Review Article

Occult leiomyosarcomas during myomectomy: what should be considered?—a narrative review

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Background and Objective: Uterine leiomyomas, the most common pelvic tumor in women during their reproductive years, and leiomyosarcomas (LMSs) are remarkably similar to each other and the preoperative distinction between the two is a challenge for gynecologists. Women present with similar symptoms and characteristics on imaging modalities is a challenge due to many overlapping features, in most cases the diagnosis is confirmed post-operatively for presumed benign disease. With the increasing use of minimally invasive techniques during surgery, misdiagnosis of LMS results in possible dissemination of malignant tissue throughout the abdominal cavity, and significant treatment delays which in turn increase morbidity and mortality. In recent years there has been debate on its prevalence and whether minimally invasive surgical techniques and morcellation are suitable to use. Food and Drug Administration's estimated prevalence of uterine LMSs is contradicted by many meta-analyses comprising more publications. This review aims to discuss the prevalence of LMS, whether there is an effective method to predict the malignant potential of a presumed benign leiomyoma, what should be considered pre and perioperatively, and how to approach inadvertent morcellation of uterine LMS.

Methods: On May 23rd, 2021 PubMed database and the Cochrane Library were searched for original articles, reviews, meta-analyses, and case reports in English published after Jan 1st, 1990. Also all publications' bibliographies were searched for relevant articles. All related articles' abstracts were reviewed by one author, then selected articles were reviewed by one other author.

Key Content and Findings: We summarized preoperative findings on imaging modalities and laboratory studies implicating malignancy, and innovative scoring systems combining these with up to 80% accuracy and in which patients morcellation is appropriate to use. Also, there are some novel studies on frozen sections' diagnostic accuracy opposing the general opinion on this subject. These novel approaches might improve preoperative detection rates and augment referral to gynecologic oncologists for optimal treatment.

Conclusions: Even though there are some promising reports, more studies with bigger cohorts are needed to determine accurate preoperative diagnostic methods. Up to date, there are no definitive diagnostic approaches.

Keywords: Leiomyosarcoma (LMS); leiomyoma; morcellation; occult leiomyosarcoma; fibroid

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Introduction

Uterine leiomyomas (fibroids or myomas) are benign tumors of the uterine smooth muscle and the most common pelvic tumor in women during their reproductive years. Approximately 70% of white women and 80% of black women are affected (1). Women with leiomyomas often present with abnormal uterine bleeding, pelvic pain, infertility, and pregnancy complications (1). The disease affects the quality of life of many women.

During routine gynecological practice, leiomyomas are encountered frequently and when symptomatic they are often treated by surgical procedures such as hysterectomy and myomectomy. Uterine leiomyomas are the most common indication for hysterectomy in the United States (2).

Uterine sarcomas are the most malignant group of uterine tumors. They are exceedingly rare, with an incidence of 0.36 per 100,000 women/year and a prevalence of 3–5% out of all uterine malignancies (3,4). The most common histological type is leiomyosarcoma (LMS) which accounts for roughly one-third of uterine sarcomas and consists of ~1% of all uterine malignancies (3). The average age at diagnosis is 64 years in white women and 62 years in black women (5), which is average about 10 years older than of a woman with a leiomyoma (1). The 5-year relative survival is between 52% and 85% for stage I disease and 18.8% to 65% for all stages, the risk of recurrence fluctuates between 45% and 73% (5,6).

Women with LMS most often present with abnormal uterine bleeding (53%), abdominal pain (35%), and palpable abdominal mass (14%); which are very similar to leiomyomas (6). Sarcomas do not have any pathognomonic features on any imaging technique and there are no validated radiological criteria established. Since presenting symptoms and characteristics on imaging modalities are remarkably similar to leiomyomas, the preoperative distinction between the two is a challenge for gynecologists.

Minimally invasive techniques for both hysterectomy and myomectomy have been around for years and reduce operative morbidity compared to laparotomy. They offer less pain and blood loss, shorter postoperative hospital stay, quicker recovery, and smaller incisions (7). The main challenge of these techniques is the requirement to remove large masses through small openings. Manuel morcellation has been used as a solution for a long time. In 1993 the first electric morcellator was found and in 1995 it has been approved by the Food and Drug Administration (FDA) (8).

In 2014 FDA issued a warning against the use of morcellation techniques because of the inadvertent dissemination of an unsuspected LMS during minimally invasive surgery (MIS) since there is no reliable method to preoperatively diagnose a malignant tumor (9). They stated that for presumed benign leiomyomas, the prevalence of occult LMS is 1 in 498 women or 20 per 10,000 persons based upon their review of the literature (10). In 2020 they released an updated statement requiring the use of a tissue containment system during morcellation (11). Since these statements were published, the prevalence of LMSs has been a subject of debate and has been contradicted by many meta-analyses comprising more publications (12,13). Inflated numbers published by the FDA might cause unnecessary concern among clinicians and decrease the use of MIS which in turn causes an increase in operative morbidity.

Even though the majority of women with uterine masses have benign leiomyomas, one of the greatest challenges in gynecological practice is the differential diagnosis of uterine leiomyoma and LMS preoperatively. Accurate preoperative evaluation of patients with leiomyoma is critical. This review aims to discuss, in the light of current literature, the prevalence of LMS, whether there is an effective method to predict the malignant potential of a presumed benign leiomyoma, what should be considered pre and perioperatively, and how to approach inadvertent morcellation of uterine LMS. We present the following article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-45/rc).

Methods

On May 23rd, 2021 PubMed database and the Cochrane Library were searched for original articles, reviews, meta-analyses, and case reports in English published after Jan 1st, 1990 using the terms “leiomyoma”, “uterine”, “leiomyosarcoma”, “sarcoma”, “morcellation”, “occult”, “prevalence”, “frozen”, “biopsy”, “preoperative imaging”, “preoperative diagnosis”, “hysterectomy”, “myomectomy” either alone or in combination. After duplicate studies were eliminated, all related articles’ abstracts were reviewed by one author (SF), then selected articles were reviewed by one other author (YES, ST). In case of a disagreement, all authors debated until a mutual decision was made. Also all publications’ bibliographies were searched for relevant

Table 1 The search strategy summary

Items	Specification
Date of search	May 23rd, 2021
Databases and other sources searched	PubMed database and the Cochrane Library were used, also all publications' bibliographies were searched for relevant articles
Search terms used	Either alone or in combination; "myoma", "leiomyoma", "uterine", "fibroid", "leiomyosarcoma", "sarcoma", "morcellation", "occult", "malignancy", "prevelance", "frozen", "biopsy", "imaging", "preoperative diagnosis", "hysterectomy", "myomectomy"
Timeframe	Manuscripts published after Jan 1st, 1990
Inclusion and exclusion criteria	Original articles, reviews, meta-analyses, and case reports in English were included
Selection process	All articles' abstracts were reviewed by one author (SF), then selected articles were reviewed by one other author (YES, ST). In case of a disagreement, all authors debated until a mutual decision was made

articles. The search strategy is summarized in *Table 1* and detailed search strategy used while searching PubMed database is in Table S1.

The prevalence of occult LMS

Since the 2014 FDA statement, the prevalence of occult LMS has been the subject of debate. FDA stated that for presumed benign leiomyomas, the prevalence of occult LMS is 1 in 498 women or 20 per 10,000 persons based upon their review of the literature (10). Pritts *et al.* conducted a meta-analysis of 134 studies (64 prospective and 70 retrospective) and found the estimated prevalence to be 5.1 in 10,000 (1 in 1,961) surgeries. When restricted to only prospective analyses, their estimated prevalence was 1.2 LMS per 10,000 surgeries (1 in 8,300) (12). In another 2017 meta-analysis conducted by Agency for Healthcare Research and Quality (AHRQ), a cumulative prevalence estimate, including both retrospective and prospective studies, is fewer than 1–13 per 10,000 surgeries (<1/10,000 to 1/770) (13). In both meta-analyses, the prevalence is much lower than previously stated by the FDA.

Nevertheless, it is conceivable why the FDA estimate was higher for several reasons: FDA's assessment was based solely on hysterectomies, LMS prevalence increases with age, and women undergoing hysterectomy are generally older than those undergoing myomectomy (14). The FDA analysis was limited to studies in which an occult LMS was found, studies of women undergoing surgery for presumed benign leiomyomas in which no LMSs were identified were excluded from the analysis (12,15). FDA excluded studies with less than 100 subjects in it which severely limited their evidence base, especially considering how rare LMSs are (12). Also, FDA only included studies in which the sole indication was presumed benign leiomyomas, if multiple indications were listed by the author the study was excluded and was unavailable for analyses (12).

The most prominent superiority of these mate-analyses to the FDA review is that these meta-analyses included studies with both malignant and benign outcomes while the FDA analysis excluded the studies in which no LMSs were identified. The 2015 Pritts meta-analysis included 133 studies and 30,193 women. In addition to the studies included in the Pritts analysis, 27 newer studies were included in the 2017 meta-analysis conducted by AHRQ, which included a total of 160 studies and 136,195 women. Both analyses included both myomectomies and hysterectomies and excluded the studies in which the results were not specified as LMSs. They both used a Bayesian binomial random effect specification to estimate the prevalence and conducted separate analyses for prospective and retrospective studies. AHRQ presented 5 different models, including but not limited to a model restricted to studies with high certainty of histopathologic evaluation, and another with corrected Pritts data. Regardless of the model, all their estimates were lower than the FDA's.

Diagnostic methods

Biochemical markers

Since there are no reliable laboratory markers in the preoperative diagnosis of LMSs, many biochemical markers, and their utility in the differential diagnosis of LMSs from

leiomyomas, have been studied. Although not specific, many articles suggest that serum CA125 or lactate dehydrogenase (LDH) are elevated in uterine LMS (16-18). Other studies have investigated neutrophil to lymphocyte ratio (NLR) and preoperative hyperphosphatemia (18,19) but to date, there are no reliable preoperative markers.

Juang *et al.* compared the preoperative serum CA125 values of 42 patients with uterine LMS to 84 patients with uterine leiomyomas as controls. Even though they reported a significant overlapping between early-stage LMS and the leiomyoma group, they found that serum CA125 values were significantly increased in the LMS group. The optimal cut-off values of serum CA125 were 162 and 75 U/mL for the premenopausal group and the postmenopausal group, respectively (16). In another study, Duk *et al.* have found elevated levels of serum CA125 levels in 40% of the patients with uterine sarcomas but found no difference in serum CA125 levels between histologic sarcoma subtypes (17).

Di Cello *et al.* have retrospectively compared the preoperative serum LDH values of 43 patients with uterine sarcomas and 2,211 patients with uterine leiomyomas. They found that patients with uterine sarcomas, compared to the leiomyoma group, have higher values of LDH3, LDH4, and LDH5 isoenzymes and lower values of LDH1 and LDH2 isoenzymes. They believed LHD1 and LDH3 to be the best diagnostic markers for uterine sarcomas. They created the Uterine mass Magna Graecia (U.M.G.) risk index, combining these two isoenzymes. The risk index was defined as U.M.G. = LDH3 + (24/LDH1) with a cutoff value of 29 and had a 99.6% specificity (9 false positives in the leiomyoma group) and 100% sensitivity (18). Goto *et al.* analyzed serum LDH values of 140 patients. 10 with LMSs and 130 with degenerated leiomyomas and with LDH 3 both sensitivity and specificity of over 90% and diagnostic accuracy of 92.1% were acquired (20).

Jitsumori *et al.* reviewed 7 cases of uterine LMS and found two cases with preoperatively elevated alkaline phosphatase (ALP). In both cases, ALP levels returned within the normal range postoperatively and increased upon recurrence. LMS cells showed positive staining for ALP. They found no correlation between serum ALP and LDH or ALP and CA125; and ALP, CA125, and LDH were thought to be independent tumor markers (19).

NLR defined as the neutrophil count divided by the lymphocyte count has been proven to be beneficial in the preoperative diagnosis and as a prognostic marker in colon and ovarian cancers. Kim *et al.* compared NLR to CA125 in the differential diagnosis of uterine sarcomas from uterine leiomyomas. They retrospectively reviewed 55 cases of uterine sarcomas and matched to 165 patients with leiomyomas and 165 patients with adenomyosis in terms of age, body mass index (BMI), and uterine volume. Neutrophil count, the NLR, and serum 125 levels were found to be higher in the sarcoma group, while lymphocyte count was lower. There was no difference in the NLR, WBC counts, and serum CA125 levels among different histological subtypes in the sarcoma group. With a cut-off value of 2.12 for the NLR and 14.5 U/mL for CA125, compared to serum CA125, the NLR had a higher sensitivity (80% *vs.* 53.8%), specificity (70.3% *vs.* 31.8%), positive predictive value (14% *vs.* 4.7%), and negative predictive value (98.3% *vs.* 92.1%) for LMSs (20/55 patients). Despite the NLR having a low positive predictive value, it might be a helpful diagnostic tool in case of suspicious uterine masses (21).

Imaging

According to the European Society of Gastrointestinal Endoscopy (ESGE), sarcomas do not have any pathognomonic characteristics on any imaging technique, and there are no validated radiological criteria, but there are certain characteristics to LMSs that could cause suspicion preoperatively (22). A solitary, large (bigger than 8 cm), oval-shaped, highly vascularized, irregular, and heterogeneous mass and central necrosis combined with degenerative cystic changes (without calcification) should raise suspicion of LMS (22,23).

In routine gynecological practice, ultrasonography is the most frequently used imaging method. Comparing grayscale and Doppler ultrasonography findings of uterine leiomyomas to uterine sarcomas in a series of studies, Hata *et al.* reported an enlarged uterus with heterogeneous internal echo on grayscale ultrasonography and a normal resistance index (RI) value with high peak systolic velocity on Doppler ultrasonography. For peak systolic velocity, a cut-off value of 41 cm/s had a detection rate of 80% for uterine sarcomas (24,25). Aviram *et al.* had a similar report. They compared 98 patients with leiomyomas to 6 patients with uterine LMS and 7 patients with malignant mixed mesodermal tumor (MMMT). In terms of sonographic appearances and RI values, there were no significant differences between the leiomyoma and LMS groups, however, mean RI values of MMMT were significantly lower than leiomyomas' (26). However, Kurjak *et al.*

reported a different outcome. They compared 10 cases with uterine sarcoma to 1,850 patients with leiomyomas and 150 healthy patients. There was no difference between right and left uterine artery RI values but, between groups, the RI values were the lowest for the sarcoma group and the highest for the normal uterus group. With a cut-off value of 4.0 for the RI, a sensitivity, specificity, positive predictive value, and negative predictive value of 90.91%, 99.82%, 71.43%, and 99.96%, respectively, were noted for sarcoma detection (27).

For the evaluation of endometrial and myometrial vascularization, Doppler ultrasonography is used. Exacoustos *et al.* compared grayscale and Doppler ultrasonography findings of 8 patients with uterine LMS to 225 patients with benign leiomyomas. In their study LMSs were larger, 88% were larger than 8 cm in diameter, and 50% of LMSs had degenerative cystic changes. 88% of LMSs had increased peripheral and central vascularity in Doppler ultrasonography while vessel regularity and RI remained similar between groups. For the ultrasonographic diagnosis of LMS, a diameter larger than 8 cm and marked central vascularity together had a sensitivity, specificity, positive predictive value, and negative predictive value of 75%, 98%, 60%, and 99% respectively (28).

Magnetic resonance imaging (MRI) has a wide range of functions in medical practice, also has an irreplaceable role in the preoperative evaluation of potential gynecological malignancies. Sahdev *et al.* conducted a retrospective review of 25 scans of 22 patients with uterine sarcomas, 11 of whom had LMSs. In their series LMSs presented as large heterogenous masses with areas of cystic necrosis and hemorrhage. All except one replaced the normal anatomical structure of the uterus, which appeared as a large endometrial mass, it stemmed from the myometrium and invaded the endometrium as it was later discovered via the histological assessment (29). In another series by Tanaka *et al.*, in which they reviewed the scans of 9 patients with LMS, 3 patients with smooth muscle tumors of uncertain malignant potential, and 12 patients with leiomyomas. Of the malignant cases, 9 showed an HH pattern, and 11 had well-demarcated unenhanced areas with high signal intensity on T2WI. These two findings together on MRI had 72.7% sensitivity, 100% specificity, 100% positive predictive value, and 80% negative predictive value, with an overall accuracy of 87% (30).

Diffusion-weighted magnetic resonance imaging (DWI) is an MRI sequence that creates contrast in MRI images by using the diffusion of water molecules. There are some studies suggesting DWI may help differentiate between benign and malignant tumors of the uterine smooth muscle. In a 2015 study by Tasaki *et al.*, the images of 168 lesions—159 leiomyomas, 6 LMSs, and 3 smooth muscle tumors of uncertain malignant potential (STUMPs)—were analyzed. Mean tumor size was 13.6 cm for LMSs, 8.9 cm for STUMPs, and 6.4 cm for leiomyomas. All 6 LMSs and 2 out of 3 STUMPs showed high signal intensity on both T2WI and DWI but 29 leiomyomas were also in this group (31). Lerner *et al.* investigated the utility of DWI combined with LDH to detect LMSs, they had only 2 cases of LMSs in their cohort. Out of 142 abnormal MRIs, 2 were true positives, 3 were STUMPs, and one was another gynecologic cancer. MRI alone had a sensitivity of 100%, specificity of 67%, a negative predictive value of 100%, but a positive predictive value of 1%. Twenty-three patients had both abnormal MRI and LDH results and only 2 were true positives (8.6%) but all 203 patients with both negative results were true negatives (32).

In 2002, Goto *et al.* combined the use of contrast-enhanced magnetic resonance imaging (CE MRI) with serum LDH values in the differential diagnosis of LMS and degenerated leiomyoma in a prospective study. In their cohort, they had 10 patients with LMSs and 130 patients with degenerated leiomyomas. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 100%, 99.2%, 90.9%, 100%, 99.3%, respectively (20). Lin *et al.* compared CE MRI with DWI in the differential diagnosis of LMS/STUMP from leiomyomas in a prospective study with a cohort of 33 patients (25 leiomyomas and 8 LMSs/STUMP). Compared to DWI, CE MRI had higher diagnostic accuracy (94% *vs.* 52%), specificity (96% *vs.* 36%), and positive predictive value (88% *vs.* 33%). On the other hand, DWI had both higher sensitivity (88% *vs.* 100%) and negative predictive value (96% *vs.* 100%) (33).

Thomassin-Naggara *et al.* retrospectively assessed the ability of MRI in the differential diagnosis of malignant uterine smooth muscle tumors (25 patients) from leiomyomas (26 patients). They had 3 patients with LMS in their cohort. They found high b_{1000} signal intensity, intermediate T2-weighted signal intensity, mean ADC, patient age older than 44.8 years, intra-tumoral hemorrhage, endometrial thickening, T2-weighted signal heterogeneity, menopausal status, enhancement heterogeneity, and the non-myometrial origin on MRI to be prognostic features of

malignancy, especially the use of DW signal intensity, mean DC, and T2 signal intensity in a multivariate model analysis had a diagnostic accuracy of 92.4% (34).

Umesaki *et al.* presented 3 cases of LMS whom they evaluated with Doppler ultrasonography, MRI, and 18-F-Fluorodeoxyglucose positron emission tomography (FDG-PET). All patients' MR imaging showed high-intensity areas on both T1 and T2 weighted images and all patients had positive PET results. One patient with stage IV disease had positive serum CA 125 and LDH values and intra-tumoral blood vessels were visualized (35).

Molecular bio-imaging techniques

Survivin is a protein present in fetal development but is absent in differentiated adult cells (36). It is expressed in malignant cells but due to overlaps with normal controls, it cannot be applied as a biomarker in the diagnostic process (37). In a recent study done by Shalaby *et al.*, they have checked *in vivo* in a preclinical animal model, using bioluminescence based molecular imaging techniques, whether the survivin promoter gene expression in LMS cells can be detected and was able to distinguish leiomyoma cells from LMS cells by the significant difference in survivin gene expression with high specificity (38). Even though their results are very promising, there is a lack of well-optimized chemiluminescence-based robust human imaging devices so the clinical adaptations of this method are extremely limited (39).

Transcervical needle biopsy

Since using the transabdominal route to obtain a biopsy from a pelvic mass has the risk of puncturing the bowel, the transvaginal approach is seen as the optimal route to reach pelvic masses but the utility of needle biopsies in LMSs is not clear (40).

Kawamura *et al.* analyzed 351 biopsies and used a cut-off value of 2, according to Bell's criteria (41,42). The sensitivity, specificity, and positive and negative predictive values were 100%, 98.6%, 58%, and 100%, respectively. All 7 sarcomas were diagnosed by needle biopsy, and 5 false-positive cases with a score of 2 were either atypical leiomyomas or smooth muscle tumors of low malignant potential. All 333 patients with a score of 0 had benign disease (42). Whether potential spread of sarcoma cells by puncturing the tumor is possible or not is not clear.

Endometrial sampling

Endometrial sampling is a minimally invasive technique, highly effective in detecting endometrial pathologies but in uterine sarcomas, its diagnostic accuracy might be as low as 35% (43).

In a retrospective analysis by Bansal *et al.*, among the 72 patients with sarcomas, preoperative endometrial biopsy suggested an invasive tumor in 86% (62/72) and correctly predicted the histologic diagnosis in 64% (46/72). In LMSs, its accuracy rate was 67%. There were no differences between the accuracy of Pipelle biopsy and uterine curettage (44).

In a more recent 2021 study, 58.2% (46/79) of LMSs were detected preoperatively. The rate of diagnosis was higher (66.7% *vs.* 31.6%) in patients that underwent sampling with hysteroscopic guidance (45).

Regarding uterine LMSs, the accuracy of endometrial sampling is low, but since it is already indicated preoperatively in patients with abnormal uterine bleeding, it might be a helpful tool for the clinician.

Risk assessment

Risk factors associated with LMSs are post-menopausal status, increasing age, black race, tamoxifen use (5 years or longer), a history of pelvic irradiation, a history of childhood retinoblastoma, and hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome (46). Regarding parity and age at menarche or menopause, data is inconclusive (46).

Preoperative scoring systems

There is an urgent need for a risk assessment tool in patients with uterine masses. In 2014 Nagai *et al.* came up with a scoring system for uterine sarcomas called novel PREoperative Sarcoma Score (PRESS). Out of 63 patients with suspected uterine sarcomas, 15 had malignant disease. There were no significant differences in serum CA 125 values, tumor size, and Doppler ultrasonography RI values between the two groups. Rapid tumor growth was more common in the leiomyoma group. Age, serum LDH values, endometrial cytology findings were placed as 2 points and MRI finding as 1 point. Out of 7 points, the optimal cut-off value was 3 points. When PRESS was interpreted as 3 points or higher, the sensitivity, specificity, positive predictive value, negative predictive value, and

diagnostic accuracy were 80%, 85%, 63%, 93%, 84%, respectively (47).

Lentz *et al.* identified 117 patients with occult uterine sarcomas and 234 women were randomly selected as controls out of a cohort of 45,461 patients. They found women with solitary myomas, a larger uterus, >50% growth, blood loss requiring transfusions, and pain requiring hospital admission or opioids were more likely to have sarcomas. The final risk assessment model consisted of age, race/ethnicity, body mass index, number of myomas, uterine growth, uterine weight, pelvic pain level, and blood transfusion. Using a risk level of 0.5% as a threshold had 60% sensitivity and 88% specificity (48).

Recently Zhang *et al.* prepared a scoring system for uterine LMS. Forty-five patients with LMS and 180 patients with leiomyoma as controls were enrolled retrospectively. Tumor size larger than 7 cm (2 points), serum LDH value of 193 U/L (2 points), age over 40 years (1 point), NLR higher than 2.8 (1 point), and number of platelets greater than 298×10^9/L (1 point) were included in the model. The optimal cut-off value was determined as 4 points out of 7 with a sensitivity of 80% and specificity of 78%. In a subpopulation of patients younger than 40 years of age, 3 out of 6 was established as the cut-off value and had 71% sensitivity and 88% specificity (49).

Intraoperative gross characteristics and frozen section

Sarcomas might have different gross characteristics compared to leiomyomas which might raise suspicion of malignant tissue during operation. Some of these are a loss of the usual whorl pattern, a homogeneous texture, ill-defined margins, a yellow color, a softer less resilient tumor, an absence of a bulging surface, extrauterine extension of a uterine tumor, and intraoperative discovery of an unusual growth pattern. However, these characteristics are also present in degenerated leiomyomas or after GnRH treatment (24,46,50,51).

A reliable diagnosis of LMS is not possible through intraoperative frozen section (52,53) although some recent studies are proving otherwise. Lok *et al.* analyzed 112 frozen sections of uterine smooth muscle tumors and acquired an accurate diagnosis of LMS in 8 cases out of 9, the misdiagnosis being a myxoid LMS (50). There is still room for further studies with larger sample sizes. In any case, frozen section should always be performed intraoperatively if a uterine sarcoma is suspected.

Morcellation

Minimally invasive surgical techniques have been around for quite some time. The main challenge of these techniques is the requirement to remove large masses through small openings. En bloc removal via the vaginal opening (after hysterectomy) or posterior cul-de-sac has been and is still being used. Also, manual morcellation has been used as a solution for a long time. Since the approval of electric morcellators in 1995, they have been used in gynecological practice (8).

Who to morcellate?

FDA's updated statement in 2020 required the use of a tissue containment system, compatible with the laparoscopic power morcellator, during morcellation of presumed benign leiomyomas. They stated that even in bag morcellation is contraindicated when the tissue is suspected or known to have malignancy, the patient is post-menopausal and/or older than 50 years of age, and en bloc removal of the tissue is possible via the vagina or a mini-laparotomy incision (11).

Turkish Society of Minimally Invasive Gynecologic Oncology advised that patients over the age of 35 should be treated with caution and ones with risk factors for uterine LMS should be examined with advanced imaging methods (8).

American College of Obstetricians and Gynecologists recommends evaluating the patient preoperatively to identify malignancy of the uterus; with imaging, cervical cancer screening, and endometrial tissue sampling; and afterward deciding the surgical route via a shared decision-making process with the patient. They state that morbidity risk associated with laparotomy should be weighed against the risk of disseminating occult malignancy through morcellation (15).

Contained morcellation

To prevent the dissemination of malignant tissue throughout the peritoneum, the use of containment bags has been suggested but there is no definite evidence that contained morcellation is superior to other strategies and the significance of this technique is not validated.

A 2021 systematic review by Pepin *et al.* identified 20

studies that evaluated containment bags and 13 (65%) reported no loss of bag integrity. Rates of bag damage/leakage ranged from 0% to 40.6% (54). In a pilot study evaluating a small number of patients, leiomyoma cells were detected in 83.3% (20 out of 24) of patients even after in-bag morcellation (55).

In a 2016 pilot study, in which containment bags were not used, 30% of samples acquired after morcellation showed residual leiomyoma cells, of which half was already present after the myomectomy closure, before morcellation (56), which shows that irrespective of morcellation, malignant cells may disseminate into the abdominal cavity after a uterine incision.

Although both studies regarding cell spillage included in this review were limited to a few patients (20 and 24 patients), they both found leiomyoma cells in the peritoneum irrespective of morcellation. In the retrospective study by Takeda *et al.* (55), leiomyoma cell sheets were identified trapped on the surface of a defoaming sponge equipped in the reservoir of an intraoperative red blood cell salvage device which collected both blood and peritoneal washing fluid during in 83% of their cases. They performed laparoscopic myomectomies on all their patients and morcellated the leiomyomas by hand with scalpels in a contained bag. They hypothesized they have detected a much higher rate compared to other studies because of the "superior capability of defoaming sponge to concentrate the targeted leiomyoma cells on its surface from larger amounts of washing fluid, in comparison to simple collection from 100–500 mL of irrigated washing fluid". The retrospective nature of the study combined with their high detection rate might suggest a selection bias. In their prospective study, Toubia *et al.* (56) performed peritoneal washings 3 times during the surgery: the beginning of the procedure once the peritoneal cavity was accessed laparoscopically, after the myoma was excised and the myometrial incision closed, and after uncontained power morcellation. They have performed uncontained morcellation despite the FDA recommendations, but the prospective nature of the study and three separate peritoneal washing samples collected makes it more credible.

In a recent review, the Turkish Society of Minimally Invasive Gynecologic Oncology stated that even though tissue containment bags are assumed to prevent dissemination, there is not enough evidence to prove their efficacy and that they should be used with caution (8).

Outcomes after morcellation

Regarding outcomes of occult LMS after morcellation, data is inconsistent. In a series of 56 patients comprised of stage I and II disease, tumor morcellation was significantly associated with poorer outcomes. In morcellation and no morcellation groups, the recurrence rate was 53% *vs.* 32%, 5-year disease-free survival was 40% *vs.* 65%, 5-year overall survival was 46% *vs.* 73% and death was 44% *vs.* 16%, respectively (57). In a 2015 systematic review by Pritts *et al.*, during the earlier stages poorer outcome was observed when the tumor was morcellated *vs.* removed en bloc. They found the overall data was insufficient to determine whether one specific type of morcellation was more worrisome than others and hypothesized that morcellation might not increase true tumor burden by dissemination of tumor throughout the peritoneum, and any type of tumor penetration will enhance the hematogenous spread of malignant cells (58). A 2017 review found no difference between outcomes of power *vs.* non-power morcellation and no difference in the 5-year survival no matter the form of removal (59). A 2016 retrospective analysis found an increased 1-year mortality rate in power and non-power morcellation groups compared with no morcellation for all stages (60). For stage I LMSs, there was no difference for 3-year disease-free survival and 3-year overall survival between the power morcellation, non-power morcellation, and no morcellation groups (60). In the 2017 meta-analysis by AHRQ, the relative 5-year survival after power morcellation, scalpel morcellation, and no morcellation was 30%, 59%, and 60%, respectively. They suggested that even though survival after power morcellation was considerably lower, even without evident tumor disruption, the hematogenous and microscopic spread is possible (13).

Management of occult LMS after morcellation

Management of occult uterine malignancy after inadvertent morcellation presents a predicament since there is a paucity of literature. In a retrospective case series of 17 patients by Einstein *et al.*, out of three patients with morcellated LMSs, two underwent completion surgery, of which one received adjuvant chemoradiation therapy. Both patients who underwent completion surgery were upstaged. They hypothesized that upstaging could be due to incorrect staging after the initial surgery, progression of malignancy

during the time interval between the initial and completion surgeries (mean interval to completion surgery was 63 days, range between 41–132 days), or histology of the tumor since both patients were diagnosed with LMS. They believe completion surgery has possible advantages such as accurate staging, the ability to customize postoperative treatments, and preventing complications related to excessive therapies (61). Park *et al.* published a case series of 56 patients with uterine LMS, of which 53 underwent surgery for presumed benign leiomyomas. There were 31 patients in the no-morcellation group and 25 in the morcellation group. Out of the 25 patients in the morcellation group, 6 underwent completion surgery (none were upstaged), 13 received chemotherapy and 1 received concurrent chemoradiation therapy (57). In a 2016 case series of 45 sarcoma patients (of which 18 have LMSs) by Lee *et al.*, two had LMSs that were morcellated. Re-exploration surgery was performed on both patients, none had disseminated disease. In all patients, the mean time interval between initial and completion surgeries was 18 days, the upper limit being 21 days. They think uterus preserving surgeries are a viable option for women with presumed benign disease as long as completion surgeries are performed immediately (62). Tantitamit *et al.* conducted a literature review of 23 studies in 2018 and stated that time to completion surgery and overall survival correlates negatively and the mortality rate is worse with late re-exploration (>30 days) (63).

According to National Comprehensive Cancer Network guidelines, adjuvant chemotherapy after morcellation, even without evidence of dissemination, should be considered (64). Regardless of morcellation, when uterine LMS is diagnosed abdominal, pelvic, and thoracic imaging should be performed on all patients since hematogenous metastasis to the lungs, bone, and liver are common. For recurrences, FDG PET scans should be performed (65).

Summary

No test can accurately diagnose or rule out uterine sarcomas preoperatively. Most of the time the diagnosis is not made until pathologic evaluation of the tissue is performed. With that in mind, there are some clinical indicators and preoperative methods that might raise the suspicion of malignancy. All studies covered in this review, including samples, measures, sensitivity, specificity, and diagnostic accuracy are listed in *Table 2*.

Regarding the prevalence of LMSs, there are different reports in literature ranging from 1/498 to less than 1/10,000. FDA's estimated prevalence of 1/498 is countered by several newer meta-analyses comprising more publications. Regardless, when operating on a presumed benign leiomyoma, the risk of an occult malignancy should always be cognizant of.

If laparoscopy is performed, morcellation should be limited to presumed benign leiomyomas. When morcellation is appropriate only contained morcellation should be executed and it should be kept in mind that even with contained morcellation, the risk of dissemination cannot be prevented completely. Although both studies regarding cell spillage included in this review were limited to a few patients (20 and 24 patients), they both found leiomyoma cells in the peritoneum irrespective of morcellation. Morcellation is contraindicated in women over the age of 50 and post-menopausal women. Also, before the operation, the risks of both laparotomy and laparoscopy, and the risk of occult malignancy and its inadvertent dissemination through morcellation should be discussed with the patient and a joint decision should be made.

When morcellation is inadvertently performed on occult LMS, re-exploration surgery should be completed within 30 days and systemic chemotherapy should be considered.

Most of the studies included in this review are retrospective. There might be an absence of data on potential confounding factors and controls might not be representative of the general population. Also in retrospective studies causation cannot be determined, only association. It is a challenge for clinicians to conduct prospective studies due to the low prevalence of LMSs but prospective multicenter studies reporting preoperative ultrasonographic characteristics and complete histopathologic evaluation of each subject would be invaluable.

Even though there are some promising reports, large-scale prospective studies focusing on both biochemical/molecular and imaging markers of LMS are urgently needed. Up to date, there are no definitive diagnostic approaches.

Table 2 Screening studies

#	Article title	Year	Sample size (n)		Measure	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
			Benign	Malignant				
1	Potential role of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and leiomyosarcoma (16)	2006	84	42	Serum CA125	N/A	N/A	N/A
2	CA 125 in serum and tumor from patients with uterine sarcoma (17)	1994	NA	33	Serum CA125	N/A	N/A	N/A
3	A more accurate method to interpret lactate dehydrogenase (LDH) isoenzymes' results in patients with uterine masses (18)	2019	2,211	43	Serum LDH 3 +(24/LDH 1)	100	99.6	N/A
4	Hyperphosphatasemia in leiomyosarcoma of the uterus: Two case reports and a literature review (19)	2017	NA	2	Serum ALP	N/A	N/A	N/A
5	Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus (20)	2002	130	10	Serum total LDH	100	87.7	88.6
					Serum LDH 3	90	92.3	92.1
					MRI	100	96.9	97.1
					Dynamic MRI	100	87.5	90.5
					LDH & MRI	100	99.2	99.3
6	Neutrophil to lymphocyte ratio for preoperative diagnosis of uterine sarcomas: a case-matched comparison (21)	2010	330	55	NLR	80	70.3	60.6
					CA125	53.8	31.8	49.6
7	Sonographic findings of uterine leiomyosarcoma (24)	1990	N/A	1	Ultrasonography	N/A	N/A	N/A
8	Uterine sarcoma: can it be differentiated from uterine leiomyoma with Doppler ultrasonography? A preliminary report (25)	1997	41	5	Color & pulsed Doppler sonography	N/A	N/A	N/A
9	Uterine sarcomas versus leiomyomas: Gray-scale and Doppler sonographic findings (26)	2005	98	13	Gray-scale & Doppler sonography	N/A	N/A	N/A
10	Uterine sarcomas versus leiomyomas: Gray-scale and Doppler sonographic findings (27)	1995	2,000	10	Right and left uterine artery RI values	90.91	99.82	N/A
11	Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma? (28)	2007	225	8	Gray-scale & Doppler sonography	75	98	98
12	MR imaging of uterine sarcomas (29)	2001	N/A	22	MR images	N/A	N/A	N/A
13	Smooth muscle tumors of uncertain malignant potential and leiomyosarcomas of the uterus: MR findings (30)	2004	12	12	MR images	72.7	100	87
14	Differential diagnosis of uterine smooth muscle tumors using diffusion-weighted imaging: correlations with the apparent diffusion coefficient and cell density (31)	2014	159	9	MR images	N/A	N/A	N/A
15	Magnetic Resonance Imaging to Rule out Leiomyosarcoma in Patients Undergoing Surgery for Leiomyomas: A Real World Experience in an Unenhanced Patient Population (32)	2019	569	2	MRI	100	67	N/A
16	Comparison of the diagnostic accuracy of contrast-enhanced MRI and diffusion-weighted MRI in the differentiation between uterine leiomyosarcoma/ smooth muscle tumor with uncertain malignant potential and benign leiomyoma (33)	2016	25	8	MRI (CE MRI *vs.* DWI)			
					CE MRI	88	96	94
					DWI	100	36	52

Table 2 (*continued*)

Table 2 (*continued*)

#	Article title	Year	Sample size (n)		Measure	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
			Benign	Malignant				
17	How to differentiate benign from malignant myometrial tumours using MR imaging (34)	2013	26	25	MRI	N/A	N/A	92.4
18	Positron emission tomography with 18F-fluorodeoxyglucose of uterine sarcoma: a comparison with magnetic resonance imaging and power Doppler imaging (35)	2001	N/A	3	FDG-PET, MRI, power Doppler imaging	N/A	N/A	N/A
19	Molecular bio-imaging probe for non-invasive differentiation between human leiomyoma versus leiomyosarcoma (38)	2020	Animal model		Survivin gene expression	N/A	N/A	N/A
20	Transcervical needle biopsy for the differential diagnosis between uterine sarcoma and leiomyoma (42)	2002	351	7	Transcervical needle biopsy	100	98.6	N/A
21	The role of endometrial biopsy in the preoperative detection of uterine leiomyosarcoma (43)	2016	N/A	68	Endometrial sampling (both Pipelle biopsy and D/C)	N/A	N/A	35.3
22	The utility of preoperative endometrial sampling for the detection of uterine sarcomas (44)	2008	N/A	72	Endometrial sampling (both Pipelle biopsy and D/C)	N/A	N/A	64
23	Endometrial Sampling for Preoperative Diagnosis of Uterine Leiomyosarcoma (45)	2021	N/A	79	Endometrial sampling with *vs.* without H/S guidance	N/A	N/A	66.7 *vs.* 31.6
24	Novel uterine sarcoma preoperative diagnosis score predicts the need for surgery in patients presenting with uterine mass (47)	2014	48	15	Preoperative Scoring System	80	85	84
25	Prediction of occult uterine sarcoma before hysterectomy for women with leiomyoma or abnormal bleeding (48)	2020	234	117	Preoperative Scoring System	60	88	N/A
26	Preoperative clinical characteristics scoring system for differentiating uterine leiomyosarcoma from fibroid (49)	2020	180	45	Preoperative Scoring System	80	78	N/A
27	Intraoperative Frozen Section Biopsy of Uterine Smooth Muscle Tumors: A Clinicopathologic Analysis of 112 Cases With Emphasis on Potential Diagnostic Pitfalls (50)	2021	103	9	Intraoperative frozen section	N/A	N/A	88.8
28	Identification of leiomyoma cell sheets in peritoneal washings retrieved by an intraoperative red blood cell salvage device during laparoscopic-assisted myomectomy with in-bag manual tissue extraction: A pilot study (55)	2018	24	0	Intraoperative peritoneal washing and lost blood	N/A	N/A	N/A
29	Peritoneal washings after power morcellation in laparoscopic myomectomy: a pilot study. Journal of minimally invasive gynecology (56)	2016	20	0	Intraoperative peritoneal washing samples	N/A	N/A	N/A

CA125, cancer antigen 125; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; MRI, magnetic resonance imaging; NLR, neutrophil to lymphocyte ratio; RI, Resistance Index; CE, contrast enhanced; DWI, diffusion weighed imaging; FDG-PET, positron emission tomography with ^{18}F-fluorodeoxyglucose; D/C, dilation and curettage; H/S, hysteroscopic; N/A, not applicable.

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Footnote

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Supplementary

Table S1 Detailed search strategy of PubMed database

Dates covered	Date searched	Hits	Search terms
1990-2021	May 23rd, 2021	121,264	Sarcoma
1990-2021	May 23rd, 2021	9,285	Leiomyosarcoma
1990-2021	May 23rd, 2021	5,441	Uterine sarcoma
1990-2021	May 23rd, 2021	2,407	Uterine leiomyosarcoma
1990-2021	May 23rd, 2021	1,713	Uterine leiomyoma and prevalence
1990-2021	May 23rd, 2021	303	Preoperative diagnosis and uterine sarcoma
1990-2021	May 23rd, 2021	293	Occult sarcoma
1990-2021	May 23rd, 2021	178	Preoperative diagnosis and uterine leiomyosarcoma
1990-2021	May 23rd, 2021	74	Occult leiomyosarcoma
1990-2021	May 23rd, 2021	74	Preoperative imaging and uterine leiomyosarcoma
1990-2021	May 23rd, 2021	73	Occult sarcoma and prevalence
1990-2021	May 23rd, 2021	54	Occult leiomyosarcoma and morcellation
1990-2021	May 23rd, 2021	52	Occult leiomyosarcoma and hysterectomy
1990-2021	May 23rd, 2021	39	Occult leiomyosarcoma and myomectomy
1990-2021	May 23rd, 2021	35	Occult leiomyosarcoma and prevalence

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