FDA Updated Assessment of The Use of Laparoscopic Power Morcellators to Treat Uterine Fibroids

December 2017

Executive Summary

FDA's Center for Devices and Radiological Health (CDRH)'s most recent assessment of using laparoscopic power morcellators (LPM) to treat presumed uterine fibroids confirms concerns outlined in our 2014 safety communication which discouraged the use of these products for that use. Women with unsuspected uterine sarcoma who undergo morcellation of presumed benign fibroids are at risk for mechanical spread of cancerous tissue and worsened clinical outcomes. As part of the FDA's ongoing efforts, CDRH conducted an updated review to assess:

- the prevalence of sarcoma in women undergoing myomectomy or hysterectomy for presumed benign uterine fibroids;
- clinical outcomes for patients who were diagnosed with cancer following morcellation (power or manual) during myomectomy or hysterectomy to treat presumed uterine fibroids; and,
- differences in patient outcomes for women who have undergone electric power morcellation compared to manual (e.g., scalpel) morcellation and/or no morcellation.

In addition, we reviewed Medical Device Reports (MDRs) received by FDA for dissemination of malignancy following LPM use as well as information related to changes in rates of hysterectomy or myomectomy procedures performed since our 2014 communication.

Key to our reassessment are data suggesting the prevalence of uterine sarcoma in women undergoing surgery for presumed fibroids to be in the range of approximately 1 in 225 to 1 in 580 and that for leiomyosarcoma (LMS) to be approximately 1 in 495 to 1 in 1100, depending on the analytical methodology used. In addition, there continues to be evidence for differences in patient outcomes (e.g., disease-free survival and overall survival) between those with occult malignancy who receive morcellation and those who do not receive morcellation.

While minimally invasive surgery conveys several advantages over open surgery for women with fibroids including reduced recovery time and rate of wound infection, the use of LPMs during these surgeries poses a risk due to unsuspected uterine sarcoma. The FDA continues to caution against the use of LPMs in the majority of women undergoing myomectomy or hysterectomy for treatment of fibroids.

Background

Uterine sarcomas are uncommon neoplasms of mesenchymal origin and account for 3-5% of all uterine malignancies.[1,2] The most common histologic types are leiomyosarcomas (LMS, 63%), endometrial stromal sarcomas (ESS, 21%), adenosarcomas (6%), undifferentiated sarcoma (5%), and smooth muscle tumors of uncertain malignant potential (STUMP).[3,4,5] Carcinosarcoma, a mixed mesenchymal and epithelial tumor, is now regarded as a subset of endometrial carcinoma. In general, uterine sarcomas are associated with poor prognosis with recurrence rates approaching 60%.[6] While women with localized

[1] Ebner, F., et al., Is open surgery the solution to avoid morcellation of uterine sarcomas? A systematic literature review on the effect of tumor morcellation and surgical techniques. Arch Gynecol Obstet, 2015. 292(3): p. 499-506.
[2] Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiololgy and end results program, 1978-2001: an analysis of 26,758 cases. Int J Cancer 2006: 119:2922-30.
[3] Tropé CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus. A review. Acta Oncologica, 2012; 51:694-705.
[4] Abeler VM, Røyne O, Thoresen S, Danielsen HE, Nesland JM, Dristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology 2009; 54:355-365.
[5] Kurman RJ, Carcanigiu ML, Herrington S, Young RH. World Health Organization classification of tumours of the female reproductive organs. IARC, Lyon, 2014.
[6] Ruengkhachorn I, Phithakwatchara N, Nawapun K, Hanamornroongruang S. Undiagnosed uterine sarcomas identified during surgery for presumed leiomyoma at a national tertiary hospital in Thailand: a 10-year review. Int J Gynecol Cancer 2017; 27:973-978.

disease have a 5-year survival rate of 71.3%, the rate is lower for women with regional disease (37.3%) or distant metastasis (12.3%).[7] Stage of disease[8] is the most important prognostic factor for such sarcomas; however, prognosis may also be impacted by tumor size, mitotic index (MI), and tumor cell necrosis.

In December 2013 FDA began receiving voluntary MDRs describing dissemination and upstaging of undiagnosed uterine sarcomas following the use of LPMs in the surgical treatment of women with presumed uterine fibroids. An FDA review and analysis of data available at that time estimated that 1 in 350 women undergoing hysterectomy or myomectomy for the treatment of presumed fibroids may have an occult uterine sarcoma, and 1 in 498 may have an occult LMS specifically. These rates were higher than had traditionally been quoted (e.g., as uncommon as 1 in 10,000). The analysis also suggested worsened outcomes (e.g., disease recurrence) after morcellation procedures. In April 2014, FDA issued a safety communication warning against the use of LPMs during most surgeries for fibroids. Following an open public meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee, FDA issued an updated safety communication and Immediately-in-Effect Guidance document in November 2014. The latter recommended the addition of the following key statements to the labeling of LPMs with gynecological or general indications:

- *Contraindication: Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy*

- *Contraindication: Laparoscopic power morcellators are contraindicated for removal of uterine tissue containing suspected fibroids in patients who are:*
  - *peri- or post-menopausal, or*
  - *candidates for en bloc tissue removal, for example, through the vagina or via a mini-laparotomy incision.*

- *Boxed Warning:*

> ***WARNING*: Uterine tissue may contain unsuspected cancer. The use of laparoscopic power morcellators during fibroid surgery may spread cancer, and decrease the long-term survival of patients. This information should be shared with patients when considering surgery with the use of these devices.**

Purpose

This document is intended to provide a review of information which has been published subsequent to FDA's 2014 analyses. It consists of:

- An evaluation of the prevalence of occult sarcoma (and LMS specifically) in women undergoing myomectomy or hysterectomy for presumed benign uterine fibroids;
- An evaluation of patient outcomes (e.g., disease-free survival and overall survival) in women diagnosed with an occult malignancy following morcellation (power or manual) during myomectomy or hysterectomy for the treatment of presumed uterine fibroids; and
- An evaluation of differences in patient outcomes for women undergoing power morcellation compared to manual (e.g., scalpel) morcellation and/or no morcellation.

[7] Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine sarcoma: analysis of 13,089 cases based on surveillance, epidemiology, and end results database. Int J Gynecol Cancer 2016; 26:1098-1104.
[8] American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Seventh edition. Springer, New York, 2010.

In addition, this document provides

- A review of MDRs received by FDA for dissemination of malignancy following LPM use;
- A summary of data related to changes in rates of types of hysterectomy/myomectomy procedures following FDA's 2014 actions; and
- A summary of advantages/disadvantages of laparoscopic compared to open abdominal myomectomy and hysterectomy.

Methods

Prevalence of Sarcoma in Presumed Benign Uterine Leiomyomas (Fibroids)

PubMed and EMBASE were searched to identify publications in English between April 1, 2014 and April 15, 2017 using combinations of the following search terms: unexpected, occult, malignancy, sarcoma, leiomyosarcoma, hysterectomy, myomectomy, fibroid, leiomyoma, cancer, histology, and histopathology. We included studies whose stated research objective(s) included the determination of the rate of occult sarcoma in women undergoing surgery for presumed fibroids. Posters and abstracts were not included, nor were studies of women which included surgeries for non-leiomyoma related primary indications (e.g., pelvic organ prolapse, pain) unless data were separately presented for those with a primary indication of fibroids. Twenty-three (23) studies were included in the analyses. For both uterine sarcoma and LMS, estimates were generated using a fixed effect model and a random-effects model using a generalized linear mixed model in SAS 9.4 (PROC GLIMMIX). The fixed effect model assumes that there is one true event rate which is shared by all included studies. The random effects model, however, allows for the possibility that the true event rate may vary between studies (e.g., the event rate might be higher in studies with older subjects). Since it is not clear whether we can assume that the true event rate varies from study to study, both models were used, and the results for both models will be presented.

Impact of Morcellation on Disease-Free and Overall Survival Outcomes

PubMed was searched to assess the impact of morcellation using a LPM or non-power method (i.e., hand/scalpel) on overall survival and disease free survival (or disease recurrence), in patients who underwent laparoscopic treatment of fibroids via hysterectomy and/or myomectomy and who were diagnosed with an occult sarcoma. The search was limited to English articles published January 1, 2014 through December 31, 2016. The following search terms were used: morcell* AND fibroid. Records were reviewed for eligibility, and excluded for: non-clinical study (i.e., commentary, letter to the editor, non-systematic review, animal studies); case report or case series; feasibility study; no patients with occult malignancy; no use of laparoscopic morcellation (i.e., hysteroscopic morcellation); no patient data; no data on outcomes (disease recurrence, disease free survival, or overall survival after initial surgery).

MDRs Associated with Dissemination of Malignant Tissue in Association with LPM Use

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and malfunctions. Although MDRs are a valuable source of information, they may include incomplete, untimely, unconfirmed, duplicate or biased data. Furthermore, a rate of an event cannot be determined due to potential under-reporting and lack of information about frequency of device use. MDRs associated with LPMs received through April 17, 2017 were reviewed.

Results

Prevalence of Sarcoma in Presumed Uterine Leiomyomas (Fibroids)

A total of 23 studies were included in the current analyses.[9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,,24,25,26,27,28,29,30,31] Summaries of these publications are provided in table format in Appendix A (uterine sarcoma overall) and Appendix B (LMS). The number of subjects per study ranged from 232 to 137,717. The rate of unsuspected uterine sarcoma in each individual study ranged from 0% to 1.48%, and for LMS from 0% to 0.51%. The estimated rates of unsuspected uterine sarcoma and LMS during myomectomy or hysterectomy for presumed fibroids, based on these 23 newer publications, are shown in Table 1 below.

Table 1. Estimated Prevalence of Unsuspected Uterine Sarcoma and Leiomyosarcoma (2014-2017 Publications)

	Fixed Effect Model % (95% CI)	Random Effects Model % (95% CI)
Uterine Sarcoma (General)	0.328 (0.303-0.352)	0.277 (0.172-0.445)
Leiomyosarcoma (LMS)	0.175 (0.148-0.202)	0.134 (0.089-0.202)

[9] Damasco M, Chan, P, Slonim M et al. Incidence of malignancy and fibroid variants at surgery for presumed benign symptomatic fibroids. Journal of Minimally Invasive Gynecology, 2017; 24(4):659-664.

[10] Bean E, Cutner, A, Holland T et al. Laparoscopic Myomectomy: A single-center retrospective review of 514 patients. Journal of Minimally Invasive Gynecology, 2017, 24:485-493.

[11] Raine-Bennett T, Tucker L, Zaritsky E et al. Occult uterine sarcoma and leiomyosarcoma. Incidence of and survival associated with morcellation. Obstet Gynecol. 2016; 127(1):29-39.

[12] Paul P, Rengarag, V, Das T, et al. Uterine sarcomas in patients undergoing surgery for presumed leiomyomas: 10 years' experience. Journal of Minimally Invasive Gynecology. 2016; 23:384-389.

[13] Gao Z, Li, L, Meng, Y. A retrospective analysis of the impact of myomectomy on survival in uterine sarcoma. PLOS ONE, 2016; DOI:10.1371/journal.pone.0148050.

[14] Agrawal P, Agrawal, R, Chandrakar, J. To assess the safety of morcellation for removing uterine specimen during laparoscopic and vaginal hysterectomies for leiomyomas. J Obstet Gyn India, 2016; 66:567-72.

[15] Mettler, M, Maass, N, Abdusattarova, K et al. Frequency of uterine sarcomas in patients admitted for uterine fibroids surgery. J Turk Ger Gyn Assoc. 2017; doi:10.4247/jtgga.2016.0248 [epub ahead of print].

[16] Mahnert N, Morgan D, Campbell D et al. Unexpected gynecologic malignancy diagnosed after hysterectomy performed for benign indications. Obstet Gynecol 2015; 135 (2):397-405.

[17] Zhang J, Li, T, Zhang J et al. Clinical characteristics and prognosis of unexpected uterine sarcoma after hysterectomy for presumed myoma with and without transvaginal scalpel morcellation. Int J Gyn Cancer, 2016; 26(3):456-463.

[18] Bojahr B, De Wilde R, Tchartchaian, G. Malignancy rate of 10,731 uteri morcellated during laparoscopic supracervical hysterectomy (LASH). Arch Gynecol Obstet, 2015; 292:665-672.

[19] Mao, J, Pfeifer, S, Zheng, X et al. Population-based estimates of the prevalence of uterine sarcoma among patients with leiomyomata undergoing surgical treatment. JAMA Surgery, 2015; 150(4): 368-370.

[20] Zhao, W, Bi, F, Li, D, Tang Q. Incidence and clinical characteristics of unexpected uterine sarcoma after hysterectomy and myomectomy for uterine fibroids: a retrospective study of 10,248 cases. OncoTargets and Therapy, 2015; 8:2943-2948.

[21] Tan A, Salfinger, S, Tan J, Cohen P. Morcellation of occult uterine malignancies: an Australian single institution retrospective study. Australian and NZ J Obstet and Gyn, 2015; 55:503-506.

[22] Brohl, A, Li, L, Andikyan V et al. Age-stratified risk of unexpected uterine sarcoma following surgery for presumed benign leiomyoma. The Oncologist. 2015; 20: 433-439.

[23] Zhang J, Zhang J, Dai, Y et al. Clinical characteristics and management experience of unexpected uterine sarcoma after myomectomy. Int Journal of Gyn and Obstet, 2015; 130: 195-199.

[24] Vercellini P, Cribiu, F, Bosari, S et al. Prevalence of unexpected leiomyosarcoma at myomectomy: a descriptive study. Amer J Obstet & Gyn, 2016; 214(2):292-294.

[25] Oduyebo, T, Hinchcliff, E, Meserve, E et al. Risk factors for occult sarcoma among women undergoing minimally invasive gynecologic surgery. Journal of Minimally Invasive Gyn Surgery, 2016; 23:34-39.

[26] Rodriguez, A, Asogly M, Sak M, et al. Incidence of occult leiomyosarcoma in presumed morcellation cases: a database study. European J Obstet & Gyn and Reprod Biology, 2016; 197:31-35.

[27] Lieng M, Berner, E, Busund, B. Risk of morcellation of uterine leiomyosarcomas in laparoscopic surpacervical hysterectomy and laparoscopic myomectomy, a retrospective trial including 4791 women. Journal of Minimally Invasive Gynecology, 2015; 22:410-414.

[28] Picerno, T, Wasson, M, Rios, A et al. Morcellation and the incidence of occult uterine malignancy. Int J Gynecol Cancer, 2016:26:149-155

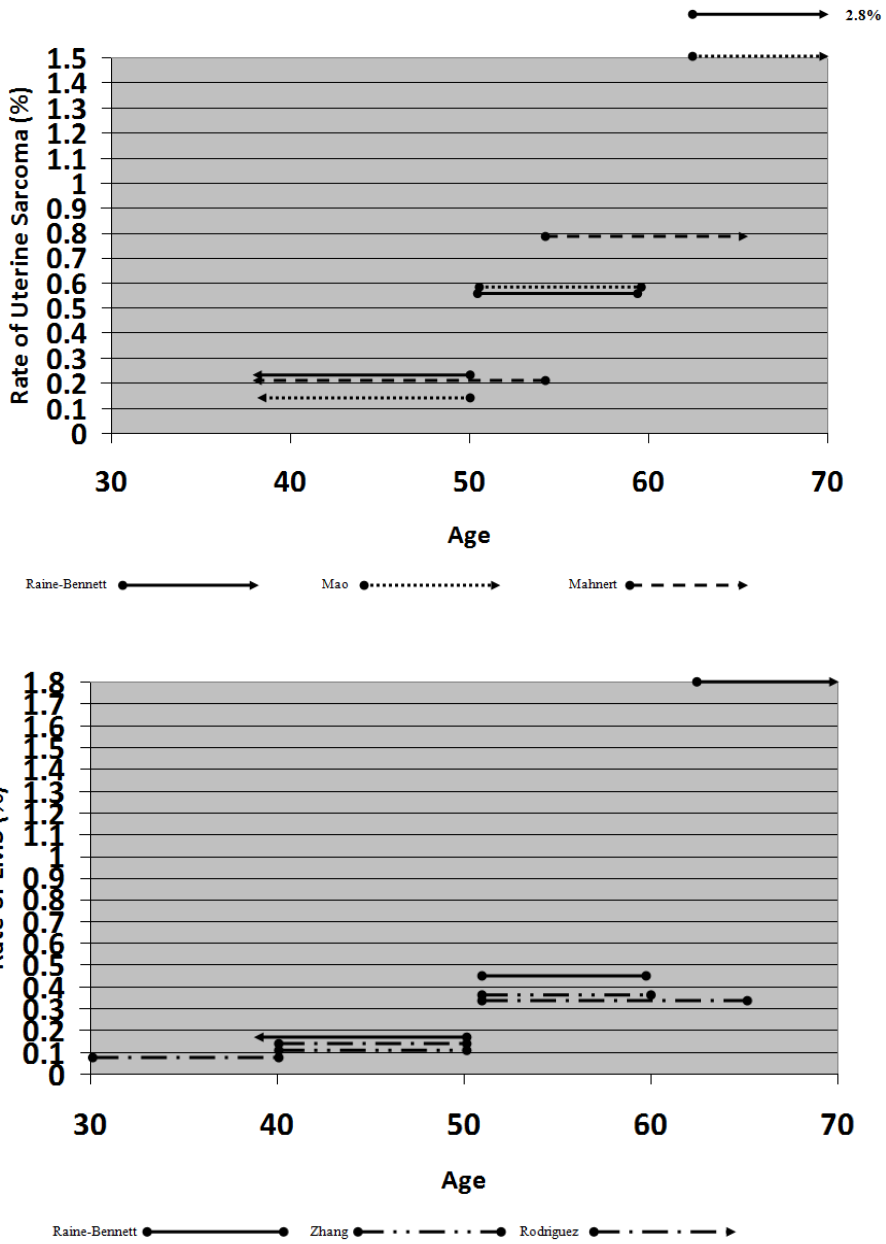
[29] Balgobin, S, Maldonado, P, Chin, K et al. Safety of manual morcellation after vaginal or laparoscopic-assisted vaginal hysterectomy. J Min Inv Gyn, 2016: 23(4):542-547.

[30] Rechberger, T, Miotla, P, Futyma, K et al. Power morcellation for women undergoing laparoscopic supracervical hysterectomy – safety of procedure and clinical experience from 426 cases. Ginekologia Polska, 2016; 87:546-551.

[31] Cormio G, Loizzi V, Ceci O et al. Unsuspected diagnosis of uterine leiomyosarcoma after laparoscopic myomectomy. J Obstet & Gyn, 2015; 35:21--212

Five of the 24 publications[11,16,17,19,26] stratified rates by age ranges. As shown in Figure 1 below, these data suggest increases in rates of occult sarcoma with age for women undergoing surgery for presumed fibroids with rates approaching 2-3% for women over age 60.

Figure 1. Rates of uterine sarcoma (top) and LMS (bottom) by age ranges



Raine-Bennett also calculated incidence rates by race/ethnicity[11]. In that review, for occult uterine sarcomas in general, rates ranged from 0.28% for African-American women to 0.36% for Caucasian and Hispanic women to 0.44% in Asian (and "other") women. For LMS specifically, rates ranged from 0.22% in African-American women to to 0.23% in Caucasian and Hispanic women, to 0.28% in Asian (and "other") women.

Impact of Morcellation on Disease-Free and Overall Survival Outcomes

Literature published 2014-2016 was reviewed to assess the impact of morcellation using power or manual methods on overall survival (OS) and disease free survival (DFS)/disease recurrence, in patients undergoing laparoscopic myomectomy or hysterectomy for fibroids and who were diagnosed with an occult malignancy. A total of 27 articles were included in our analyses.

Studies with Comparisons between Groups

Twelve (12) studies[11,13,17,20,23,27,32,33,34,35,36,37] reported survival outcomes for patients receiving morcellation versus those who did not. For our review, in studies where both power and manual techniques were employed or morcellation type was not specified, the term "combined morcellation" is used. All 12 studies included subjects diagnosed with uterine malignancy (sarcomas and/or STUMP) after surgery and 11 of the 12 included greater than one year of follow-up. All were retrospective studies with variable follow-up times. In addition, relatively small sample sizes may have resulted in wide confidence intervals and/or results which showed trends but did not reach statistical significance.

Several of these studies provide some evidence for differences in disease recurrence and OS between morcellation and non-morcellation patient groups. For patients with LMS, Raine-Bennett[11] reported crude risk ratios associated with power morcellation compared to no morcellation for disease recurrence at one, two, and three years as 2.38 (95% CI: 1.05-5.38), 1.45 (no 95% CI provided), and 1.88 (95% CI: 1.50-2.37) respectively. For nonpower morcellation compared to no morcellation these ratios were 1.39, 0.97, and 0.98 at those same time points respectively (all not statistically significant). The authors noted that the probability of 3-year DFS was lower for power morcellation (0.19, 95% CI: 0.01-0.54) than non-power (0.51, 95% CI: 0.30-0.69) or no morcellation (0.54, 95% CI: 0.42-0.64). Regarding OS, at one year, the power morcellation group was associated with a higher risk of death compared to no morcellation (crude RR = 4.75, 95% CI: 1.03-22.0). At two and three years, the crude risk ratios were 1.13 and 1.64 respectively. For nonpower morcellation, the crude risk ratios for death were 3.04, 1.26, and 0.82 at one, two and three years respectively.

George[33] reported an association between combined morcellation and disease recurrence when compared to no morcellation in patients with LMS (OR=3.14, 95% CI: 1.5-6.5). Median RFS was 10.8 months and 39.6 months (p=0.02) respectively. Cusido[32], in a cohort with 57% ESS, reported higher rates of local disease recurrence (75.0% vs 17.2%) and any disease recurrence (87.5% vs 37.9%) in a combined morcellation group compared to a non-morcellation group. The median time to recurrence was 10.4 months and 70.3 months respectively (p=0.018). The authors also reported a difference in DFS in power versus vaginal/non-power versus no morcellation groups (6.3 versus 11.9 versus 149.9 months, p = .002). Lee[34] reported 33.3% sarcoma recurrence for the combined morcellation group compared to 13.4% in the non-morcellation group (p=.048), after a median of 41 months follow-up. Gao's[13] cohort of 59 myomectomy subjects (54% ESS) revealed a trend for worse 5-year recurrence-free survival (24.1% combined vs 43.6% no morcellation) and 5-year overall survival (OS) (37.8% vs 43.1%) following morcellation. Median RFS was 66 months in the morcellation group and 90 months in the no morcellation group. Lin[35] reported an adjusted hazard ratio of 2.43 (95% CI: 0.70-8.40) for lower disease free survival (DFS) and 2.94 (95% CI: 0.83-10.39) for lower OS, for morcellation compared to no morcellation groups in LMS subjects matched for tumor size. Five year DFS was reported as 0% in the morcellation group

[32] Cusido, M., et al., Impact of surgery on the evolution of uterine sarcomas. J Minim Invasive Gynecol, 2015. 22(6): p. 1068-74.
[33] George, S., et al., Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. Cancer, 2014. 120(20): p. 3154-8.
[34] Lee, J.Y., et al., Outcomes of uterine sarcoma found incidentally after uterus-preserving surgery for presumed benign disease. BMC Cancer, 2016. 16(1): p. 675.
[35] Lin, K.H., et al., Clinical outcome affected by tumor morcellation in unexpected early uterine leiomyosarcoma. Taiwan J Obstet Gynecol, 2015. 54(2): p. 172-7.
[36] Tan-Kim, J., et al., Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation. Am J Obstet Gynecol, 2015. 212(5): p. 594 e1-10.
[37] Yuk, J.S., et al., Comparison of survival outcomes in women with unsuspected uterine malignancy diagnosed after laparotomic versus laparoscopic myomectomy: A national, population-based study. Ann Surg Oncol, 2016. 23(4): p. 1287-93.

and 58.9% in the non-morcellation group. Five-year OS was 19.5% and 53.4% in the two groups respectively. Yuk[37] (n=126) reported that estimated survival rates at 3 years did not vary between groups (93.8% vs. 93.8%). Zhang[17] reported one case of recurrence (1/7, 14.3%) in the combined morcellation group for hysterectomy patients with unexpected uterine sarcoma (72% ESS), compared to no cases (0/11, 0%) in the no morcellation group. Zhang[23] reported no recurrences in a myomectomy morcellation group (0/5, 0%, mean follow-up 31.2 months) compared to one case (1/4, 25%, mean follow-up 40.5 months) in the non-morcellation group for patients with unexpected uterine sarcoma. Zhao[20] (n=48, 60% ESS), assuming all laparoscopic myomectomies included power morcellation, reported 16.7% and 22.2% recurrence rates for subjects with ESS for laparoscopy and laparotomy groups respectively at an average follow-up of 30 months, although only 33 cases were followed.

Studies without Comparison Groups

Seven studies presented outcomes for patients who underwent morcellation and were diagnosed with an occult malignancy.[18,21,24,38,39,40,41] At follow-up times of 1-4 years, a number of patients diagnosed with LMS experienced disease recurrence and/or death across five of the 7 studies. Oduyebo[41] reported that 61.5% of patients with LMS experienced a local recurrence and a third of the LMS patients died. Comparatively, the outcomes for malignancies other than LMS showed fewer recurrences and no deaths.

Systematic Reviews

Four systematic reviews included discussions related to DFS or OS following morcellation. All reviews evaluated between four and seven original research articles, depending on their search criteria and types of sarcoma evaluated. Articles in the reviews had some degree of overlap. Ebner[42] concluded that most available data indicated a benefit for en-bloc resection of LMS in terms of reduced rates of recurrences, and both prolonged DFS and OS. Singh[43] stated that the literature reported a worse prognosis in patients initially treated with a surgical approach involving tumor disruption. Pritts[44] concluded that en bloc removal may result in improved survival and less recurrence, but that the data were "highly biased and of poor quality" and there was "no reliable evidence that morcellation, power or otherwise, substantially results in tumor upstaging or that there is any evidence that any single type of morcellation is more worrisome than another." Pereira[45] focused on patients who underwent a second surgery after power morcellation, and concluded "there is some evidence highlighting the long-term sequelae related to the growth and propagation of these dispersed tissue fragments in the form of parasitic leiomyomata, iatrogenic endometriosis, and cancer progression."

[38] Brown, J., et al., Laparoscopic supracervical hysterectomy with morcellation: should it stay or should it go? J Minim Invasive Gynecol, 2015. 22(2): p. 185-92.
[39] Ehdaivand, S., et al., Incidental gynecologic neoplasms in morcellated uterine specimens: a case series with follow-up. Hum Pathol, 2014. 45(11): p. 2311-7.
[40] Graebe, K., et al., Incidental power morcellation of malignancy: a retrospective cohort study. Gynecol Oncol, 2015. 136(2): p. 274-7.
[41] Oduyebo, T., et al., The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol, 2014. 132(2): p. 360-5.
[42] Ebner F., et al., Is open surgery the solution to avoid morcellation of uterine sarcomas? A systematic literature review on the effect of tumor morcellation and surgical techniques. Arch Gynecol Obstet, 2015. 292(3): p. 499-506.
[43] Singh, S.S., et al., Technical update on tissue morcellation during gynaecologic surgery: its uses, complications, and risks of unsuspected malignancy. J Obstet Gynaecol Can, 2015. 37(1): p. 68-81.
[44] Pritts, E.A., et al., Outcome of occult uterine leiomyosarcoma after surgery for presumed uterine fibroids: a systematic review. J Minim Invasive Gynecol, 2015. 22(1): p. 26-33.
[45] Pereira, N., et al., Electric morcellation-related reoperations after laparoscopic myomectomy and nonmyomectomy procedures. J Minim Invasive Gynecol, 2015. 22(2): p. 163-76.

Decision Analyses

There were four decision analysis papers identified by the search and relevant to the topic.[46,47,48,49] Decision analyses are constructed using parameters estimated from published literature and tested using a hypothetical cohort of subjects. Siedhoff[47] used estimated risks of transfusion, wound infection, vaginal cuff dehiscence, venous thromboembolism, hernia, occult LMS incidence (0.12%), procedure-related death, and death from LMS, and predicted more deaths from LMS for laparoscopic hysterectomy (LH) than abdominal hysterectomy (AH), but more hysterectomy-related deaths for AH. In sum, this resulted in more estimated total deaths for AH than LH (103 vs. 98 per 100,000). The LH group was predicted to have an additional one month of quality adjusted life time over five years compared to AH. The model predicted lower overall mortality for LH with any type of morcellation when compared with AH. In 2016, Siedhoff[48] updated the model using an estimated incidence of occult LMS of 0.17% and found that overall mortality was similar between LH and AH, but slightly favoring AH. The model favored the LH group for women age <50, but strongly favored the AH group for women ≥50 years old. Rutstein[46] reported 4.99 quality adjusted life years (QALY) over five years for the LH group compared to 4.91 for the AH group. Wright[49] found that LH without morcellation was associated with more QALY compared to either AH or LH with power morcellation. The authors reported a small advantage in number of overall deaths and QALYs for LH for women <40 years old, and for QALYs for women 40-49 years old. There was an advantage in overall deaths, cancer associated deaths, and QALYs for AH for women over 50 years old.

Medical Device Reports (MDRs) Received By FDA

Through April 17, 2017, FDA received 262 MDRs describing dissemination of malignant cells in association with LPMs. Of these, 18 specifically claimed that the device was associated with upstaging of disease, or that the patient was diagnosed with Stage III or IV disease following the surgery. Due to the level of information provided in a given report it is not always possible to determine which reports are citing the same event, and therefore duplicate reports may be included. In addition, the submission of an MDR does not prove causality between the device and the reported event(s). Mean patient age was 48.8 years and LMS was specifically reported as the tumor type in 146 reports. The earliest MDR submission occurred in December 2013 and described an event from October 2013. Table 2 below provides the number of MDRs received by year from 2013 to 2017 (through April 17, 2017).

Table 2: Number of MDRs Received by Calendar Year

Year of Receipt	MDR Reports
2013	9
2014	31
2015	82
2016	127
2017 (Through 4/17/17)	11
Total	**262**

The year of MDR receipt does not necessarily correlate with the date of the actual surgical procedure as reports are commonly submitted to FDA months to years after the event occurred. Only 5 of the 262 events occurred after FDA's November 2014 safety communication and guidance issuance; none of the reports were associated with a surgery that took place in 2016 or 2017.

[46] Rutstein, S.E., et al., Cost-effectiveness of laparoscopic hysterectomy with morcellation compared with abdominal hysterectomy for presumed myomas. J Minim Invasive Gynecol, 2016. 23(2): p. 223-33.
[47] Siedhoff, M.T., 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(5): p. 591 e1-8.
[48] Siedhoff, M.T., et al., Laparoscopic hysterectomy with morcellation vs abdominal hysterectomy for presumed fibroids: an updated decision analysis following the 2014 Food and Drug Administration safety communications. Am J Obstet Gynecol, 2016.
[49] Wright, J.D., et al., Economic and survival implications of use of electric power morcellation for hysterectomy for presumed benign gynecologic disease. J Natl Cancer Inst, 2015. 107(11).

Changes in Hysterectomy/Myomectomy Procedures

Several publications, using information from individual facilities, regional, and/or national databases, sought to describe changes in procedures in the months/years subsequent to FDA's 2014 activities when compared to those prior.[50,51,52,53,54,55,56] Three of these specifically focused on women with fibroids as the indication for the procedure.[54-56] Table 3 below presents the changes in percentages of various hysterectomy and myomectomy procedures as cited in those publications. (Where data for multiple years was presented individually, the table below presents data for 2013 versus 2015).

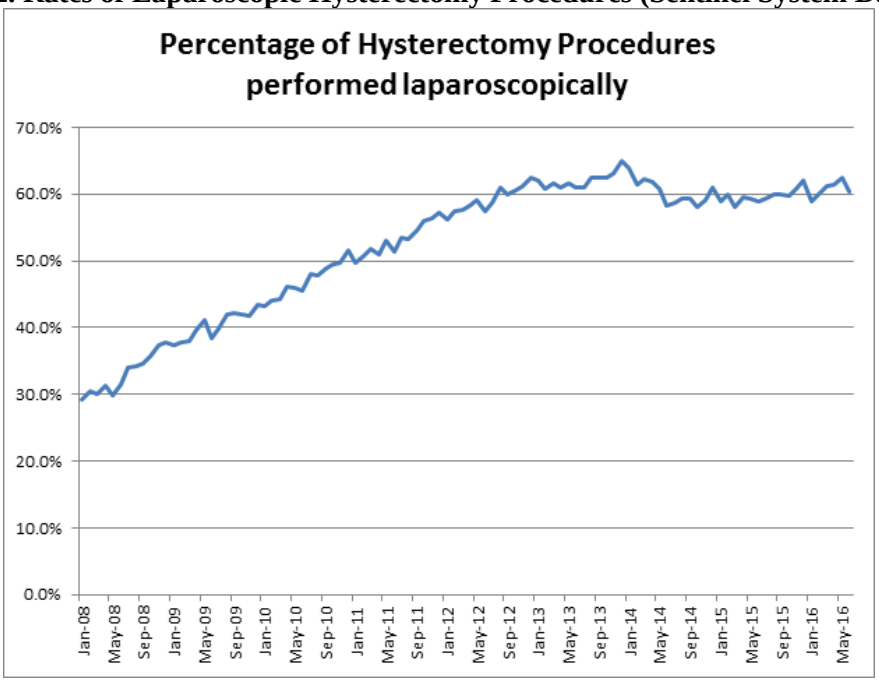
Table 3. Changes in Procedure Types (Pre- and Post-2014 FDA Actions)- Medical Literature

	Barron[50]	Wright[51]	Harris[52]	Zaritsky[53]	Ottarsdottir[54]	Stentz[55]	Pereira[56]
Abdominal Procedures	14.3% → 20.1%	27.1% → 31.8%	22.9% → 24.6%	11.5% → 6.9%	19.0% → 29.0%	49.1% → 60.0%	
Laparoscopic Procedures			55.2% → 51.1%	66.3% → 69.7%	71.3% → 65.3%	50.9% → 40.0%	
Minimally Invasive Surgery Procedures	85.7% → 79.9%	59.7% → 56.2%					47.3% → 48.1%
Supracervical Hysterectomy – Lap	13.9% → 5.6%		11.0% → 4.5%				
Vaginal Hysterectomy	9.7% → 7.1%		21.9% → 24.3%	22.2% → 23.4%	5.6% → 2.3%		
LPM use		13.7% → 2.8%		11.4% → 0.02%			

FDA also reviewed data from the Sentinel System which leverages existing electronic health care data from multiple sources, covering over 425 million person-years. FDA's analysis was limited to women with a prior diagnosis of fibroids who were identified as having had a hysterectomy or myomectomy using appropriate CPT and ICD codes. Procedures associated with malignancy were excluded. The use of morcellators was identified using HCPCS Level II code C1782, "Morcellator". Data revealed that between 2008 and April 2014, the use of morcellators in hysterectomies increased to 0.7-0.8 procedures per 1,000 eligible women. After April 2014, the rate fell to < 0.1 procedures per 1,000. In addition, prior to 2014 the rate of hysterectomies performed laparoscopically rose from 30% in 2008 to over 60% in early 2014. After that time point, as shown in Figure 2 below, the rate plateaued at approximately 60%.

[50] Barron, K et al. Association of the US Food and Drug Administration morcellation warning with rates of minimally invasive hysterectomy and myomectomy. Obstet & Gyn, 2015; 126(6): 1174-1180.
[51] Wright, J et al. Trends in use and outcomes of women undergoing hysterectomy with electric power morcellation. JAMA, 2016; 316: 877-878.
[52] Harris, J et al. Practice patterns and postoperative complications before and after US Food and Drug Administration safety communication on power morcellation. Amer J Obstet & Gyn, 2016; 98.e1-98.e13.
[53] Zaritsky E et al. Minimally invasive hysterectomy and power morcellation trends in a west coast integrated health system. Obstet & Gyn. 2017 May 5. doi: 10.1097/AOG.0000000000002034.
[54] Ottarsdottir H et al. Trends in mode of hysterectomy after the US Food and Drug Administration power morcellation advisory. Obstet & Gyn 2017 Jun;129(6):1014-1021. doi: 10.1097/AOG.0000000000002058.
[55] Stentz, N et al. Changes in myomectomy practice after the US Food and Drug Administration safety communication on power morcellation. Obstet & Gyn 2017 Jun;129(6):1007-1013. doi: 10.1097/AOG.0000000000002035.
[56] Pereira, N. Temporal trends in minimally invasive myomectomy before and after the US Food and Drug Administration recommendations against electric morcellation. Int J Gyn Obstet, 2017; 137(3):295-300.

Figure 2. Rates of Laparoscopic Hysterectomy Procedures (Sentinel System Data)



Several of the publications referenced in Table 3 also reported on changes in rates of surgical complications associated with hysterectomies and/or myomectomies following FDA's 2014 communications. Harris[52], reporting on data from the Michigan Surgical Quality Collaborative, cited slight increases in rates of "all major postoperative complications" (4.4% to 5.0%, p=0.18), for major postoperative complications excluding blood transfusions (2.2% to 2.8%, p=0.015), and 30-day hospital readmission (3.4% to 4.2%, p=0.025) but no change in rates of surgical reoperations (2.2% to 2.3%, p=0.59). Other authors did not see increases in complications. Wright[51], using data from the Perspective Database, noted that "paradoxically, although the rate of abdominal hysterectomy increased, no change in the rate of major peri-operative complications were found." For the first quarter of 2013 and the first quarter of 2015, the overall complication rates were 8.3% and 8.4% respectively. In addition, the rates of intra-operative complications decreased for abdominal hysterectomies (7.0% to 6.1%), for MIS hysterectomies (4.4% to 4.1%) and for vaginal hysterectomies (4.7% to 4.2%). Using data from the Partners Research Patient Data Registry to report on patients undergoing hysterectomy for fibroids, Ottarsdottir[54] also noted a decrease from 2013 to 2015 in rates of intra-operative complications (3.4% to 2.3%), readmission (2.6% to 2.3%), and reoperation (1.5% to 0%). Stentz[55] evaluated myomectomies using the American College of Surgeons National Surgical Quality Improvement Program database and despite seeing an increase in the proportion of abdominal procedures, noted that composite morbidity (transfusion, wound dehiscence, wound infection, UTI, sepsis/shock, DVT/PE) "remained constant over time" with a rate of 11.5% prior to FDA's communication and 11.7% afterwards. Thirty-day rates for reoperation remained similar (0.7% and 0.9%) as did those for readmission (1.7% and 1.7%). Pereira et al[56] also reviewed cases of myomectomies at a New York facility and noted no changes in rates of intra-operative or post-operative complications.

Laparoscopic Compared to Abdominal Myomectomy and Hysterectomy

A recently updated Cochrane review including 47 trials examined the advantages and disadvantages of LH versus vaginal hysterectomy (VH) and AH for benign gynecological disease.[57] The authors concluded that although LH has "no advantages" over VH, it does have "some advantages over AH" including fewer days to return to activities (mean difference 13.6 days), reduced length of hospital stay,

[57] Aarts J, Nieboer TE, Johnson N, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015; 8: CD003677.

and decreased rate of wound/abdominal wall infection (OR = 0.29, 95% CI 0.12-0.71). LH, did however, have higher rates of urinary tract (bladder or ureter) injury when compared to AH (OR=2.44, 95% CI 1.2-4). Several other outcomes showed clinical trends, but did not reach statistical significance including lower rates of bleeding (OR=0.45) and bowel injury (OR=0.21) for LH as well as longer operating time, and higher rates of vascular injury (OR=1.76) and vaginal cuff infection (OR=1.43). Another recent Cochrane review of 9 trials evaluated MIS techniques versus open myomectomy for fibroids.[58] When compared to open myomectomy, MIS techniques provided advantages in post-operative pain and fever, as well as length of hospital stay, but resulted in longer operating time. In both Cochrane reviews, authors rated the quality of the evidence as "very low to moderate" with main limitations including small subject numbers, poor information about study methods, and wide confidence intervals. Hurst reported that compared to open myomectomy, laparoscopic myomectomy is associated with less operative blood loss and post-op pain, faster recovery and fewer adhesions.[59] Seidhoff's[47] decision model predicted lower rates of postoperative transfusion, venous thromboembolism, and wound infection for LH versus AH.

Summary

As part of FDA's ongoing efforts to consider the benefits and risks of LPMs in women undergoing laparoscopic myomectomy or hysterectomy for presumed uterine fibroids, we have undertaken an evaluation of data which has become available following our 2014 FDA safety communication and guidance. Peer-reviewed scientific literature served as the main source of data for our analyses. Limitations of these publications include reliance on retrospectively collected data, studies which were heterogeneous (e.g., patient population, type of procedure, type of morcellation (power, non-power), tumor pathology, patient ages, and subject follow-up), and, for outcomes studies, small sample sizes. However, at the current time, these data are the highest level of evidence available.

In estimating the prevalence rates of occult uterine sarcoma and LMS in women undergoing surgery for presumed benign fibroids, we identified and assessed 23 studies which sought to address this question and which were published since our 2014 safety communication. For uterine sarcomas in general, use of a fixed effect model resulted in an estimate of 0.328% (95% CI: 0.303-0.352%) corresponding to approximately 1 in 305 women with an expected range of 1 in 284 to 1 in 330 women. Application of the random effects model resulted in a rate of 0.277% (95% CI: 0.172-0.445%), corresponding to approximately 1 in 360 women, with an expected range of approximately 1 in 225 to 1 in 580 women. For LMS, the fixed effects model resulted in an estimate of 0.175% (95% CI: 0.148%-0.202%), corresponding to approximately 1 in 570 women with an expected range of approximately 1 in 495 to 1 in 675, whereas the random effects model provided a rate of 0.134% (95% CI: 0.089%-0.202%) corresponding to 1 in approximately 750 women, with an expected range of approximately 1 in 495 to 1 in 1100. These estimates are consistent with those cited by FDA in 2014. Limited data showed an increase in occult sarcoma with age for both uterine sarcoma and LMS with significant increases noted for women $\geq$60 years of age.

Evaluation of patient outcomes following morcellation was based on data from 27 studies, including 12 which involved comparisons between patients who received morcellation versus those who did not. These publications continue to provide evidence for differences in patient outcomes between groups, including for power morcellation versus non-power or no morcellation.

Since the receipt of its first MDR in December 2013 related to dissemination of malignant cells in association with the use of LPMs during gynecological surgery, FDA has received 262 similar reports. Five note an index procedure which was performed following FDA's November 2014 communication.

[58] Bhave C, Franik S, Pouwer A et al. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. Cochrane Database of Systematic Reviews 2014; 10:CD004638.
[59] Hurst BS, Matthews ML, Marshburn PB. Laparoscopic myomectomy for symptomatic uterine myomas. Fertil Steril 2005; 83(1): 1-23.

Recent literature describes changes in practice patterns regarding hysterectomy/myomectomy following FDA's 2014 actions. It generally suggests that the percentage of women undergoing open abdominal procedures is higher than prior to 2014 although reported absolute and relative percentage changes varied between reports. Two reports showed a large decrease in the use of LPMs. However, it also appears that minimally invasive surgical techniques remain a common procedure. Data from the Sentinel System also showed a reduction in the use of LPMs and suggest a "flattening" of the rates for laparoscopic procedures (which had been increasing) and open procedures (which had been decreasing). Despite changes in routes of surgery, data on rates of complications also varied, with several noting no significant changes in peri-operative complications.

While minimally invasive surgery conveys several significant advantages over open surgery for women with fibroids, the use of LPMs during these surgeries poses a risk due to the potential presence of unsuspected sarcoma in this population. FDA continues to caution against the use of LPMs in the majority of women undergoing myomectomy or hysterectomy for treatment of fibroids. The Agency also continues to recommend that the advantages and risks of using LPMs during fibroid surgery be thoroughly discussed between the patient and physician before surgery. FDA continues to actively encourage and engage in research to evaluate outcomes for a range of treatment options for fibroids and support the development of safer alternatives for providing a minimally invasive approach.

Appendix A. Studies reporting rates of unsuspected uterine sarcomas in women undergoing surgery for fibroids

Author	Year Published	Study Years	Procedure(s)	Country	Total Patients	Number of Occult Uterine Sarcomas	Rate of Occult Uterine Sarcoma Per 100 (95%CI)
Damasco[9]	2017	2004-2013	Hysterectomy or Myomectomy	Australia	1878	6	0.32 (0.06-0.57)
Bean[10]	2017	2004-2015	Myomectomy	U.K.	514	1	0.19 (0.00-0.58)
Raine-Bennett[11]	2016	2006-2013	Hysterectomy	U.S.	34,728	125	0.36 (0.30-0.42)
Paul[12]	2016	2004-2014	Hysterectomy or Myomectomy	India	2678	8	0.30 (0.09–0.51)
Gao[13]	2016	2005-2014	Hysterectomy or Myomectomy	China	3986	59	1.48 (1.11-1.86)
Agrawal[14]	2016	2011-2015	Hysterectomy or Myomectomy	India	232	0	0.00 (0.00-1.29)
Mettler[15]	2016	2003-2015	Hysterectomy or Myomectomy	Germany	2269	1	0.04 (0.00-0.13)
Picerno[30]	2016	2006-2013	Hysterectomy or Myomectomy	U.S.	258	0	0.00 (0.00-1.16)
Rechberger[32]	2016	2011-2015	Hysterectomy	Poland	334	0	0.00 (0.00-0.90)
Mahnert[16]	2015	2013	Hysterectomy	U.S.	1325	5	0.38 (0.05-0.71)
Zhang[17]	2015	2009-2013	Hysterectomy	China	3021	18	0.60 (0.32-0.87)
Bojahr[18]	2015	1998-2014	Hysterectomy	Germany	8720	4	0.05(0.00-0.09)
Mao[19]	2015	2008-2011	Hysterectomy or Myomectomy	U.S.	137,717	412	0.30 (0.27-0.33)
Zhao[20]	2015	2008-2014	Hysterectomy or Myomectomy	China	10,248	48	0.47 (0.34-0.60)
Tan[21]	2015	1990-2015	Hysterectomy or Myomectomy	Australia	734	2	0.27 (0.00-0.65)
Brohl[22]	2015	2005-2014	Myomectomy	U.S.	2075	6	0.29 (0.06-0.52)
Zhang[23]	2015	2009-2013	Myomectomy	China	4248	9	0.21 (0.07-0.35)

Appendix B. Studies reporting rates of unsuspected uterine LMS in women undergoing surgery for fibroids

Author	Year Published	Study Years	Procedure(s)	Country	Total Patients	Number Occult LMS	Rate of Occult LMS Per 100 (95% CI)
Damasco[9]	2017	2004-2013	Hysterectomy or Myomectomy	Australia	1878	0	0.00 (0.00-0.20)
Bean[10]	2017	2004-2015	Myomectomy	U.K.	514	1	0.19 ().00-0.58)
Raine-Bennet[11]	2016	2006-2013	Hysterectomy	U.S.	34,728	81	0.23 (0.18-0.28)
Paul[12]	2016	2004-2014	Hysterectomy or Myomectomy	India	2678	5	0.19 (0.02-0.35)
Gao[13]	2016	2003-2014	Hysterectomy or Myomectomy	China	3986	17	0.43 (0.22-0.63)
Vercellini[26]	2016	1999-2013	Myomectomy	Italy	2356	1	0.04 (0.00-0.13)
Agrawal[14]	2016	2011-2015	Hysterectomy or Myomectomy	India	232	0	0.00 (0.00-1.29)
Oduyebo[27]	2016	2005-2012	Hysterectomy or Myomectomy	U.S.	1573	3	0.19 (0.06-0.56)
Mettler[15]	2016	2003-2015	Hysterectomy or Myomectomy	Germany	2269	0	0.00 (0.00-0.13)
Picerno[30]	2016	2004-2015	Hysterectomy or Myomectomy	U.S.	258	0	0.00 (0.00-1.16)
Balgobin[31]	2016	2006-2013	Hysterectomy	U.S.	435	0	0.00 (0.00-0.69)
Rechberger[32]	2016	2011-2015	Hysterectomy	Poland	334	0	0.00 (0.00-0.90)
Zhang[17]	2015	2009-2013	Hysterectomy	China	3021	5	0.17 (0.02-0.31)
Rodriguez[28]	2015	2002-2011	Hysterectomy or Myomectomy	U.S.	13,964	19	0.14 (0.07-0.20)
Lieng[29]	2015	2000-2013	Hysterectomy or Myomectomy	Norway	4791	6	0.13(0.03-0.23)
Zhao[20]	2015	2008-2014	Hysterectomy or Myomectomy	China	10,248	13	0.13 (0.06-0.20)
Tan[21]	2015	1990-2015	Hysterectomy or Myomectomy	Australia	734	2	0.27 (0.00-0.65)
Brohl[22]	2015	2005-2014	Myomectomy	U.S.	2075	2	0.10 (0.00-0.23)
Zhang[23]	2015	2009-2013	Myomectomy	China	4248	1	0.02 (0.00-0.07)
Cormio[31]	2015	2000-2010	Myomectomy	Italy	588	3	0.51 (0.00-1.09)