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SPECIAL ARTICLE

Uterine Sarcomas: Pre- and Intra-operative Considerations

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ABSTRACT

Uterine leiomyomas are the most common indication for hysterectomy and myomectomy. Compared with the laparoscopic approach, the abdominal approach for hysterectomy is associated with a higher risk of a venous thromboembolic event, blood transfusion, prolonged hospital stays, wound pain, and infection. Unfortunately, some women with uterine mass undergoing surgery had unexpected uterine sarcomas. Spreading an unexpected uterine sarcoma during a hysterectomy or myomectomy can worsen the prognosis. Thus, a pre-operative diagnosis of uterine sarcomas is relatively challenging. Obstetrician-gynecologists should pre-operatively discuss the possibility of malignancy of the disease, risk, and benefit of the operative approach with the patient with a uterine mass. In this article, we reviewed the concerns of uterine sarcomas in patients with a uterine mass in terms of the disease incidence, pathological and clinical features, pre-operative evaluation tools such as biomarkers and imaging, intra-operative gross evaluation, and the roles of the intra-operative tissue containment system.

Keywords: hysterectomy, leiomyoma, myomectomy, power morcellation, uterine sarcoma.

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Introduction

Uterine leiomyoma is the most common benign tumor, affecting more than 50% of all reproductive women. Hysterectomy and myomectomy are used worldwide via open and minimally invasive surgery (MIS). For the past three decades, MIS has generally been accepted as having advantages over the conventional open approach of a lower complication rate, shorter hospital stay, less blood loss, and more rapid recovery[1, 2]. Morcellation is a surgical technique for reducing the size of the uterine or myomas into pieces or strips to facilitate tissue removal. A power morcellation of the unexpected uterine sarcomas significantly increases intraperitoneal spreading and is an independent poor prognostic factor for recurrence and death[3-5]. In response, the U.S. Food and Drug Administration (FDA) issued a safety communication in November 2014 warning "against the use of laparoscopic

power morcellators in the majority of women undergoing myomectomy or hysterectomy for the treatment of fibroids"[6]. After that, the rate of open surgery increased, and the rate of MIS decreased significantly from the study used by the American College of Surgeons National Surgical Quality Improvement Program database. The major and minor 30-day complication rates among women undergoing open hysterectomy for uterine fibroids increased significantly after the warning[7]. In February 2020, the FDA updated a safety communication "laparoscopic power morcellation for myomectomy or hysterectomy can be performed only with a tissue containment system". The additional recommendations included that clinicians should not use the laparoscopic power morcellations when the tissue is known or suspected malignancy, in patients who are postmenopausal or older than 50 years of age, or candidates for removal of tissue (en bloc) through the vagina or via a mini-laparotomy incision[8]. In December 2020, the FDA also published updated recommendations "the clinicians should be aware of the spread of benign uterine tissue when used an uncontained power morcellation, conducted a thorough pre-operative screening and shared decision-making, discuss the risks and benefits of all relevant treatment options with patients"[9].

However, a pre-operative diagnosis for uterine sarcomas is relatively problematic. This article aimed to review an estimated incidence, clinical and tumor characteristics, pre-operative evaluation methods such as biomarkers and imaging, and intra-operative concerns that may impact the risk of malignancy among women undergoing surgery for benign uterine leiomyomas.

Incidence

Uterine sarcomas are rare tumors that account for 3-7% of all uterine cancers[10]. Soft tissue sarcomas are uncommon tumors. About 40% of leiomyosarcomas among women were uterine in origin—an estimated incidence of 0.36 per 100,000 woman-years worldwide[11]. In 2021, the American College of Obstetricians and Gynecologists (ACOG) summarised that the risk of an unexpected leiomyosarcoma ranges from 1 in 498 to less than 1 in 10,000[2]. The Agency for Healthcare Research and Quality (AHRQ), including data from 136,195 women in 160 studies, reported that the risk of unexpected leiomyosarcoma might range from 1 in 770 surgeries to less than 1 in 10,000 surgeries for presumed symptomatic leiomyomas[12]. In Thailand, a retrospective review from two tertiary-care institutes reported that the incidence of uterine sarcomas was 0.37% in women with uterine mass undergoing surgery at Ramathibodi Hospital and 0.2% in women undergoing hysterectomy for presumed leiomyomas at Siriraj Hospital[13, 14].

Pathological features

The tumor stage is the most important prognostic factor. The International Federation of Gynecology and Obstetrics (FIGO) classification and staging system 2009 has specified uterine sarcomas reflecting their different biologic behavior; 1. leiomyosarcomas and endometrial stromal sarcomas; 2. adenosarcomas; and 3. carcinosarcomas (malignant mesodermal mixed tumors, MMMT) (Table 1)[15]. Carcinosarcomas account for 50% of the uterine sarcoma, followed by leiomyosarcomas (30%), endometrial stromal sarcomas (15%), and undifferentiated sarcomas (5%)[16]. However, carcinosarcoma was then reclassified as carcinomas of the endometrium due to biphasic neoplasm characteristics composed of malignant epithelial and mesenchymal elements. Moreover, the recent data confirm that the sarcomatous component is derived from carcinoma or a divergent stem cell differentiation[17].

Thus, leiomyosarcomas are the most common subtype of uterine sarcomas. It often presents with a huge mass or with leiomyomas. The cut surface is typically soft, bulging, fleshy, necrotic, and hemorrhagic, lacking the prominent whorled appearance of leiomyomas[16]. Surgeons may be concerned about leiomyosarcomas while opening gross specimens intra-operatively. The role of frozen section is unclear. Artifacts caused by the freeze-drying of tissue may cause alterations in cellular appearance which is a potential source of interpretational error in frozen section. Furthermore, the result from frozen section do not have immediate therapeutic consequences in many cases[18]. The histology in permanent section

shows the constellation of hypercellularity, severe nuclear atypia, and high mitotic rate generally exceeding 15 mitotic figures per 10 high-power fields (M.F./10 HPF)[16, 19]. They are very aggressive and have poor prognoses. In the early stage of tumors confined to the uterus, recurrence rates range from 53 to 71%[10]. First recurrences occur in the lungs in 40% of patients and the pelvis in only 13%[20].

Table 1. FIGO staging for uterine sarcomas (2009)[15].

Stage	Definition
(1) Leiomyosarcomas and endometrial stromal sarcomas[a]	
I	Tumor limited to the uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvis tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(2) Adenosarcomas	
I	Tumor limited to the uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half of myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvis tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to the pelvis and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(3) Carcinosarcomas Carcinosarcomas should be staged as carcinomas of the endometrium	

[a] Note: Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis associated with ovarian/pelvic endometriosis should be classified as independent primary tumors.

Clinical features

Many retrospective studies review clinical presentations and associated factors of uterine sarcomas. Leiomyosarcomas tend to occur in old age. The study from the Ottawa Hospital reported the mean age in women with sarcomas as 62.1 ± 10.1 years (mean ± S.D.)[21]. Postmenopausal status and representing symptoms such as abnormal uterine bleeding, postmenopausal bleeding, palpable mass, rapid growth mass, and single uterine mass are reported as independently associated with increased risk of uterine sarcoma[13, 14, 21-25]. A definition for rapid growth is still indescribable and relies on subjective clinical assessment[13, 21]. The higher uterine weight, more than 2,000 grams, was reported progressively increased the incidence by 15% (2 in 13 patients)[26].

Pre-operative evaluation

Occult uterine sarcomas are rare but aggressive. According to the non-specific clinical manifestations and even endometrial histological detection, additional modalities encourage distinguishing between benign and malignant as well as access degree, severity, or staging of diseases. With significantly advanced and raised management of leiomyomas, non-surgical treatment, or even MIS, the optimized pre-operative assessments, in terms of detected potential malignancy, are the most important. Here are the pre-operative investigation tools used in clinical decision-making nowadays.

- **Biomarkers**

No available serum marker could differentiate between leiomyomas and uterine sarcomas. Some studies showed that a decreased hemoglobin, neutrophilia, or increased neutrophil-to-lymphocyte ratio would likely lead to sarcomas[27, 28]. However, Carcinoma antigen-125 (CA 125) and lactate dehydrogenase (LDH) may play a role in the pre-operative diagnosis of uterine sarcomas and usually interpret as their results along with other diagnostic imaging[22]. The diagnostic accuracy of combined LDH and magnetic resonance imaging (MRI) was 100% compared with 93.1% in MRI alone and 95.2% in dynamic MRI[29].

- **Imaging**

- Ultrasonography and computerized tomography (C.T.) scan

The feasible ultrasonography or C.T. scan facilitates identifying discriminating features of a uterine mesenchymal subtype is not easy. Due to both benign and malignant tumors originating from the mesenchymal cell, the tumors and normal myometrial tissue are usually revealed in the same manner in both modalities. Moreover, detecting invasive or metastasis as malignant potency cannot be easier. Currently, ultrasonographic or C.T. scan diagnostic criteria are not proper and valuable[15, 30].

- MRI

MRI is the best-distinguished tool for the differential diagnosis of soft tissue tumors. Although it is considered limited accuracy, some interesting features or analytical techniques can help diagnose pre-operatively. In the common malignant type, leiomyosarcomas are presented with infiltrating myometrium and an ill-defined margin. Recently studies reviewed some essential checklists on MRI that are applicable (Table 2)[31]. These features of consideration are the tumor border, enhanced features in contrast media, and endometrial thickening.

Table 2. Summary of typical MRI features for uterine mesenchymal tumors[30].

	LMS	ESS	UES	AS	Leiomyoma	Endometrial carcinoma
Localization	Myometrium	Generally, endometrium; can be located in myometrium	Generally, endometrium; can be located in myometrium	Endometrium	Myometrium	Endometrium
Margin	Irregular and ill-defined	Irregular and nodular	Markedly irregular and nodular	Regular and well demarcated	Regular	Regular or irregular
T1 signal	Hypointense and heterogeneous (hemorrhage, calcification)	Hypointense	Heterogeneous	Predominantly, hypointense, heterogeneous	Low-to-intermediated signal; high signal foci-hemorrhagic degeneration	Hypo-to-isointense signal to normal endometrium
T2 signal	Intermediate-to-high signal	Hyperintense and heterogeneous; bands of a low signal corresponding to preserved myometrium	Heterogeneous (extensive hemorrhage and necrosis)	Multiseptated cystic appearance; can show multiple small hyperintense foci	Low signal (non-degenerated); high signal-cystic, myxoid degeneration	Hyperintense and heterogeneous relative to normal endometrium
Contrast enhancement	Early and heterogeneous	Moderate (more intense than endometrial carcinoma) and heterogeneous	Marked (generally more intense than usual myometrium) and heterogeneous	Marked (generally isointense compared to normal myometrium) and heterogeneous	Variable	Hypointense compared to normal myometrium
DWI	Generally, more restrictions (lower ADC value) than leiomyomas	High signal and low ADC	High signal and low ADC	Low signal (low-grade nature)	Variable; generally higher ADC values than LMS	High signal and low ADC

LMS: leiomyosarcoma, ESS: endometrial stromal sarcoma, UES: undifferentiated endometrial sarcoma, AS: adenosarcoma, DWI: diffusion-weighted imaging, ADC: apparent diffusion coefficient

Uterine sarcoma typically has some degree of invasion that is always seen as an irregular or ill-defined border on MRI. The incidences are 80.6-100% in uterine sarcomas compared with 3.8% in atypical leiomyomas[32]. In a previous study, this finding on MRI showed 78-84% sensitivity and 86-91% specificity of leiomyosarcoma[33].

Due to necrosis, the contrast media in the MRI study reveals a lack of contrast enhancement in this area, which is often central. Uterine sarcomas usually demonstrate heterogenous enhancement, a typical central unenhanced finding[31]. The 95-100% sensitivity and 68-73% specificity on contrast media MRI in pre-operatively detecting leiomyosarcoma were reported[33]. Although the area of hyalin, cystic or red cell degeneration found in typical leiomyomas are not specifically enhanced characteristics, together with assessed signal intensities (S.I.) in both standard T1 and T2 weight imaging (W.I.), have some unique S.I. characteristics[31]. Without a specific enhanced response in degenerating leiomyomas, degenerative leiomyomas may be partially separated. In addition, the unenhanced area of necrosis in sarcomas, mean, and ratio of contrast enhancement are increased earlier than in degenerating leiomyoma groups[32].

Heterogeneous hypo-intensity on T1W.I. is commonly manifested in leiomyosarcoma[34]. Although subacute hemorrhagic necrosis, presenting methemoglobin, demonstrates the area of hyperintensity T1W.I., only 1.3-18% of leiomyomas are found compared to 18-94% of sarcoma[31, 33, 35]. Furthermore, central or intralesional hemorrhage resulted in an increase of 7.38 times sarcomas risk over non-malignant lesions[36]. Without clinical red degeneration, e.g., painful or systemic inflammation such as fever, subacute tumor hemorrhage with a high-intensity area is highly suspicious of sarcomas. However, tumors with acute or chronic hemorrhage are seldom identified with this feature. On T2W.I., the uterine sarcoma frequency shows intermediate-to-high S.I., but intrauterine hemosiderin, caused by bleeding, results in a low T2 S.I. dark area[31, 34]. The overlapping high T2 S.I. in degenerative leiomyoma and leiomyosarcoma may confuse the interpretation, so the correlated analysis together with T1WI and characteristic of enhancement is valuable.

For the endometrial stromal sarcomas and adenosarcoma, uncommon subtypes of uterine sarcoma usually involve the endometrial part resulting in endometrial lining irregularity.

High diffusion-weighted imaging (DWI) S.I. and low apparent diffusion coefficient (ADC) values are highly suspected leiomyosarcoma[32, 37]. In the aforementioned red cell degeneration area, restricted diffusion of DWI area on T1 and T2 W.I. should be used for interpretation, especially in cellular leiomyoma and sarcoma. Table 3 summarizes the MRI features for the atypical leiomyoma[38].

Table 3. Summary of typical MRI features for atypical leiomyoma[37].

	Typical leiomyoma	Hyaline & cystic degeneration	Red degeneration	Lipo-leiomyoma	Cellular leiomyoma	Sarcoma
Border	Well defined	Well defined	Well defined	Well defined	Well defined	Lobulated or irregular
Enhancement	Heterogeneous	Heterogeneous with no enhancement in degeneration	Heterogeneous with no enhancement in degeneration	Heterogeneous	Homogeneous	Heterogeneous – with irregular outline/invasion
T1WI SI	Low	low	Hemorrhage high	Fat high with saturation on fat-saturated T1WI	Low	Low with high S.I. in areas of hemorrhage
T2WI SI	Low	High in cystic areas	Variable depending on the age of hemorrhage	Variable gave the fat-containing component	Intermediate	Intermediate and heterogeneous
Endometrial thickening	None	None	None	None	None	Direct involvement/irregular or thickened
Restricted diffusion	No	No	No	No	Yes	Yes

T1WI SI: T1 weighted imaging signal, T2WI SI: T2 weighted imaging signal

Intra-operative evaluation

Histopathological findings in each specific type of benign and malignant mesenchymal uterine tumors can be partially distinct from gross descriptions. In the group of non-malignant tumors, leiomyomas are subdivided into lipoleiomyoma, apoplectic or hydropic leiomyoma, dissecting leiomyoma, cellular leiomyoma, myxoid leiomyoma, epithelioid leiomyoma, symplastic leiomyoma, leiomyomatosis, or Not Otherwise Specified (NOS)[39]. NOS, or typical leiomyoma, is the most common benign intra-operative uterine tumor, found with well-circumscribed, unencapsulated, bulging, firm, white, and whirling on the cut surface that is less likely to be malignant with these features[39, 40]. On the other hand, other gross appearances defined differently from typical leiomyoma are atypical leiomyomas. Atypical leiomyomas may have some gross features that mimic uterine sarcoma. Some typical leiomyomas with degeneration or infarction mimic gross malignant characteristics.

Degenerated leiomyomas typically are seen as hyalin, cystic, or red cell degeneration. Red degeneration is well-circumscribed, bulging, retained whirling, and softening beefy-red color. In contrast, leiomyoma with infarction is dull-white or dull-yellowish[39]. Other atypical leiomyomas such as lipoleiomyoma, apoplectic leiomyoma, or cellular leiomyoma are usually found and hard to distinguish from uterine sarcoma. The mixture of lipocytes in smooth muscle tumors with a variable of bright yellowish lipoleiomyoma or softened yellowish well-circumscribed cellular leiomyoma is frequently assumed to be malignant potential uterine tumors[40].

The roles of intra-operative tissue containment systems

Because of the unreliable pre-operative diagnosis methods and intra-operative gross pathological documentation of uterine sarcoma, additional intra-operative containment bag morcellation was recommended[2, 8]. The tissue containment systems were then developed. PneumoLiner, a tube-like plunger containment bag, was approved by U.S. FDA in 2016; however, it has not been proven to reduce the risk of cancer spreading during the power morcellation[41] (Fig. 1)[42]. Using only in pre-menopausal women undergoing myomectomy or hysterectomy for non-fibroid related indications with pre-operative risk stratification and appropriate evaluations should be considered[2, 41]. Other systems are also available, e.g., EcoSac 230, Steri-Drape Isolation bag, LapSac Surgical Tissue Pouch Cook Medical, Anchor TRS-200, or EndoCatch 15 mm[43]. However, the perforation or leakage of the bag is a rising concern. Alternative approaches to morcellation in the bag removing intact specimens through the vagina or proper abdominal incision may be reduced the risk of spreading or leakage[44].

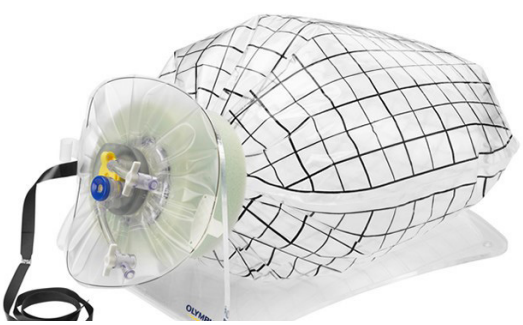

Fig. 1. PneumoLiner, The tissue containment systems[42].

Conclusion

Pre-operative diagnosis of uterine sarcomas in women with uterine mass undergoing hysterectomy and myomectomy is still problematic. Moreover, the intra-operative gross features of uterine sarcomas can mimic some types of leiomyomas. The surgeons, especially the gynecologic endoscopists, should discuss a higher procedural risk of hysterectomy or myomectomy with intra-abdominal tissue spillage and the risk of unexpected uterine sarcomas. The intra-operative containment systems play roles in reducing tumor spillage, although the perforation or leakage of the systems is worried. Further investigation is needed to improve the accuracy of pre-operative diagnostic methods and the security of intra-operative containment systems.

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