THE INTERNATIONAL SOCIETY FOR GYNECOLOGIC ENDOSCOPY

ISGE STATEMENT AND ACTIONS TAKEN FOR ASSESSING THE RISK OF LAPAROSCOPIC MORCELLATION OF OCCULTED SARCOMAS DURING HYSTERECTOMY AND MYOMECTOMY.

Uterine leiomyoma is the most common benign gynecologic neoplasm that affects women of reproductive age [1]. Surgical procedures commonly employed to treat symptomatic uterine fibroids include myomectomy or total or sub-total hysterectomy. When performed using minimally invasive techniques, these procedures reduce the risks of intraoperative and postoperative morbidity and mortality [2]; although, in order to remove these bulky lesions from the abdominal cavity through laparoscopic ports it has to be used a laparoscopic power morcellator, a device with rapidly spinning blades to cut the uterine tissue into fragments so that it can be removed through a small incision [3].

The US Food and Drug Administration (FDA) issued a safety communication [4] on 17 April urging doctors not to use laparoscopic power morcellation for hysterectomies or removal of uterine fibroids over concerns that the technique may spread occult uterine sarcomas beyond the uterus.
In fact, a new FDA analysis estimated that about 1 in 350 women having a hysterectomy or myomectomy for fibroids has an undetected uterine sarcoma, although American Cancer Society estimates that only about 1600 of the 52,000 cases of uterine cancer newly diagnosed each year turn out to be uterine sarcomas. According to some studies, FDA warns that there is a risk that the device's rapidly spinning blades will disperse tumor tissue within the pelvis and abdomen, disseminating the disease and greatly reducing the woman's chances of survival [5]. In addition, samples obtained via morcellation may be more difficult to evaluate, complicating diagnosis and staging [4].

The ACOG, ESGE and AAGL statements have and will come in response to the FDA safety notice discouraging the use of laparoscopic power morcellation in hysterectomy or myomectomy [6-8].
Therefore, patients being considered for minimally invasive surgery performed by laparoscopic or robotic techniques who might require intracorporeal morcellation should be appropriately evaluated for the possibility of coexisting uterine malignancy.
According to the above FDA safety communication, Seidman et al. observed that unexpected diagnoses of leiomyoma variants or atypical and malignant smooth muscle tumors occurred in 1.2% of cases using power morcellation for uterine masses clinically presumed to be "fibroids".

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The only prospective study assessing the risk of morcellating a sarcoma in case of laparoscopic myomectomy has found 1 case out of 2050 procedures (0.04%) [9].

It is evident that it is important to conduct a thorough patient evaluation before choosing the type and route of operation, using appropriate measures to diagnose a malignancy before surgery [10].

The ACOG statement, issued May 9 in conjunction with its special report, "Power Morcellation and Occult Malignancy in Gynecologic Surgery," presented a recent review and analysis of the scientific evidence regarding power morcellation and undetected malignancy in gynecologic surgery. It is recommended that physicians should consider risk factors, such as patient age, menopausal status, uterine size, and presence of rapid uterine growth, as well as a history of treatments such as tamoxifen or pelvic radiation and hereditary conditions, such as Lynch syndrome or hereditary leiomyomatosis and renal cell cancer [6].

Also biochemical evaluations may aid in the diagnosis of uterine leiomyosarcoma. Some studies focused on the correlation between LDH levels and especially its isoenzyme 3 and the pathological diagnosis of LMS [11], revealing that patients with LMS often have somewhat increased serum LDH levels [12]. For instance, Goto et. al observed an abnormally increased level of total LDH and LDH3 in all patients with LMS (LDH3, sensitivity and specificity 90% and 92.3%) [11].

Although preoperative clinical evaluation could improve the detection of cancer, it has some limitations, confirming the need for further research to develop reliable tools for preoperative diagnosis of an occult malignancy.

To date, there is no single correct approach to evaluate uterine leiomyomas. Various options are available and differ considerably in cost and inconvenience to the woman [13].

The vast majority of LMs are discovered and evaluated via sonography, using the trans-abdominal and transvaginal routes, due to its accessibility and relatively low cost. Ultrasonography allows correct assessment of the number, volume, location, and vascularity of the LM and in skilled hands can detect fibroids as small as 5 mm on transvaginal ultrasound [1, 14].
In the last decades, several studies focused their attention on the detection of sonographic parameters, which could be used in distinguishing between a benign and a malignant uterine smooth muscle tumor [15-18].
Exacoustos et al. proposed a subjective semi quantitative assessment (vascular score) of the blood flow examined with directional PDI (Power Doppler Imaging), which was similar to that proposed for adnexal masses according to previously published reports and confirmed by the IOTA Consensus Group, revealing that the increased central and peripheral vascularity

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had a sensitivity, specificity, and positive predictive value of 100%, 86%, and 19% in the diagnosis of LMS; volume of the mass was also estimated using the following formula: V = length x width x diameter x 0.52 and their results suggested that LMS were significantly larger than the other tumors [19].

Because of the above clinical and ultrasonographic findings, physicians could decide to further investigate the suspected lesion before surgical intervention.
In fact, differential diagnosis between LM and LMS is becoming increasingly important because of the availability of more conservative treatment modalities, such as uterine artery embolization (UAE) and MR guided focused ultrasound (MRgFUS) [1].

MRI provides a better image in delineating the exact location and characteristic of the leiomyomas but should be considered only for women in whom the nature of the pelvic mass is uncertain after level II pelvic ultrasound and clinical assessment. In fact, MRI is far more expensive and less accessible than ultrasound, and it is therefore impractical to use as a method of investigation in all cases [1, 16].
The differentiation from sarcoma is made by the total necrosis of the tumor and the presence of a peripheral rim, which corresponds to the obstructed veins showing low signal intensity on T2 and high signal intensity on T1WI [20].
Tanaka et al. reported that the highest accuracy in diagnosing non benign smooth muscle tumors of the uterus is expected when more than 50% of the tumor shows high signal on T2WI, any small area of high signal is seen within the tumor on T1WI, and there are some unenhanced pocket-like areas after administration of contrast materials [21].
Goto et al. compared conventional MRI findings along with post-enhancement behavior (dynamic MRI) or degenerated leiomyomas (DLM) and leiomyosarcomas (LMS), revealing a specificity, accuracy and PPV of 96.9, 97.1, and 71.4% for MRI, and 87.5%, 90.5% and 71.4% for dynamic MRI. Both sensitivity and NPV were 100%. In particular, they highlighted the importance of obtaining the dynamic images at 40-80 s after Gadolinium administration because no enhancement was observed in the early phase at nearly 60 s in DLM whereas LMS rapidly enhanced at 20-90 s [11].
However, other studies did not confirm these results [22], revealing that differentiation between benign and malignant myometrial tumors may be difficult if only based on the signal intensity of conventional non-enhanced and post-contrast MR sequences.
In a recent study Sato et al. proposed to introduce DWI imaging and the corresponding ADC values in the evaluation of these tumors. Diffusion-weighted imaging (DWI) is a relatively recent technique based on the diffusion motion of water molecules and the image reflects the diffusion of hydrogen molecules; high-intensity signal is evident in places with reduced diffusion. DWI can also provide quantitative measurement of apparent diffusion coefficient (ADC) values, these are considered to be influenced by the nuclear-to-cytoplasm ratio and cellular density in solid tissues [23]. Decreased ADC values of malignant tumors compared

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with normal tissues or benign lesions have been previously reported for various organs [24, 25, 26].
Sato et al affirmed that cases with low signal intensity on DWI may be regarded as uterine leiomyoma, while intermediate to high signal intensity may indicate uterine leiomyosarcoma. For this reason, in patients with parenchymal areas of intermediate to high signal intensity, ADC values was evaluated, revealing that the mean ADC value for the leiomyosarcoma lesions was significantly lower than that of the leiomyoma nodules [23]. They concluded that a combination of signal intensity on DWI and ADC could be used to further narrow the diagnosis and classify patients into two groups (low risk group and high-risk group).
Another study observed that the combination of ADC and TCR (tumor–myometrium contrast ratio) is significantly better compared to the ADC value or TCR alone in differentiating uterine sarcomas and leiomyomas, with no overlap (sensitivity 100%, specificity 100%) [26].

MR spectroscopy (MRS) MRS imaging provides metabolic information specific to its tissue type along a 2D or 3D spectrum based on the chemical shift phenomenon. In cancer, the choline metabolite profile is characterized by an elevation of phosphocholine and total choline containing compounds [27]; this elevation is increasingly used as an endogenous biomarker of cancer.
Takeuchi et al showed in 14 malignant cases of 32 myometrial lesions that the tCho concentration in malignant tumors was significantly higher than that in benign lesions, although these tumors were mixed endometrial and myometrial lesions.
They suggest that a combined diagnosis using T2-WI and tCho concentration may help for differentiation [28].
Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with pharmacokinetic analysis is a minimally invasive imaging method that measures changes in tissue microvascular properties and has been widely used in research or early phase clinical trial settings to provide assessment of tumor therapeutic response, as many cancer drugs affect tumor vasculature directly or indirectly. The quantitative approach for DCE-MRI data analysis using pharmacokinetic models allows extraction and mapping of quantitative parameters of tumor biology *in vivo* [29].
These new techniques may provide clues to optimize the treatment of patients with malignant diseases of the uterus but major problem of both intra-abdominal MRS and DCE-MRI is motion, which is largely due to respiration and intestinal peristalsis [30].

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Although all these newly developed techniques are by now easily available, an effort should be made to focus on how they are applicable.
In fact, it is impractical to use MRI of the uterine lesion as a method of investigation in all cases.
Therefore, a preoperative algorithm should be proposed in order to avoid the occurrence of unexpected LMS diagnosed on the pathological post-operative examination; this should be done starting from clinical and ultrasonographic findings suspected of LMS and only in highly suspected cases by a pelvic MRI examination.

CLINICAL RISK CRITERIA, also according to the above ACOG report, are:

- Age: > 35 years (women younger than age 35 years seem to have the lowest incidence.
  The mean age of the patients with LMS was significantly higher than that of patients with LM. The highest incidence of uterine sarcoma is in women over age 65).
- Postmenopausal status.
- Uterine size.
- Rapid uterine growth.
- Certain treatment (tamoxifene or pelvic radiation).
- Hereditary conditions (Lynch syndrome or hereditary leiomyomatosis and renal cell cancer).

Symptoms:

- Hyper-poli-menorrhea.
- Abnormal genital bleeding.
- Dysmenorrhea.
- Palpable abdominal mass.
- Lower abdominal pain.
- Lumbago.
- Pressure symptoms (pollakiuria, dysuria, bowel symptoms).

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All patients have to undergo:

- LDH and isoenzyme 3[10],
- Pap smear.
- Hysteroscopy with biopsy in any case of uterine bleeding plus Ca 125

ULTRASOUND PROTOCOL AND US CRITERIA

Patients are examined by transvaginal and/or trans-abdominal sonography with Gray-scale imaging, color and directional PDI, using a convex trans-abdominal 2.5–5.5-MHz transducer and a 5.5–8.5-MHz vaginal probe. Number of any uterine masses is reported and the longitudinal, transverse, and anterior-posterior diameters are measured. Volume of the mass is estimated using the following formula: V = length x width x diameter x 0.52.
Gray-scale imaging is also used to evaluate absence or presence of calcifications, presence of cystic necrosis or hemorrhage and to describe the echo pattern of the lesion (homogeneous or inhomogeneous).
A subjective, semi quantitative assessment of the amount of blood flow within the examined lesion
is made with power Doppler images (color score), describing the vascularity of the central and peripheral region of the lesion as marked, moderate, mild, or not appreciable.
A score of 1 is given when no blood flow is found
A score of 2 is given when only minimal flow was detected
A score of 3 is given when moderate flow is present;
A score of 4 is given when numerous vessels are present.
The score for both central and peripheral region are combined with a maximum vascular score of 8 [21].

II levels ultrasound criteria:

- echo pattern (homogeneous or inhomogeneous with mixed echogenic and poor echogenic parts).
- necrotic, cystic, hemorrhagic changes.
- single lesion.
- presence or absence of central vascularization.
- distribution of tumoral vascularization: a high vascularity score (≥ 7).
- size: diameter > 8 cm.
- Presence or absence of calcifications.

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Patients evaluated clinically, with blood test assays and US examination and considered "Low risk" will undergo directly to surgery.

The other patients will be selected for MRI evaluation.

MRI PROTOCOL AND IMAGES ANALYSIS

MRI provides a better image in delineating the exact location and characteristic of the leiomyomas but should be considered only for women in whom the nature of the pelvic mass is uncertain after II level pelvic ultrasound and clinical assessment. In fact, MRI is far more expensive and less accessible than ultrasound, and it is therefore impractical to use as a method of investigation in all cases.
All MRI examinations are performed on a 1.5 o 3 T unit. T1, T2-weighted and DWI images are acquired; ADC maps are derived from the DWI images. Conventional MR images are reviewed regarding the following items; size of the tumor (the greatest diameter), signal intensity (SI) of the tumor on T1- and T2-weighted images, the tumor margin, endometrial involvement, intratumoral hemorrhage and unenhanced areas in the tumor. Tumor-myometrium contrast ratio (TCR) is also evaluated.
The SI on DW images is judged as high when it shows equal or higher signal than that of the endometrium and on the basis of this finding, patients are included in the DWI intermediate- or high-intensity group and in the DWI low intensity group; DWI intensity is compared to the corresponding ADC values.
A dynamic contrast-enhanced MRI (DCE-MRI) study with pharmacokinetic analysis is also performed.
Correlation between conventional MRI findings (T1 and T2-weighted images), DWI intensity and corresponding ADC values, and dynamic contrast-enhanced MRI (DCE-MRI) with pharmacokinetic analysis study is evaluated in order to exclude or suspect the presence of a leiomyosarcoma.

However, we only consider FT (cut off: > 39.5 mL.min−1.100 mL−1), V_b (13.4%) and rAUC (>0.28) for predicting malignancy, as previously reported [21].

Only the patients who are considered "low risk" after MRI imaging will undergo MIS involving an intra-abdominal morcellation, unless the morcellation can be carried out in a contained bag.

Proper Informed Consensus has to be given to the patient explaining the potential risk of sarcoma morcellation and upstaging and the difficulties we are encountering to give an actual risk (given the heterogeneity of papers that leads to inadequate or confounding data). A risk sharing process has to be undertaken. According to the AAGL Statement, these risks should be weighed against the benefits of MIS. The risks of laparotomy should be noted, including wound infections, blood transfusions, longer recovery and the potential for life threatening complications such as venous thrombotic disease (31)

Histological evaluation after myomectomy, hysterectomy or supra cervical hysterectomy will be recorded and computed for statistics analysis.

ISGE has designed a prospective multicenter trial ON RISK OF UNASPECTED LEIOMYOSARCOMA DURING LAPAROSCOPIC MYOMECTOMY OR HYSTERECTOMY.

The study will involve at least 4 University Centers in Italy, 1 in Belgium, 1 in the United States.
Other Centers have requested to apply and are under evaluation.

Given that the results of this trial will never be available in the next recent times and no one is negating the benefits of MIS for the patients (Level 1) (31),

It is in the meantime **recommended to perform Total Laparoscopic Hysterectomies instead of Supracervical Hysterectomies, morcellating the specimen through the vagina, possibly in a bag.**

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There are not EBM data showing that supracervical hysterectomy is better than total hysterectomy (Cochrane Mata-analysis, 2010) [32].
All the patients have to have pap-smear evaluation, at least 2nd Level US examination, LDH assessment, hysteroscopy with endometrial biopsy in case of AUB.

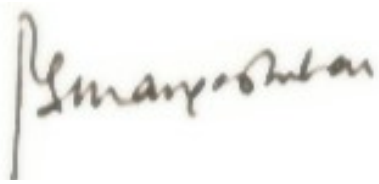
It has to be given preference to Supracervical Hysterectomy only in case of POP repair after having been evaluated the endometrium of the patient and at least performed LDH assessment and 2nd Level US, and of course pap smear.

In case of myomectomy, after a 2nd level US, LDH and its iso-enzyme 3 assessment, MRI diffusion weighted Imaging and ADC values in suspected myomas,

laparoscopic morcellation could be performed in low risk patients.

Techniques for single or multiport laparoscopic morcellament in contained new designed sturdy bags have already been described by ISGE Board Members and their safety will be studied.

ISGE President Dr. P. Mangeshikar



ISGE Medical Director Dr. O. Sizzi

ISGE Task Force: *Ornella Sizzi, Alfonso Rossetti, Bruno van Herendael, Lucia Manganaro, Chuck Miller, Matteo Saldari, Giuseppe Florio, Alessandro Loddo, Stefano Bettocchi*

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