



## Special Article

# Morcellation during Uterine Tissue Extraction: An Update

The Tissue Extraction Task Force Members

From the AAGL, Cypress, California.

## Introduction and Background

Morcellation is a mechanism to reduce the size of large tissue specimens with the intent to remove them via small openings in the body and has been used in gynecologic surgery for over 90 years. While traditionally performed manually via scalpel or scissors, surgeons have more recently employed electromechanical morcellation devices in conjunction with laparoscopic surgery. The first electromechanical morcellation device was approved by the US Food and Drug Administration (FDA) in 1995; over the succeeding two decades numerous such devices have been developed and marketed.

In response to concerns about the risk of dissemination of occult malignancy at the time of morcellation, particularly in leiomyosarcoma (LMS), the FDA issued a safety communication in 2014 warning against the use of electromechanical morcellators during most surgeries for fibroids [1]. This was followed by a guidance document in November 2014 that stated that such electromechanical morcellators are contraindicated (1) in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy and (2) for removal of uterine tissue containing suspected fibroids in patients who are perimenopausal, postmenopausal, or candidates for en bloc removal [2]. The FDA also issued a black box warning for labeling all electromechanical morcellators that read: "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" [1,2].

Following release of the above report, the American Association of Gynecologic Laparoscopists (AAGL) created a task force that subsequently produced a review of key issues involved in this evolving controversy; the document provided critical assessment of the research available at that time

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as well as recommendations for future investigation [3]. There has been a great deal of research related to various aspects of the morcellation debate published in the years since the FDA report. With many new, high quality studies emerging in the last few years, the FDA felt a reappraisal of the literature was warranted and in December 2017, published an updated assessment of the role of electromechanical morcellation in surgeries for presumed uterine fibroids [4]. In the same month, the Agency for Healthcare Research and Quality of the Department of Health and Human Services (AHRQ) issued a robust report on the management of uterine fibroids that included considerable attention devoted to the morcellation issue [5].

Given the proliferation of new data and more critical analysis of prior data, an update of the previous AAGL position statement on the topic of morcellation and tissue extraction was warranted. As opposed to the earlier 2014 position paper, the current review is not a comprehensive treatise of morcellation and tissue extraction. Instead, the focus is on those areas where the research and debate over the last few years are most likely to have impacted conclusions and future directions.

## Prevalence of Uterine Cancer and Sarcomas

The presence of undiagnosed uterine cancer in morcellated specimens has been documented as a major concern by federal agencies, physicians, and patients. Indeed, uterine cancer may be present in morcellated hysterectomy specimens as frequently as in 1 of 350 procedures [1,6,7]. However, the vast majority of these malignancies are endometrial carcinomas and can be diagnosed preoperatively in most cases with appropriate evaluation. Furthermore, morcellation of endometrial cancer has not been shown to affect prognosis (see below).

Uterine sarcomas account for only 3% to 5% of all uterine cancers [8,9]. The largest histologic subgroup of uterine sarcomas is LMS, which represents 63% of all uterine sarcomas [10]. Leiomyosarcomas are difficult to distinguish from benign leiomyomas preoperatively and thus represent a risk to the woman undergoing surgery for presumed benign pathology.

As such, it is important to know the prevalence rate for LMS in women with presumed uterine fibroids who proceed to surgery.

The FDA initiated the first attempt to determine this rate via a systematic review and meta-analysis in 2014 [1]. Using evidence from 9 publications, it was concluded that the rate of LMS was 1 in 498 surgeries [1]. However, this analysis had significant limitations. First, the FDA performed a targeted query using only the search terms “uterine cancer” AND “hysterectomy or myomectomy” AND “incidental cancer or uterine prolapse, pelvic pain, uterine bleeding, and uterine fibroids”. Using “uterine cancer” as a required search term necessitates the presence of uterine cancer in the manuscripts available for analysis, while those studies without uterine cancers would be overlooked. Second, only studies with more than 100 subjects were included in the analysis. Third, studies that examined other types of surgical patients were excluded, even if the surgeries for presumed fibroids were extractable. Fourth, only English language articles were included. Fifth, the agency’s meta-analysis included an unpublished abstract and a letter to the editor [11,12]. Sixth, eight of the nine included study datasets were retrospectively collected. Recently, the FDA updated their initial analysis but failed to correct the shortcomings in the original report [4]. An analysis of 23 studies (all retrospective) published after the original report found the prevalence rate of occult uterine sarcoma to be between 1 in 495 and 1 in 1100 surgeries [4].

In contrast, Pritts and colleagues published a meta-analysis in 2015 producing radically different results [13]. This review was more comprehensive than the FDA report. All peer-reviewed studies from 1980 to 2014 regarding surgery for uterine fibroids were reviewed, with nearly 5000 abstracts and over 1000 manuscripts reviewed and analyzed. Only studies with complete reporting of pathologic findings in all patients were included. Studies of all sizes and languages were considered leading to the inclusion of 133 studies (134 datasets). The meta-analysis showed a prevalence rate of 1 in 1700 for the 70 retrospective datasets, 1 in 8300 for the 64 published prospective datasets (prospective cohort and randomized clinical trials), and an overall prevalence rate for all 133 studies (134 datasets) of 1 in 2000 surgeries. These data have recently been updated by the AHRQ of the US Department of Health and Human Services for all studies through 2017 [5]. Using the data and methodology from the Pritts report [13], the AHRQ added an additional 106,002 surgeries from 27 studies [5]. They found a prevalence rate of LMS to be 1 in 1429. More importantly, they also analyzed the studies according to reliability of the data. Using only those studies considered to have highly reliable histopathology in all patients, the rate of LMS was determined to be <1 in 4000 surgeries [5].

Evidence-based medicine requires the use of the best available evidence to make clinical decisions [14]. The best such evidence regarding the rate of LMS in patients undergoing surgery for presumed fibroids is approximately 1 in 1500 and may be as low as <1 in 4000 procedures.

Another type of sarcoma is endometrial stromal sarcoma (ESS), which represents approximately 1% of all uterine cancers and 21% of all uterine sarcomas [10]. Most ESS is diagnosed preoperatively owing to the patient presenting with excessive bleeding followed by evaluation via imaging and/or biopsy, but some will be mistaken for benign fibroids and operated on for this reason. Published reports have provided rates ranging from 1 in 1214 to 1 in 5059, with most suggesting a rate between 1 in 2000 to 3000 [11,15–20].

A final issue is the personalization of patient risk based on specific factors. This has primarily been examined in women with presumed fibroids found to have LMS, with analysis of age as a confounding variable. Five studies have examined this issue, with the estimated prevalence in 60- to 70-year-old patients being approximately 7- to 9-fold higher than that of 40- to 50-year-old women [17,21–24]. Thus, the older the patient with presumed fibroids, the greater the risk by far that the tumor is in fact malignant.

### Impact of Morcellation on Tissue Dissemination and Survival

There is a possibility that electromechanical morcellation (and indeed any type of morcellation) may spread disease throughout the abdomen and pelvis resulting in a higher stage of disease than originally presented prior to surgery (referred to as “upstaging”). This is difficult to demonstrate in women undergoing surgery for presumed benign fibroids in that patients are not staged at the initial surgery because the sarcoma is undiagnosed. It is likely that in some percentage of patients disseminated disease already exists at the time of initial surgery and is simply not identified.

Overall survival for women with uterine tumors vary by tumor type. While most uterine tumors result in high 5-year survival rates, only 40% of LMS patients will survive 5-years [25,26]. Even early stage LMS patients suffer from poor outcomes, with over 70% of patients with stage I to II LMS and removed intact tumors exhibiting recurrence in the first 2.5 years after diagnosis, and a median survival of 52 months [27].

Investigation as to the influence of morcellation on disease-free survival and overall survival has been limited. Four systematic reviews were published in 2015, each including between four and seven original research articles [8,28–30]. All agreed that some data suggested tumor disruption will lead to poorer prognosis, although the small number of patients, the heterogeneity of the studies, the poor quality of data, and even misrepresentation of data in some instances make meta-analysis unreliable and conclusions difficult to draw. None of these reviews provided evidence that outcomes following electromechanical morcellation differ from those following manual morcellation or even that seen when the tumor is merely penetrated by sharp instruments [8,28–30].

The best available analysis is found in the 2017 AHRQ report [5]. Twenty-eight studies from 14 countries provided data regarding disease progression in women who had LMS identified at the time of initial surgery for presumed fibroids, and for

whom the method of tumor removal was known and survival time data could be extracted [5]. Seven hundred and fifteen women were treated from 1980 to 2015. Five-year overall survival was found to be 30% with electromechanical morcellation, 59% in women undergoing manual morcellation, and 60% with no use of morcellation. While estimates appear to favor manual or no morcellation, no statistically significant difference could be discerned [5].

As noted above, patients with other malignancies and benign tumors that may be mistaken for uterine fibroids undergo morcellation. The majority of these malignancies can be detected preoperatively with protocol-driven testing. However, no data exist to show decreased survival or poorer clinical course when other types of tumors undergo morcellation, including electromechanical morcellation. A systematic review of cases from 1980 to 2016 [15,16,31–41] revealed 19 patients who underwent inadvertent morcellation of endometrial adenocarcinomas. Of the 18 who underwent power morcellation, there were no recurrences. The remaining patient with vaginal morcellation did have a local recurrence but no evidence of disease at 7.5 years of follow-up. A review of 44 cases of morcellation of ESS with inadvertent morcellation revealed that of 17 procedures performed with the power morcellator, there was only one recurrence (with no evidence of disease at 8.25 years) [15,16,31–41]. Eight of the remaining 27 cases with other types (or unknown types) of morcellation exhibited recurrence. In women with smooth muscle tumors of uncertain malignant potential (STUMPs), 19 women had undergone power morcellation with one recurrence [15,16,31–41]. These results were recently confirmed by Raspagliesi and associates, who examined outcomes of women with morcellation of malignancies and STUMPs [42]. For endometrial adenocarcinomas, ESS, and STUMPs no statistical difference in outcomes was noted following morcellation of any type.

In summary, the very limited literature addressing survival suggests that electromechanical morcellation may affect LMS outcome, but this has not yet been proven. Furthermore, LMS has a substantial mortality risk regardless of the method of tumor removal. No data suggest a worsening of outcomes with other types of atypical or malignant tumors.

### **Patient Assessment and Evaluation for Leiomyosarcoma**

Fibroids are extremely common, occurring in almost 80% of all women [43]. The baseline risk of LMS for all women in the general population is about 1 in 25,000 [26]. While risk factors that increase the likelihood of LMS have been identified, the absolute increases in risk are extremely small. Women of African descent have an increased risk of benign fibroids and a similarly increased risk of LMS, approximately 1 in 14,000 [43].

The risk of any uterine cancer in women undergoing hysterectomy with an electromechanical morcellator increases substantially as the patient ages. Compared with women <40 years of age, the prevalence of undetected uterine cancer is

5-fold higher at 50 to 54 years and 36-fold higher in women >65 years old [7]. Similarly, increasing age is a significant risk factor for uterine cancer in women undergoing myomectomy [44]. Fibroids most commonly decrease in size after menopause owing to a decline in ovarian hormones. Consequently, a postmenopausal woman presenting with a new or growing uterine fibroid should raise suspicion for sarcoma. However, postmenopausal women who are treated with estrogen may be at risk for a small increase in the size of previously identified fibroids. Discontinuing estrogen for a short trial to evaluate if the fibroid decreases in size should be considered.

Tamoxifen appears to increase the baseline risk for LMS of 1 in 25,000 women to 1 in 6000 women who use tamoxifen for 5 years or longer [45]. Premenopausal women with fibroids that do not decrease in size following 3 months of treatment with gonadotropin-releasing hormone or uterine artery embolization should raise suspicion for LMS [46]. Other risk factors include a history of pelvic irradiation, a history of childhood retinoblastoma, hereditary leiomyomatosis, or renal cell carcinoma [3].

While screening tools have proven effective for most malignancies of the uterus, LMS has proven to be particularly difficult to detect preoperatively. As outlined previously, the use of standard testing for the clinical assessment of suspected fibroids will frequently miss a diagnosis of LMS [1]. Indeed, recent data confirms this finding: in Norway, more than half of uterine LMS are unidentified before surgery [47,48].

Imaging studies have traditionally been of limited value in the preoperative diagnosis of LMS, but recent advances suggest more promise in the techniques than previously considered. Ultrasonography and magnetic resonance imaging (MRI) have been used in the past to document rapid growth in uterine size, with the presumption that this is suggestive of LMS. However, fibroids can significantly increase or decrease in size during the reproductive years [49]. Of 371 women with rapidly growing uteri who underwent hysterectomy or myomectomy for presumed fibroids, none were found to have LMS by current World Health Organization diagnostic criteria [50]. Furthermore, a systematic review of 26 studies found that a history of rapid uterine enlargement was documented in only 15 of 580 patients (2.6%) with uterine sarcomas [50]. Thus, while rapid uterine fibroid growth increases the risk of LMS, documentation of this will result in preoperative diagnosis in very few patients.

Although computed tomography (CT) and MRI have been fairly unreliable in diagnosing LMS preoperatively, they do have value in suggesting a greater possibility of malignancy, with MRI suggesting malignancy in 81% and CT in 60% [48]. However, specificity is low when used alone for diagnostic purposes.

Goto et al discussed promising data regarding the use of dynamic gadopentetate dimeglumine-enhanced MRI in conjunction with serum lactic acid dehydrogenase (LDH) isozyme 3 to help distinguish degenerating fibroids from sarcoma [51].

These findings resulted from a study population with particularly high pretest probability of disease and have not been confirmed in a large cohort of women undergoing surgery for presumed fibroids.

Diffusion-weighted imaging (DWI), a form of MRI, has been used to help diagnose LMS. Malignant lesions have more dense cellularity and larger nuclei, causing the cells to restrict motion of water molecules (Brownian motion) in such tissue. One DWI study of 16 women with pathologically confirmed LMS and 26 with degenerating fibroids, reported sensitivity and specificity of 100% and 90% [52]. Other studies, however, show conflicting results [53,54]. Magnetic resonance imaging with LDH enzyme levels and DWI are both promising, but further research is needed to better define their role in preoperative assessment.

A small study using positive emission tomography with (18)F-fluorodeoxyglucose correctly identified 5 of 5 uterine sarcomas [55]. Unfortunately, no further investigation has been completed, and the generalized diagnostic potential for this technique remains unknown.

If historic risk factors or imaging studies can suggest an increased likelihood of LMS, a test to confirm the presence or absence of this malignancy would be desirable. The use of imaging-directed needle biopsy may prove to be a secondary testing step. Three studies have tested the possibility of transcervical, transvaginal, or transabdominal biopsy before surgery, and all have shown excellent results [56–58]. The most recent publication involved 63 patients, of which 38 underwent surgery [58]. Sensitivity, specificity, and positive and negative predictive values were 91.7%, 100%, 100%, and 96.2% respectively [58].

While the use of preoperative biopsy is enticing, the obvious concern lies in the inability to access all presumed fibroids in patients with multiple or oddly placed tumors. It should also be considered that the mere act of puncturing the pseudocapsule of a potential LMS could itself be a source of dissemination of malignant cells.

As leiomyosarcomas are often histologically heterogeneous, the diagnosis may be missed if the wrong area is sampled and histology alone is used to determine malignancy. Nonetheless, the use of biopsies in the patient considered to be at increased risk for LMS may prove to be of clinical value, and further investigation is warranted.

Today, multiple new techniques are being used to more accurately diagnose these tumors [59–61]. Telomerase activity in needle biopsies has been shown to be a useful diagnostic marker for malignancy [59]. Immunohistochemical tests for LMP2, Ki-67, and CD34, either alone or in combination, have also been shown to improve diagnostic accuracy [60,61].

## Related Issues

Residual disease at the end of surgery is a predictor for survival and prognosis in many cancers, notably ovarian cancer, head and neck cancers, gastrointestinal cancers, and lung

cancer. The goal of most cancer surgery is to minimize residual disease. One approach to minimizing tissue spread during morcellation is the use of containment bags, which create an enclosed system within which uterine and fibroid specimens can be fragmented and extracted following myomectomy or hysterectomy. Contained tissue extraction can be performed using either power morcellation or manual morcellation with a scalpel via minilaparotomy or colpotomy.

Initial studies on contained power morcellation demonstrated feasibility with either a single-port or multiport approach [62–64]. Additional operative time may be required to incorporate the contained power morcellation technique, on average 20 to 26 additional minutes according to two retrospective studies [65,66]. In 2016, the FDA approved the first tissue containment system for use with the single-port approach and power morcellation; of note this is indicated for use only in premenopausal fibroid patients or women undergoing hysterectomy for non-fibroid related indications [67]. Additional containment systems have been developed, including a multiport containment bag that is currently available for use in Europe [68].

Various techniques for contained vaginal and contained minilaparotomy manual morcellation have been reported as well [69–75]. Comparisons across the various modalities of contained tissue extraction have demonstrated similar perioperative outcomes and low risk of complications, with some variability in terms of relative operative time [76,77].

The relative effectiveness or protection afforded by various containment systems and techniques is unknown, and leakage has been reported when bag integrity is tested after contained morcellation [74,78]. Such leakage has unknown clinical significance. Although the use of containment systems is thought to decrease the burden of tissue dissemination, the degree of protection compared with open or uncontained specimen fragmentation is still unclear. Longer term follow-up and rigorous prospective evaluation is needed to further assess the theoretical advantages of this approach.

Laparoscopic myomectomy involves considerable dissection and manipulation of the uterus and fibroid before morcellation. In such cases, smooth muscle cells and tissue fragments have been shown to be present in the pelvis and abdomen before morcellation [79]. A recent study investigated the utility of careful removal of tissue fragments and irrigation with 3 liters of sterile saline or water following myomectomy and morcellation and found no residual tissue or cells in washings following the procedure [80]. Thus, it seems highly prudent, whether a containment bag has been used or not, to meticulously search for tissue fragments and copiously irrigate and suction the pelvis and abdomen.

Although concern has been expressed regarding tumor spread with tissue morcellation during abdominal surgery, the procedure has been used for decades during vaginal hysterectomy with little controversy. However, there are no data to suggest that vaginal morcellation is less risky than uterine morcellation via any other route. Furthermore, while morcellation at laparoscopy or minilaparotomy allows subsequent

inspection and irrigation of the abdomen and pelvis, this is not possible when performing vaginal surgery. Vaginal surgery with uterine extraction by morcellation should not be considered a safer alternative to intra-abdominal morcellation.

If LMS is inadvertently found, time to reoperation may be important. Many of the cited studies examining survival following diagnosis of occult LMS report lengthy intervals to reoperation (if the intervals are reported at all), with one study reporting a mean interval of 20 months [40]. It is likely that the longer the delay until reoperation, the more likely that the residual tumor will implant, grow, invade blood vessels, and/or spread to distant sites. One study found that for women undergoing myomectomy or supracervical hysterectomy who were unexpectedly found to have LMS, there was no adverse impact on survival if the completion surgery was performed within 21 days [81].

Finally, if the risk of malignancy in an individual case is considered high, fibroids should be removed intact to be evaluated for cancer. This would preclude such procedures as uterine artery embolization and high-intensity focused ultrasound, any medical treatments, and even observation without medical or surgical intervention. However, for women at average risk of LMS, excluding these treatment options (including morcellation) seems impractical as well as potentially detrimental to their health.

## Ethics and Informed Consent

A device or procedure is deemed ethical if there is some value to a portion of the population. While harm may also result, this does not invalidate the potential value. However, to ethically provide a procedure or use a device that also potentially produces harm, a thorough understanding of the potential risks and benefits to the patient must be known and articulated to the patient.

The ethics involved in the use of morcellation in general, and electromechanical morcellation in particular, hinge upon the existence of value inherent to the procedure and appropriate informed consent by the patient. Minimally invasive surgery provides a clear advantage in many situations, and is often facilitated by morcellation of tissue [3]. While laparotomy is a reasonable alternative that would eliminate the need for morcellation, the procedure carries its own clearly defined risks, some of which are serious and life threatening [82].

The value of electromechanical morcellation may be more difficult to define. Use of such devices clearly result in faster minimally invasive procedures. However, this may seem ethically questionable in the event that electromechanical morcellation is found to be significantly more harmful than other morcellation techniques. Further research into this area will determine if electromechanical tissue removal is in fact more adverse than other types of morcellation, in which populations this may be the case, and whether or not this additional risk (if it exists) can be modified by additional devices or technical improvement.

To perform surgery with morcellation of any type requires informed consent. The components of a thorough and complete informed consent were outlined in our previous publication and include the following [3]:

- Discussion of the possibility of dissemination of tissue in the peritoneal cavity, which may increase severity of treatment and worsen prognosis.
- Discussion of the possibility of increased difficulty in rendering a complete pathologic evaluation.
- Discussion of potential injuries unique to the equipment and procedure.

Such a process is the essence of the ethical principle of autonomy: presented with the facts of risks, benefits, and alternatives to a surgical procedure, the patient has the right to accept or decline the surgery. No one should be forced to undergo surgery with morcellation against their will or without their knowledge; patients must agree to the procedure. Proper informed consent is not just a document signed with vague and confusing rhetoric. It is a process of detailed explanation both in conversation and in writing, with the goal of achieving clarity in the above issues with the patient. When true informed consent is achieved, autonomy by the patient is preserved.

Evidence-based medicine should be discussed with the patient when determining treatment decisions [14]. This is a critical component of appropriate informed consent.

The use of the best evidence provides a starting point for discussion of options, including an accurate assessment of their risks and benefits. However, physicians must keep in mind that the best available evidence is a moving target, and the surgeon has the obligation to present the patient with the most up-to-date and accepted data available.

## Summary

Considerable research has been performed since the original FDA safety communication, with the goal of better understanding of risks, benefits, and role of morcellation in gynecologic surgery. In some areas previously held dogma was confirmed; in others, surprising findings have become apparent. Pronouncements made as recently as 4 years ago have proven less robust than expected as new, higher quality research has become available. A careful evaluation of the existing medical literature on this subject allows the discerning practitioner to incorporate evidence-based medicine into the decision-making process regarding morcellation.

The AAGL recommends the following guidelines related to morcellation:

- Morcellation should not be used in the setting of known malignant or premalignant conditions.
- An appropriate preoperative evaluation of all patients in whom morcellation is being considered should be performed. This should include up-to-date pap screening according to the most

recent national guidelines, appropriate image analysis of myometrium and any fibroids, and evaluation of the endometrium by either tissue sampling and/or imaging.

- Increasing age significantly increases the risk of uterine LMS, and alternatives to morcellation are advised in postmenopausal women.
- Growth of fibroids is expected prior to menopause and is not, by itself, a reliable sign of malignancy.
- If a woman is considered high risk for malignancy, morcellation should be avoided if possible. Myomectomy should also be discouraged.
- For women desiring uterine preservation in whom LMS is found, only final pathologic evaluation should be used before recommending and performing hysterectomy.
- Use of a containment bag may mitigate the risk of tissue spread during morcellation.
- Informed consent should be obtained in all patients considering morcellation, with specific risks and benefits of the procedure explained and discussed. The best available evidence should be used when reviewing these risks and benefits. The gynecologic community should invest in determining an evidence-based standard of informed consent for alternatives to laparotomic hysterectomy and myomectomy for presumed fibroids [83].

## Conclusions

It is the opinion of the AAGL that all existing methods of tissue extraction have risks and benefits. The magnitude of these risks and benefits are currently in flux, as more and better studies populate the medical literature. Today there is no evidence that universal elimination of any type of morcellation serves the intended purpose of protecting patients. However, as new evidence emerges, physicians should modify patient selection and surgical technique to minimize established risks and optimize benefits of the procedure. We have attempted to provide the most accurate, up-to-date information to assist the gynecologic community in providing sound options and thorough informed consent. In this way, quality care can be provided to patients in need of uterine surgery.

## Statement of Approval by the AAGL Board of Directors

This report was approved on February 24, 2018 by the AAGL Board of Directors who have no commercial, proprietary, or financial interest in the products or companies described in this report.

## Tissue Extraction Task Force

The members of the Tissue Extraction Task Force have no commercial, proprietary, or financial interest in the products or companies described in this report.

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