveness, and patient satisfaction with each procedure.

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Disclosure

Dr David Eisenstein reports surgical proctor from hologic, outside the submitted work. Mr John Carlow and Mrs Laura Kemp report personal fees from Hologic, Inc., during the conduct of the study. The authors report no other conflicts of interest in this work.

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