AAGL *Advancing Minimally Invasive Gynecology Worldwide*

Morcellation During Uterine Tissue Extraction

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I. Introduction: Minimally Invasive Surgery, Morcellation and the Scope of the Problem

The benefits of minimally invasive surgery (MIS) for treating a variety of gynecologic conditions are well documented [1-10]. Nearly half of the estimated 400,000 inpatient-based hysterectomies performed annually in the United States for benign indications employ these innovative techniques [11]. Thousands more women benefit from MIS in uterus-sparing procedures such as myomectomy. The ability to offer less invasive surgery to women often requires the removal of large tissue specimens through small incisions, which may be facilitated by morcellation. The term morcellation encompasses a variety of surgical techniques, some used in concert with specific devices, used to enable removal of large specimens from the peritoneal cavity, avoiding the need for laparotomy.

Manual morcellation with a scalpel or electro-mechanical morcellation (EMM) with a device specifically designed to fragment tissue specimens should only be considered in women at low risk for a gynecologic malignancy and when an appropriate preoperative assessment is suggestive of a benign disorder. When occult malignancy is inadvertently encountered, EMM hinders the ability to perform a comprehensive histopathological evaluation of a uterine specimen. Additionally, dissemination of tumor or uterine fragments, either benign or malignant, throughout the intraperitoneal cavity may necessitate further surgical interventions or other treatment and may worsen prognosis [12-24]. The possibility of this complication may have been previously underestimated.

Multiple factors may limit our understanding regarding the full scope of potential risks associated with tissue morcellation. First, although it is possible to diagnose most uterine cancer cases preoperatively, rare subtypes of uterine cancer (i.e. sarcomas) may mimic the appearance of benign myomas on imaging. Second, preoperative diagnostic testing may not discriminate between benign and malignant conditions in these cases [25,26]. Third, morcellator device safety and critical understanding of how to mitigate morcellator-associated injury continues to evolve. However, despite our incomplete understanding of these issues, MIS employing morcellation remains safe when performed by experienced, high-volume surgeons in select patients who have undergone an appropriate preoperative evaluation.

While the U.S. Food and Drug Administration (FDA) approved the first electromechnical morcellation device in 1995, it recently issued a statement discouraging the use of "power" or electromechanical morcellation for hysterectomy and myomectomy in most women with uterine myoma [27]. The Administration cited safety concerns, specifically the potential for dissemination of occult uterine cancer that may occur with the morcellator technology. The FDA's recommendations must be taken very seriously, as patient safety and avoiding preventable harm are of paramount importance. However, the studies analyzed by the FDA in formulating this recommendation were not stratified by risk factors for sarcoma and were not necessarily performed in the setting of reproductive-age women with presumed benign leiomyomata [13,28-35]. Further, in addition to the risk-benefit ratio of morcellator technology per se, one must also consider the implications of alternative surgical options for women if morcellator use is suspended nationwide. The alternatives for women with large uteri or uterine myomas would, in some cases, involve abandoning MIS or the ability to morcellate and potentially deny the clear benefits this approach provides to hundreds of thousands of women around the world each

year. In considering these scenarios, laparotomy as an alternative carries its own set of clearly defined risks, some of which are serious and life threatening. In an effort to minimize all associated procedural risks, research aimed at optimizing MIS approaches in the greatest number of women and the development of diagnostic tools to identify more accurately those women who may be potentially harmed by morcellation are urgently needed.

With any surgical technology or intervention, unanticipated risks may not be realized for years after implementation. Thus, surgical innovation should be linked with ongoing safety evaluation [16]. To ensure that gynecologic surgeons have the ability to provide MIS for the majority of their patients in a safe manner, AAGL convened a task force to conduct a critical appraisal of the existing evidence related to the practice of uterine tissue extraction and morcellation in the setting of hysterectomy and myomectomy. Recommendations for the gynecologic surgeon are provided herein and areas in need of further investigation are identified.

Definitions and Points of Clarification:

- This review exclusively addresses the practice of uterine tissue extraction, and not extraction of other reproductive organs.
- This review primarily focuses on uterine leiomyosarcoma (LMS) because of its unique clinical features and how those relate to morcellation (e.g. its aggressive nature and ability to mimic benign uterine leiomyoma). To provide a global and comprehensive review, other tumor types and complications related to EMM are highlighted as well.
- For the purposes of this review, morcellation will refer to any surgical technique involving fragmenting a surgical specimen into smaller pieces. Electromechanical Morcellation (EMM, also known as "electronic" morcellation, "electric-generated" morcellation, and "power" morcellation) is a specific subtype of morcellation in which tissue is mobilized through a spinning or electrosurgical blade to cut it into smaller strips. The specifics are not yet fully delineated in the literature, but various methods of morcellation may have inherent differences in risk profile.
- The technique under question by the FDA is EMM (or "power" morcellation). Other methods of tissue extraction that will be reviewed in this document include contained (in a specimen retrieval bag) or uncontained morcellation, mini-laparotomy, laparotomy and vaginal extraction.
- The use of specimen retrieval pouches or bags for contained morcellation (electromechanical or otherwise) will be addressed in this review, but data regarding comparative safety of this approach do not yet exist.
- Minimally invasive surgery (MIS) as defined in this article encompasses vaginal, conventional laparoscopic, single-site laparoscopy or robotic surgical approaches.
- The quality of evidence and strength of the recommendations made in this document were assessed using United States Preventive Services Task Force (USPSTF) guidelines (Appendix) and are outlined throughout the manuscript [36].

II. Defining the Issue

Minimally Invasive Surgery in Gynecology

Several prospective studies demonstrate that minimally invasive surgical approaches (MIS) to hysterectomy for gynecologic conditions confer improved surgical and disease-related outcomes compared with laparotomy [1] (Level I). The benefits of MIS are well-documented and include fewer perioperative complications, shorter hospital stays, less pain, improved quality of life and a faster return to work [1-10]. In many instances, both vaginal and laparoscopic hysterectomy can be safely performed as an outpatient procedure. A Cochrane systematic review analyzed 27 randomized clinical trials comparing laparoscopic or vaginal hysterectomy to abdominal hysterectomy [1] (Level I). Significantly shorter hospital stays and speedier return to normal activities, as well as other improved secondary outcomes (less blood loss, fewer abdominal/incisional infections or febrile episodes), were achieved in women who underwent either vaginal or laparoscopic surgery.

Given the abundance of Level I data that strongly support the use of a vaginal or laparoscopic approach for hysterectomy when possible, both the American College of Obstetrics and Gynecology (ACOG) and the AAGL issued position papers on the route of hysterectomy for benign disease [9,10]. In 2011, the AAGL recommended "that most hysterectomies for benign disease should be performed either vaginally or laparoscopically and that continued efforts should be taken to facilitate these approaches. Surgeons without the requisite training and skills required for the safe performance of vaginal or laparoscopic hysterectomy should enlist the aid of colleagues who do or should refer patients requiring hysterectomy to such individuals for their surgical care."

Approximately half of the estimated 400,000 hysterectomies completed annually in the United States for benign indications are performed via a MIS approach [11]. Many more women undergo minimally invasive

myomectomy surgery and likely thousands more would benefit from having their uterine surgery performed via this route. However, frequently the uterine specimen is too large to be removed intact through the vagina or a laparoscopic incision, and thus morcellation is needed to successfully complete the procedure. Manual or electromechanical morcellation has been used for decades to aid in tissue extraction and is the primary subject of this review.

Morcellation: Methods of Tissue Extraction

Morcellation Techniques

Currently there are three general categories of uterine morcellation: (1) vaginal morcellation with a scalpel through a culdotomy or colpotomy, (2) minilaparotomy/ laparoendoscopic single site (LESS) morcellation with a scalpel, and (3) electromechanical morcellation. The former two approaches have been used for decades, but it is not known at this time if they share equivalent risks as EMM regarding dissemination of an occult malignancy. Each technique outlined above can be performed within a specimen retrieval bag.

There is no one agreed-upon definition of "mini-laparotomy," but, in general, a small abdominal incision can be used to extract uterine tissue [37,38] (Level III). This can be performed using a LESS incision, by extending a trocar incision, or by making an incision in another location (e.g. Pfannenstiel or suprapubic). A circumferential, self-retaining retractor (e.g. Alexis® Wound Protector/ Retractor, Applied Medical, Rancho Santa Margarita, CA; SurgiSleeve™ Wound Protector, Covidien, Mansfield, MA; Mobius® Abdominal Retractor, CooperSurgical, Trumbull, CT) can be used to provide an expanded area for retrieval through these small incisions. The size and location of these types of incisions may afford different risks such as infection and incisional hernia. Furthermore, any type of open morcellation through an abdominal incision may involve exposure of the tissue to the peritoneal cavity, presenting a similar risk of specimen fragments remaining in the intraperitoneal cavity.

Vaginal morcellation can be performed during a vaginal hysterectomy before the specimen is completely detached or following complete detachment of a specimen (uterus or uterine myoma) during a vaginal hysterectomy, total laparoscopic hysterectomy, and after creation of a culdotomy incision when performing laparoscopic supracervical hysterectomy or laparoscopic myomectomy [39,40]. Vaginal morcellation techniques include coring, bivalving, myomectomy, and wedge resection [41,42] and can be performed within a specimen retrieval bag [43,44] (Level III).

Electromechanical Morcellator Devices

Electromechanical morcellators are used to reduce the volume of large tissue masses into smaller, more manageable fragments that can be removed through laparoscopic incisions. They are used in gynecologic surgery, but have been described in other surgical specialties as well, including general surgery and urology [45-48] (Level III). Manual, electromechanical, and electrosurgical morcellators work by motor-coring, peeling, or dividing tissue with energy. Although morcellation technique during laparoscopic surgery was described earlier, [49] EMM using a hand-held laparoscopic device was first used in 1993 [50]. Since that time, there has been significant innovation in technology and surgical technique [51-57] (Level III). A variety of morcellators approved by the FDA for use in uterine surgery is available, featuring differences in blade diameter, cutting speed, weight, morcellation rate, and mechanism of action.

All existing morcellator devices employ either a laparoscopic port or are passed through a 12-20 mm laparoscopic incision. Although their small blade diameter can result in a prolonged morcellation time to extract large tissue specimens, data suggest that some morcellator devices may work more efficiently than others [58,59] (Level III). Specifically, those having motor-peeling features demonstrate the fastest potential morcellation capabilities [60,61] (Level I).

Visceral organ (bowel, genitourinary, others) and major vessel injury due to the tenaculum or blade itself have been reported, some of which have resulted in patient death [16] (Level III). The incidence of these complications cannot be determined as the number of EMM procedures performed annually is not known and not all complications are reported. Device-specific comparisons related to patient safety, risk of spread of an undetected uterine malignancy, and intraperitoneal tissue fragment dissemination in general is lacking. There are no data to suggest any one device is associated with higher risk than another, and surgeon experience is probably the most significant factor related to morcellator-related injuries [16] (Level III).

The Morcellation Problem and Undetected Uterine Malignancies

The AAGL has maintained for several years (and reiterated in the 2011 position statement on route of hysterectomy) that morcellation is contraindicated in settings "where uterine malignancy is either known or suspected" [10]. However, the dilemma with morcellation is that even with our diagnostic acumen and tools, uterine malignancy may not always be identifiable during preoperative evaluation. Although it is possible to reliably diagnose most uterine cancer cases preoperatively,

rare subtypes, such as sarcomas, may mimic the radiographic appearance of benign uterine myomas, and other preoperative diagnostic testing may not always discriminate between benign and malignant conditions. A review of the malignancies in question and the ability to diagnosis them preoperatively are discussed in the following sections.

Uterine Cancer and Sarcomas

Uterine cancer is the most common gynecologic malignancy in the United States, with over 50,000 new cases and almost 8,600 deaths from the disease in each year [62]. The risk of endometrial cancer increases significantly with age, obesity and unopposed estrogen exposure [63-65] (Level II-2). It is an uncommon diagnosis in women before the age of 40, with a peak between ages 75 and 90 and a median age of diagnosis of 66 [64] (Level II-2). However, the vast majority of endometrial cancer cases is heralded by abnormal bleeding and usually can be diagnosed with imaging and endometrial sampling. Therefore, with appropriate preoperative evaluation performed by gynecologic surgeons, most women with endometrial cancer will be diagnosed prior to hysterectomy, referred to an oncologist, and morcellation will be avoided.

Even less common in reproductive-aged women and the general population is uterine LMS, an aggressive and rare subtype of uterine cancer with an incidence of 0.36 per 100,000 woman-years in the United States from 1979 to 2001 [66] (Level III). LMS and other uterine sarcomas are rare, accounting for only 7-8% of all uterine cancers [67]. Approximately 60% of patients present with stage I disease. (68) Risk factors for uterine sarcoma are not nearly as well understood as those for endometrial cancer, but include advanced age, radiation and tamoxifen use [66,69-73] (Level III, Table 1). The overwhelming majority of women diagnosed with uterine cancer will be postmenopausal. Uterine sarcomas represent a heterogeneous group of tumors with very different clinical presentations, responses to therapy, and outcomes.

The largest histologic subgroup of sarcomas is LMS, accounting for 43% of sarcomas [67]. LMS represents a particular challenge in gynecology, as it behaves aggressively and can be difficult to distinguish from benign myomatous disease. It is estimated that between 1 in 400 and 1 in 1,000 hysterectomy specimens for presumed benign uterine myoma will ultimately be confirmed as LMS. but the data informing this estimate are arguably incomplete and are not stratified by patient risk factors for sarcoma, including age and race [13,28-30] (Level III). In its statement, the FDA estimated 1 in 350 women undergoing hysterectomy or myomectomy for the treatment of fibroids is found to have an unsuspected uterine sarcoma. It should be noted, however, that the nine studies (including 1 abstract and 8 manuscripts) informing its assessment were all referral-center, single-institution, retrospective studies and included only between 104 and 1429 patients [13,28-35]. The reports were from five countries, span several decades, and had varying histopathologic criteria (e.g. the number of mitoses per high powered field) to define sarcoma. Postmenopausal women were included, and some women were diagnosed preoperatively, indicating they were not MIS candidates to begin with and thus morcellation would not have been performed. One study included only morcellation cases and thus its denominator was different from the others [13]. It is premature to conclude definitely the actual risk of encountering an occult sarcoma during MIS for presumed fibroids, and newer, more comprehensive studies are needed to better inform this risk.

Prognosis of Patients with LMS

Overall survival for women diagnosed with LMS is universally poor, with only 40% alive at 5 years. (67,70) Recurrence rates and survival outcomes are poor even in the setting of early stage disease. In a recent retrospective, multi-institution study of women with apparent stage I-II uterine LMS whose uteri were removed intact, 71.8% experienced a recurrence in the first 2.5 years after diagnosis and median overall survival was only 52 months for the entire cohort [12]. Randomized controlled trials outlining optimal treatment strategies for early stage uterine LMS are ongoing but few data are currently available to guide clinicians. However, it is clear from retrospective studies that even in the setting of aggressive surgical and chemotherapeutic treatment, women diagnosed with either early or advanced stage LMS have dismal survival outcomes.

Morcellation, and especially EMM, may lead to disruption and possible dissemination of an unrecognized sarcoma, which can result in parasitic implants in the peritoneal cavity. Such iatrogenic dissemination of disease may have an adverse impact on patient prognosis. One study reviewing 1091 surgeries involving EMM at a single institution encountered 12 instances of unexpected pathology (1.2%) [13] (Level III). The authors noted 10 cases of uterine myoma variants, including atypical uterine myoma and stromal tumor of undetermined malignant potential (STUMP), as well as one case of endometrial stromal sarcoma (ESS) and one LMS. Of the 10 cases of atypical uterine myomas and STUMPs, 5 underwent re-exploration and 4 of those had intraperitoneal tumor dissemination. The two re-explored patients with sarcoma did not have dissemination. However, a rate of only 0.1% for uterine sarcoma was observed for cases in

which hysterectomy using EMM had been performed at the institution. At interval laparoscopy for both in-house and consultative cases (patients who underwent their original hysterectomy at another hospital and was referred to a cancer center for further care), intraperitoneal dissemination of tumor was identified in 64% of patients, including 4 of 7 with LMS. Only LMS was associated with mortality. Although only small single-center retrospective studies, evidence regarding outcomes of patients that underwent intraperitoneal morcellation of unsuspected LMS demonstrate an increased risk of recurrence and shorter progression-free survival when compared with en bloc resection [12,13,24]. The most recent of these demonstrated an increased recurrence with laparoscopic hysterectomy plus uncontained EMM, compared to total abdominal hysterectomy (11 months vs 40 months recurrence-free survival) [24]. The mean age of the patients in this study was 53 years old, however, and thus benign leiomyoma as a preoperative diagnosis for some of these women may have been a faulty presumption (Level III).

Women with uterine cancer other than sarcoma, appear to fare better after uterine morcellation [15,74]. The largest report of patients with undiagnosed endometrial cancer found in morcellated specimens includes 8 women [15] (Level III). Six of them were re-explored; none had residual disease; seven were alive without disease an average of 20 months following the second surgery. In patients who underwent supracervical hysterectomy, there was no extension of disease to the cervical stump, which was removed at the second surgery. There are no studies that evaluate differences in survivorship in patients who underwent EMM of previously undiagnosed endometrial cancers.

Dissemination of Benign Disease

In addition to the spread of occult malignancy, fragments of benign tissue may also be disseminated during EMM. Disseminated tissue fragments may implant on organs in the abdominal cavity, with the potential for peritonitis, intra-abdominal abscesses, and intestinal obstruction requiring re-operation or additional interventions [16] (Level III). The true incidence of such complications is not known, but case reports have appeared with increasing frequency in the literature [17-19]. In one series, iatrogenic myomas were found on the appendix, implanted on the bladder, and in retroperitoneal spaces after EMM [20]. Similarly, scattered peritoneal leiomyomatosis throughout the pelvis has been identified following EMM [21]. In patients without prior evidence of endometriosis, de novo endometriosis and adenomyosis have also been reported after EMM [22,23].

Summary/Recommendations for "Defining the Issue"

- With comprehensive preoperative evaluations, most women with uterine cancer will be diagnosed prior to hysterectomy surgery (Level II).
- It is estimated that between 1 in 400 and 1 in 1,000 women who undergo hysterectomy for presumed benign uterine myoma will be diagnosed with LMS, based on data from single-center, retrospective studies (Level III).
- The prognosis of patients with LMS is universally poor and may be worsened in the setting of EMM (Level III). Other risks, including spread of benign tissue and visceral injury, can occur with EMM, indicating the need for careful training, experience and skill when using this technique (Level III).
- There are no data to suggest any one EMM device is associated with higher risk than another, and surgeon experience is probably the most significant factor related to morcellator-related injuries (Level C).

III. Preoperative Evaluation, Intraoperative Diagnosis, and Postoperative Pathologic Analysis

Preoperative Evaluation

A discussion of preoperative evaluation must first note that patients undergoing hysterectomy, myomectomy, or alternative uterine procedures represent a heterogeneous group and indications for the procedure vary. The initial evaluation of any patient should start with a thorough history and physical exam, particularly noting a patient's menopausal status. A common consideration regarding sarcoma includes a history of rapid uterine growth, but evidence suggests this is not a reliable predictor. One single-institution series of 1332 women undergoing surgery for presumed uterine myoma found a 0.23% risk of sarcoma overall, as compared to 0.27% in those reporting rapid growth [29] (Level III).

Cervical cancer screening should be followed per current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines prior to hysterectomy [75]. Morcellation of the uterus in patients with known cervical dysplasia should be avoided.

Patients with symptomatic abnormal uterine bleeding (AUB) present with a different risk profile from asymptomatic women. For example, while office endometrial sampling has reported cancer detection rates as high as 95%, this rate was demonstrated in symptomatic women with confirmed endometrial malignancies [76,77] (Level II-3). In contrast, women who undergo hysterectomy as a part of the repair for pelvic organ prolapse (POP) are typically postmenopausal or do not have AUB as a

secondary complaint. In this group of women, office endometrial sampling proved to be a less effective screening tool [78] (Level III), possibly related to the low prevalence of disease [74,79,80] (Level III). Women with abnormal bleeding should be sampled according to ACOG guidelines [81]. When evaluating routine endometrial screening in asymptomatic postmenopausal patients with POP undergoing uterine morcellation as a portion of their surgery, a decision tree model demonstrated neither endometrial biopsy nor ultrasound were cost-effective [82] (Level III). Others, however, have documented occult uterine pathology in 1-3% of these women [74,79,80]. As noted above, while one should not use morcellation if malignancy is suspected, the risk of morcellation in the setting of endometrial cancer seems to be different than that of leiomyosarcoma. Occult LMS has been found in low-risk patients [80] (Level III) but office biopsy is an ineffective screening tool for LMS (Level B).

There are limited data regarding diagnosing LMS with endometrial sampling. In an older single-institution series, LMS was identified in 3 of 8 (37.5%) patients with preoperative endometrial biopsy or curettage [28] (Level III). A more recent study reported a better detection rate of some invasive uterine sarcomas (not limited to LMS). The false negative rate in this cohort was 14% [83] (Level II-C).

Pelvic ultrasonography and sonohysterography represent the mainstay of imaging for endometrial pathology, but these modalities are not infallible. In women with postmenopausal bleeding, an endometrial echo of >4mm indicates possible intrauterine pathology. However, there is no evidence this applies to asymptomatic postmenopausal women with a thickened endometrial echo [84]. Similarly, ultrasound may identify features suggestive of sarcoma, such as mixed or poor echogenic areas with central necrosis [85]. Doppler velocimetry (color) can reveal irregular vessel distribution, low impedance to flow, and high peak systolic velocity [25]. If a sarcoma is expected after ultrasound evaluation, magnetic resonance imaging (MRI) can be helpful in further evaluation [26]. Unfortunately, the features that suggest LMS on MRI (large size, tissue signal heterogeneity, central necrosis, and ill-defined margins) are features that can also be consistent with benign degenerating uterine myomas. Significant change in size between interval scans, in addition to these features, should raise concern.

A prospective imaging study evaluating 130 patients with degenerating uterine myoma and 10 women with LMS, described a protocol that utilized dynamic gadopentetate dimeglumine-enhanced (Gd-DTPA) MRI combined with serum analysis of LDH and LDH isoenzyme 3, to differentiate the two processes. The specificity, positive and negative predictive values and diagnostic accuracy of dynamic imaging with serology compared to MRI alone and dynamic MRI was 100%, 100%, 100%, 100%, respectively [86] (Level II-2). However, these data have not been replicated, nor do they address non-degenerating uterine myomas. Accordingly, these findings cannot be widely integrated into clinical practice. More recently, a small retrospective study that examined 81 specimens, including 5 cases of LMS, offered greater differentiation between LMS and benign uterine myoma; however, the ability to specify atypical or cellular myoma was more difficult [87] (Level III). Confirmation of these data in a larger study may lead to greater insight of its utility as a diagnostic tool.

Although there is no definitive diagnostic modality that reliably identifies LMS in the setting of uterine myoma, occasionally cases will be identified preoperatively [88]. Every effort should be made to do so with existing diagnostic capabilities, as some cases will be identified prior to surgery (Level C).

Table 1 Risk factors for uterine sarcoma

Variable	Effect
Age	Mean age of diagnosis: 60 (69)
Black race	Two fold higher incidence rate of LMS (70)
Tamoxifen	Prolonged tamoxifen use, defined as five years or more (71)
Pelvic Irradiation	Association is especially strong for carcinosarcoma (72)
Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome	Rare autosomal dominant syndrome. Uterine sarcomas associated with HLRCC are often found in younger women (116)
Survivors of childhood retinoblastoma	Higher risk for sarcomas in general, including uterine sarcoma (73)

Intraoperative Assessment to Identify an Underlying Cancer

The role of intraoperative assessment to identify an unsuspected uterine malignancy can be difficult. Frozen section of the endometrium by intraoperative dilation and curettage immediately preceding hysterectomy is not commonly used or recommended, as the presence of blood and mucin in the sample may result in a significant amount of artifact, limiting the microscopic diagnosis (Level III). Other considerations such as intraoperative needle biopsy of a mass could lead to sampling error, missed diagnosis, or inadvertent cellular dissemination and exposure to adjacent structures or the peritoneal cavity [89] (Level III). Currently, there are no reliable gross characteristics that can distinguish a benign myoma or endometrial stromal nodule from a sarcoma, which can only be confirmed with microscopic evaluation [89] (Level III).

Postoperative Pathologic Assessment

The postoperative pathologic assessment of an undiagnosed cancer after morcellation can be very challenging. Indeed, in certain scenarios, a definitive diagnosis cannot be reached. There are several pathologic disorders that are difficult to distinguish from sarcoma if the surrounding tissue is detached from the tumor itself. Specifically, a benign endometrial stromal nodule (ESN) has the same histologic features as an endometrial stromal sarcoma (ESS), a low grade sarcoma with metastatic potential [90-92] (Level III). Both exhibit densely uniform stromal cells with minimal cellular pleomorphism, mild nuclear atypia, and rare mitotic figures. While ESS typically has distinct finger-like projections into the myometrium and vascular invasion, ESN has a well-defined architectural feature without evidence of myometrial or vascular invasion. This border may be lost with morcellation, leading to a misdiagnosis.

For patients with undetected endometrial adenocarcinoma, a morcellated specimen similarly presents a challenge for the pathologist. Even when the diagnosis of cancer can be confirmed histologically, the depth of myometrial invasion, critical to assessing metastatic risk and adjuvant treatment, cannot be quantified [93] (III). The inability to make this specific and accurate assessment, along with the potential for missing the diagnosis altogether in an architecturally distorted specimen following morcellation, [74] may lead to suboptimal treatment in these women.

Postoperative Management

The majority of women diagnosed with a uterine sarcoma are informed following surgery for a presumed benign uterine myoma, only after final pathology is confirmed. If the uterus is removed intact, reoperation for surgical staging is not typically recommended. Follow-up imaging with computer tomography (CT) of the chest, abdomen and pelvis can help guide adjuvant therapy. For patients who are pre-menopausal and do not desire ovarian preservation, a bilateral salpingoophorectomy (BSO) can be considered (Level C). For those who underwent myomectomy or supracervical hysterectomy, a subsequent operation is required for total abdominal hysterectomy or simple trachelectomy with BSO (Level C). Further, in settings where EMM was performed, reoperation to ensure that any residual peritoneal disease is resected is considered [14] (Level C).

Summary and Recommendations for "Preoperative Evaluation, Intraoperative Diagnosis, and Postoperative Pathologic Analysis"

- Preoperative diagnosis of uterine sarcoma presents a greater challenge than other uterine malignancies. Currently, there are no reliable preoperative diagnostic tools to differentiate malignant mesenchymal tumors of the uterus from their benign counterparts (Level III).
- When considering uterine surgery and route of hysterectomy or myomectomy, a detailed history, with special attention to age, menopausal status, abnormal bleeding, estrogen exposure, a history of tamoxifen use, and pelvic irradiation, will help guide the clinician regarding to risk of uterine malignancy and choice of surgical approach (Level A).
- When morcellation is considered prior to hysterectomy, an endometrial evaluation should be performed. Endometrial sampling and imaging can be useful in the preoperative setting in diagnosing unrecognized uterine pathology and ascertaining a woman's candidacy for morcellation (Level C).
- Given the higher incidence of uterine cancer or sarcoma in postmenopausal women, increased caution should be exercised when considering morcellation in this cohort.
- Should preoperative imaging suggest focal endometrial pathology, hysteroscopy with directed sampling is recommended. If suspicion for occult endometrial malignancy remains high after clinical evaluation, alternatives to morcellation should be employed (Level C).
- Uterine tissue morcellation should only be performed when there is no suspicion of malignancy (Level C).
- In women for whom an unsuspected malignancy was morcellated, reoperation to ensure optimal resection of residual peritoneal disease may be considered (Level C).

IV. Alternatives in Managing and Extracting Uterine Pathology

Expectant Management

As many as 80% of women will have uterine myoma during their lifetime, [94] (Level III) many of which will have been diagnosed incidentally. For most women with clinically suspected myoma, the risk of LMS is very small and current literature does not support the need for surgical intervention. Expectant management remains a reasonable option for women with asymptomatic uterine myoma [95] (Level A).

Hysteroscopic Retrieval

Tissue such as polyps or submucosal uterine myomas can be resected sharply, with electrosurgical devices or with hysteroscopic morcellation devices (e.g. MyoSure®, Hologic, Bedford, MA; TRUCLEAR ®, Smith & Nephew, London, UK). Hysteroscopic morcellation differs from abdominal morcellation because it occurs within the uterus; however, in the absence of tubal ligation, tissue fragments could be introduced into the peritoneal cavity retrograde via the fallopian tubes. As a diagnostic procedure, hysteroscopy does not change outcomes in the management of endometrial adenocarcinoma, [96,97] (Level II-2) but the effect of hysteroscopic transmission of a uterine mesenchymal tumor to the peritoneal cavity has not been well-delineated.

LMS has been reported in women undergoing hysteroscopic resection of presumed submucous myoma. (98,99) A review of the literature focusing on intracavitary lesions in both symptomatic and asymptomatic peri- to postmenopausal women revealed disease that was either completely or mostly resected at the original hysteroscopic procedure. At the time of subsequent hysterectomy, minimal to no residual disease was documented and no women had succumbed to their disease at time of publication [100] (Level III). These procedures did not include the use of hysteroscopic morcellators.

The risk of removing a uterine mesenchymal tumor during hysteroscopic morcellation of a presumed uterine myoma has not been quantified, but likely happens more rarely than when performing an abdominal procedure for presumed uterine myoma. Hysteroscopy remains an appropriate manner to remove symptomatic submucosal uterine myomas in premenopausal women and need not be exchanged for definitive treatment (i.e. hysterectomy) simply to avoid morcellation (Level A). As with intraperitoneal cases, if intrauterine pathology encountered during hysteroscopy is expected to be malignant, EMM should not be used (Level C).

Laparotomy

The proportion of minimally invasive hysterectomies (vaginal, laparoscopic, robotic) performed in the US compared to laparotomy continues to increase, [101] (Level III) including those for large uteri, [102] (Level III) where morcellation of some form is required. Compared to laparotomy, a minimally invasive approach is associated with well-established decreased risk of both major and minor complications including transfusion of blood products, wound infection, hernia and venous thromboembolic events. These techniques afford women improved cosmesis, shorter length of stay and convalescence, and lower direct and indirect costs [1-10] (Level I). In general, death after hysterectomy is rare, but the risk may be substantially higher after abdominal hysterectomy compared with a laparoscopic approach [8] (Level III).

Vaginal Extraction

Tissue extraction can also be accomplished following myomectomy via a culdotomy incision [39,40,59]. With hysterectomy, laparoscopy has significant advantages compared to laparotomy, but vaginal hysterectomy remains the optimal route in appropriate candidates. [9,10]. In many cases, a bulky uterus can still be removed intact through the vagina, but if morcellation is required, it can often be performed outside the pelvis, and coring has the theoretical advantage of leaving the uterine serosa intact. Although one series included patients with vaginal morcellation of LMS [33] and two comparative studies examining morcellation in the setting of occult LMS included both EMM and manual (scalpel) morcellation, [12,24] there are no data regarding LMS dissemination specifically with vaginal extraction. There are limited early reports, however, that vaginal extraction with bi-valve morcellation in a specimen retrieval bag may be a safe means of removing the enlarged uterus with endometrial cancer [43,44]. These findings need to be confirmed in larger studies.

Alternative and Interventional Procedures for Uterine Myoma

Treatment options for women with uterine myoma continue to expand with emerging technologies, many of which do not involve removal of the myoma itself, and are uterus-preserving by definition. These include uterine artery embolization (UAE) [103] and myoma ablation techniques such as focused ultrasound (MRgFUS), [104] radiofrequency ablation (HALT procedure), [105] and others not yet approved for use by the FDA.

Evidence surrounding the diagnosis of LMS following these alternative treatments consists only of case reports

and primarily focuses on UAE [106-112] (Level III). The majority of women described in these reports were premenopausal and had pre-procedural screening with MRI. Only two reports involve MRgFUS, [113,114] one of which was aborted due to suspicious imaging findings, and none have been reported in context of the HALT procedure. Tumor size, when reported, was at least 9cm in maximum dimension. Time to diagnosis ranged from immediate to 60 months following the initial procedure. Long-term outcomes for all women following surgical staging were not readily available, but on two occasions, the lesion documented upon re-presentation was significantly larger than its original size. Based on the small number of reports, no conclusive recommendations can be made. However, since most imaging protocols require pre-procedural MRI, this may represent a venue for further research focusing on radiologic diagnostic features of myomatous disease.

With regard to the various forms of myomectomy, the number of case reports or series is likewise low, in part because women undergoing myomectomy tend to be younger and there is also potential for underreporting. When performed laparoscopically, EMM can disseminate malignant disease, [12,13] but insufficient evidence is available to make further recommendations, especially since the majority of patients undergoing myomectomy will be of a younger age than those undergoing hysterectomy. One trial reported follow-up on younger women who underwent abdominal myomectomy, diagnosed postoperatively with LMS, and managed without re-intervention because of childbearing interest. Seven of the eight patients were alive at a mean of 42 months, and 3 of these women conceived and delivered at term. One was noted to have recurrent disease at the time of cesarean delivery and ultimately died from her malignancy [115]. Some of the patients in this series, however, may have had what is now characterized as stromal tumor of unknown malignant potential (STUMP).

Specimen Retrieval Pouches

Investigators are examining the safety and feasibility of using EMM within a specimen containment system, but current data are limited. In theory, this approach may help with the problem of tissue dissemination. Additionally, there are technical challenges associated with the approach:

- Variability in size, shape, and weight of uterine tissue makes placing the specimen into the bag challenging.
- Puncturing the bag in some cases of multiport laparoscopy can be a risk.
- Visualization of the mass within the bag may be suboptimal.
- Visualization of vital structures external to the bag may be obscured.
- Advanced laparoscopic skills are required to avoid complications performing EMM inside a bag.

A variety of specimen retrieval pouches are available on the market. Although this approach makes intuitive sense from a patient safety perspective, there is no evidence to date that EMM within a bag improves prognosis in the setting of unsuspected malignancy. Use of a containment system in vaginal and abdominal cases is being entertained as well. A recent study of 12 endometrial cancer patients whose uteri (mean weight 291±80 grams) were morcellated vaginally in a bag after laparoscopic hysterectomy demonstrated no evidence of local or distant recurrence at a median follow-up of 18 months; these cases were not stratified by grade [44] (Level III). Another report on a similar technique described successful outcomes for 8 endometrial cancer patients with mean uterine weight 255 grams [43]. Contained vaginal morcellation of pre-invasive or invasive specimens appears to permit rapid uterine extraction and may avoid unnecessary laparotomy in women with larger uteri. However, it remains uncertain whether this technique maintains the architectural integrity to facilitate adequate pathologic analysis or preserves oncologic outcomes, both of which must be confirmed in larger studies.

Summary and Recommendations for "Alternatives in Managing and Extracting Uterine Pathology"

- It is possible that different risk profiles exist among the various methods of morcellation, but specific data are lacking with respect to these differences (Level C).
- Hysteroscopy remains an appropriate manner to remove symptomatic submucosal uterine myoma in premenopausal women and need not be exchanged for definitive treatment (i.e. hysterectomy) simply to avoid morcellation (Level A).
- Women with asymptomatic uterine myoma can be managed expectantly (Level A).
- Laparoscopy has well-documented advantages over laparotomy regarding surgical complications and patient outcomes (Level A).
- Sarcomas have been diagnosed after alternative uterine-preserving treatments such as UAE. The same challenges in preoperative diagnosis of uterine sarcoma apply to these surgical alternatives (Level C).
- The use of morcellation within specimen retrieval pouches for containment of benign or malignant uterine tissue requires significant skill and experience, and the use of specimen retrieval pouches should be investigated further for safety and outcomes in a controlled setting (Level C).

V. Informed Consent

Informed consent is not simply signing a document providing permission to operate, but it is also a process of information sharing and dialogue between surgeon and patient regarding risks, benefits, and alternatives regarding a specific procedure. With regard to all forms of tissue morcellation, the following risks should be included in the discussion:

- Dissemination of malignant tissue in the peritoneal cavity, which may worsen prognosis.
- Dissemination of benign tissue, which may result in untoward health consequences, including the need for re-operation or additional treatments.
- Rendering complete pathologic evaluation of a tissue specimen more difficult.
- Injury to adjacent organs unique to the technique of morcellation.

These risks should be weighed in the context of the benefits of a minimally invasive approach as well as the risks and benefits of expectant management or laparotomy as alternatives. The risks of laparotomy should be noted, including wound infection, blood transfusion, longer recovery periods and the potential for life threatening complications such as venous thromboembolic disease (Level A).

VI. A Critical Appraisal of the Sarcoma and Morcellation Literature

The uterine cancer, LMS, and morcellation reports referenced in this document (and the same studies reviewed by the FDA in their recent safety announcement concerning morcellation) were critically appraised [13,28-35]. Concerns regarding the interpretation of these data arose and warranted further discussion. All studies regarding uterine LMS outcomes in the setting of morcellation are single-institution and retrospective, and more than half of them contain fewer than 1,000 patients. The true incidence of LMS in the setting of hysterectomy for benign disease could not be calculated in some studies since the overall hysterectomy (denominator) was not known. Most studies were conducted at high-volume academic medical or cancer centers, where referrals for treatment of patients with complex conditions, comorbidities or rare tumors are frequently made. The incidence of uterine pathology and rare tumor types such as LMS tend to be higher in academic medical centers and may not reflect cancer incidence rates in the general population. Several reports did not clarify whether the hysterectomy and morcellation procedures were performed at their respective centers or were referred from an outside hospital for uterine sarcoma treatment. Additionally, many of these studies were not stratified by sarcoma risk factors and were not necessarily performed on patients who would have been MIS candidates in the first place. Whether all candidates underwent a comprehensive preoperative evaluation and were appropriate candidates for a minimally invasive procedure remain unclear. However, several of the reports suggested that many of the women who underwent morcellation were menopausal and that rate of uterine LMS increased sharply with increasing age. Therefore, one should be particularly careful when considering morcellation in postmenopausal women, especially if the presumed preoperative diagnosis is uterine fibroids. Prospective and population-based studies are needed to develop a better understanding of morcellator safety in different patient cohorts (e.g. women with large fibroids planning laparoscopic hysterectomy or myomectomy versus women with pelvic organ prolapse planning laparoscopic supracervical hysterectomy and sacrocolpopexy) and identify a population of women undergoing uterine surgery who may be at high risk of an unrecognized uterine cancer.

VII. Future Directions: Discovery and Innovation

The significant burden uterine myoma contribute to women's health, along with what little is known regarding (1) the true incidence of LMS in a population of women undergoing uterine surgery for apparent benign disease, (2) the ability to detect uterine sarcoma pre-operatively, and (3) the risks of morcellation in the setting of heterogeneous patient cohorts, indicate research and funding are urgently needed to better understand these issues and optimize treatment strategies for women undergoing uterine surgery. Future directions in discovery and innovation may include:

- Patient-centered research regarding integration of new technologies in minimally invasive gynecologic surgery with respect to safety, outcomes and quality of life.
- Research to develop and implement better diagnostic tools to identify uterine malignancies preoperatively, especially sarcomas.
- Collaboration with device manufacturers to stimulate clinically-directed innovation focused on contained morcellation systems and instrumentation to facilitate safe removal of specimens.
- Defining the comparative risks and benefits of laparotomy versus minimally invasive surgery with morcellation of uterine tissue.
- A nationwide prospective surgical database for the acquisition of consistent and reliable information for the accurate quantification of outcomes data with regard to uterine surgery.
- A more rigorous system for mandatory adverse

event reporting and device surveillance that involves professional societies, device manufacturers, and regulatory agencies such as the FDA.
- A system for timely dissemination of hazards and concerns regarding devices and procedural complications.
- Addressing educational needs with didactic and hands-on training opportunities regarding safe tissue extraction.

VIII. Summary

It is well known that minimally invasive gynecologic surgery has significant advantages for women compared to laparotomy. Indeed, hundreds of thousands of women worldwide benefit from minimally invasive approaches to hysterectomy and myomectomy every year. Occasionally, morcellation, a surgical technique involving fragmenting a surgical specimen into smaller pieces, is required for extraction of large uterine tissue specimens, which may expose patients to increased morbidity in certain circumstances. This is particularly true in cases of unrecognized malignancy, where intra-abdominal dissemination of cancer may worsen the prognosis. However, the risk of occult malignancy appears extremely low, especially in reproductive-aged women.

A critical review of the literature supports that tissue morcellation can be performed safely and effectively by properly trained and experienced surgeons in appropriately screened and selected patients.

AAGL recommends consideration of the following guidelines related to morcellation:

- Morcellation should not be used in the setting of known malignant or pre-malignant conditions, or in risk-reducing surgery.
- Morcellation should only be considered in patients if the appropriate evaluation of the myometrium (with or without fibroids) is reassuring, and appropriate evaluation of the cervix and endometrium is also reassuring.
- For patients in whom preoperative evaluation results in an increased suspicion for malignancy, alternatives to morcellation should be employed, including laparotomy.
- As the risk of malignancy, including undetectable malignancy, is increased in postmenopausal women, alternatives to morcellation should be considered in this patient population.
- When electromechanical morcellation (EMM) is planned or considered likely, the specific risks of encountering an undetected malignancy and the likelihood of worsening the patient's prognosis, should be discussed in a patient-centered manner as part of the informed consent process so that the patient can actively be involved in the decision whether to use EMM. Patient autonomy must be respected.
- The use of morcellation within specimen retrieval pouches for containment of benign or malignant uterine tissue requires significant skill and experience, and the use of specimen retrieval pouches should be investigated further for safety and outcomes in a controlled setting.

IX. Conclusion

It is the opinion of the AAGL that all existing methods of tissue extraction have benefits and risks, which must be balanced. At this time, we do not believe there is a single method that can protect all patients; therefore, all current methods of tissue extraction should remain available. We believe that an understanding of the issues reviewed in this document will allow surgeons and hospitals to make the most appropriate, informed choices regarding utilization of tissue extraction in individual patients undergoing uterine surgery.

STATEMENT OF APPROVAL BY THE AAGL BOARD OF TRUSTEES

This report was approved on May 6, 2014 by the members of the Board of Trustees 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. The members are:

Ted L. Anderson, MD, PhD, Vanderbilt University Medical Center; Christopher S. Awtrey, M.D., Beth Israel Deaconess Medical Center; Amanda N. Fader, M.D., Johns Hopkins Medical Institution; Kathy J. Huang, M.D., New York University; Kimberly A. Kho, MD, MPH, University of Texas Southwestern Medical Center; Franklin D. Loffer, M.D., AAGL Medical Director; Marie Fidela R. Paraiso, M.D., Cleveland Clinic Foundation; Harry Reich, M.D.; Matthew T. Siedhoff, MD, MSCR, University of North Carolina at Chapel Hill; Andrew I. Sokol, M.D., MedStar Washington Hospital Center/Georgetown University School of Medicine; Pamela T. Soliman, MD, MPH, University of Texas M.D. Anderson Cancer Center; M. Jonathon Solnik, M.D., Cedars-Sinai Medical Center; Ray A. Wertheim, M.D. Greenbrier Ob-Gyn/Inova Fair Oaks Hospital.

Appendix		Quality of Evidence and Strength of Recommendations: US Preventive Services Task Force [36]
I		Evidence obtained from at least one properly designed randomized controlled trial
II		Evidence obtained from non-randomized clinical evaluation
	II-1	Evidence obtained from well-designed, controlled trials without randomization.
	II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research center.
	II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III		Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Recommendations, based on the highest level of evidence found in the data, are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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Russell R. Broaddus, M.D., University of Texas M.D. Anderson Cancer Center; R. Wendell Naumann, M.D Carolinas Health Care Centers.

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