

## **An open letter to the FDA regarding the use of morcellation procedures for women having surgery for presumed uterine fibroids.**

In November, 2014 the FDA ruled that power morcellation was contra-indicated in "the majority of women" having surgery for uterine fibroids due to the potential risk of spreading occult uterine sarcoma. Although problems with this ruling were immediately apparent, the passage of time has allowed for more clarity on the related medical issues.

### **Prevalence of Leiomyosarcoma among women having surgery for presumed uterine fibroids**

The prevalence of occult leiomyosarcoma among women with fibroids is critical for every patient. All medical procedures have potential risk and the patient's understanding of risk is the foundation of medical decision-making.

The FDA estimated that for every 458 women having surgery for fibroids, one woman would be found to have an occult leiomyosarcoma (LMS). 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 where cancer was not found or discussed were not identified. Nine studies, all but one of which were retrospective, were analyzed including a non-peer-reviewed letter to the editor and an abstract from an unpublished study. (Leung, Rowland) 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 non-peer-reviewed data are excluded, the FDA identified 8 cases of LMS among 12,402 women having surgery for presumed leiomyomas, a prevalence of 1 in 1,550 (0.064%).

Pritts et al. recently published a more rigorous meta-analysis of 133 studies and determined that the prevalence of LMS among women having surgery for presumed fibroids was 1 in 1,960, or 0.051%. All peer-reviewed reports in which surgery was performed for presumed fibroids were analyzed, including reports where cancer was not found. Inclusion criteria required that histopathology results be explicitly provided and available for interpretation. Among the 26 randomized control trials analyzed, 1,582 women had surgery for fibroids and none were found to have LMS. Bojahr et al., recently published a large population-based prospective registry study and reported 2 occult LMS among 8,720 women having surgery for fibroids (0.023%). In summary, the re-analyzed FDA dataset 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 RCT's 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 support the FDA's estimated prevalence of LMS among women having surgery for presumed fibroids and those at risk for morcellation of a leiomyosarcoma.

## Prognosis for women with morcellated LMS

Leiomyosarcoma, removed intact without morcellation have a poor prognosis. Based on SEER data, the 5 year survival of Stage I and II LMS is only 61%. (Kosary) Whether morcellation influences the prognosis of women with LMS is not known and the biology of this tumor has not been well studied. Distant **metastasis occurs** early in the disease process, primarily hematogenous dissemination. Four frequently quoted published studies examine survival following 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. reported only one of the 25 morcellated cases had laparoscopic surgery with power-morcellation. Eighteen women had a laparoscopically-assisted vaginal hysterectomy with scalpel-morcellation performed through the vagina, one had a vaginal hysterectomy with scalpel-morcellation and 5 had mini-laparotomy 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. Since the number of non-referred 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., none of the patients had power-morcellation. Four women had an abdominal myomectomy, four had a hysteroscopic myomectomy with tissue confined within the uterine cavity, two had a laparoscopic hysterectomy with scalpel-morcellation, four had a supra-cervical abdominal hysterectomy with cut-through at the cervix and two had an abdominal hysterectomy with injury to the uterus with a sharp instrument. When comparing the outcomes for women with morcellated and non-morcellated LMS, Morice et. al., found no difference in recurrence rates or over-all and disease-free survival at six months. In the only study to compare use of power- with scalpel-morcellation in women with LMS, Oduyebo et. al. 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). Notably, a life table analysis of the above studies showed no difference in survival between morcellation methods. (Pritts)

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 mini-laparotomy procedures. Morcellation within containment bags have recently been utilized 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 FDA 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." This statement is not consistent with current evidence. Moreover, a severe restriction of morcellation, including vaginal and mini-laparotomy morcellation, would limit women with symptomatic leiomyomas to one option, total abdominal hysterectomy. For women with fibroids larger than a 10-week pregnancy size, which most often require either scalpel or power-morcellation in order to remove tissue, a ban on morcellation would eliminate the following procedures:

- vaginal hysterectomy (scalpel morcellation)
- mini-laparotomy hysterectomy (scalpel morcellation)
- laparoscopic hysterectomy (scalpel morcellation)
- laparoscopic supra-cervical hysterectomy (cervix cut-through)
- open supra-cervical hysterectomy (cervix cut-through)
- laparoscopic myomectomy (power morcellation)
- mini-laparotomy myomectomy (scalpel morcellation)
- hysteroscopic myomectomy (intrauterine morcellation)
- uterine artery embolization (no specimen and will delay diagnosis)
- high-intensity focused ultrasound (no specimen and will delay diagnosis)

## If abdominal hysterectomy is recommended to women with fibroids, will women be better off?

By focusing exclusively on the risk of LMS, the FDA failed to take into account other risks associated with surgery. Laparoscopic surgery uses small incisions, is performed as an outpatient procedure (or overnight stay), has a faster recovery (2 weeks versus 4-6 for open surgery) and is associated with lower mortality and fewer complications. These benefits of minimally invasive surgery are now well-established in gynecologic and general surgery. Using published best-evidence data, a recent decision analysis showed that, comparing 100,000 women having laparoscopic hysterectomy with 100,000 having open hysterectomy, the group having laparoscopic surgery would experience 20 fewer peri-operative deaths, 150 fewer women would have a pulmonary or venous embolus and 4,800 fewer women would have a wound infection. (Seidhoff) Importantly, women having open surgery would have 8,000 fewer quality-of-life years. A recently published study found that in the eight months following the FDA safety communication, utilization of laparoscopic hysterectomies decreased by 4.1% ( $p=0.005$ ) and both abdominal and vaginal hysterectomies increased (1.7%,  $p=0.112$  and 2.4%,  $p=0.012$ , respectively). (Harris) Major surgical complications (not including blood transfusions) significantly increased from 2.2% to 2.8% ( $p=0.015$ ), and the rate of hospital readmission within 30 days also increased from 3.4% to 4.2% ( $p=0.025$ ). **These observations merit consideration as**

women weigh the pros and cons of minimally-invasive surgery with morcellation versus 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 re-examining relevant issues. We respectfully suggest that the following clinical recommendations be considered:

- The risk of LMS is higher in older post-menopausal women and greater caution should be exercised prior to recommending morcellation procedures for these women.
- Preoperative consideration of LMS is important and women age 35 or older with irregular uterine bleeding and presumed fibroids should have an endometrial biopsy, which occasionally may detect LMS prior to surgery. Women should have normal results of cervical cancer screening.
- Ultrasound or MRI findings of a large irregular vascular mass, often with irregular anechoic (cystic) areas reflecting necrosis, may cause suspicion of LMS.
- Women wishing minimally-invasive procedures with morcellation, including scalpel-morcellation via the vagina or mini-laparotomy, or power-morcellation using laparoscopic guidance, should understand the potential risk of decreased survival should LMS be present. Open procedures should be offered to all women who are considering minimally -invasive procedures for "fibroids".
- Following 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.
- Further investigations of a means to identify LMS pre-operatively should be supported. Likewise, investigation into the biology of LMS 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 LMS and women choosing minimally-invasive surgery could be re-assured that they do not have LMS.

Respecting women who suffer from leiomyosarcoma, we conclude that the FDA directive was based on a misleading analysis. Consequently, more accurate estimates regarding the prevalence of LMS among women having surgery for fibroids 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 in order to select the procedure which is most appropriate for her.

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