GYNECOLOGY

Laparoscopic hysterectomy with morcellation vs abdominal hysterectomy for presumed fibroid tumors in premenopausal women: a decision analysis

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OBJECTIVE: The purpose of this study was to model outcomes in laparoscopic hysterectomy with morcellation compared with abdominal hysterectomy for the presumed fibroid uterus and to examine short- and long-term complications and death.

STUDY DESIGN: A decision tree was constructed to compare outcomes for a hypothetical cohort of 100,000 premenopausal women who underwent hysterectomy for presumed fibroid tumors over a 5-year time horizon. Parameter and quality-of-life utility estimates were determined from published literature for postoperative complications, leiomyosarcoma incidence, death related to leiomyosarcoma, and procedure-related death.

RESULTS: The decision-tree analysis predicted fewer overall deaths with laparoscopic hysterectomy compared with abdominal hysterectomy (98 vs 103 per 100,000). Although there were more deaths from leiomyosarcoma after laparoscopic hysterectomy (86 vs 71 per 100,000), there were more hysterectomy-related deaths with abdominal hysterectomy (32 vs 12 per 100,000). The laparoscopic group had lower rates of transfusion (2400 vs 4700 per 100,000), wound infection (1500 vs 6300 per 100,000), venous thromboembolism (690 vs 840 per 100,000) and incisional hernia (710 vs 8800 per 100,000), but a higher rate of vaginal cuff dehiscence (640 vs 290 per 100,000). Laparoscopic hysterectomy resulted in more quality-adjusted life years (499,171 vs 490,711 over 5 years).

CONCLUSION: The risk of leiomyosarcoma morcellation is balanced by procedure-related complications that are associated with laparotomy, including death. This analysis provides patients and surgeons with estimates of risk and benefit on which patient-centered decisions can be made.

Key words: abdominal hysterectomy, fibroid tumor, laparoscopic hysterectomy, morcellation

Cite this article as: Siedhoff MT, Wheeler SB, Rutstein SE, et al. Laparoscopic hysterectomy with morcellation vs abdominal hysterectomy for presumed fibroid tumors in premenopausal women: a decision analysis. Am J Obstet Gynecol 2015;212:591.e1-8.

Hysterectomy is the most common procedure performed in nonpregnant women in the United States; leiomyomata (fibroid tumors) is the indication for a significant proportion of these.[1] Surgeons increasingly are using laparoscopy for hysterectomy.[2] For all laparoscopic supracervical hysterectomies and total laparoscopic hysterectomies in which the specimen is too large to be removed intact vaginally, the uterus must be morcellated (ie, cut into pieces that will fit through small incisions). If morcellation is not contained in a retrieval bag, tissue may be unintentionally left behind, which can lead to spread of benign or malignant tissue.[3,4]

EDITORS' ★ CHOICE

Morcellation has come under scrutiny regarding the risk of disseminating occult leiomyosarcoma, which was highlighted by a recent Food and Drug Administration safety notification.[5] Unlike other gynecologic malignancies, leiomyosarcoma is difficult to distinguish from benign disease preoperatively and bears a poor prognosis.[6] Retrospective studies suggest a worse prognosis with morcellation of leiomyosarcoma compared with intact removal of the uterus.[7,8]

Laparoscopic hysterectomy affords shorter hospital stay and convalescence compared with abdominal hysterectomy. In addition, laparoscopic hysterectomy is associated with less pain, lower blood loss, and lower rates of wound

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Received Oct. 20, 2014; revised Jan. 21, 2015; accepted March 3, 2015.

The authors report no conflict of interest.

Presented at the 43rd annual Global Congress of Minimally Invasive Gynecology of the American Association of Gynecologic Laparoscopists, Vancouver, BC, Canada, Nov. 17-21, 2014.

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0002-9378/free • http://dx.doi.org/10.1016/j.ajog.2015.03.006

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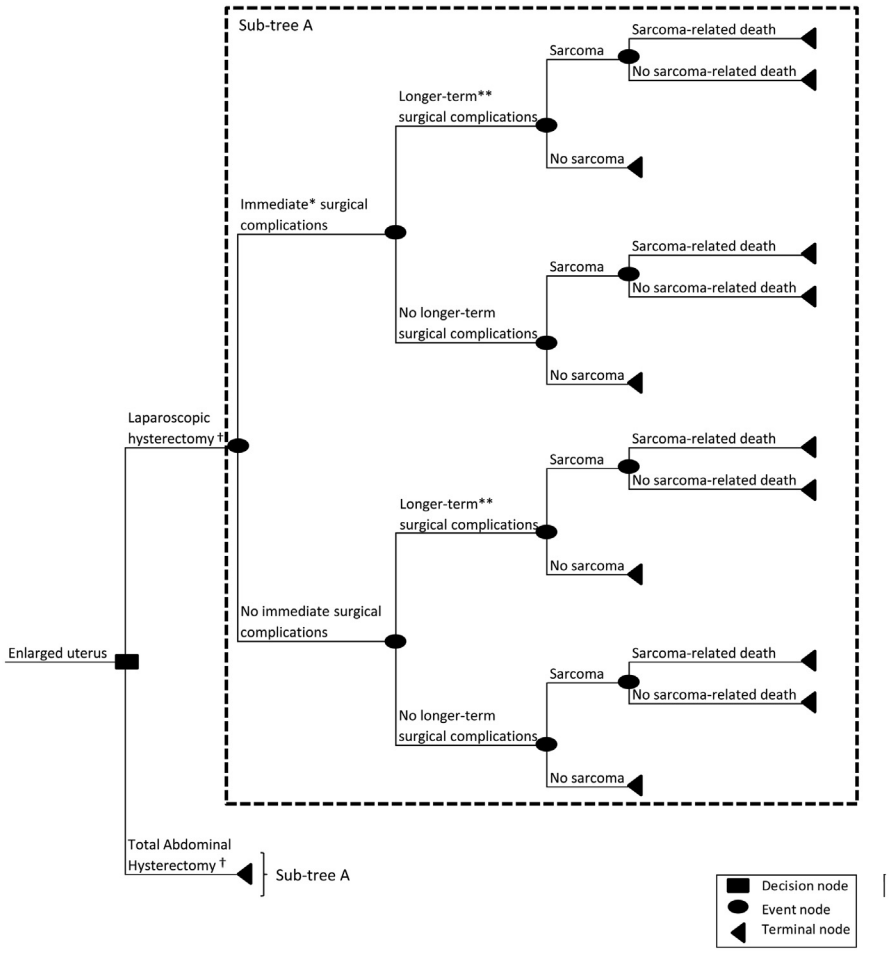
FIGURE 1
Decision tree



†In all possible branches, an individual could have an immediate post-operative death due to hysterectomy
* Immediate surgical complications include: need for transfusion, abdominal wound infection, and vaginal cuff dehiscence
** Longer-term surgical complications include: venous thromboembolism and hernia

Premenopausal women whose condition requires hysterectomy for an enlarged uterus could undergo laparoscopic or abdominal hysterectomy. In either approach, death could occur immediately after the procedure. Women who survive the procedure could experience immediate surgical complications (blood transfusion, wound infection, or vaginal cuff dehiscence) and/or longer term surgical complications (hernia and venous thromboembolism). Women who had occult leiomyosarcoma at the time of the procedure would undergo treatment, after which point they could recover or die (sarcoma-related death).

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infection, incisional hernia, and venous thromboembolism.[9] On the other hand, abdominal hysterectomy avoids the risk of morcellating leiomyosarcoma. To provide physicians with better estimates of health outcomes when they consider these surgical approaches, we conducted a decision analysis that compared laparoscopic hysterectomy to abdominal hysterectomy for the management of the enlarged uterus with presumed benign leiomyomata in premenopausal women and examined mortality rates, surgical complications, and quality of life.

Materials and Methods

We constructed a decision tree to compare outcomes of laparoscopic hysterectomy with morcellation with abdominal hysterectomy for women with an enlarged uterus because of presumed benign leiomyomata (Figure 1). We assessed a hypothetical cohort of 100,000 premenopausal women, because approximately 200,000 hysterectomies are performed for leiomyomata annually in the United States.[1] It made clinical sense that roughly one-half of those procedures could involve uteri large enough to require morcellation if considered for laparoscopic hysterectomy. The decision tree model was constructed using Excel 2010 (Microsoft Corporation, Redmond, WA) and TreePlan (TreePlan Software, San Francisco, CA).

Women who underwent both laparoscopic and abdominal hysterectomy were at risk for potential surgical complications, each represented as unique and independent health states in the model. Morbidity and mortality outcomes were evaluated over a 5-year time horizon. This study was considered exempt from review by the Institutional Review Board at the University of North Carolina at Chapel Hill because it involved analysis of existing published data. Three of the authors (S.W., S.R., and M.S.) were responsible for analyzing data.

Base-case estimates and ranges for each parameter and transition probabilities that govern movement between branches in the decision tree were determined by published literature review (Table 1). In the selection of estimates, preference was given to higher-quality studies and more recent publications that reflected advances in surgical practice. Surgical complications in the model included transfusion, abdominal wound infection, vaginal cuff dehiscence, venous thromboembolism, incisional hernia, leiomyosarcoma, death from leiomyosarcoma, and death from hysterectomy. Febrile episodes and vaginal cuff infections were considered but were believed to be better represented by identifiable and more objective diagnoses, wound infection, and cuff dehiscence. Major visceral and vascular adverse events were not included because they are rare and not significantly different between laparoscopic and abdominal hysterectomy.[10]

TABLE 1
Parameter estimates, hysterectomy for presumed leiomyomata

Parameter	Laparoscopic hysterectomy estimate	Range	Abdominal hysterectomy estimate	Range	Sources	Level of evidence[a]
Transfusion	0.024	0.013–0.035	0.047	0.043–0.047	Nieboer et al[9]	I
					Wallenstein et al[14]	
					Wiser et al[15]	
Wound infection	0.015	0.00055–0.015	0.063	Not varied	Nieboer et al[9]	I
					Wallenstein et al[14]	
Vaginal cuff dehiscence[b]	0.0064	0.0002–0.0089	0.0029	0.0015–0.006	Hur et al[30]	II-2
					Koo et al[31]	
					Ucella et al[32]	
Venous thromboembolism	0.0069	0.003–0.009	0.0084	0.0072–0.0084	Wallenstein et al[14]	I
					Wiser et al[15]	
					Nieboer et al[9]	
					Ritch et al[33]	
					Harrki-Siren et al[34]	
Hernia[c]	0.0071	0.0014–0.09	0.0880	0.045–0.098	Brown and Goodfellow[35]	I
					Bickenbach et al[36]	
					Le Huu Nho et al[37]	
					Hussain et al[38]	
					Swank et al[39]	
Occult leiomyosarcoma incidence[d]	0.0012	0.0007–0.0049	—	—	Seidman et al[4]	II-3
					Leibsohn et al[17]	
					Parker et al[19]	
					Kamikabeya et al[22]	
					Leung and Terzibachian[23]	
Procedure-related death	0.00012	0.000096–0.00012	0.00032	0.00032–0.00038	McPhersonet al[13e]	II-3
					Wallenstein et al[14f]	
					Wiser et al[15]	
Death from leiomyosarcoma[g]	0.72	Not varied	0.59	Not varied	Kosary[26]	III

[a] US Preventative Services Task Force level of evidence for highest-quality source; [b] A weighted average was used because the incidence was low and the difference varied between groups among candidate studies; [c] It was assumed that most candidate fibroid uteri that were large enough to need morcellation during laparoscopic hysterectomy would require a vertical midline incision if removed by laparotomy. The rate of incisional hernia after hysterectomy was not readily identified in the gynecologic literature and thus was extrapolated from general surgery reports. The incidence of hernia with a transverse incision that was reported in a Cochrane review was used for the lower estimate in sensitivity analysis; [d] The same estimate and range was used for the incidence of occult leiomyosarcoma in laparoscopic and abdominal hysterectomy; [e] Used only for the abdominal hysterectomy estimate; [f] Used only for the laparoscopic hysterectomy estimate; [g] The abdominal hysterectomy group was assigned the 5-year death rate for International Federation of Obstetrics and Gynecology stage I-II leiomyosarcoma and laparoscopic hysterectomy was assigned the 5-year death rate for stage III leiomyosarcoma according to Surveillance, Epidemiology, and End Results reports.[26]

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Mortality rates because of hysterectomy were reflected in the literature as a short-term outcome and were not categorized by a specific cause (eg, fatal embolic event). With the exclusion of older studies that were conducted when safety and prophylactic measures (eg, infection, venous thromboembolism) were different from modern practice,[11,12] estimates of 0.00012 (laparoscopic hysterectomy) and 0.00032 (abdominal hysterectomy) were derived from 3 larger and more recent series.[13-15]

In terms of occult malignancy, we focused on leiomyosarcoma in particular because it mimics benign myomatous disease. Other more rare uterine mesenchymal tumors have diverse biologic behavior, and the impact of morcellation on these tumors is unknown.

Cervical cancer is almost always a known preoperative diagnosis, and the risk of tissue dissemination appears to be less serious with endometrial cancer.[16] Ten sources were considered regarding the incidence of leiomyosarcoma among women who undergo hysterectomy for presumed fibroid tumors (Table 2).[4,17-25] Quality and the degree to which the study population mirrored that for our decision analysis was evaluated based on year of publication, menopausal status, number of subjects, geographic location, and pathologic criteria that were used to determine leiomyosarcoma diagnosis. An estimate of 0.0012 (6/5084 cases) was derived from what were considered the 4 highest quality sources that reported mean estimates of 0.0008,[19] 0.0007,[22] 0.0009,[4] and 0.0023.[23] The range for sensitivity analysis included those sources with sample size >1000:0.0007[22] to 0.0049.[17]

Leiomyosarcoma mortality estimates were derived from Surveillance, Epidemiology, and End Results reports.[26] First, we assumed that women with metastatic disease generally would be identified preoperatively and not be candidates for our hypothetical cohort. In rare cases when it was not identified, surgical approach, with or without morcellation, would not change their stage (IV) nor impact overall survival, which would be driven by the distant metastases. Therefore, occult leiomyosarcoma that was detected at the time of hysterectomy would be represented in the model by an International Federation of Obstetrics and Gynecology stage I or II (confined to the pelvis) diagnosis, with a 5-year mortality rate of 0.59. Second, we assumed morcellation could lend the same prognosis as spontaneous cancer spread; thus, the laparoscopic group was assigned a stage III (extra-pelvic disease) prognosis, with a 5-year mortality rate of 0.72 (ie, all laparoscopic patients were given a worse prognosis than abdominal patients).

In the model, morcellation indicated the cutting of uterine tissue to facilitate laparoscopic removal. Data are lacking regarding safety differences between various morcellation techniques that prevented the stratification by type of morcellation. The few studies that demonstrate survival differences in patients with leiomyosarcoma who underwent surgery with and without morcellation include a heterogeneous set of extraction modalities.[7,8]

Health state utilities capture health-related quality of life and are measured on a scale of 0-1, where 0 represents death and 1 represents 1 year of life in perfect health. Each year of life spent at that health state then can be quantified in quality-adjusted life years. Using published literature, we derived utility estimates for each health state represented in the model and the average duration of each health state (Table 3).

To account for the possibility of experiencing multiple clinical events, each with varying duration and morbidity, we divided the 5-year (60-month) period into 1-month increments and used a selective weighted average to calculate 1-month utilities for each distinct pathway in the tree. We then summed across 5 years to obtain 5-year quality-adjusted life years for the laparoscopic and abdominal branches. To more accurately reflect real-world clinical scenarios, the model was built to reflect the fact that women could experience multiple clinical adverse events simultaneously (eg, require a transfusion and have a wound infection). If events overlapped in time, the worse utility estimate was assigned for that period. We further assumed that death because of hysterectomy occurred immediately postoperatively (ie, at the beginning of our study window). Accordingly, these persons contributed a utility weight of 0 to the model. For leiomyosarcoma-related deaths, these persons experience the quality-adjusted life-years associated with first- and second-line

TABLE 2
Rate of leiomyosarcoma for women who underwent surgery for presumed fibroid tumors

Study	Publication year	Study years	Country	Age, y	Leiomyosarcoma Cases, n	Total patients, n	Rate of leiomyosarcoma
Leibsohn et al[17]	1990	1983-1988	United States	36-62	7	1429	0.0049
Reiter et al[18]	1992	1986-1989	United States	42 (mean)	0	104	0.0
Parker et al[19a]	1994	1988-1992	United States	22-86	1	1332	0.0008
Takamizawa et al[20]	1999	1983-1997	Japan	26-75	1	923	0.0011
Sinha et al[21a]	2008	1998-2005	India	34 (mean)	2	505	0.0040
Kamikabeyaet al[22]	2010	1987-2008	Brazil	Not reported	1	1364	0.0007
Rowland et al[24b]	2011	2006-2011	United States	Not reported	3	1115	0.0027
Leung and Terzibachian[23]	2012	1999-2005	France	34-77	3	1297	0.0023
Seidman et al[4a,c]	2012	1999-2010	United States	Not reported	1	1091	0.0009
Theben et al[25]	2013	2005-2010	Germany	28-81	2	1584	0.0013

[a] Included myomectomies; [b] Abstract only; [c] Denominator included only morcellated cases.

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TABLE 3
Utilities

Parameter	Estimate	Range[a]	Duration, mo	Source
Hysterectomy for fibroid tumors[b]	0.9	0.72–1.0	6	O'Sullivan et al[40]
Transfusion	0.48	0.38–0.58	1	Klarenbock et al[41]
Wound infection	0.607	0.49–0.73	1	Chatterjee et al[42]
Vaginal cuff dehiscence	0.54	0.43–0.65	1	Chatterjee et al[42]
Venous thromboembolism	0.8	0.64–0.96	12	Spangler et al[43]
Hernia	0.77	0.62–0.92	24	Hynes et al[44]
Leiomyosarcoma (1st 6 months chemotherapy)[c]	0.76	0.61–0.91	6	Reichardt et al[45]
Leiomyosarcoma progression (additional 6 months chemotherapy)[d]	0.66	0.53–0.79	12	Reichardt et al[45]
Leiomyosarcoma progression (palliative care)[e]	0.71	0.57–0.85	36	Health Quality Ontario[46]
Alive	1.0	Not varied	Varies	—

[a] Range based on ±20% of base-case utility; if +20% exceeded 1.0, the utility was assigned a value of 1.0; [b] Decrement applied only to abdominal hysterectomy; [c] For women with leiomyosarcoma diagnosed at time of surgery, we presumed all would receive a minimum of 6 months of chemotherapy (approximately 6 cycles); responders would get no more treatment and return to normal health; [d] Nonresponders after 6 months would get additional chemotherapy (up to 12 months); [e] Nonresponders after 12 months of chemotherapy would go on to palliative care and ultimately die of the disease.

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chemotherapy and subsequent palliative care and are assumed to die in year 5 of the model, with the use of 5-year survival estimates.

Deterministic (1-way univariate) sensitivity analyses were performed to assess the robustness of the assumptions in the decision model,[27] which included surgical complications, the probability of leiomyosarcoma, and probability of death from hysterectomy. The range of clinical outcomes (eg, transfusion, wound infection) was evaluated by varying the input for each clinical event to its minimum and maximum. Given the limited reports on utilities for the health states in our model, we performed a sensitivity analysis by varying the utility by 20% higher and lower than each base-case estimate.

RESULTS

The decision analysis predicted fewer overall deaths with laparoscopic hysterectomy compared with abdominal hysterectomy (98 vs 103 per 100,000; Table 4). Although there were more deaths from leiomyosarcoma after laparoscopic hysterectomy (86 vs 71 per 100,000), there were more hysterectomy-related deaths with

TABLE 4
Clinical outcomes per 100,000 women who underwent hysterectomy for presumed fibroid tumors

Outcome	Laparoscopic hysterectomy, base-case (range)[a]	Abdominal hysterectomy, base-case (range)[a]	Incremental difference (laparoscopic–abdominal)
Leiomyosarcoma cases	120	120	n/a
Leiomyosarcoma deaths	86 (50–353)	71 (41–289)	15
Hysterectomy-related deaths	12 (10–12)	32 (28–32)	−20
Total deaths	98 (60–365)	103 (69–321)	−5
Transfusion	2400 (1300–3500)	4700 (4300–4700)	−2300
Venous thromboembolism	690 (30–900)	840 (720–840)	−150
Vaginal cuff dehiscence	640 (200–890)	290 (150–600)	350
Abdominal wound infection	1500 (55–1500)	6300 (6300)	−4800
Hernia	710 (140–900)	4500 (4500–9800)	−8090
Quality-adjusted life years	499,171 (499,062–499,280)	490,711 (482,733–486,270)	8460

n/a, not applicable.

[a] Sensitivity analyses were conducted with the use of the ranges that are outlined in Tables 1 and 3 (ie, the 1-way sensitivity analysis for each input).

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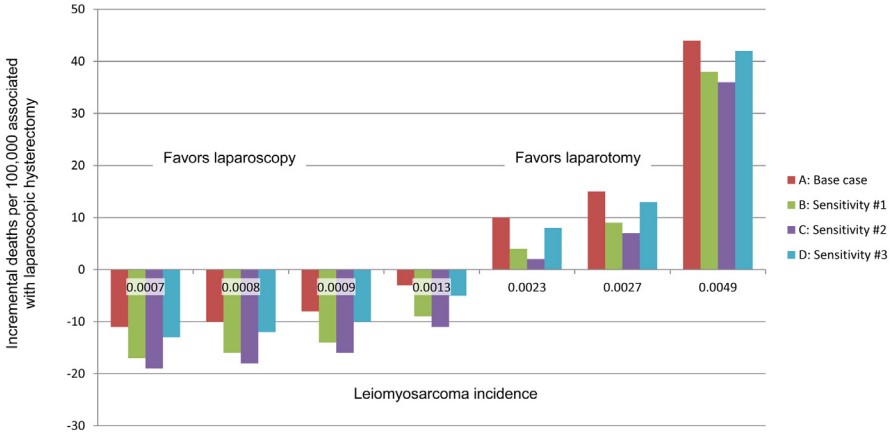
abdominal hysterectomy (32 vs 12 per 100,000). For surgical complications, the laparoscopic group had lower rates of transfusion (2400 vs 4700 per 100,000), wound infection (1500 vs 6300 per 100,000), venous thromboembolism (690 vs 840 per 100,000), and incisional hernia (710 vs 8800 per 100,000), but a higher rate of vaginal cuff dehiscence (640 vs 290 per 100,000), compared with the abdominal group.

In terms of quality of life, the laparoscopic group resulted in 499,171 quality-adjusted life years, compared with 490,711 in the abdominal group (incremental difference, 8460 additional quality-adjusted life years gained among women who underwent laparoscopic hysterectomy). Stated another way, on average, women who undergo laparoscopic hysterectomy experience an additional 0.85 quality-adjusted life years over 5 years (1.02 months), compared with women who undergo abdominal hysterectomy.

In the sensitivity analysis, our results were relatively robust to varying risks of postoperative complications, leiomyosarcoma, and hysterectomy-associated deaths across predefined ranges in the published literature (Table 4). With the lowest estimate of leiomyosarcoma (0.007), the incremental difference in the number of deaths per 100,000 ranged from 11−19 more with abdominal hysterectomy, varying the rate of procedure-related death. With the high estimate (0.0049), the number ranged from 36-44 more deaths with laparoscopic hysterectomy. The incremental difference in death associated with laparoscopic hysterectomy was most conservative with the base-case estimates of procedure-related death (Figure 2). A hypothetical leiomyosarcoma incidence of 0.0015 would provide equivalent deaths between laparoscopic and abdominal groups, assuming base-case estimate for procedure-related death.

Quality-adjusted life year differences were robust across a ±20% utility range for sensitivity analysis. For example, if the hysterectomy utility estimate was, in fact, 0.72 rather than 0.9, the difference in total quality-adjusted life years over 5 years would be 16,438, with laparoscopic hysterectomy patients experiencing an additional 0.16 quality-adjusted life years over 5 years (1.97 months). Even without a decrement for hysterectomy, there remained a difference of 4312 quality-adjusted life years (0.52 months). There was no scenario in which a 20% adjustment in base-case utility resulted in more quality-adjusted life years for abdominal hysterectomy.

FIGURE 2
Incremental deaths per 100,000 that were associated with laparoscopic hysterectomy



Incremental deaths per 100,000 that were associated with laparoscopic hysterectomy by varying the candidates for leiomyosarcoma incidence that was used in the sensitivity analysis. At an incidence of 0.007, 0.008, 0.009, and 0.0013, there were more deaths per 100,000 that were associated with abdominal hysterectomy. At an incidence of 0.023, 0.027, and 0.049, there were more deaths per 100,000 that were associated with laparoscopic hysterectomy. Base-case estimate: abdominal hysterectomy mortality rate, 0.00032; laparoscopic hysterectomy mortality rate, 0.00012. Sensitivity analysis estimate #1: abdominal hysterectomy mortality rate, 0.00038; laparoscopic hysterectomy mortality rate, 0.00012. Sensitivity analysis estimate #2: abdominal hysterectomy mortality rate, 0.00038; laparoscopic hysterectomy mortality rate, 0.000096. Sensitivity analysis estimate #3: abdominal hysterectomy mortality rate, 0.00032; laparoscopic hysterectomy mortality rate, 0.000096.

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Comment

Using base-case estimates, our decision analysis predicted lower overall mortality rates from laparoscopic hysterectomy with morcellation than abdominal hysterectomy for the treatment of the presumed fibroid uterus in premenopausal women. Abdominal hysterectomy was associated with more postoperative complications and lower quality of life.

The strength of the study includes its design as a decision analysis, which is a strategy that is particularly helpful when a comparative prospective study is challenging. In this case, it would not be feasible to conduct a randomized trial to compare laparoscopic hysterectomy with morcellation with abdominal hysterectomy because leiomyosarcoma is so rare. Further, the analysis incorporated death because of the procedure itself, not simply death that is associated with morcellation of leiomyosarcoma. Insight was also provided for multiple clinical outcomes, which offered more information to guide surgeons in counseling women on approach for hysterectomy for fibroid tumors. Last, outcomes were assessed by comprehensive literature review, and sensitivity analyses supported the model's conclusions, which added confidence to the applicability of these findings to a clinical setting.

Any discussion of risk that is associated with morcellation of presumed leiomyomata is limited by the paucity of data regarding the incidence of occult leiomyosarcoma in this setting. Currently available reports include very small numerators and denominators when the high number of uterine surgeries for fibroid tumors that occurred during the respective time periods are considered.[4,17-25] The studies span several decades, with varying pathologic criteria to define leiomyosarcoma, and include data from 5 different countries. Some women in the reports were identified preoperatively, and some reports included older postmenopausal women. The population therefore does not necessarily reflect those who are at risk, because morcellation would not have been performed in the first place. Thus, limitations in the literature suggest our estimate was conservative, and updated estimates of leiomyosarcoma risk in this population are unlikely to alter the direction of our conclusions. Although the high end of leiomyosarcoma incidence in sensitivity analysis changed the direction of favorable mortality rates to abdominal hysterectomy, consideration of all the available literature suggests that it is fair at least to grant near-equivalent mortality rates, with outcomes other than death still clearly favoring laparoscopy. Further, our estimates of death from the procedure itself were the most conservative of the candidates that were available in sensitivity analysis.

Data are limited regarding the specific impact of morcellation of occult leiomyosarcoma. The model assumed that the behavior of a morcellated leiomyosarcoma would mimic that of spontaneous disease spread. A better understanding of the impact of leiomyosarcoma morcellation could alter the conclusions of our model, either positively or negatively.

The results are subject to uncertainty in the estimates of rare events such death. In particular, in the absence of randomization, unmeasured factors could influence the relationship between type of surgery and death. Further, randomized trials that involved the specific target population were not always available, so we attempted to account for this uncertainty by conducting sensitivity analyses and varying point estimates of these events with ranges reported in existing literature.

Data were also limited in the assignment of utilities to various complications that are associated with hysterectomy, but our findings were robust to a 20% manipulation of the estimates. In all scenarios, laparoscopic hysterectomy was favored in terms of quality of life.

Finally, this analysis was conducted specifically on clinical outcomes. Assessment of cost associated with surgery is notoriously difficult, but monetary estimates for the procedure and associated postoperative events could add depth to the consideration of approach for hysterectomy to treat leiomyomata. Not all clinical outcomes were assessed, but more recent literature suggests that the rate of visceral injury is not different between laparoscopic and abdominal hysterectomy.[10] The outcomes included in our study are not as likely to change based on improvement in technique (eg, venous thromboembolism) and, if anything, would favor a laparoscopic approach (eg, blood loss).

Morcellation is currently one of the most debated issues in gynecologic surgery, both in the media and in the medical arena, prompted by a recent Food and Drug Administration safety notification[5] and the response of several large obstetrics and gynecology organizations regarding its use.[28,29] The Food and Drug Administration report emphasizes risk that is associated with morcellation, nearly to the exclusion of the benefits of minimally invasive surgery for leiomyomata.[9,15] The benefits could be further improved by reducing the risk that is associated with morcellation (eg, specimen containment) rather than abandoning minimally invasive treatment for fibroid tumors. Better understanding of risk factors for leiomyosarcoma, new diagnostics to preoperatively distinguish benign from malignant myomata, and enhanced methods of tissue extraction represent potential avenues for improvement in the safety and care of women with uterine disease. ■

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