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***Management of Uterine Fibroids and Sarcomas: the Palermo Position Paper***

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Short Title: Management of Uterine Fibroids and Sarcomas

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**Abstract**

**Background**

Uterine fibroids are benign monoclonal tumors originating from the smooth muscle cells of the myometrium, constituting the most prevalent pathology within the female genital tract. Uterine sarcomas, although rare, still represent a diagnostic challenge and should be managed in centers with adequate expertise in gynecological oncology.

**Objectives**

This article is aimed to summarize and discuss cutting-edge elements about the diagnosis and management of uterine fibroids and sarcomas.

**Methods**

This paper is a report of the lectures presented in an expert meeting about uterine fibroids and sarcomas, held in Palermo in February 2023.

**Outcome**

Overall, the combination of novel molecular pathways may help to combine biomarkers and expert ultrasound for the differential diagnosis of uterine fibroids and sarcomas. On the one hand, molecular, and cellular maps of uterine fibroids and matched myometrium may enhance our understanding of tumor development compared to histologic analysis and whole tissue transcriptomics and support the development of minimally invasive treatment strategies; on the other hand, ultrasound imaging allows in most of the cases a proper mapping the fibroids and to differentiate between benign and malignant lesions, which needs appropriate management.

**Conclusions and Outlook**

The choice of uterine fibroid management, including pharmacological approaches, surgical treatment, or other strategies such as High-Intensity Focused Ultrasound (HIFU), should be carefully considered taking into account the characteristics of the patient and reproductive prognosis.

**Introduction**

This is a brief report of the lectures presented in an expert meeting about uterine fibroids (known also as leiomyomas or myomas) and (leiomyo)sarcomas, held in Palermo in February 2023. Each section reflects the content of one lecture presented at the meeting; each one of the authors revised the text for amendments and gave final approval for its publication.

**Somatic mutation landscape in fibroids**

The first exact genetic driver change in fibroids was described in 1995 when – guided by cytogenetic analyses – Schoenmaker et al. scrutinized recurring translocations resulting in overexpression of the oncogenic transcription factor HMGA2 [1]. The availability of high-throughput sequencing 15 years later allowed systematic nucleotide-level analyses and has resulted in the identification of a small number of mutually exclusively mutated fibroid driver genes. In 2011, specific MED12 gene mutations, in particular in codon 44, were discovered in a large proportion of uterine fibroids [2]. In subsequent studies, the proportion of mutated tumors has varied, likely due to sample selection bias as MED12 fibroids tend to be smallish in size. In an extensive sample set of 2263 tumors exceeding 1 cm in diameter, 77% of fibroids carried a MED12 mutation [3]. These mutations disrupt the interaction between MED12 and CDK8 [4] and cause tumorigenic changes in the landscape of the regulatory genome, and transcriptome [3,5]. More rarely, mutations occur in fumarate hydratase [6,7], as well as genes encoding proteins of the SRCAP complex [3] and neddylation genes [8]. A deletion at the COL4A5/COL4A6 locus, resembling one observed in germline of patients with Alport syndrome with leiomyomatosis, drives uterine fibroids by upregulation of near-by growth factor gene IRS4 [9]. Large chromosomal imbalances contribute to genesis of fibroids, 7q deletions targeting at least CUX1 transcription factor being the most frequent event [1,9]. Moreover, other genetic aberrations have been reported in fibroids, albeit as rare events. The driver genes carry important clues to pathogenesis of fibroids. Most lesions arise from aberrant chromatin function, and particular areas poised to change their transcriptional status are commonly affected [3]. Myometrium is highly responsive to external cues such as hormonal and environmental factors associated with menstrual cycle and pregnancy, and poised chromatin can be envisioned to bear exceptional importance in the homeostasis of myometrial cells. Such plasticity gone awry could be a powerful facilitator of fibroid development, perhaps explaining the frequent occurrence of the condition.

**What does single-cell transcriptomics tell us about fibroids?**

The clinical symptoms and morphological/histological signs of rare uterine sarcomas overlap with those of uterine fibroids. This convergence renders the discrimination between malignant and benign myometrial tumors a challenging aspect of the diagnostic process [10].

Omics-based approaches that categorize uterine fibroids and sarcomas based on their genomic, epigenomic, and transcriptomic profiles have prompted the development of a new molecular classification system [11–13]. Unfortunately, most studies involve the evaluation of whole tissue samples and inherent heterogeneity within and between tumors limits any mechanistic and therapeutic insight [14,15]. Innovative technologies such as single-cell RNA sequencing, single-cell proteomics, and spatial transcriptomics have supported the creation of distinctive identities for each cell type as well as the detection of novel cell types and the identification of their functions in specific areas within organs [16,17]. Overall, these advancements provide a better understanding of the cellular and molecular heterogeneity of various cell types.

Recently, single-cell transcriptomics and proteomics allowed to create a multi-omic profile of uterine fibroids and matched myometrium to understand the complex molecular processes underpinning tumorigenesis [10]: cell integration through single-cell myometrium anchors identified five biologically relevant cell clusters (supported by 52,909 cells), which included smooth muscle, endothelial, fibroblast, and perivascular cells; spatial transcriptomics demonstrated specific relationships between cells and their relative locations within the tissue. Interestingly, while uterine fibroids and matched myometrium possessed broad similarities in cellular composition, they displayed differential gene expression compared to each studied cell population. These data also provided evidence for the dysregulation of MAPK, PI3K-Akt, and proteoglycan pathways in smooth muscle, endothelial, fibroblast, and perivascular cell types.

Overall, molecular, and cellular maps of uterine fibroids and matched myometrium may enhance our understanding of tumor development compared to histologic analysis and whole tissue transcriptomics and support the development of minimally invasive treatment strategies.

**Liquid biopsy biomarkers in uterine sarcoma**

A liquid biopsy is easy, less invasive, and can better captures tumor heterogeneity as compared to one single tissue biopsy [18]. Blood-based liquid biopsies can focus on circulating tumor cells (CTC), cell-free circulating tumor DNA (ctDNA), microRNA (miRNA), non-coding RNA (ncRNA), circulating immune cells, extracellular vesicles and proteins. An overview on liquid biopsies in uterine sarcoma has recently been published [19]. Currently, the blood-based liquid biomarkers that can be employed in clinical practice are lactate dehydrogenase (LDH), cancer-antigen 125 (CA-125) and neutrophil-to-lymphocyte ratio (NLR).

LDH as a final step in anaerobic glycolysis, is upregulated through oncogenes (biological phenomenon known as Warburg effect). LDH levels can also be increased in non-cancerous conditions, such as tissue injury, necrosis, hypoxia, hemolysis, myocardial infarction and hepatitis [20]. Six out of the eight retrospective studies report an increased level of LDH in uterine sarcoma. There is a substantial overlap in LDH levels between uterine sarcomas and degenerated or atypical uterine fibroids [21].

CA-125 is a known biomarker for ovarian cancer, but CA-125 levels are also raised in benign pathology including endometriosis or infection, and during pregnancy. Only three out of six retrospective studies show a significant increase in CA-125 levels in uterine sarcoma cases. CA-125 levels in the early stages of leiomyosarcoma overlap with those in uterine fibroids [21,22].

The interaction between cancer cells and immune cells (immunoediting) [23] is reflected by the NLR, which mirrors the balance between immunosuppression and immune stimulation. A high NLR has been associated with adverse overall survival [24]. So far, three retrospective studies have shown the potential of NLR in distinguishing uterine sarcoma from uterine fibroids [21]-

Although, based on retrospective studies, LDH and NLR are potentially useful markers in the diagnosis of a uterine sarcoma, there is a strong need for prospective studies on liquid biopsy biomarkers validating their role in clinical practice.

**Uterine fibroids and sarcomas: diagnosis and classification**

Three distinct categories of myometrial lesions exist, encompassing benign entities such as fibroids and adenomyosis, alongside malignant sarcomas. The correct differentiation between fibroids and sarcomas is crucial for the patients' management and prognosis.

Fibroids are very common (> 50%), benign and may either be managed expectantly or, in case of symptoms, medically or by (minimally invasive) surgery, minimising surgical, cosmetic and psychological morbidity. Uterine sarcomas are rare (5/10000), but highly malignant requiring prompt and radical surgery, taking care to avoid any spilling of cancer cells into the abdominal cavity [25].

On ultrasonography fibroids are well-defined, usually round-shaped lesions [26]. Often multiple fibroids are present. The location within/adjacent to the myometrium is reported according to the FIGO (International Federation of Gynecology and Obstetrics) classification [27]: from a totally intracavitary FIGO type 0 lesion to a pedunculated subserous FIGO type 7 fibroid (Fig. 1). The number of lesions, their size (measured in three perpendicular planes, their location (anterior, posterior, fundus, left, right) and the proximity of the uterine artery should be recorded. A precise mapping of the fibroid is important for optimal follow-up or to decide on the surgical approach.

On ultrasound scan, the echogenicity of a well-defined myometrial lesion may be uniform (hypoechogenic, isoechogenic or hyperechogenic as compared to the adjacent myometrium) or non-uniform (heterogenous, with echogenic areas or calcifications, or with (irregular) anechoic (cystic) areas). Often shadowing is present from the edge of the lesion (edge shadow) or behind the lesion (internal shadows). Internal shadows may be subtle, fan shaped or strong and obliterating any retrolesional structure.

At Color/Power Doppler examination, fibroids typically present circumferential vascularisation. Internal vascularisation may also be present and varies from absent/low grade to extensive. Internal vascularisation is correlated with the fibroid's growth potential [28]. As opposed to fibroids, in adenomyosis, the lesion is often ill-defined and the vascular pattern is typically translesional, with vessels crossing the adenomyotic area.

Uterine sarcomas are often large or fast-growing, solitary, oval shaped or lobular lesions with inhomogeneous echogenicity [25,29,30]. Calcifications and fan-shaped shadowing is uncommon. Signs of central necrosis with formation of irregular cystic areas are highly suspicious for a malignant myometrial lesion. At Color/Power Doppler examination, sarcomas are often – at least partly - highly vascularised with an irregular/chaotic vascular pattern (Fig. 2 and Tab. 1).

**Diagnosis of malignant disease prior to surgery by imaging**

A standardized sonographic approach to myometrial lesions should be always performed according to MUSA (Morphological Uterus Sonographic Assessment) criteria [26]. Although there is an excellent intra- and inter-rater agreement in the sonographic assessment of uterine fibroids [31], the ultrasound appearance of uterine fibroids can vary significantly due to the wide range of histologic variants in particular in cases of degenerated fibroids. This unusual appearance can simulate the presence of sarcoma. As a matter of fact, differential diagnosis between uterine fibroids and sarcomas can be particularly challenging [32,33]. Ultrasonographic suspicion features could be of particular importance in these cases such as the presence of large tumors, non-homogeneous echogenicity, internal irregular cystic areas, rich and intralesional vascularization and absence of shadowing or calcifications [30]. Uterine fibroids may resemble uterine sarcomas in some cases. In a recent published study, Cabezas et al. [34] conclude that approximately 5% of benign uterine fibroids may exhibit sonographic suspicion of sarcoma based on Ludovisi et al. study [30]. Although it is a small percentage, it is not negligible.

Magnetic resonance (MR) imaging is also a useful diagnostic tool [35], which could be of particular importance in preoperative mapping when the uterus extends beyond the pelvis and the use of standard ultrasonography is limited or when the ultrasonographic appearance is suspect based on Ludovisi's criteria. The appearance of sarcomas is variable including large heterogeneously enhancing mass, with central T2 hyperintensity indicative of necrosis, but also homogeneously low-signal mass, similar to a fibroid [35]. Moreover, also the 18-fluoro-d-glucose positron emission tomography (18FDG PET) has been attempted as a diagnostic tool and could eventually be useful; however, current data are limited [36].

Based on a consensus conference on the management of uterine sarcomas published on behalf of SIGO (Italian Society of Obstetrics and Gynecology) [37] we suggest, although no radiological criteria to differentiate atypical fibroids from uterine sarcomas are definitively established, that a myometrial lesion with "suspicious" signs for sarcoma at ultrasound requires further diagnostics.

**Pharmacological treatments of uterine fibroids**

Medical management primarily aims to reduce heavy menstrual bleeding (HMB) and pain (dysmenorrhea, chronic pelvic pain) due to uterine fibroids (Tab. 2). First-line symptomatic medical management is based on the use of non-hormonal medical options such as non-steroidal anti-inflammatory agents (NSAIDs) and tranexamic acid due to their general availability, low cost, and limited adverse effects. In general, long-term hormonal medical treatment aims to improve symptoms due to uterine fibroids in patients without immediate desire for pregnancy (as these drugs interfere with ovulation) or in patients without a desire for pregnancy wishing to avoid or postpone surgical treatment [38].

Combined estrogen-progesterone oral contraceptives (COCs) and progestins are hormonal options that can be used cyclically or continuously in the form of pills, vaginal rings, or transdermal patches. These drugs act by keeping the endometrium thin, thereby decreasing the amount of endometrial shedding during the menstrual cycle. Although these drugs are well tolerated, women should be informed of treatment-related potential adverse effects, such as nausea, headache, and irregular bleeding [39]. The levonorgestrel-releasing intrauterine device (LNG-IUD) causes amenorrhea and/or improvement of menorrhagia and anemia in up to 50%-60% of patients with HMB due to uterine fibroids at 6-12 months [40].

GnRH agonists have traditionally been used to induce amenorrhea in most women (> 98%) with uterine fibroids, also leading to a 35%-65% decrease in fibroid size within 3 months of treatment initiation. GnRH agonists have mainly been used as presurgical therapy for uterine fibroids. In fact, their use has been shown to improve both preoperative and postoperative hemoglobin levels, reduce operative time, and shorten the duration of hospital stay [41]. The main drawback of GnRH treatment is the induced hypo-estrogenic state, which can cause menopause-related side effects and lead to a loss of bone mineral density (BMD). These adverse effects can be reduced by adding appropriate add-back therapy (ABT), especially for treatments with GnRH agonists lasting longer than 6 months [42]. Ulipristal acetate (UPA; 5 mg/day; only approved in Europe) is a selective progesterone receptor modulator (SPRM), which has been initially approved for the pretreatment therapy of uterine fibroids [43]. UPA acts at the level of peripheral progesterone receptors by inducing apoptosis, inhibiting cellular proliferation of the fibroid, and thinning the endometrial lining. UPA has been associated with 25%-50% fibroid shrinkage and greater than 90% uterine bleeding control in randomized control (PEARL and VENUS) trials. However, this drug faced criticism due to its temporary suspension in 2017 and 2020 after an apparent association with liver injury. Currently, the European Medicines Agency (EMA) has restricted UPA use as long-

term intermittent treatment in women who were not eligible for surgery. Before, during, and after cessation of this therapy, liver function needs to be evaluated monthly [44].
GnRH antagonists represent a relatively new alternative for the treatment of moderate to severe symptoms of uterine fibroids. The advantages of these drugs are an oral route of administration, the avoidance of the initial flare occurring with GnRH agonists, and a lower induced hypo-estrogenic impact. In phase III clinical trials, elagolix (Elaris Trials), linzagolix (Primrose trials), and relugolix (Liberty trials) have demonstrated excellent control of fibroid-related HMB, while also preserving BMD in long-term regimens [45–47]. Recently, linzagolix has become the first GnRH antagonist approved by EMA at multiple doses (100-200 mg) with or without ABT for treating moderate to severe symptoms related to uterine fibroids. While at the lower dose associated with ABT this drug may be adopted for controlling symptoms in a long-term regimen, its short-term use (<6 months) at the higher dose without ABT could be indicated in women for whom ABT is not recommended or in clinical situations when a reduction of uterine and fibroid volume is primarily desired [47]. If, until now, the objective of studies on current pharmacological strategies for uterine fibroids has been to obtain only long-term symptom relief, the possibility of using GnRH antagonists with multiple dosing schedules with or without ABT opens up multiple clinical evaluations, including short-term treatments to achieve a rapid volumetric reduction of fibroids. This possibility also presents an opportunity to evaluate medical strategies for improving fertility outcomes, both for spontaneous conception and assisted reproduction, in patients with uterine fibroids that may impair implantation.

**High frequency ablation intervention and non-surgical approaches**
The intramural fibroids are a dilemma in the treatment of fibroids. In particular, intramural (FIGO type 3, 4, and 5, as FIGO type 2-5) fibroids are difficult to remove. With a hysteroscope, these fibroids cannot be reached and a laparoscopic procedure will cause a uterine scar with a recovery time of several weeks [48].
Nowadays, women opt more and more for a minimal invasive treatment while retaining their uterus. Magnetic resonance-guided-guided high-intensity focused ultrasound (MRg-HIFU) treatment, uterine artery embolization (UAE) and radiofrequency (RF) ablation technology are examples of non-surgical minimally invasive treatments. UAE has been evaluated in large RCT's with long follow-up. The Emmy trial compared UAE with hysterectomy up to 10 years of follow up [49]. In about two thirds of UAE-treated patients with symptomatic uterine fibroids a hysterectomy could be avoided. Health-related quality of life after uterine artery embolization or hysterectomy remained comparably stable. The FEMME trial compared UAE with laparoscopic myomectomy [50]. Among women with symptomatic uterine fibroids, myomectomy resulted in greater improvement in quality of life than UAE. The differences in costs and quality-adjusted life-years were very small. Future research should involve women who are desiring pregnancy.
The HIFU technology has several implementations: MR-HIFU and ultrasound-guided HIFU. A systematic review of this technology for treating fibroids stated that HIFU could be an effective and safe treatment option for patients affected. However, one of its side effects, skin burns, requires further research and discussion. Additional studies involving more randomized controlled trials are warranted [51].
Last decade, high frequency ablation has been implemented as a minimally invasive technology to treat fibroids [52,53]. The ablation technology consists of radio frequent current. Different approaches have been described: laparoscopic, percutaneous, transvaginal and transcervical. All procedures are ultrasound-guided. All these techniques have been evaluated in a systematic review [54], showing a consistent improvement of health-related quality of life and a reduction of symptoms after all RF ablation treatments. The transcervical RF ablation has been evaluated retrospectively showing high satisfaction; however, there was 24% of hysteroscopic reintervention rate to remove the ablated fibroid tissue from the uterine cavity, after which the whole fibroid was removed [55].
Reproduction after the HIFU, UAE and RF fibroid ablation has been evaluated in a systematic review [56]. The pooled estimate of pregnancies was 17.31% to 44.52% after UAE, 18.69% to 78.53% after HIFU, and 2.09% to 7.63% after RF ablation. These minimally invasive uterine-sparing treatment options for fibroids are a good approach for women with a future desire for pregnancy, with comparable reproductive outcomes among the different techniques. More research is needed to draw strong conclusions.
However, these three minimally invasive treatments have not been compared to each other in prospective or randomized trials. To compare results, it would be nice to have uniform core outcome parameters of fibroid treatment, so future studies would add more comparable outcomes, aiming to compare the satisfaction, reproduction outcome, effectiveness, and cost-effectiveness of these three minimally invasive techniques.

**Management of uterine fibroids during pregnancy**

Uterine fibroids may increase the risk of adverse maternal–fetal outcomes, including miscarriage, preterm delivery, fetal growth restriction, fetal malpresentation, placental complications, premature rupture of membranes [57,58]. Furthermore, uterine fibroids are known to be associated with high risk of complications during labor and delivery, such as uterine atony, abnormalities of uterine contractile activity, and postpartum haemorrhage [59]. In addition, under the influence of hormonal changes of pregnancy, uterine fibroids can undergo colliquation and cause pelvic pain that often responds poorly to pharmacological approaches available for use during pregnancy [60]. Overall, the rate of uterine fibroid growth during pregnancy is still unclear: on the one hand, the increase of pregnancy-related hormones does not always cause an increase in the size of uterine fibroids [61]; on the other hand, a systematic review highlighted that uterine fibroids seem to be subject to a non-linear trend of modifications during pregnancy and puerperium, with a systematic enlargement during the first trimester of pregnancy, while inconsistent evidence is available about the changes of uterine fibroids during second and third trimesters [62]. From the clinical point of view, submucosal fibroids as well as large intramural fibroids may have the most significant impact on pregnancy, due to mass-effect, compression of the intrauterine space and, in case of fibroids placed below the placenta, they may be associated with reduced blood supply to the placental-fetal unit and cause fetal growth restriction as well as increased risk of placental abnormalities and abruption [63]. Conversely, subserosal fibroids, especially small ones, does not affect the uterine cavity environment and play only a minimal effect on pregnancy course. Nevertheless, large subserosal and intramural fibroids may both cause compression of the adjacent organs such as ureters (leading to hydroureteronephrosis), bladder (causing frequent urination and urgency), and bowel (leading to altered defecation) [64]. After the publication of the FIGO classification system (Fig. 1, see [27]) more data are now becoming available on FIGO type 3, characterized by its complete myometrial development while encroaching the endometrium [65]: indeed, accumulating evidence suggests that FIGO type 3 fibroids are significantly associated with a lower implantation rate, cumulative pregnancy rate, and live birth rate; furthermore, their deleterious effect on the outcome of IVF increases further with increasing size and number [66]. Considering the anatomical features of FIGO type 3 fibroids, an unique "hybrid" between a submucous and an intramural fibroid, hysteroscopic approach may be considered a safe and feasible approach if performed by an expert gynecological endoscopist [67].

Among the limited approaches available for the management of fibroids during pregnancy, the use of acetylsalicylic acid for the management of pain is considered safe, whereas data about other painkillers are less robust to ensure safety [68]. Surgical approaches include myomectomy in case of cesarean section: although it may be associated in some cases with increased risk of severe uterine bleeding [69], a recent systematic review suggests that with appropriate hemostatic techniques and when performed by experienced surgeons, cesarean myomectomy may be safe and feasible in selected patients with fibroids, regardless of size and locations, except if they are located at the cornual or close to large vessels, and in the absence of uterine atony during surgery [70]. In addition, the presence of fibroids, as well as their size and location, should be carefully evaluated when a cesarean section is planned, since it may increase the surgical complexity due to their potential association with difficult access to the lower uterine segment, complicated fetal extraction, laceration or organ damage and abnormal placentation [71].

In selected cases of uterine fibroids with severe symptoms when other treatment options have failed and there is high risk of adverse maternal–fetal outcomes, myomectomy during pregnancy could be considered as last resource [72] by laparotomy or even by laparoscopy (especially in case of subserosal/pedunculated fibroids) [73], although the risk/benefit ratio should be carefully evaluated since this procedure is associated with an increased risk of obstetric complications [74].

**Hysteroscopic myomectomy**

The effect of fibroids on fertility depends on their size and location; moreover, fibroids may affect both reaching and maintaining a pregnancy [75]. The level of evidence published till today is scarce and based mostly on not randomized studies.

Based on the evidence, we know that subserosal fibroids do not appear to have an impact on fertility and that submucosal fibroids have been shown uniformly to have a negative impact on rates of implantation, clinical pregnancy, miscarriage, live birth/ongoing pregnancies [76].

The impact of intramural fibroids is controversial and again based on few studies with low level of evidence [77]. There is some evidence that supports the fact that intramural fibroids can lead to cavity involvement by making

its distortion or being in contact with it [78], therefore potentially affecting fertility. Also intramural fibroids of more > 4 cm or multiple have a negative effect [79]. Thus, a surgical removal intramural fibroids of more than 4 cm, and especially of submucosal fibroids, could bring an improvement in fertility [80].
The approach for the removal of submucosal fibroids is by hysteroscopy techniques and based on finding the cleavage plane, specifically the pseudocapsule. It can be performed by resection, morcellation or enucleation. The enucleation process entails meticulous dissection along the pseudocapsule plane, particularly in FIGO type 1 or 2 fibroids, until the intramural segment of the fibroid achieves liberation [81,82]. Subsequently, in instances such as FIGO type 0 fibroids, the fibroid may be allowed to reside freely within the uterine cavity following the cutting of the pedicle [83].
Why is it important to preserve the pseudocapsule in patients that wish to become pregnant? By dissecting through this plane the integrity of the myometrium is preserved, we avoid thermal damage or injury of the muscle and by this, we could reduce the risk of post-surgical fibrosis and synechia [84]. The surgical approach based on pseudocapsule preservation should become routine.

**Laparoscopic myomectomy**
Laparoscopic myomectomy represents a minimally invasive and fertility-preserving approach, with clear benefits in term of faster recovery and better cosmetic outcomes compared with laparotomy, sharing the same indications (mainly symptoms/signs that are not resolved by pharmacological treatments).
Pharmacological preparation before laparoscopic myomectomy, including the administration of GnRH-a, could be useful to reduce fibroid volume and intra-operative blood loss, although the best strategy is yet to be elucidated [85].
In addition, different pharmacological (such as vaginal or rectal misoprostol, intramyometrial vasopressin injection, bupivacaine and epinephrine subserosal injection, intravenous oxytocin infusion) hemostatic techniques proved to be useful to reduce intra-operative blood loss [41], although comparative analyses do to not allow to identify the best strategy over the others and we should take into account that intramyometrial vasopressin injection may cause adverse cardio-pulmonary events. Similarly, some non-pharmacological hemostatic techniques, such as the use tissue sealants [86], temporary uterine artery occlusion [87], and tourniquet loop [88] may also be considered adequate strategy to reduce intra-operative blood loss and, consequently, the need for transfusion and the risk of unplanned hysterectomy. From a technical perspective, both single-site [89] and robotic [90] approaches can be considered feasible and safe options: although both were not associated with longer operative time compared with standard laparoscopic myomectomy, robotic surgery is associated with higher costs. In addition, barbed sutures may be associated with better peri-operative outcomes compared with conventional sutures [91]. Nevertheless, we currently need robust comparative analyses to evaluate reproductive and obstetric outcomes after single- vs. multi-layer suture; waiting for further and more robust evidence, we suggest suturing in as many layers as needed based on the depth of the defect. Robust data suggested that laparotomic approach and uterine cavity opening are associated with the risk of developing intrauterine adhesions [92], so these points should be taken into account during the counseling. After the warning of the Food and Drug Administration (FDA) in 2014 [93], it is mandatory to perform bag-contained specimen extraction in case of power morcellation: anyway, in-bag transvaginal extraction of the surgical specimens has comparable surgical outcomes than in-bag power morcellation [94]. Finally, laparoscopic myomectomy is not associated with worse reproductive and obstetric outcomes compared with laparotomic approach [95], and vaginal delivery after laparoscopic myomectomy can be considered feasible and safe [96], with a waiting time for pregnancy of at least 3 months after surgery as precautionary measure to allow proper uterine healing and reduce the risk of uterine rupture.

**How to manage unexpected malignant diseases**
Myomectomy and hysterectomy for uterine fibroids represent the most common and widely performed gynecological surgical procedures worldwide. Different approaches may be used to perform these procedures: open, vaginal, or endoscopic (laparoscopic and robotic) surgery. Morcellation is a surgical technique that allows to decrease the size of the uterus or fibroids into smaller pieces to extract them through small incisions. The 2014 FDA warning underlined that about 0.3% of patients undergoing surgery for benign disease could have uterine sarcomas [97]. A 2017 review conducted by the Agency for Healthcare Research and Quality (AHRQ) estimated that the prevalence of unexpected uterine sarcoma is likely to be lower, showing that at the time of surgery for presumed symptomatic fibroids the range was between <1 and up to 13 per 10,000 surgeries [98]. In June 2022,

the FDA released an updated Safety Communication confirming these previous recommendations pointing out the importance of the use of tissue containment systems in order to minimize the risk of dissemination, although the safety of this procedure is still an object of investigation [99,100]. Uncontained morcellation of unexpected uterine sarcomas can modify the natural history of the disease causing disseminated sarcomatosis thus leading to worse oncologic survival outcomes compared to women whose lesions are extracted intact [101]. There is no clear evidence or guideline about the proper management of an uncontained morcellated unexpected malignancy after an endoscopic procedure. Surgical re-exploration after morcellation is an option to ascertain the potential spread of the disease in the abdominal cavity, however no definitive data are available to support this procedure and no conclusive recommendation can be suggested [102,103]. Among those patients who underwent myomectomy, radical surgery including hysterectomy should be offered [102,103]. Data on the fertility-sparing treatment of patients after tumorectomy are scanty. Highly selected patients with early stage disease (FIGO stage IA) may be candidate in tertiary referral center after proper counseling and explaining that the procedure is experimental and cannot be considered as standard [37].

## Statements

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

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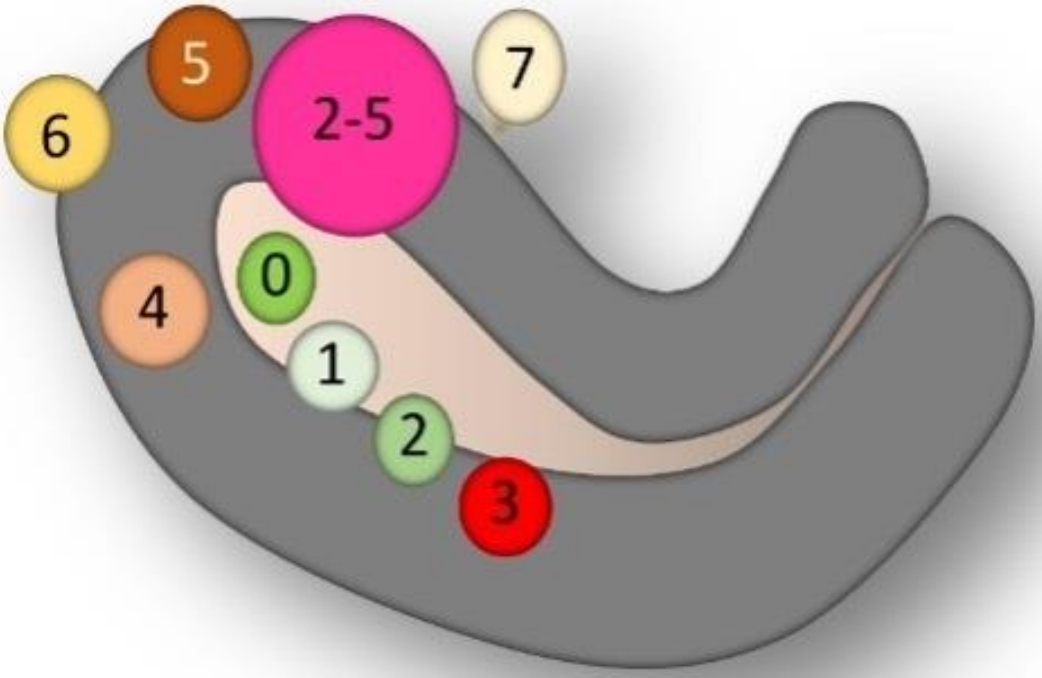
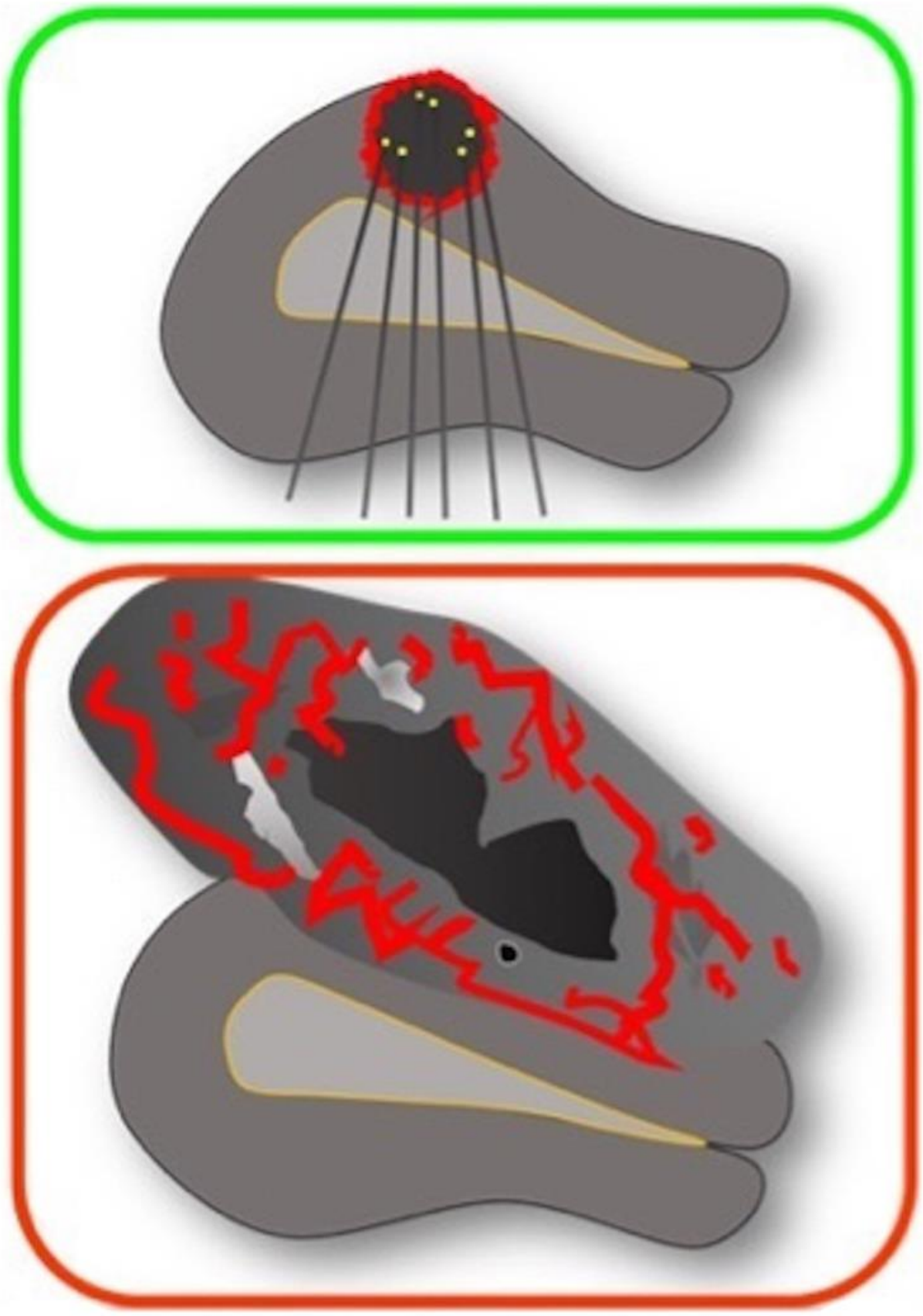
**Figure Legends**

Fig. 1. FIGO staging of uterine fibroids (adapted from: *Munro MG, et al. Int J Gynaecol Obstet 2011; 113:3-13*).

Fig. 2. Schematic illustration of the ultrasonographic features of fibroids (top) and uterine sarcomas (bottom).





Tab. 1. Ultrasonographic features of fibroids and uterine sarcomas.

| FEATURE | FIBROID | LEIOMYOSARCOMA |
|---|---|---|
| **Number** | Multiple | Solitary |
| **Shape** | Round | Oval / lobulated |
| **Echogenicity** | Calcifications | Inhomogenous |
| **Fan shaped shadowing** | Frequent | Rare |
| **Irregular cystic areas**<br>**Central necrosis** | Rare | Frequent |
| **"*Cooked*" appearance** | No | Frequent |
| **Vessels** | Circumferential flow | Irregular vessels<br>Score 3-4 |
| **Size** | Variable | ≥ 8 cm<br>Fast growing |

Tab. 2. Pharmacological strategies for uterine fibroids.

| Drug class | Mechanism of action | Advantages | Disadvantages |
|---|---|---|---|
| **Non-steroidal anti-inflammatory drugs** | Inhibition of the enzyme cyclooxygenase and lowering the production of pro inflammatory prostaglandins. | • Effective in improving dysmenorrhea and pelvic pain.<br>• Not expensive. | • Mainly action on pain symptoms but it does not regularize the menstrual cycle.<br>• Contraindicated in women with known hypersensitivity to this class of medications, active gastric or peptic ulcers, or advanced renal disease. |
| **Tranexamic acid** | Prevention of fibrin degradation at the level of the plasminogen lysine receptor site, favoring pro-coagulant mechanisms which lead to a reduction in menstrual blood flow. | • Effective in improving heavy menstrual bleeding.<br>• Not expensive. | • Mainly action on current bleeding but it does not regularize the menstrual cycle.<br>• Possible onset of adverse effects including gastrointestinal and musculoskeletal symptoms<br>• Contraindicated for patients with color blindness, active bleeding, and history of intravascular clotting. |
| **Estroprogestins and progestins** | Maintenance of a thin endometrium and decrease of the amount of endometrial shedding during the menstrual cycle. | • Not expensive.<br>• Multiple routes of administration are available (pills, vaginal rings, or transdermal patches). | • Need a review of medical eligibility criteria (age, smoking, history of venous thrombosis, and migraines with aura).<br>• Not effective in reducing fibroid size or characteristics.<br>• Higher LNG-IUD expulsion rate (especially with fibroids larger than 3 cm) |
| **Ulipristal acetate** | Action at the level of peripheral | • Effective in inducing a 25%- | • As anovulation is seen in 80% during UPA |

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|---|---|---|---|
| | progesterone receptors on myomas by inducing cellular apoptosis, inhibiting proliferation of the fibroid, and thinning the endometrial lining. | 50% of fibroid shrinkage and highly effective in obtaining a decrease of uterine bleeding with an amenorrheic status (elevate scientific evidence).<br>• Oral administration. | treatment, the use of a reliable form of birth control (contraception) is recommended.<br>• Contraindicated for patients with asthma and liver impairment.<br>• Expensive. |
| **GnRH agonists** | After an initial stimulation, binding to the GnRH receptor, block of endogenous GnRH activity and direct suppression of LH and FSH production. | • Effective in inducing a 25%-50% of fibroid shrinkage and highly effective in obtaining a decrease of uterine bleeding with an amenorrheic status within 3 months of treatment initiation (elevate scientific evidence).<br>• Monthly or trimestral schedule of administration. | • Not oral rout of administration.<br>• Expensive.<br>• Relevant rate of AEs (i.e., hot flushes, mood swings, vaginal dryness, decreased libido, sleep disturbances), and bone mineral density loss without ABT. |
| **GnRH antagonists** | Rapid binding to the GnRH receptor, blocking endogenous GnRH activity and directly suppressing LH and FSH production. | • Oral route of administration.<br>• Possibility of multiple doses for each drug (low and high dose) with or without ABT.<br>• Avoidance of the initial flare of GnRH agonists.<br>• Lower hypo-estrogenic | • Expensive.<br>• ABT necessary for alleviating hypo-estrogenic- related AEs (i.e., hot flushes, mood swings, vaginal dryness, decreased libido, sleep disturbances), particularly if they are given at higher dose for long period.<br>• The need of a concomitant reliable |

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| | | impact than GnRH agonists. | form of birth control is controversial. |
| **Aromatase inhibitors** | Inhibition of the aromatization of androgens to estrogens which results in thinning of the endometrial lining and reduced menstrual bleeding. | • Oral route of administration. | • Low scientific evidence to support their use.<br>• Relevant rate of AEs (i.e., myalgia, osteoporosis). |

ABT= add-back therapy; AE= adverse effect; LNG-IUD= levonorgestrel-releasing intrauterine device; GnRH= Gonadotropin Releasing Hormone.