Risk of minimal access surgery in uterine leiomyosarcomas: a narrative review

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Abstract: The aim of this paper is to review latest evidences concerning the risk of minimal access or minimally invasive surgery, with detail on incidence and impact of occult leiomyosarcoma (LMS) morcellation at treatment time for presumed benign conditions. Mini-invasive surgery includes techniques in which abdominal wall integrity is preserved (laparoscopy, robotic) and its advantages compared to laparotomy are well known (lower hospital stay, wound infection incidence, recovery time). Morcellation refers to the division of tissue into smaller pieces or fragments and is often used to facilitate the removal of specimens through small incisions. LMS is a rare tumour with aggressive behaviour, but morcellation seems to decrease patients' prognosis further. Iatrogenic damages to other organs from power morcellation are also reported. In 2014 a Food and Drug Association (FDA)-warning banned the use of morcellation in peri- and post-menopause and "candidates for en bloc tissue removal". After this ban, gynaecologists partially revised their surgical procedures. The real occult LMS incidence varies deeply in literature, with 0.08–1.2% range, mixing premalignant and malignant diseases, different histotypes and surgical techniques. Preoperative differential diagnosis between leiomyoma and LMS is challenging despite progresses in gynaecological imaging. Nevertheless, more efforts should be done to define an "high risk patient" based on anamnesis, symptoms, clinical and radiological information [both with magnetic resonance imaging (MRI) or an accurate ultrasound investigation by an expert sonographer], in order to avoid abdominal cells spread at the time of surgery. In bag morcellation could be a feasible and safe alternative to open surgery in selected cases. Every institution should review its surgical protocols in the diagnosis and treatment of myometrial masses, valuating pros and cons of laparoscopic/robotic approach for presumed fibroids. Risks and benefits should be widely discussed with the patient.

Keywords: Occult uterine sarcoma; morcellation; laparoscopic surgery; leiomyosarcoma (LMS); morcellation injuries

Introduction

Myometrial lesions and mini-invasive surgery

Benign myometrial lesions [leiomyoma (LM), myoma, fibromyoma or fibroid] are the first cause of gynaecological surgery between women aged 35 to 50 (1). They are often, but not always, symptomatic due their volume, giving abnormal uterine bleeding, dysmenorrhea, pelvic pain, vesical pressure and LMs are found in 10% of patients with an history of infertility (2).

After medical treatments failure, the first option is surgery and the treatments should be offer to the patient depending on her desire of pregnancy, site and volume of myomas. Myomectomy is a surgical approach to treat symptomatic uterine fibroids in women desiring fertility-sparing procedures while hysterectomy is performed in perimenopausal patients. Historically it was performed with a laparotomic access. Actually, both procedures are offered to the patient by mini-invasive approach.

Gynaecologists were pioneers in laparoscopy and advantages of mini-invasive surgery are well known. In almost all series reported in literature concerning myomectomy or hysterectomy, parameters as hospital stay, blood loss, wound infection or dehiscence, postoperative pain and recovery time are significantly reduced compared to laparotomic approach (3,4). Regarding hysterectomy, also the vaginal approach demonstrated good results, but it's not indicated in enlarged uterus (5). According to some studies, exclusion criteria for laparoscopic myomectomy are the presence of more than four fibromas to remove in different uterine regions (in order to avoid multiple uterine incisions) and maximal mass diameter 12 cm on preoperative evaluation (6). In the event of large fibroids and/or large uterus treated with a mini-invasive approach, the tissue needs to be fragmentated in small parts to permit the removal through the small incisions. In case of hysterectomy, a vaginal morcellation with scalpel can be performed. In the setting of laparoscopic/robotic myomectomies (or supracervical hysterectomies) an intrabdominal morcellation is usually performed and the small pieces are taken off from the biggest trocars. In all cases the removal through some centimetres laparotomic access with manual morcellation is an alternative, but partially nullifying the benefits of mini-invasive techniques in term of possible complications and aesthetic results. Transvaginal morcellation through a posterior colpotomy has also been described. To avoid mini-laparotomic approach and hand mechanical morcellation with scalpel,

in 1993 electronic morcellation (or power morcellation) system were introduced and began to be widely used. This equipment cuts the specimen in small pieces with electrical energy, reducing operative times. The procedure gained success worldwide and became the main system used in laparoscopic myomectomy/hysterectomy for benign conditions. After some incidental findings of occult malignancies morcellated, arose doubts in literature about its implications, as recurrence risk, upstaging and survival outcomes or possible obstacle to the pathologist interpretations and diagnosis. Regarding myometrial masses, on the other hand, despite the progresses in gynaecological ultrasound and magnetic resonance, the differential diagnosis between leiomyosarcoma (LMS) and myoma on preoperative evaluation, remains still challenging. Consequently, some patients with LMS could be treated initially with conservative surgery.

Uterine sarcomas

LMS is an aggressive malignant tumour and represents nearly 70% of all uterine sarcomas and 1.5% of all uterine cancers (7). Endometrial stromal sarcoma (ESS), adenosarcoma and undifferentiated endometrial sarcomas are different histological entities. Several histologic variants of LM and a premalignant form were described. The so called "smooth muscle tumours of uncertain malignant potential (STUMP)" is characterized by cytologic atypia but its risk of recurrence is debated and prognosis is unclear (8,9).

LMS frequently recurs and tends to locally spread or to send distant metastases, mostly to lungs. The median age at diagnosis of LMS is 54 years and risk factors are black race, previous pelvic irradiation, Li-Fraumeni and hereditary retinoblastoma genetic syndrome (10). As previously discussed in this number, these tumours tend to have a weak response to adjuvant therapies (11).

The prognosis is principally related to the stage of disease, with a 66% overall 5 years survival reported (12). Norwegian data shown even worse results, with a 5-year overall survival no better than 51% in stage I tumours and 25% in stage II (13).

Staging for LMS and ESS are described in *Table 1*.

In 2014, an FDA statement (than with revisions in 2017 and 2020) banned the use of power morcellation in peri-/post-menopausal patients and in "*candidates for en bloc tissue removal*" in order to avoid the risk of spreading neoplastic cell in the abdomen (14). These restrictions severely

Table 1 FIGO Cancer Report 2018 uterine sarcomas (9)

Stage	Leiomyosarcomas and endometrial stromal sarcomas
I	Tumor limited to uterus
IA	Less than 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site1
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

FIGO, International Federation of Gynecology and Obstetrics.

reduce the indications to mini-invasive myomectomy or hysterectomy for women with fibroids and they also instigated a debate on medical-legal aspects. As consequence an 11% increase of abdominal myomectomy was observed in the following years, with a parallel increment in surgical complications and hospital readmissions (15).

An Italian survey on the argument in 2016 showed that 58.7% of surgeons changed their approach in the fear of litigation (16).

There have also been more reports by gynaecologists on confined-in-bag morcellation, a technique in which specimens are located into a bag to permit a protect vaginal or abdominal fragmentation, avoiding peritoneal cells spread. This could be probably safer, but requires a little longer operative time and major costs. The different techniques are later described. We present the following article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-11/rc).

Methods

we reviewed principal evidences reported in literature in English by consulting the PubMed, Medline, and Cochrane Systematic Review database on occult sarcoma morcellation, using the key words occult uterine sarcoma, morcellation,

mini-invasive surgery, LMS, morcellation injuries, mostly after 2014 FDA warning on the issue. Aims of the authors are to clarify incidence and oncological outcomes in the event of unsuspected LMS dissemination, description of surgical techniques for specimens' removal and morcellation (unprotect or in bag), iatrogenic complications, preoperative clinical and instrumental features of patients not eligible for morcellation. We tried to simplify the debated aspects through the most cited articles from different countries in a narrative review.

Occult LMS incidence

The real occult sarcoma incidence in the setting of gynaecological surgery for benign condition varies widely in literature, often mixing premalignant masses or different histopathology.

Citing the 2014 FDA warning "*approximately 1 in 350 women undergoing hysterectomy or myomectomy for the treatment of fibroids is found to have an unsuspected uterine sarcoma, a type of uterine cancer that includes leiomyosarcoma*". The reported LMS incidence is 1/498 (14). This data has been deeply criticized because referees to uterine sarcoma in general and come from retrospective small studies. Moreover, the cohort of women analysed was composed by different ages, unstratified for risk factors or candidates for various surgical treatments.

Seidman *et al.* observed that unexpected diagnoses of LM variants or atypical and malignant smooth muscle tumors had occurred in 1.2% of myometrial lesions clinically presumed to be "fibroids" (17). These percentages are debated. In a prospective multicentric study assessing different gynaecological and obstetrical outcomes of laparoscopic myomectomy, Sizzi and collaborators have found 2 cases of uterine sarcoma out of 2,050 procedures (0.09%) (18). A similar low incidence was reported by Mettler *et al.* They registered unsuspected uterine sarcomas in 1 of every 2,269 patients (0.044%) among those who underwent hysteroscopic, laparoscopic, but including also open myomectomies or hysterectomies to treat presumed benign uterine fibroids (19). Based on the 2017 Agency for Healthcare Research and Quality (AHRQ) report, patients may be informed that the risk of unexpected LMS may range from less than 1 in 770 surgeries to 1 in 10,000 surgeries for presumed symptomatic LMs (20). Understandably, the great variability of these data depends on the court of patients included (for example all the

Table 2 Occult uterine sarcoma incidence reported in literature

Year	Authors	%	Note
2007	Sizzi et al.	0.09	2/2,050 uterine sarcomas in laparoscopic myomectomy (18)
2012	Seidman et al.	1.2	including premalignant disease (1 ESS and 1 LMS/1091 uterine morcellation) (17)
2014/2017	FDA	0.28	All uterine sarcomas 1/352—only leiomyosarcoma 1/498, reviewed in 2017: 1/570–750 (14)
2018	Pritts et al.	0.11	Meta-analysis, 32 LMS/30,193 patients, in prospective studies maybe lower (1/8,300) (21)
2015	Nugent et al.	0.025–0.069	LMS, 1/3,906 myomectomies—1/1,465 laparoscopic myomectomies or supracervical hysterectomies (35,161 patients) (22)
2015	Lieng et al.	0.021	1 LMS/4,791 laparoscopic myomectomies or supracervical hysterectomies (23)
2017	Mettler et al.	0.044	1 ESS/2,269 hysteroscopic, laparoscopic, laparotomic surgery for presumed fibroids (19)
2017	AHRQ	0.02-0.08	Risk of LMS in 160 meta-analysis, 136,195 patients (20)
2020	Gitas et al.	0.24	4 (2 LMS + 2 ESS)/1,683 patients treated with electronical morcellation (24)
2018	Bretthauer et al.	0.36	3,6 uterine sarcomas/1,000 laparoscopic hysterectomies -retrospectively from cancer national registers (25)

LMS, leiomyosarcoma; ESS, endometrial stromal sarcoma.

patients treated for fibroids with every kind of surgery including hysteroscopy) and often are mixed LMS, all uterine sarcomas, other malignancies or also premalignant diseases (in particular STUMP)/atypical myomas. Some incidence of occult sarcoma reported in literature are summarized in *Table 2*.

Debates are also ongoing on the impact of sarcoma morcellation on oncological outcomes and common consensus are difficult to achieve. LMS is often an "incidental" diagnosis after fibroids treatments that could have caused tumour damage itself, due to surgical manipulation or cut-through. Nevertheless, prognosis is poor despite further treatments but after unprotect morcellation seems to be even worse. These facts are analysed in next paragraphs.

Surgery and morcellation techniques

Laparoscopic/robotic surgery for myomas are a minimally invasive techniques usually performed by expert Surgeons, although laparotomic surgery is still preferred in selected patients. The choice to remove myometrial masses or enlarged uterus by these approaches, depends on the surgeon experience, the size and location of presumed myomas, patients' characteristics (age, obesity)/wishes and suspicion of malignancies (4,26).

Myomas are the first indication to perform a hysterectomy, but many women wish to preserve their fertility and choose conservative treatment, although the benefits of those on reproductive function are controversial (27). Preoperative assessment includes alternative medical treatments proposal if eligible and anaemia correction if present.

For laparoscopic myomectomy the patient is positioned in Trendelenburg, so optimal pulmonary ventilation is required. After pneumoperitoneum induction, usually four 5–12 mm trocars are collocated, myomas are detected and enucleated following their capsules. Then the myometrium is sutured (*Figure 1*). In case of big masses, the extraction can be obtained through morcellation, that can be usually achieved by abdominal or by vaginal accesses.

The specimens can be fragmentated with scissors or scalpels (hand morcellation) or with electric systems usually positioned in the umbilical trocar (power morcellation). Another option is to perform a suprapubic or periumbilical mini-laparotomy. Hand morcellation and mini-laparotomy are usually facilitated by wound retractors.

Vaginal morcellation can be easily performed during laparoscopic/robotic hysterectomy, where the uterus is reduced into smaller pieces with scissors or scalpels and extracted through the upper vaginal rim (28). This is possible also during laparoscopic myomectomy but is necessary to perform a culdotomy, usually through the posterior fornix (29-31). A cohort multicenter study published in 2018 involving 316 women, reported no pelvic infection, vaginal dehiscence, or complaints of dyspareunia at the 30-day follow-up (31).

As seen, morcellation gives the advantage to remove big specimens through small incisions, but with some
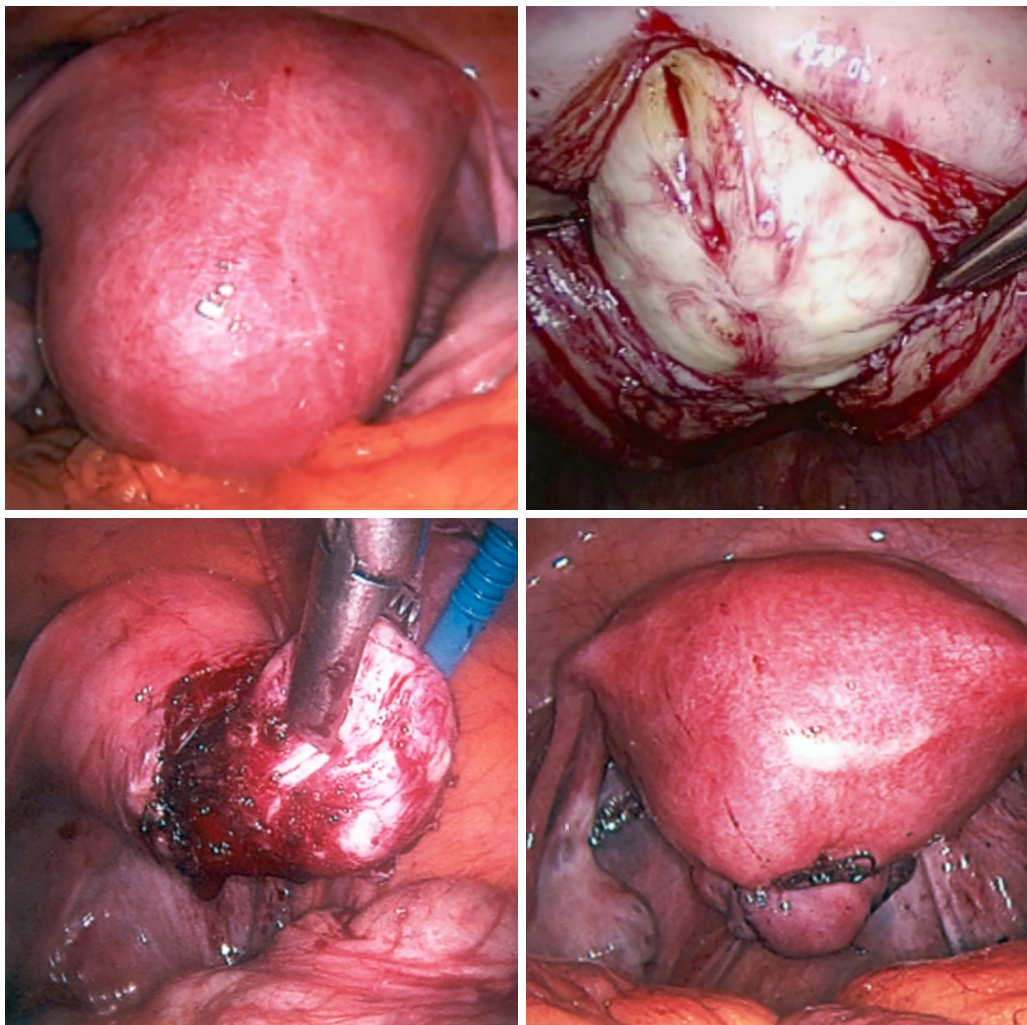
Figure 1 Laparoscopic myomectomy: corpus uteri posteriorly enlarged. Myometrium is longitudinally incised, myoma is excised following the capsule and an intracorporeal suture is performed.

implications. The principal criticisms to the technique are longer operative time and the tissue injuries, that could spread uterine cells in abdomen and also complicate the pathologist analysis.

Moreover, dissemination leads to possible peritoneal implants and parasitic myomas formation or malignancies diffusion.

Many authors proposed the use of contained bag system to reduce these complications. During laparoscopic/robotic surgery, a sterile bag is introduced through a trocar and a "pneumosac" is obtained. Contained bag system is equipped with two or three accesses that allow the introduction of the optical and the power morcellator. Fragmentation is

performed directly into the bag and small specimens are removed. Finally, the pneumosac is released, and the bag is token away.

Another possibility is to place the specimens into a bag and to perform a hand in-bag morcellation through the abdomen or the vagina, with valves exposition.

According to some Authors anyway, disadvantages are worse abdominal organ visualization when bag is insufflated, longer operative time and major costs (even if this could be a bias depending on surgeons' experience). Moreover, incidental bag rupture and indirect dissemination is possible and data on this event are missing (32).

Mechanical trauma morcellation of other organs are also

reported in literature. These complications are descripted further ahead.

Intraperitoneal dissemination and oncological outcomes

Intra-abdominal or vaginal morcellation as previously described, lead to micro or macro fragments dissemination in the peritoneal cavity.

If this fact is completely depending on morcellation technique alone is also an issue. According to some authors for example, the simple myometrial tissue manipulation during myomectomy could lead to intraabdominal seeding and lympho-vascular invasion of eventual malignant cells from undiagnosed LMS. In cytologic studies, positive washings for myometrial cells were found positive in half patients after myomectomy closures prior to morcellation. Some other studies conducted on morcellation with containment system reported a 9.2% spillage in peritoneal lavage even with intact bags (33,34). It's not probably possible to reach clear conclusions from these data, as real implication of positive washing is unknown and possible bias exist due to different bag systems used and surgeons' experience.

Even in the circumstances of benign lesions, consequences as development of endometriosis implants or parasitic myomas are described and a second surgery could be required (35). Parasitic myoma is a myoma completely separated from uterus and receiving blood supply from another structure. A systematic review by Lete et al. revealed in these patients an history of previous myomectomy or hysterectomy in 44% of cases (36). Anyway, other studies demonstrated an incidence of parasitic myomas after uncontained morcellation less than 1% (35,37). Another very rare conditions reported in literature are the peritoneal leiomyomatosis and metastatic leiomyomatosis, that are almost anecdotical situations in which myometrial tissues are found in multiple foci in the abdominal peritoneum, retroperitoneum or in distant organs. Some, but not all, cases seem to be related to previous myomas morcellement (38). Anyway, very small data on these issues are available in literature.

In the event of an occult sarcoma with unprotected morcellation and dissemination, oncological prognosis seems to be decreased. Morcellement should be considered an upstaging and, as previously seen, oncological outcomes strictly correlate with stage at diagnosis. Anyway, uterine LMS has an aggressive biological behaviour per se.

The impact of primary surgery on patients' survival has been investigated for years. In 2009, Perri et al. retrospectively collected data from women with stage I LMS, underwent previous surgery for presumed fibromas and compared the disease-free survival and overall survival between group A (total abdominal hysterectomy) and group B (any other surgery with "tumour injuries"). Kaplan-Meier curves reveals significantly better results for group A, despite further surgery and oncological therapies (39). According to Park et al. morcellation truly contributes to grave prognosis. They assessed 56 patients with stage I and II uterine LMS, 25 with and 31 without tumour morcellation. In univariate analysis, only tumour morcellation was significantly associated with poorer disease-free survival (P=0.043). Higher stage and tumour morcellation were significantly associated with poorer overall survival in multivariate analysis.

The percentage of patients with abdominal-pelvic dissemination or vaginal recurrence, was significantly greater in patients with previous morcellation (44% vs. 12.9%, P=0.032) (40).

Analogue results are reported in a retrospective study from Norway on patients with uterine sarcoma. The authors identified from the national registries 1,367 women with uterine sarcoma and compared the survival between morcellated and non-morcellated groups. Age-adjusted 10-year uterine sarcoma survival was 32.2% for women treated with morcellation compared with 57.2% for non-morcellated group. All-cause 10-year survival was 32.2% in the morcellated group and 44.1% in the non-morcellated group (25). Gao et al. reported longer 5-year recurrence-free survival and overall survival in uterine sarcoma patients who had not undergone morcellation (43.6% vs. 24.1%; 43.1% vs. 37.8%), but this did not reach statistical significance after multivariate survival analysis (41). Similarly, a retrospective study of 125 patients with LMSs revealed a 3-fold increased risk of death for those who had undergone morcellation. No significant effect was noted for those affected by uterine STUMP or other uterine sarcomas (42).

A recent retrospective publication by Gitas et al. from 3 centers in Germany on 1,683 patients treated with electronical morcellation, found 4 women (0.24%) with unexpected sarcoma (2 LMSs and 2 ESSs). They underwent laparoscopic hysterectomy because all were older than 45 years and 75% had a solitary lesion. In this study, after further treatment, all patients were alive at 5 years of follow-up (24). No unexpected malignancies were observed after laparoscopic myomectomies (probably due to bias selection as patients age).

Several recent studies have directly investigated spread

of occult LMS after morcellation within containment systems (43-47). Results are often inconsistent due to small numbers, mostly regarding just surgical outcomes of the technique. Zullo *et al.* included all randomised controlled trials comparing in-bag extracorporeal manual morcellation versus intracorporeal uncontained power morcellation during laparoscopic myomectomy in premenopausal women, finding no differences in surgical complications or postoperative diagnosis of LMS (43). In another study on 720 patients from India, no case of LMS was found and in-bag versus conventional morcellation were comparable in terms of surgery duration and blood loss (44). Steller *et al.* reported on 187 patients, with no bag-related complications (45). According to some Authors operative times seem to be slightly prolonged but this is not confirmed using modern system and power morcellator (46). Solid data on oncological safety of in-bag morcellation are missing, probably due the rarity of the event. Rationally this should guarantee no peritoneal dissemination, however, in 2018, Salman and Colleagues described a case-report of a 37 years old patient underwent laparoscopic myomectomy and in-bag morcellation for a suspected myoma histologically revealed as LMS, that recurred after only 5 months (47).

There is little evidence that performance of bilateral salpingo-oophorectomy in premenopausal women improves survival (12,48).

Morcellation injuries

As morcellations have become frequent during surgery, morcellators-related injuries increased, but true rates are difficult to define because of data inconsistency. Probably, the actual frequency is yet unknown and underestimate. Most common complications involve small and large bowel, bladder, ureteral and vascular injuries.

The most comprehensive study currently published in the literature is a systematic review by Milad *et al.* They published morcellator-related complications from 1993 to 2003. The data was taken from US FDA database. A total of 55 complications were identified: 31 injuries to the small and large bowel, 27 to large blood vessels, 3 to the kidney, 3 to the ureter, 1 to the bladder and 1 to the diaphragm. In six cases, the accidents were fatal. This study concluded that surgeon inexperience and lack of visualization due to collapse of pneumoperitoneum were the common reason for these complications (49).

In 2017, a survey of European Society of Gynaecological

Endoscopy (ESGE) members found that direct morcellator injury was a rare event. Despite the low risks, however, also the ESGE board claims that only physicians with adequate training and knowledge should perform these procedures. A total number of 221 LMS was reported among 429,777 minimally invasive surgeries (including hysteroscopic myomectomies) (50,51).

Preoperative evaluation: is possible to define a "high risk" patient?

Preoperative work up has a central role in women with myometrial masses candidate to minimally invasive surgery. Differential diagnosis between benign fibroids and sarcomas is crucial for a better counseling in order to avoid surgical complications related to an unexpected tumour (29,52-54). Although the definitive diagnosis of sarcoma is only histological, several clinical and imaging features have been identified to predict the risk of malignancy (53-55).

Clinical features

Advanced age and postmenopausal status are risk factors for all histological type of sarcoma. The median age of women at LMS diagnosis was 50–56 years (29,55,56). Below the age of 40 a sarcoma in a presumed fibroid is extremely rare. Clinical presentation of uterine sarcomas overlaps with common symptoms associated with uterine fibroids and the preoperative detection rate is low. Presenting symptoms include abnormal uterine bleeding (56%) either in the pre- or postmenopausal period, a palpable pelvic mass (54%), abdominal pain (22%), bloating or abdominal distension and urinary symptoms (52).

Rapid increase in size of a pre-existing myoma is a frequent indication for gynecological oncologist consultation, however is not typical of malignancy, occurring also in benign lesion. Both sarcoma and myoma are responsive to estrogen and gonadotropin-releasing hormone (GnRH) analogue (52,53). Malignancy should be suspected in cases of tumor growth in postmenopausal women who are not on hormone replacement therapy. No growth in 3 months may be reassuring unless caused by GnRH.

Recently, ulipristal acetate (UPA) therapy has been used worldwide for symptomatic uterine myomas demonstrating good results in reducing volume and symptoms (54). Worsening of uterine bleeding or pelvic weight despite medical treatment, were frequently reasons for the patients to choose surgery. Few cases from Italy (2), France (2),
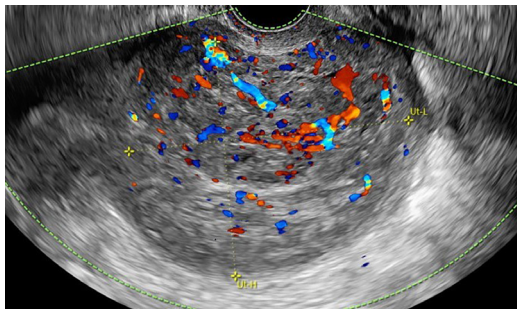
Figure 2 Transvaginal ultrasound image of single voluminous myometrial mass presenting rich vascularization and no acoustic shadowing.

Denmark (1) in which postoperative analysis revealed LMS after UPA therapy failure are reported in literature. Obviously, it is not possible to take any solid indication from these scanty data, but ineffective UPA treatment may indicate a population in which uterine LMS is more prevalent and the awareness of this possibility could avoid a delay in the diagnosis and potentially dangerous morcellation (55-58).

Imaging

Uterine sarcomas include several histological types so they may display in various morphological patterns. No imaging modality has been shown to be predictive in differentiating between myoma and sarcoma, but some features are more related to malignancy. Transvaginal ultrasound is the first-line imaging tool in evaluation of myometrial pathology (59-62). Morphological Uterus Sonographic Assessment (MUSA) statement provides a consensus on terms, definition and measurement to report myometrial sonographic features, underlying the importance of a homogenous description of the mass (63). As previously described in this number, ultrasound features of uterine sarcomas may be indistinct from those of common fibroids although they may present more frequently as solitary, large size, irregular solid mass often with anechoic area due to necrosis and irregular intralesional vascularisation (64,65). Data on ultrasound prediction of uterine sarcoma are scanty and based on small retrospective series. Recently a retrospective multicentric study describe the clinical and sonographic characteristic of 183 uterine sarcoma reviewed by a consensus meeting according to standard terminology (66). Median age was 56 years and most frequent symptom was abnormal uterine bleeding (but occurring only in almost 50% of women). Uterine sarcomas typically appear as single (80%), solid mass (79.5%), with inhomogeneous echogenicity (77.4%), sometimes with irregular cystic areas (44.6%), only 2.1% with fan shaped shadowing. The vascularisation at color Doppler is moderate or rich (67.9%) (*Figure 2*).

Magnetic resonance imaging (MRI) is an accurate imaging technique for preoperative selection in women candidate to minimally invasive surgery. T2-weighted sequences, may help evaluating lesion extent and characteristics (29,54,67). Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) values has been reported as selection criteria to stratify low or high-risk masses. Intermediate DWI and low ADC values are correlated with malignancy (68,69).

MRI findings for a suspected LMS are high signals in T2WI and abnormal signals in DWI, high signals in T1WI, undefined borders, high cell density in the mass, suggesting haemorrhage within the mass and an infiltrative growth of mass. In contrast-enhanced images, a mass that shows an early period of heterogeneous, strong contrast effect is considered to be a tumour mass. However, the haemorrhagic necrosis portion of a mass, essential for the diagnosis of LMS, is considered to be an area where contrast effects are missing (70).

The use of CT scan is not supported in evaluation of a myometrial lesion due to the diagnostic superiority of MRI. The use of positron emission tomography (PET) scanning with active metabolite usually fluorodeoxyglucose (FDG) or alphafluorobeta-estradiol (FES) has been reported in preoperative studies of suspected uterine sarcoma, but limited to small series (53,71,72).

Endometrial biopsy

As first diagnostic step an accurate ultrasound evaluation should describe also the distance between uterine mass and endometrial line leading the need of subsequent investigations. Despite imaging data, endometrial sampling is often performed in women with uterine fibroids presenting with abnormal uterine bleeding both in pre and in post menopause to exclude concomitant endometrial pathology (23,29). Preoperative endometrial biopsy found a uterine sarcoma in 3.5%, with a low predictive value reported for uterine sarcomas, as they originate in the myometrium (73). Nevertheless, endometrial sampling is recommended in preoperative work up of uterine mass involving the endometrium, especially when uterine morcellation is likely
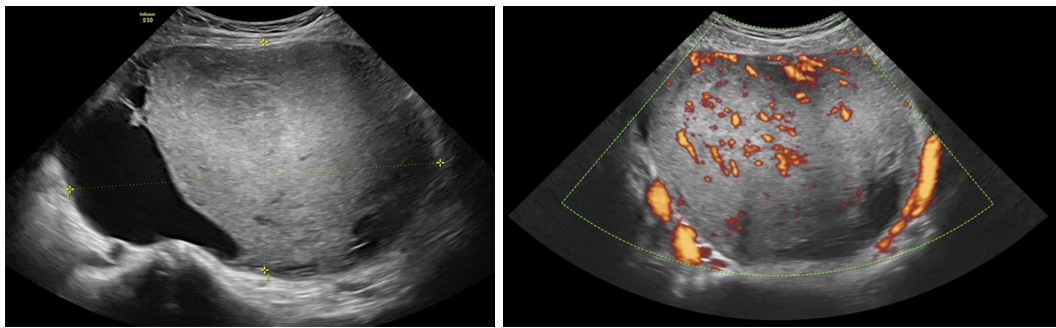
Figure 3 Single myometrial growing mass with big anechoic area, rich vascularization and minimal shadowing on ultrasound images. Post-menopausal patient.
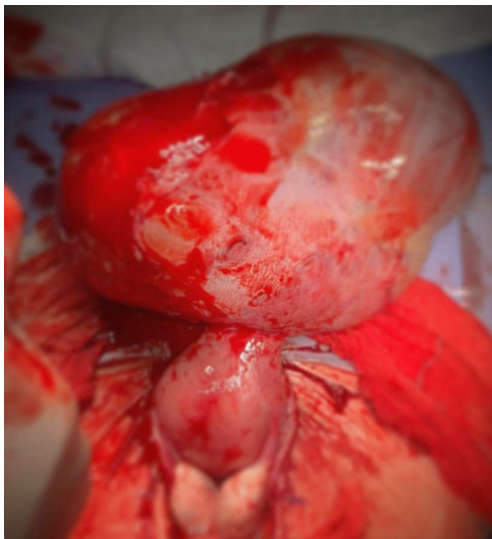

Figure 4 Laparotomic aspect of the myometrial mass previously shown at transvaginal ultrasound (*Figure 3*). Histology was myoma.

(29,52,53). The role of endometrial biopsy in asymptomatic patient with uterine fibroids is not clear (74). A good negative predictive value is reported using MRI-guided needle biopsies, no data are found on the possible spread of sarcoma cells by multiple puncturing of the sarcoma (53).

Serum markers

Serum lactate dehydrogenase (LDH) and cancer antigen (CA)-125 have been considered as markers to predict uterine sarcoma (29,75-77). Total LDH and LDH isozyme 3 may be useful in differentiating between sarcoma and myoma: an increment has been reported in prospective series (53,75). CA-125 may be increased in advanced disease, but unfortunately it has low specificity and poor positive predictive value in early stage (29,76). Considering previous cited parameters, Nagai *et al*. point out scores to predict the risk of sarcoma in a myometrial lesion (29,78,79). Predictive factors include: age over 49, high levels of LDH (>279 U/L), positive MRI and cytological findings. The accuracy, positive predictive value and negative predictive value were 93.7%, 92.3% and 94% respective. Recently an algorithm found that 7 preoperative variables on 32, were associated with increased risk of sarcoma: post-menopausal status, symptom of pressure, post-menopausal bleeding, neutrophil count (>7.5×10^9), Hb level <11.8 g/dL, endometrial biopsy positive for atypia or neoplasia, mass size >10 cm in radiological imaging (80).

In conclusion preoperative diagnosis of uterine sarcoma remains challenging but the knowledge of clinical presentation and imaging features raise the suspicious index (10,29,81,82). A transvaginal ultrasound performed by an expert sonographer is the first step in preoperative work to define the risk of malignancy of a myometrial mass. Although sonographic imaging may overlap with those of benign or degenerate fibroids, a large, solitary, solid, highly vascularised, heterogeneous myometrial tumor with necrotic changes and absence of calcifications or shadows should raise the suspicion of a sarcoma. A systematic ultrasound evaluation of the uterine cavity together with endometrial biopsy in women with abnormal uterine bleeding is recommended to rule out concomitant endometrial pathology, especially when morcellation is likely. In suspected case an MRI with contrast enhancement and serum LDH (total and isozyme 3) may help to clarify differential diagnosis. A multidisciplinary team discussion of atypical myoma cases prior to minimally invasive surgery can lead to a more appropriate management (*Figures 3,4*).

Conclusions

The percentage of women requiring surgery for presumed fibroids is extremely high in every gynaecological institution. Laparoscopic/robotic myomectomy is a feasible surgical technique for those who desire fertility-sparing treatments and if performed by well-trained surgeons, it is safe even including morcellation. The benefits of mini-invasive surgery are well recognized in literature. LMS incidence in the setting of myomectomy/hysterectomy candidates for benign conditions, seems to be lower than reported in 2014 FDA warning. A possible explanation is the selection when regarding myomectomy, of a big number of younger patients (frequently desiring pregnancy), with multiple mesenchymal lesions that show a "typical" aspect on transvaginal ultrasound. In this context, indiscriminate appeal to laparotomy is not reasonable (10,29,81,82).

Nevertheless, in the event of LMS dissemination or non-*en bloc* dissection, the oncological prognosis seems to be decreased (82), even despite further treatment and adjuvant therapies, and, as said, a preoperative differential diagnosis in myometrial lesions is still challenging.

Literature information are often controversial due bias selection of patients included in the studies with different ages, different myometrial lesions and treated with different surgical approaches.

Ultrasound evaluation in uncertain cases should be performed by an expert gynaecological Sonographer, focusing on number, volume, position, growth, vascularization, necrosis, inhomogeneity, absence of calcifications or shadowing. This diagnostic moment is fundamental not only on oncological bases, but to guide the surgical strategy too. In cases suspect for malignancies MRI could be helpful, even if limits exist because of atypical myomas (69,70).

Postmenopausal patients, especially if irregular bleeding, with single vascularized lesion are more at risk to reveal a malignant tumour and in these cases a laparotomic hysterectomy (or vaginal if feasible) is probably still to be considered. In bag morcellation could be an alternative permitting minimally invasive surgery, but clear data are missing as containment system probably cannot completely prevent cell spread. Anyway, this practice should be rationally implemented, as suggested by the 2020 FDA recommendation.

In the future we should probably define an "high risk" patient among women with myometrial pathology in order to define a restricted group of women who will benefit from avoiding morcellation: future studies should find a modality to stratify the risk of malignancy of a myometrial mass using diagnostic tools and clinical signs. Carefully inspections of morcellated specimens and washing by the pathologists are mandatory.

Patients should be deeply informed about possible surgical strategies including morcellation pros and cons (14,82,83). It could be desirable in every gynaecological unit the establishment of a "myometrial board" including gynaecological Surgeons, expert Sonographer, dedicated Radiologist and Pathologist in order to define multidisciplinary the best strategy for every patient with suspect myometrial mass.

Footnote

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