U.S. Food and Drug Administration’s Guidance Regarding Morcellation of Leiomyomas
Well-Intentioned, But Is It Harmful for Women?

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The U.S. Food and Drug Administration (FDA) is warning against the use of laparoscopic power morcellators in the majority of women undergoing myomectomy or hysterectomy for the treatment of leiomyomas because of the concern for inadvertent spread of tumor cells if an undiagnosed cancer were present. The authors, representing a 46-member review group, reviewed the current literature to formulate prevalence rates of leiomyosarcoma in women with presumed leiomyomas and to assess reliable data regarding patient survival after morcellation. The authors disagree with the FDA’s methodology in reaching their conclusion and provide clinical recommendations for care of women with leiomyomas who are planning surgery.

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In November 2014, the U.S. Food and Drug Administration (FDA) issued a safety communication severely restricting the use of power morcellators during minimally invasive surgery for women with uterine leiomyomas.1 This guidance was prompted by concern that if a patient had an undiagnosed leiomyosarcoma the morcellator might inadvertently spread tumor cells within the peritoneal cavity. We disagree with the methodology the FDA used to determine the prevalence of leiomyosarcoma among women presumed to have benign leiomyomas and the subsequent restrictions placed on the use of the morcellator, which currently deny many women the benefits of minimally invasive surgery.

Uterine leiomyomas are the most common benign uterine tumor, found in approximately 75% of all women. Leiomyomas may cause abnormal uterine bleeding, infertility, or bulk symptoms causing pelvic discomfort. Symptomatic leiomyomas constitute the indication for approximately 210,000 hysterectomies and 50,000 myomectomies annually in the United States. Genetically distinct from leiomyomas, leiomyosarcoma is a rare, aggressive cancer of the uterine muscle cells. Leiomyosarcomas account for only 1–2% of all uterine malignancies, with approximately 1,600 women diagnosed in the United States annually. Even in early-stage disease, these malignancies have a poor prognosis, primarily as a result of hematogenous spread.2 Clinically, it may be difficult to differentiate leiomyosarcomas from benign leiomyomas. Although leiomyomas tend to be most prevalent between ages 40 and 49 years, bothersome symptoms that lead to surgery for leiomyomas decrease significantly after menopause. Importantly,
the prevalence of leiomyosarcoma is 10-fold higher in women older than age 60 years when compared with women younger than age 50 years.

The preferred method of hysterectomy is vaginal hysterectomy and minilaparotomy may be performed for removal of moderate-sized uteri. Traditionally, surgery for leiomyomas has been performed through large, open abdominal incisions. Minimally invasive laparoscopic surgery, performed through small abdominal incisions, can be used to perform a hysterectomy or myomectomy and currently nearly 40% of hysterectomies are performed using minimally invasive techniques. The benefits of minimally invasive surgery have been well documented and include fewer intraoperative and postoperative complications, less postoperative pain with less need for narcotic pain medication, shorter hospital stays, and faster return to work and family.3

Morcellation, in one form or another, divides tissue into smaller pieces so that a large volume of tissue can be removed from the body through small incisions. For decades, morcellation has been commonly performed with a scalpel during vaginal and minilaparotomy hysterectomies and myomectomies. For minimally invasive procedures, instruments called power morcel- lators were developed that use electromechanical power to divide the tissue for extraction through small incisions, making many minimally invasive procedures technically feasible. Although power morcellation has come under recent scrutiny by the FDA, it should be recognized that all morcellation techniques have the potential of spreading tissue fragments.

In some women, the diagnosis of leiomyosarcoma may be suspected before surgery based on the patient’s menopausal status, imaging findings, or the results of endometrial sampling. In other women, the diagnosis may only be made by pathologic analysis of the tissue days after the myomectomy or hysterectomy. If leio- myosarcoma is present, but unsuspected, and morcellation is performed, tumor cells may be spread throughout the peritoneal cavity. The effect of morcel- lation of occult leiomyosarcoma on long-term prognosis is not known, but the presence or suspicion of retained tissue may necessitate additional surgery and chemotherapy and may worsen the prognosis. In addition to the risk of morcellating occult leiomyosarcoma at the time of surgery for presumed leiomyomas, uncommon cases of benign leiomyomatosis and morcellation of other uterine sarcomas as well as endometrial cancer have been reported.

DATA ANALYSIS
All surgical procedures have potential risks. Therefore, patients’ and physicians’ understanding of risks is the foundation of medical decision-making. Based on their review of the literature, the FDA estimated that for every 458 women having surgery for presumed leiomyomas, one woman would be found to have an occult leiomyosarcoma. We challenge this calculation. To estimate this risk, the FDA searched medical databases using the terms “uterine cancer” AND “hysterectomy or myomectomy.” Because “uterine cancer” was required, studies in which cancer was not found or discussed were not identified. Nine studies, all but one of which were retrospective, were analyzed including a nonpeer-reviewed letter to the editor and an abstract from an unpublished study. Additionally, three leiomyosarcoma cases identified by the FDA do not meet current pathologic criteria for cancer and would now be classified as benign atypical leiomyomas. If atypical leiomyomas and nonpeer-reviewed data are excluded, the FDA identified eight cases of leiomyosarcoma among 12,402 women having surgery for presumed leiomyomas, a prevalence of 1 in 1,550 (0.064%).

Pritts et al4 recently published a more rigorous meta-analysis of 133 studies and determined that the prevalence of leiomyosarcoma among women having surgery for presumed leiomyomas was 1 in 1,960, or 0.051%. All peer-reviewed reports in which surgery was performed for presumed leiomyomas were ana- lyzed, including reports in which cancer was not found. Inclusion criteria required that histopathology results be explicitly provided and available for interpre- tation. Among the 26 randomized control trials analyzed, 1,582 women had surgery for leiomyomas and none were found to have leiomyosarcoma. Bojahr et al5 recently published a large population- based prospective registry study and reported two occult leiomyosarcoma among 8,720 women having surgery for leiomyomas (0.023%). In summary, the reanalyzed FDA data set yields a prevalence of 1 in 1,550 (0.064%), the Pritts study reports a prevalence of 1 in 1,960 (0.051%) with the randomized con- trolled trials having a prevalence of 0, and the Bojahr study reported a prevalence of 2 of 8,720 (0.023%). We acknowledge that with rare events, statistical analysis may be uncertain and confidence intervals may be wide. However, these numbers do not sup- port the FDA’s estimated prevalence of leiomyosar- coma among women having surgery for presumed leiomyomas and those at risk for morcellation of a leiomyosarcoma.

Leiomyosarcoma, removed intact without mor- cellation, has a poor prognosis. Based on Surveil- lance, Epidemiology, and End Results data, the 5-year survival of stage I and II leiomyosarcoma is
only 61%. Whether morcellation influences the prognosis of women with leiomyosarcoma is not known and the biology of this tumor has not been well studied. Distant metastasis occur early in the disease process, primarily hematogenous dissemination. Four frequently quoted published studies examine survival after power morcellation. Surprisingly, virtually none of the women in these studies had power morcellation. Furthermore, the data presented in these reports are poorly analyzed and patient numbers are very small. Park et al.6 reported only 1 of the 25 morcellated patients had laparoscopic surgery with power morcellation. Eighteen women had laparoscopically assisted vaginal hysterectomy with scalpel morcellation performed through the vagina, one had vaginal hysterectomy with scalpel morcellation, and five had minilaparotomy with scalpel morcellation through small lower abdominal incisions. Seventeen of the 25 patients plotted in the published survival curve were referred to the hospital after initial diagnosis or the discovery of a recurrence at another institution. Because the number of nonreferred women with less aggressive disease or without recurrence is not known, it is not possible to determine differences in survival between patients with and without morcellation. In a study by Perri et al.,7 none of the patients had power morcellation. Four women had abdominal myomectomy, four had hysteroscopic myomectomy with tissue confined within the uterine cavity, two had laparoscopic hysterectomy with scalpel morcellation, four had supracervical abdominal hysterectomy with cut-through at the cervix, and two had abdominal hysterectomy with injury to the uterus with a sharp instrument. When comparing the outcomes for women with morcellated and nonmorcellated leiomyosarcoma, Morice et al.8 found no difference in recurrence rates or overall and disease-free survival at 6 months. In the only study to compare use of power morcellation with scalpel morcellation in women with leiomyosarcoma, Oduyebo et al.9 found no difference in outcomes for the 10 women with power morcellation and five with scalpel morcellation followed for a median of 27 months (range 2–93 months). Notably, a life table analysis of these studies showed no difference in survival between morcellation methods.10

Of note, laparoscopic-aided morcellation allows the surgeon to inspect the pelvic and abdominal cavities and irrigate and remove tissue fragments under visual control. In contrast, the surgeon cannot visually inspect the peritoneal cavity during vaginal or minilaparotomy procedures. Morcellation within containment bags has recently been used in an attempt to avoid spread of tissue. These methods have not yet been proven effective or safe, and there is concern that bags may make morcellation more cumbersome and less safe.

**WHAT THE U.S. FOOD AND DRUG ADMINISTRATION RESTRICTIONS MEAN FOR WOMEN**

The FDA communication states, “the FDA is warning against the use of laparoscopic-morcellators in the majority of women undergoing myomectomy or hysterectomy for treatment of fibroids.”1 This statement is not consistent with current evidence. Moreover, a severe restriction of morcellation, including vaginal and minilaparotomy morcellation, would limit women with symptomatic leiomyomas to one option, total abdominal hysterectomy. For women with leiomyomas larger than a 10-week pregnancy size, which most often require either scalpel or power morcellation to remove tissue, a ban on morcellation would eliminate the following procedures:

1. Vaginal hysterectomy (scalpel morcellation)
2. Minilaparotomy hysterectomy (scalpel morcellation)
3. Laparoscopic hysterectomy (scalpel morcellation)
4. Laparoscopic supracervical hysterectomy (cervix cut-through)
5. Open supracervical hysterectomy (cervix cut-through)
6. Laparoscopic myomectomy (power morcellation)
7. Minilaparotomy myomectomy (scalpel morcellation)
8. Hysteroscopic myomectomy (intrauterine morcellation)
9. Uterine artery embolization (no specimen and will delay diagnosis)
10. High-intensity focused ultrasonography (no specimen and will delay diagnosis)

By focusing exclusively on the risk of leiomyosarcoma, the FDA failed to take into account other more common risks associated with surgery. Reduced mortality and fewer complications represent well-established benefits of laparoscopic surgery. Although minimally invasive surgery with morcellation may increase operative times, the overall outcomes are improved compared with outcomes with open surgery. Using published best evidence, a recent decision analysis by Siedhoff et al.11 compared 100,000 hypothetical women having laparoscopic hysterectomy with 100,000
having open hysterectomy for presumed leiomyomas. Women having laparoscopic surgery would experience 20 fewer perioperative deaths, 150 fewer pulmonary or venous emboli, 4,800 fewer wound infections, and 8,000 more quality-of-life years. A recently published study found that, in the 8 months after the FDA safety communication, the rate of laparoscopic hysterectomy decreased by 4.1% ($P=.005$) and the rates of both abdominal and vaginal hysterectomy increased (1.7%, $P=.112$ and 2.4%, $P=.012$, respectively). Major surgical complications (not including blood transfusions) significantly increased from 2.2% to 2.8% ($P=.015$), and the rate of hospital readmission within 30 days also increased from 3.4% to 4.2% ($P=.025$). These observations merit consideration as women weigh the pros and cons of minimally invasive surgery with morcellation compared with open surgery.

**CLINICAL RECOMMENDATIONS**

Recent attention to surgical options for women with uterine leiomyomas and the risk of an occult leiomyosarcoma is a positive development in that the gynecologic community is reexamining relevant issues. We respectfully suggest that the following clinical recommendations be considered:

1. The risk of leiomyosarcoma is higher in older postmenopausal women, and greater caution should be exercised before recommending morcellation procedures for these women.
2. Preoperative consideration of leiomyosarcoma is important, and women aged 35 years or older with irregular uterine bleeding and presumed leiomyomas should have an endometrial biopsy, which occasionally may detect leiomyosarcoma before surgery. Women should have normal results of cervical cancer screening.
3. Ultrasonography or magnetic resonance imaging findings of a large irregular vascular mass, often with irregular anechoic (cystic) areas reflecting necrosis, may cause suspicion of leiomyosarcoma.
4. Women wishing minimally invasive procedures with morcellation, including scalpel morcellation through the vagina or minilaparotomy, or power morcellation using laparoscopic guidance, should understand the potential risk of decreased survival should leiomyosarcoma be present. Open procedures should be offered to all women who are considering minimally invasive procedures for “leiomyomas.”
5. After morcellation, careful inspection for tissue fragments should be undertaken and copious irrigation of the pelvic and abdominal cavities should be performed to minimize the risk of retained tissue.

6. Further investigations of a means to preoperatively identify leiomyosarcoma should be supported. Likewise, investigation into the biology of leiomyosarcoma should be funded to better understand the propensity of tissue fragments or cells to implant and grow. With that knowledge, minimally invasive procedures could be avoided for women with leiomyosarcoma and women choosing minimally invasive surgery could be reassured that they do not have leiomyosarcoma.

Respecting women who have leiomyosarcoma, we conclude that the FDA directive was based on a misleading analysis. Consequently, more accurate estimates regarding the prevalence of leiomyosarcoma among women having surgery for leiomyomas should be issued. Women have a right to self-determination. Modification of the FDA’s current restrictive guidance regarding power morcellation would empower each woman to consider the pertinent issues and have the freedom to undertake shared decision-making with her surgeon to select the procedure which is most appropriate for her.

**REFERENCES**


