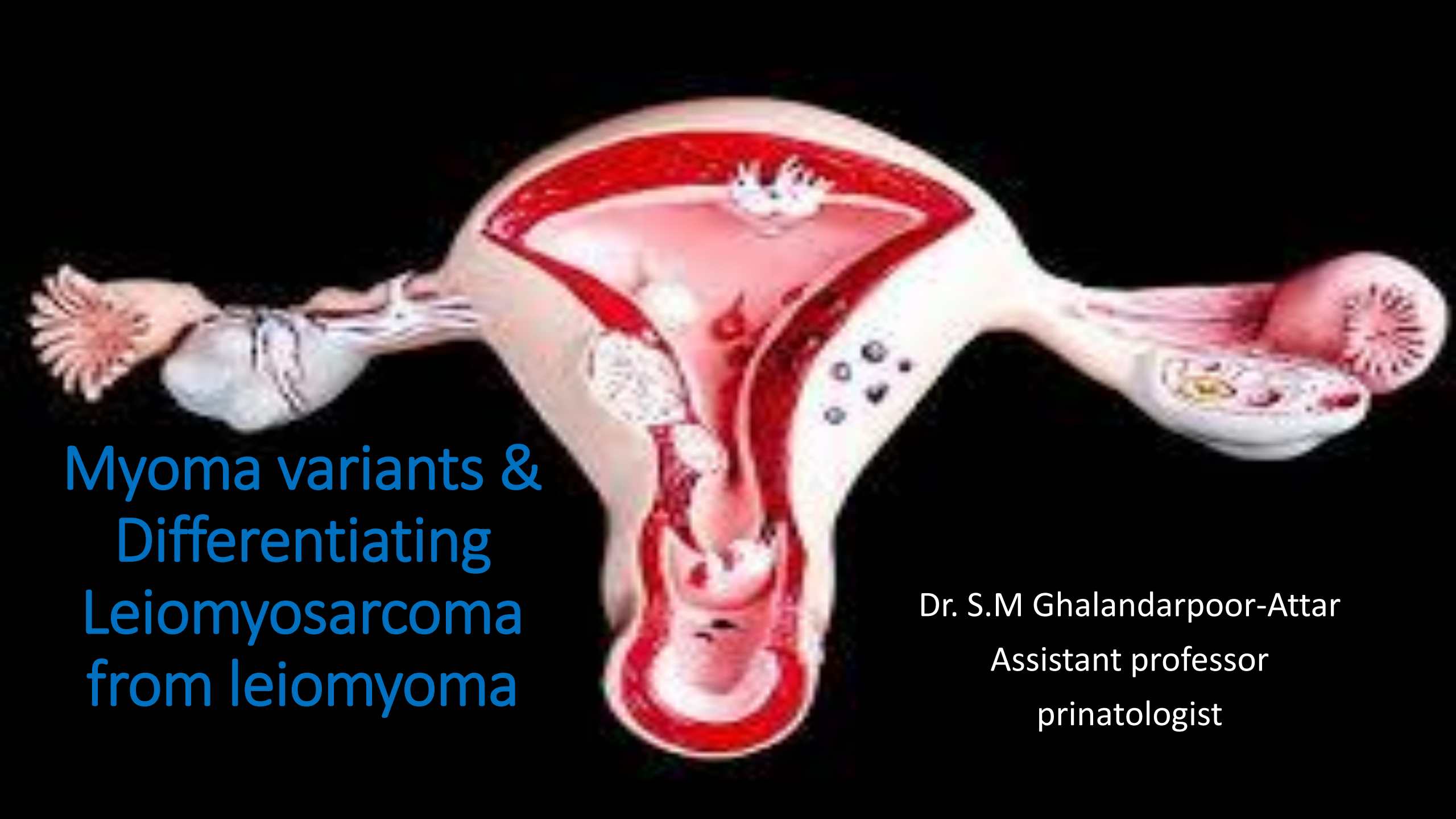
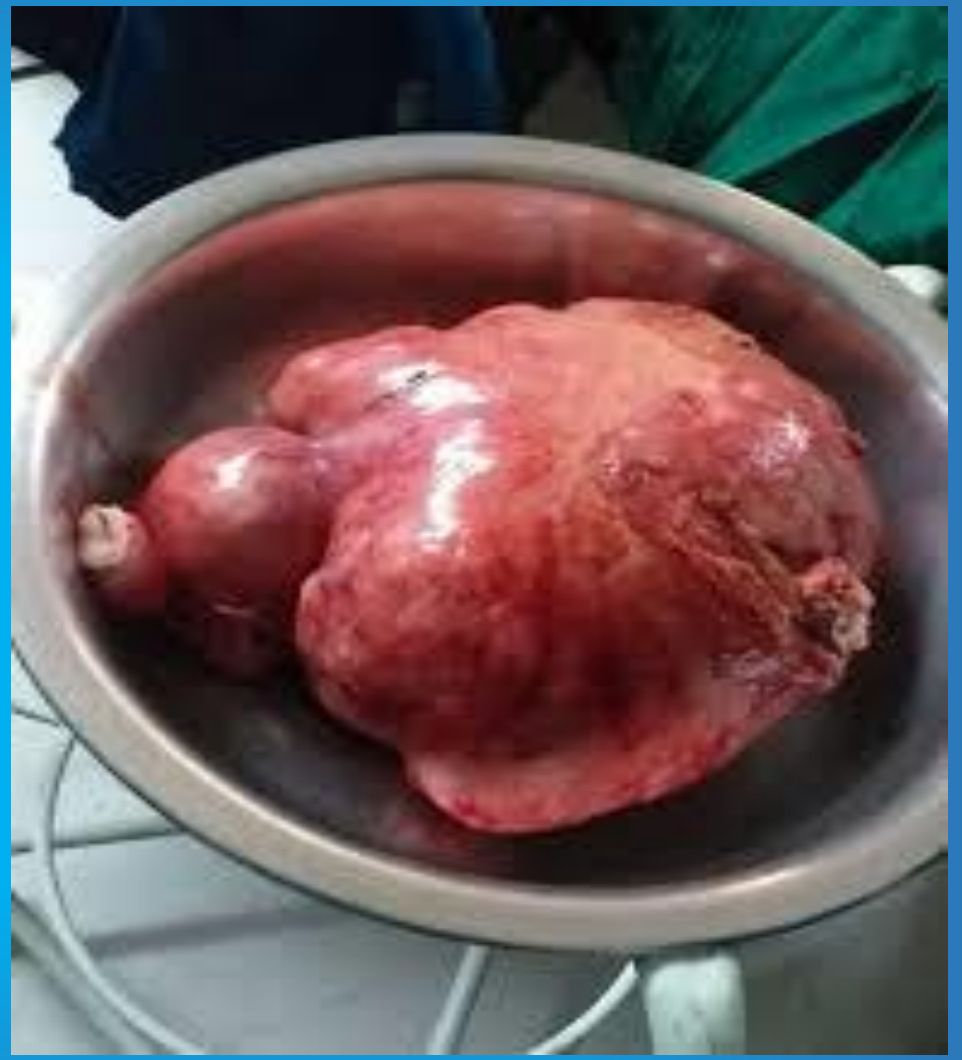


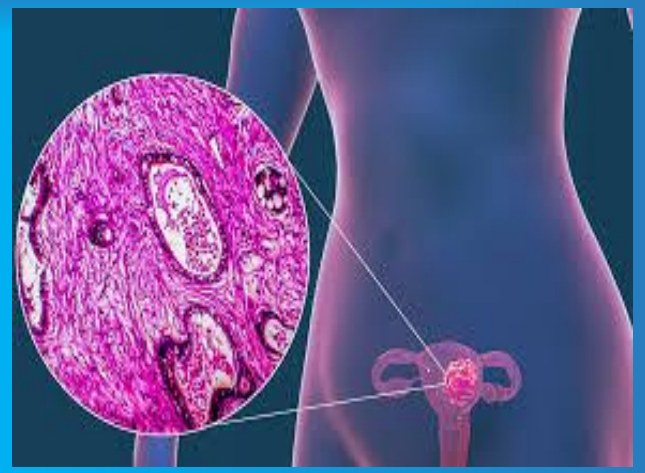
Myoma variants & Differentiating Leiomyosarcoma from leiomyoma

Dr. S.M Ghalandarpoor-Attar
Assistant professor
prinatologist

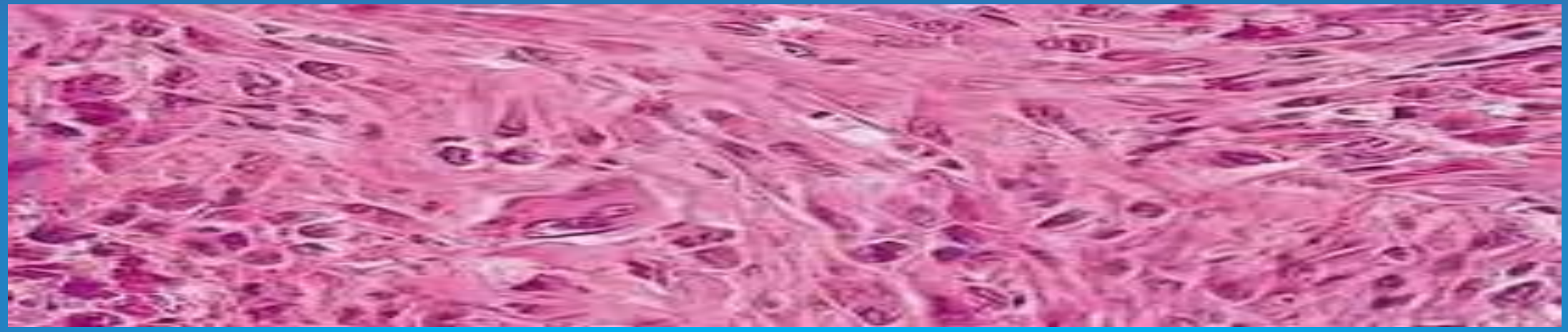
Uterine SMTs have a broad spectrum ranging from leiomyosarcomas to leiomyomas

can be distinguished based on histopathological features including the degree of cytologic atypia, mitotic count activity and presence of tumor cell necrosis





- Smooth muscle tumor of uncertain malignant potential (STUMP) encompasses a broad group of uterine neoplasms that do not meet the current histologic criteria for a diagnosis of either benign or a malignant tumor.
- It is thought that STUMP may represent a transition tumor between leiomyoma to leiomyosarcoma or possibly undiagnosed low grade Leiomyosarcoma



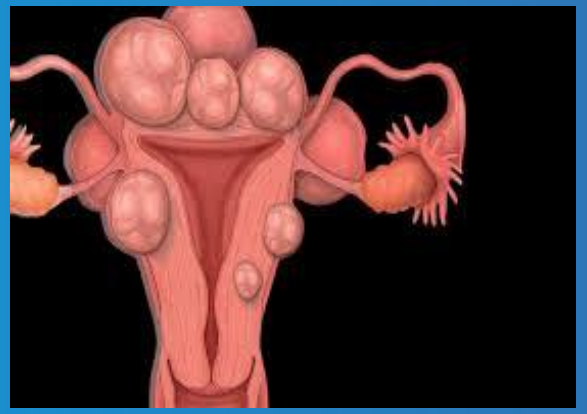
- Among women undergoing hysterectomy or myomectomy for a presumed diagnosis of leiomyoma, 0.01% receive a diagnosis of STUMP.
- The true prevalence of STUMP is difficult to determine due to the rarity of the disease and the inconsistency in diagnostic criteria.
- Treatment approaches and follow-up of these tumors have been still controversial, due to the non-aggressive behavior and prolonged overall survival rate comparing to leiomyosarcomas

- Preoperative STUMPs diagnosis with imaging modalities is not easy and there´s no specific image related to STUMPS.
- However, in front of any abdominopelvic mass it´s mandatory to perform in first line the pelvic ultrasound. In case the result don´t lead to a possible diagnosis we perform a pelvic MRI which result is better than ultrasound
- fertility sparing surgery is possible however these patients should be adequately informed of the risk of recurrence and a strict follow-up program through clinical and imaging techniques is mandatory

- Recurred STUMPs are biologically low-grade LMS. There seems to be no consensus regarding the histological features able to predict the likelihood and the clinical characteristics of a recurrence

- Ip et al suggest an intense follow-up program with an evaluation performed every 6 months in the first 5 years followed by annual surveillance for the next 5 years.
- patients treated by hysterectomy we usually perform a clinical evaluation every six months followed by a yearly total-body CT, whereas in those patients treated by uterus-sparing-surgery we perform a clinical and sonographic evaluation every 6 months and a yearly pelvic MRI coupled with chest X-ray.

the initial approach to evaluating a patient with a presumed leiomyoma in whom there is some concern of uterine sarcoma.



- ***the clinical features of benign leiomyomas and uterine sarcomas are often indistinguishable***
- **Risk factors**: Uterine sarcoma is rare and risk factors are not well defined for uterine sarcomas in general or specifically for leiomyosarcoma.

Common to both leiomyomas and sarcoma:

Race: Black race is a risk factor. The relative risk and incidence of leiomyomas is 2-3 fold greater in Black women than in White women.

Sarcoma only

- ***Increasing age and postmenopausal status***:

Benign leiomyomas are responsive to gonadal steroids and develop and grow primarily in patients of reproductive age,.

Leiomyomas typically stabilize or diminish in size following menopause.

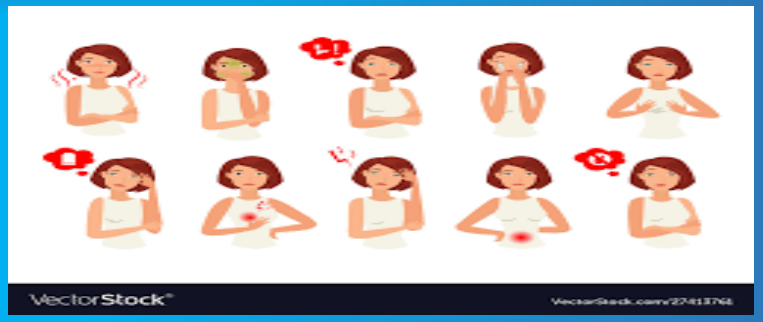
Postmenopausal estrogen therapy may be associated with modest growth of myomas and/or persistent symptoms but does not appear to induce the development of new leiomyomas

- By contrast, increasing age is a significant risk factor for uterine sarcomas. The average age at diagnosis is 60 years;
- Young age does not exclude the diagnosis of uterine sarcoma.
- for postmenopausal patients, **a new or growing uterine mass** warrants further evaluation for uterine sarcoma.
- The level of suspicion may be lower in patients who are on postmenopausal estrogen therapy and have a small increase in the size of a fibroid known to present prior to menopause. In this subgroup, a trial of discontinuing postmenopausal estrogen therapy is an option to see if regression occurs
- obtaining imaging and endometrial biopsy may also provide reassurance

- ***Tamoxifen***: Long-term use of tamoxifen (five years or more) is associated with an increase in risk of developing uterine sarcoma. In general, sarcomas present two to five years following the start of tamoxifen therapy and are often at an advanced stage at diagnosis.

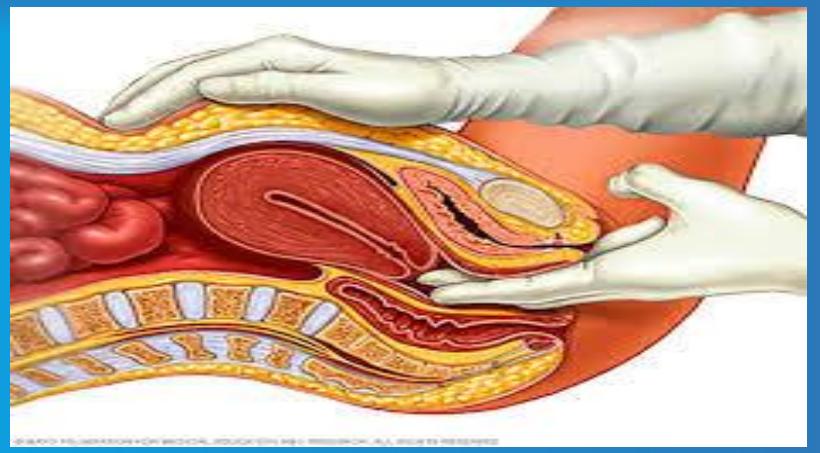
- ***Other risk factors***: pelvic irradiation, a history of childhood retinoblastoma, and hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.

Signs and symptoms



- Abnormal uterine bleeding, pelvic pain/pressure, and a pelvic mass are the primary presenting symptoms and signs for both leiomyomas and sarcoma,
- Some patients with sarcoma present with a foul-smelling vaginal discharge, but this is not a reliable indicator of malignant neoplasm since vaginal discharge is a common gynecologic symptom
- Clinical manifestations associated with metastatic neoplasm may be found in patients with sarcoma but not with ordinary leiomyomas. Uterine sarcomas spread via intraabdominal, lymphatic, or hematogenous routes. (most often to the lungs).
- Of note, some histologically benign leiomyoma variants also disseminate and must be excluded if widespread disease is found

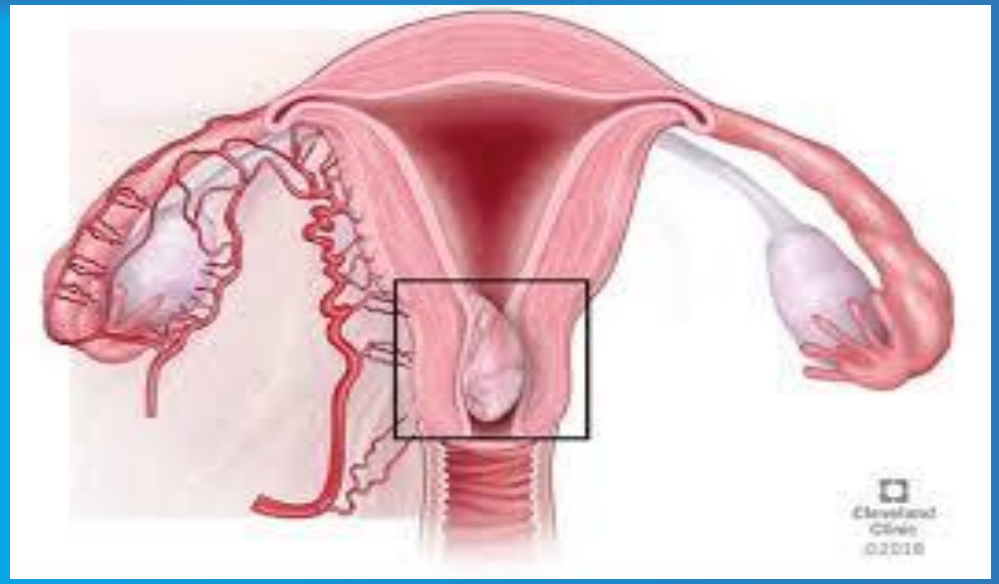
Preoperative evaluation
Pelvic examination



- A thorough pelvic examination should be performed. The size, contour, and mobility of the uterus should be noted, along with any other findings (eg, adnexal mass, cervical mass, or vaginal nodules).

- A fixed mass is more suggestive of a malignant neoplasm than a mobile mass. However, this is not pathognomonic. Among all myomectomy patients, increasing age was significantly associated with an increased risk of uterine cancer.

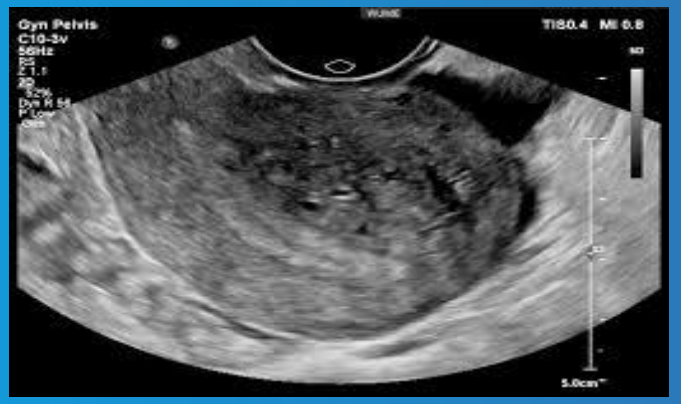
Screening and evaluation for gynecologic malignancies



- Prior to treatment for presumed leiomyomas, patients should undergo routine screening for cervical neoplasm.

- Evaluation of abnormal uterine bleeding is of critical importance

Imaging Choice



- there is no pelvic imaging modality that can reliably diagnose uterine sarcomas.
- features suggestive of sarcoma **mixed echogenic and poor echogenic parts; central necrosis; and color Doppler findings of irregular vessel distribution, low impedance to flow, and high peak systolic velocity**);
- MRI with gadolinium contrast may aid in assessing the likelihood of malignancy.
- An MRI that shows a typical fibroid (dark and homogenous in T2-weighted images) has a high negative predictive value
- High signal intensity is not a reliable indicator of uterine sarcoma.
- A consistent finding in leiomyosarcomas is the absence of calcifications.
- Neither CT nor PET-CT with FDG can reliably differentiate between leiomyomas and uterine sarcomas. While the FDG uptake is generally high in sarcomas and low in leiomyomas, the uptake varies across individual tumors.

Findings that do NOT reliably predict sarcoma

- ***1-Rapidly growing uterine mass in premenopausal patients:*** leiomyomas both grow and shrink and do so at differing rates within the same patient and even within the same uterus.
- Research on normal leiomyomas shows that growth of up to 138 percent can occur within six months. Increase in volume of ≥30 percent in a three-month period was found; rapid growth was more likely in tumors that were ≤5 cm in diameter.
- Rapid growth may occur in either a sarcoma or a benign leiomyoma. In addition, it is theoretically possible for a sarcoma to remain indolent for a long period of time and only come to diagnostic attention when a more aggressive phase of disease is entered.
- Thus, the great majority of premenopausal patients with a rapidly enlarging uterus or uterine mass do not have a sarcoma.
- By contrast, postmenopausal patients who have a uterine mass that is new or is growing at either a slow or rapid pace should be evaluated for malignancy.

- ***2- Large or solitary uterine mass*** — Retrospective studies have reported that a sarcoma is often the largest (or the only) mass within a uterus, averaging 7 to 9 cm in diameter. However, leiomyomas may also be singular and may be of any size.

Although data are limited, large uterine size (in excess of 20 gestational weeks) has also not been shown to be associated with sarcoma risk.

- ***3- biopsy techniques*** — Infrequently, both benign leiomyomas and uterine sarcomas will prolapse through the cervix and can be biopsied. accurate diagnosis of sarcoma requires sampling of multiple sites and that the procedure may spill malignant cells within the peritoneal cavity

- ***Other tests*** — There are no laboratory tests that have been found to help differentiate uterine leiomyomas from sarcoma. Some reports have mentioned use of lactate dehydrogenase (LDH), LDH isozyme 3, or cancer antigen 125.

Intraoperative evaluation — During myomectomy or hysterectomy, some characteristics of a uterine mass may raise suspicion of malignancy.

1- Gross characteristics of the mass: Potential features of sarcomas

Loss of the typical whorl pattern.

Yellow color

Soft consistency

Absence of a bulging surface when the capsule is incised.

ill-defined margins – The mass may be difficult to excise, although this may also be true of an adenomyoma or certain leiomyomas

- **Detection of such characteristics may raise the suspicion of a sarcoma but should not be the sole reason for proceeding with an unplanned hysterectomy.**

These differences are subtle, and their identification relies upon adequate surgical experience with ordinary leiomyomas.

- **Frozen section**: Frozen section analysis is not reliable for excluding uterine sarcoma. Multiple areas must be sampled, while frozen section analysis typically depends upon a limited tissue sample.
- Thus, there is a high likelihood of a false-negative result even if a sarcoma is present

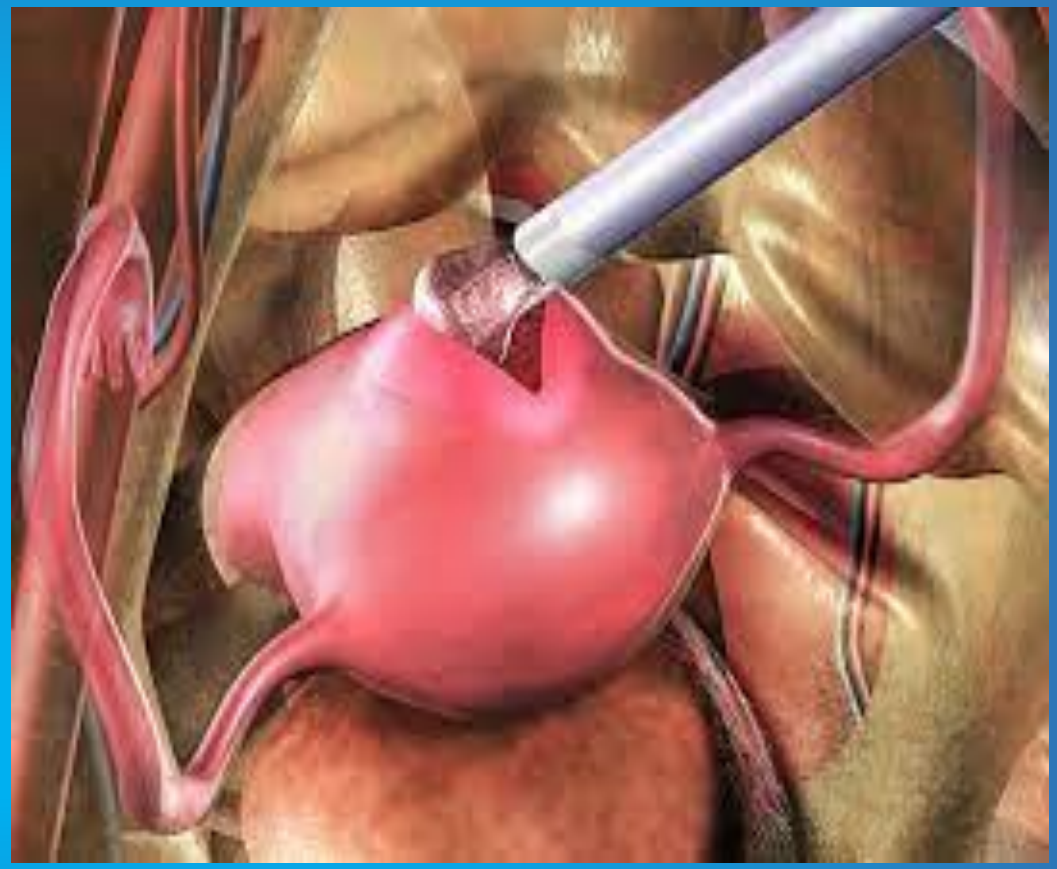
Only a definitive diagnosis of sarcoma on frozen section should influence surgical decisions

CLINICAL ISSUES

- **Do techniques that disrupt a mass disseminate tissue and worsen prognosis?**
- Surgical techniques such as myomectomy, morcellation, and supracervical hysterectomy disrupt a uterine specimen.
- malignant cells may have been disseminated or remain in uterine or cervical tissue that was not removed.
- In addition, dissemination of benign leiomyomatous tissue may result in benign tissue implants that require further treatment

- **Morcellation**

Morcellation of uterine tissue is performed in some procedures to allow removal of a large tissue block through a small laparoscopic or vaginal incision. This may be performed using an electromechanical morcellator device, as is commonly done during laparoscopy, or with a scalpel, commonly done during vaginal hysterectomy.



- Morcellation may lead to intraperitoneal spread of tumor cells, thus making prognosis of undiagnosed ULMS patients worse. Compared to open surgery group, incidence of peritoneal dissemination in stage I and II ULMS increases (44% vs. 12.9%) in morcellation group
- and 3-year overall survival rate is lower (64% vs. 73%).
- Therefore, preoperative diagnosis of ULMS, is of great significance.

- **Supracervical hysterectomy**:
- There are few data about the risk of neoplasm dissemination and worsened prognosis with supracervical hysterectomy.

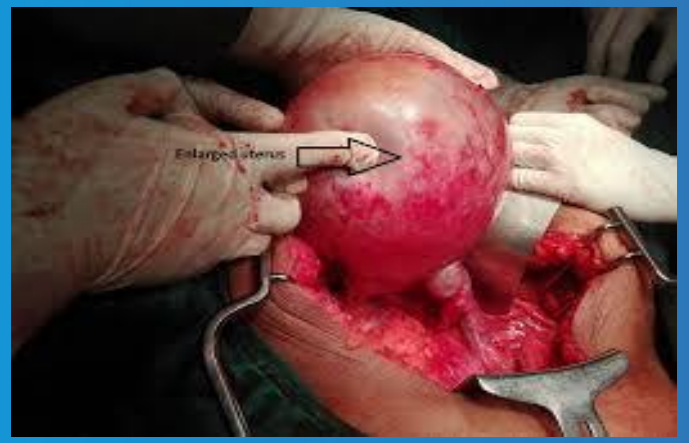
Myomectomy:

- With laparotomy, there may be multiple fibroids, and there is usually substantial exposure of myometrial tissue. With laparoscopy, the specimen is typically morcellated. Smooth muscle cells have been found in pelvic washing after myomectomy and morcellation
- There are few data about the risk of neoplasm dissemination and worsened prognosis with myomectomy. No studies have examined patients who underwent myomectomy without morcellation.

Should hysterectomy be performed to exclude uterine sarcoma?

- **For most premenopausal patients with presumed uterine leiomyomas, whether asymptomatic or symptomatic, we recommend not performing hysterectomy for the sole purpose of excluding malignant neoplasm**.
- exceptions : patients with endometrial sampling and/or magnetic resonance imaging (MRI) results that strongly suggest sarcoma, those with thoracic imaging consistent with lung metastases, those with constitutional symptoms suggestive of malignancy, or those with multiple risk factors for uterine sarcoma.
- In the rare cases in which a patient presents with a uterine mass and symptoms of lung lesions (eg, dyspnea), evidence of lung metastases on thoracic imaging greatly increases the likelihood of a malignant process. However, benign metastasizing leiomyomas is a benign condition that may also present with lung lesions

Should unplanned hysterectomy be performed based on intraoperative findings?



- It is prudent to include, at the time of preoperative consent, discussion of plans in the event of diagnosing a malignant neoplasm intraoperatively
- The only indications for hysterectomy are a definitive frozen section diagnosis of sarcoma and/or gross evidence of metastases. **Unplanned hysterectomy should not be performed in patients of reproductive age without a pathologic diagnosis of sarcoma and a documented preoperative discussion.** Additionally, because oophorectomy has not been shown to influence prognosis for leiomyosarcomas, ovarian preservation may be carried out in the case of unexpected intraoperative findings of sarcoma

Do leiomyomas progress to sarcoma?

- The consensus from genetic studies has been that most sarcomas arise independently
- Histologic studies have found rare examples that appear consistent with progression from a leiomyoma to sarcoma.
- There are no data regarding how often cellular or atypical histology are associated with such abnormal clinical behavior

Preoperative clinical characteristics scoring system for differentiating uterine leiomyosarcoma from fibroid

Guorui Zhang, Xin Yu* , Lan Z hu, Qingbo Fan, Honghui Shi and Jinghe Lang

BMC Cancer (2020) 20:514

Score	0	1	2
• Age	<40	≥ 40	–
• Myoma size	<7 cm	–	≥ 7
• NLR	<2.8	≥ 2.8	–
• LDH	<193	–	≥ 193
• Platelet	<298	≥ 298	–

Scoring	≥0	≥1	≥2	≥3	≥4	≥5	≥6	≥7
ULMS group	45	45	45	39	36	25	16	6
Control group	180	156	118	66	40	11	2	0
Total	225	201	163	105	76	36	18	6
Sensitivity	1	1	1	0.867	0.800	0.556	0.356	0.133
Specificity	0	0.133	0.344	0.633	0.778	0.939	0.989	1
Accuracy(%)	20.0	30.7	47.6	68.0	78.2	86.2	86.2	82.6

ULSM uterine leiomyosarcoma

Conclusion

- The incidence of occult ULMS was low and preoperative diagnosis was difficult.
- Age ≥ 40 years old, tumor size ≥7cm, LDH ≥ 193 U/L, NLR ≥ 2.8 and number of platelet ≥298 × 10^9/L were independent predictors of ULMS.
- The ULMS preoperative clinical characteristics scoring system could be helpful in preoperative diagnosis of occult ULMS.
- Score ≥ 4 points was a useful predictor in diagnosing ULMS from fibroid (sensitivity 0.800, specificity 0.778).

Diagnostic Algorithm to Differentiate Benign Atypical Leiomyomas from Malignant Uterine Sarcomas with Diffusion-weighted MRI

Radiology 2020; 297:361–371

- Current practice defines typical leiomyomas as masses with low signal intensity on both T2-weighted images and diffusion-weighted images. However, up to 65% of leiomyomas manifest with degenerative change and therefore will not have this typical appearance on MRI scans.

- Patients

We extracted pathology and MRI reports between January 2000 and April 2017.

inclusion criteria: *(a)* age 18 years or older; *(b)* at least one uterine mass, with atypical features for leiomyoma on MRI scans; and

(c) surgical procedure with pathologic confirmation, or MRI

follow-up for 1 year or longer in the absence of operation.

Each patient with sarcoma was matched to two control patients (ie, patients without sarcoma) from the same management year.

Four MRI features were assessed

- *(a)* presence of enlarged lymph nodes or peritoneal implants,
- *(b)* presence of focal regional or global low T2 signal intensity,
- *(c)* visual analysis of diffusion-weighted images relative to the myometrium and endometrium/lymph nodes,
- *(d)* the apparent diffusion coefficient (ADC) value.

If the tumor was heterogeneous, the highest signal intensity of the solid component was reported.

An intermediate T2 signal was defined as higher than that of gluteal muscle and lower than that of water.

DWI signal intensity was analyzed visually in three categories on the basis of the highest signal intensity within the mass. A low signal intensity was defined as lower or equal to that of the myometrium, an intermediate signal intensity as higher than that in the myometrium but lower than or equal to that in the endometrium and/or lymph nodes, and a high signal intensity as higher than that in the endometriumand/or lymph nodes.

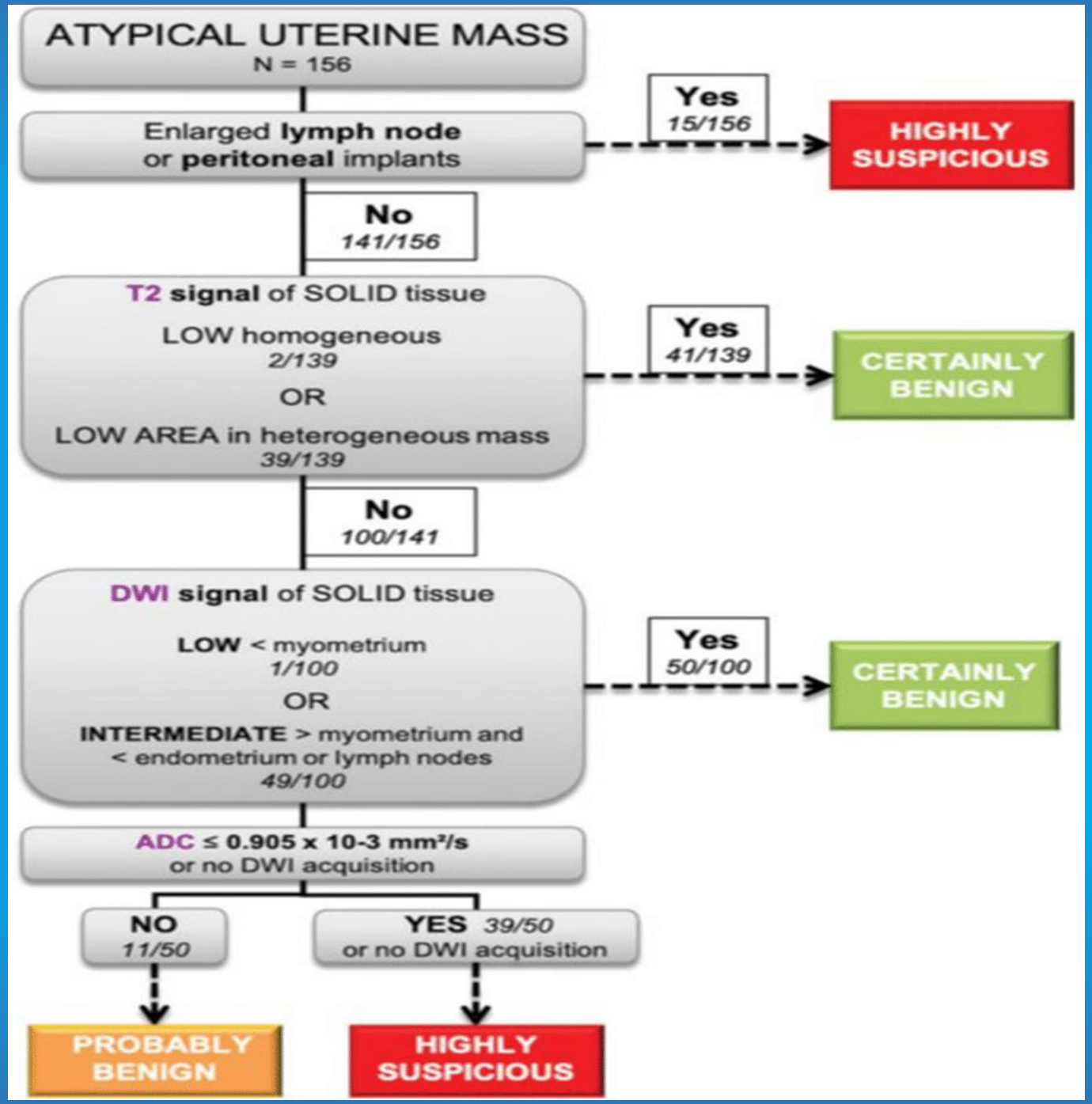
- Uterine masses were classified as

certainly benign: if they showed a global or focal area of low T2 signal and/or a low or an intermediate DWI signal

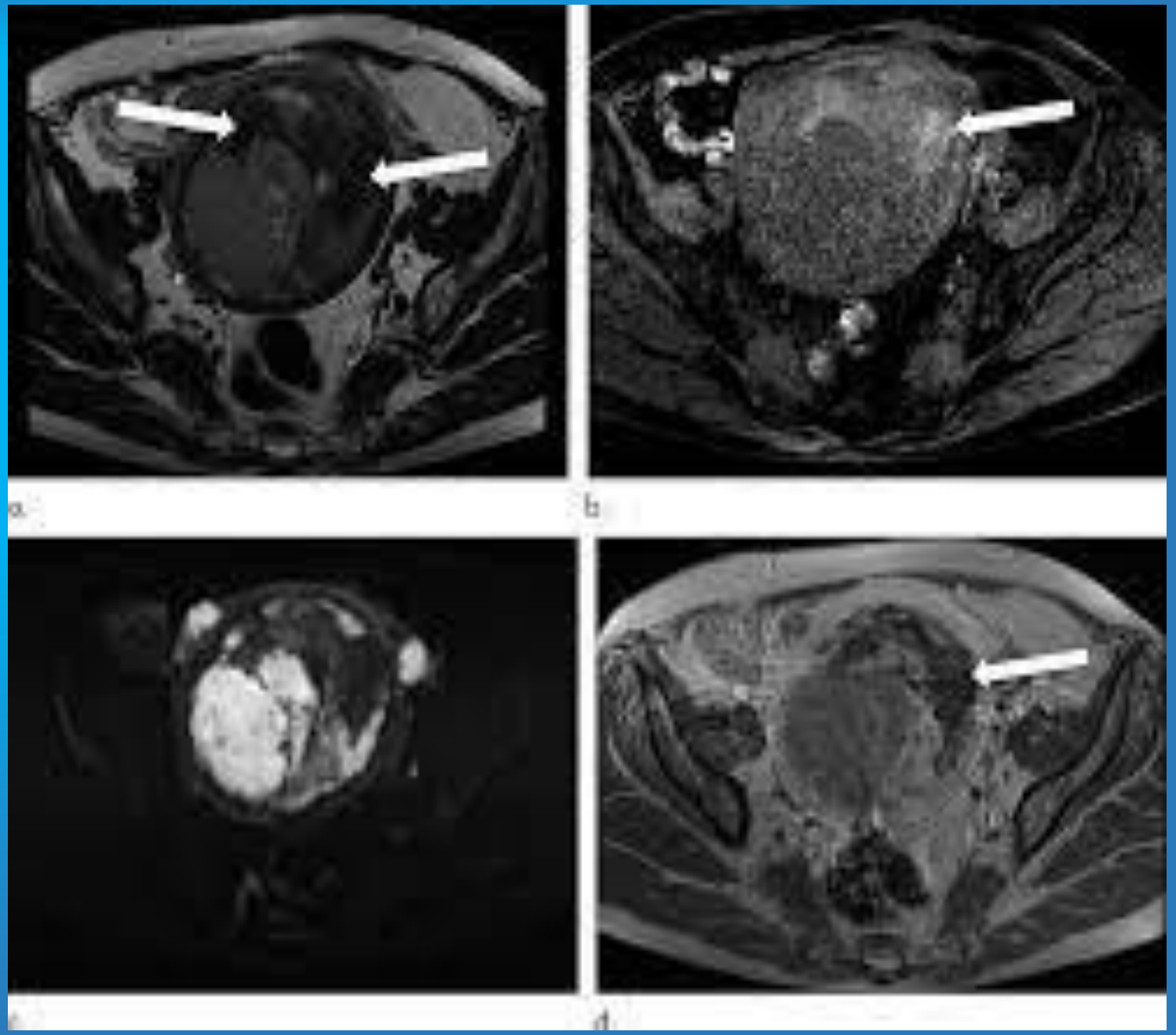
If they did not meet these criteria they were classified as probably benign.

Finally, they were classified as highly suspicious in cases with peritoneal implants or enlarged lymph nodes.

The resulting algorithm achieved a sensitivity and specificity of 98% and 96%, respectively


ATYPICAL UTERINE MASS
N = 156
Enlarged lymph node or peritoneal implants
Yes 15/156
HIGHLY SUSPICIOUS
No 141/156
T2 signal of SOLID tissue
LOW homogeneous 2/139
OR
LOW AREA in heterogeneous mass 39/139
Yes 41/139
CERTAINLY BENIGN
No 100/141
DWI signal of SOLID tissue
LOW < myometrium 1/100
OR
INTERMEDIATE > myometrium and < endometrium or lymph nodes 49/100
Yes 50/100
CERTAINLY BENIGN
ADC ≤ 0.905 x 10-3 mm²/s or no DWI acquisition
NO 11/50
YES 39/50 or no DWI acquisition
PROBABLY BENIGN
HIGHLY SUSPICIOUS

MRI scans in 52-year-old postmenopausal woman undergoing hormone therapy, with abnormal vaginal bleeding and palpation of pelvic mass.
MRI scans show uterine mass on **(a)** axial T2-weighted image, **(b)** axial T1-weighted image with fat suppression,
(c) axial diffusion-weighted image (*b* = 1000 sec/mm2), and **(d)** axial T1-weighted image with fat suppression and gadolinium chelate injection. Figure represents example of leiomyosarcoma with low T2 signal intensity because of hemorrhage (arrows), which should not be confused with low T2 signal intensity in tissue associated with benign leiomyoma. Area manifesting low T2 signal intensity can be identified as hemorrhage because it manifests high T1 signal intensity and does not demonstrate enhancement after injection of contrast material.



Preoperative Blood Inflammatory Markers for the Differentiation of Uterine Leiomyosarcoma from Leiomyoma

Cancer Management and Research 2021:13

- Laboratory tests were performed within 1 to 2 weeks prior to surgery. Variables such as NLR, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and monocyte-to-lymphocyte ratio (MLR) were calculated

- Significant differences were observed between the LMS and LM groups for the following variables: age at diagnosis, menopausal status, WBC count, ANC, CRP, LDH, and NLR
- Older or postmenopausal patients with a high WBC count, high ANC, high serum CRP, high serum LDH, and high NLR were more likely to be diagnosed with LMS.

Pre - & Postmenopause	LMS, Median (IQR) (n=79)	LM, Median (IQR) (n=257)	*P*-value
Age (years)	54	44	< 0.001
Postmenopause (%)	46 (58.2)	41 (16.0)	< 0.001
BMI (kg/m^2)	24.65	23.72	0.145
Overweight(≥23kg/m^2)	49 (62.0%)	142 (55.5%)	0.369
WBC (per μL)	6690.0	5805.0	< 0.001
ANC (per μL)	4314.1	3387.6	< 0.001
CRP (mg/dL)	1.00	0.04	< 0.001
LDH (U/L)	425.0	185.5	< 0.001
NLR	2.36	1.91	< 0.001
Premenopause	**LMS, Median (IQR) (n=33)**	**LM, Median (IQR) (n=216)**	***P*-value**
BMI (kg/m^2)	23.98	23.53	0.438
Overweight(≥23kg/m^2)	20 (60.6)	116 (54.0)	0.598
WBC (per μL)	6230.0	5770.0	0.141
ANC (per μL)	3970.7	3388.9	0.092
CRP (mg/dL)	0.69	0.04	0.005
LDH (U/L)	387.5	175.0	<0.001
NLR	2.30	1.95	0.089

Note: P-values for comparisons of medians were obtained using the Mann–Whitney-*U* test.
Abbreviations: LMS, uterine leiomyosarcoma; LM, uterine leiomyoma; IQR, interquartile range; WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio.

Key features to identify sarcomas – BET1T2ER Check!

Radiol 2021; **94**: 20201332.

B: Borders

- An irregular or poorly defined border is a key suspicious feature

74–84% sensitivity and 86–91% specificity for LMS

E: Enhancement

The addition of intravenous contrast medium increases the diagnostic accuracy of uterine sarcomas.

Myometrially based uterine sarcomas typically demonstrate heterogenous enhancement with irregular, often central, areas lacking contrast enhancement due to necrosis.

central unenhanced areas on MRI gave a 95–100% sensitivity and 68–73% specificity for LMS

In addition, uterine sarcomas demonstrate different enhancement characteristics to leiomyomas with sarcomas demonstrating increased mean contrast enhancement and early enhancement ratios compared to leiomyomas

T1: *T*1 weighted imaging

- presence of hemorrhage: Intraregional hemorrhage has a high sensitivity (95–100%) and specificity (82–95%) for LMS.
- An additional factor that helps in characterization is that when hemorrhage does occur in a fibroid, it is usually due to a typical hormonal insult such as pregnancy or oral contraceptive use and the patient typically presents with an expected history of pain and systemic upset such as fever and leukocytosis

If imaging is required in pregnancy to confirm diagnosis of red degeneration of myoma and exclude differential causes of fever and pain such as appendicitis, then the diagnosis can be made on *T*1WI and *T*2WI alone without the addition of intravenous contrast medium.

T2: *T*2 weighted imaging

low T2 signal intensity dark areas can be caused by flow voids or intra-lesion hemosiderin.

sensitivity (79–84%) and specificity (86%) for this feature in the diagnosis of LMS

These features should not be confused with normal low T2 signal seen in benign leiomyomas and, correlation with *T*1WI and enhancement is helpful.

High T2 signal intensity has been reported by many groups but there can be considerable overlap with degenerating leiomyomas

In summary, the signal intensity on *T*2WI in sarcomas is variable as it depends upon the areas of necrosis, soft tissue, flow voids and haemosiderin.

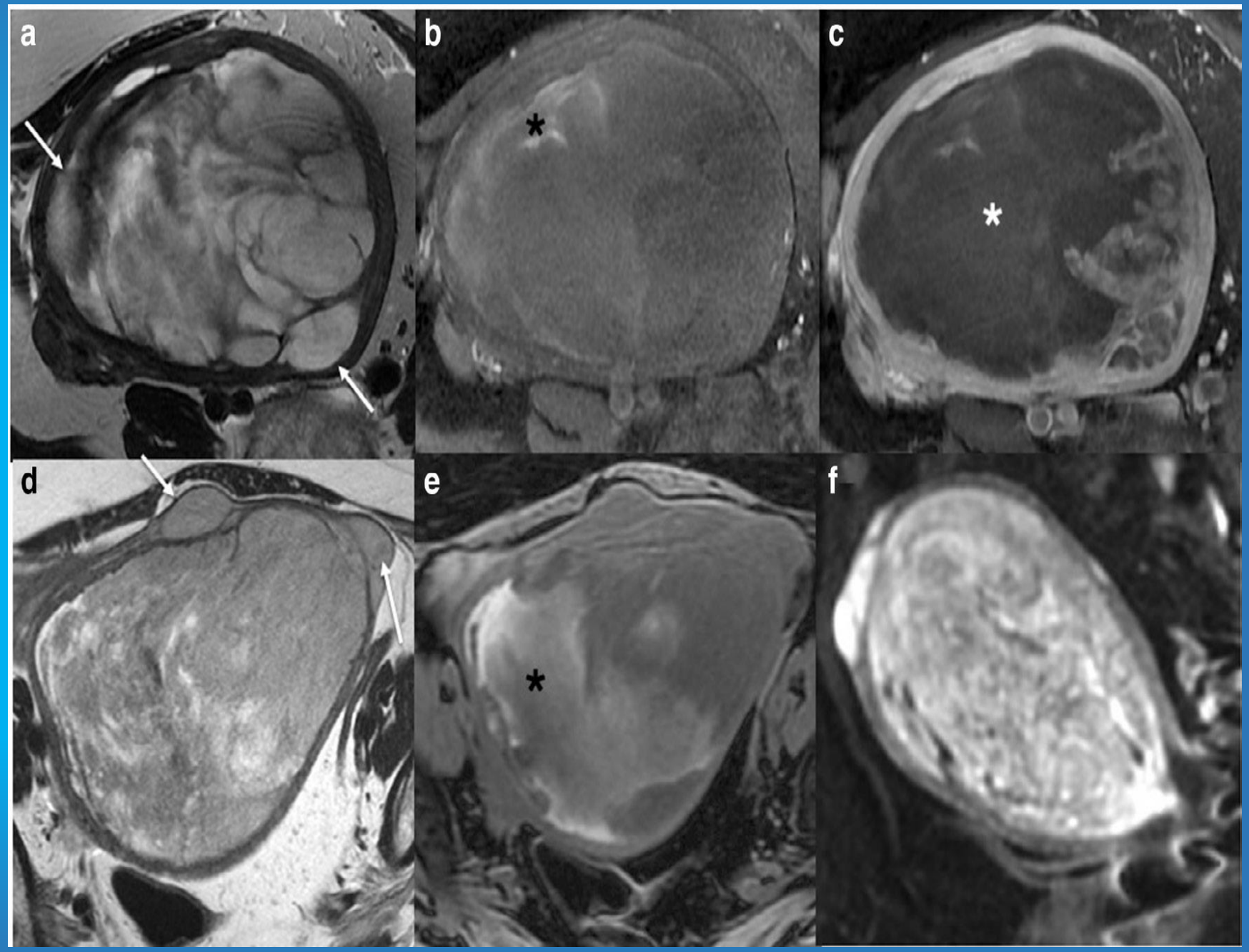
E: Endometrial involvement

Adenosarcomas and ESS have a high propensity for endometrial involvement, the aggressive nature of LMS, means that although it originates within the myometrium it can also involve the endometrium in up to 35–50% of cases, resulting in loss or irregularity of the endometrial stripe. The outline of the lesion with the endometrium is therefore vital to assess as is the serosal surface for the same reason in cases suspicious for LMS

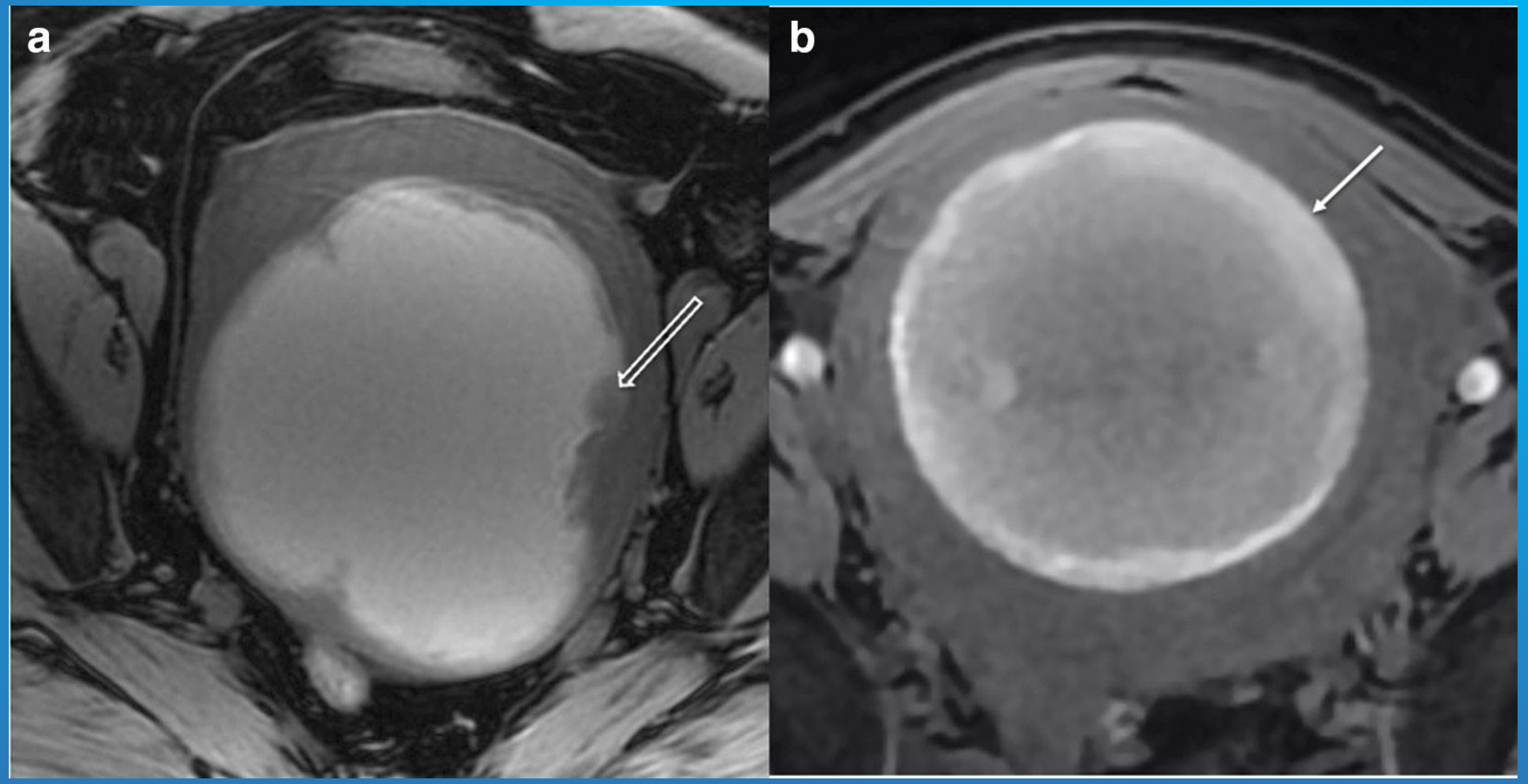
R: Restricted diffusion

High diffusion-weighted imaging (DWI) SI greater than that of endometrium, and low ADC values (cut-off value: 0.79–1.27 × 10^3 mm2 s−1) have been found in LMS. However, the routine use of ADC value on its own is limited due to overlap with cellular leiomyoma values. Different cut-off values have been suggested.

Axial T2 (a) and T1 fat saturated image without (b) and with gadolinium contrast medium (c) MRI of a low grade ESS. The ESS demonstrates myometrial invasion with irregular nodular borders (a, white arrows), heterogeneous T2 signal, intralesional hemorrhage (b, black *), and central poor enhancement (c, white *). Axial *T*2W (d), axial T1 fat saturated image (e) and DWI (f)
MRI of a uterine adenosarcoma. The adenosarcoma demonstrates myometrial invasion with irregular borders (d, white arrows), heterogenous T2 signal, intralesional haemorrhage (e, black *), and restricted diffusion. (f). ADC maps not shown..



Comparison of imaging in LMS (a) and red cell degeneration of benign fibroid (b): Axial *T*1W fat saturated MRI of two intrauterine lesions. Lesion (a) has diffuse hyperintense *T*1W fat saturated signal with and irregular intermediate T1 signal border and soft tissue projecting into the lesion (open white arrow). Lesion (b) has an intermediate to high *T*1W fat saturated signal intensity with a hyperintense smooth rim and clear distinction of the margin with no internal projections (closed white arrow) in a 40-year- old lady. Surgical histology of lesion (a) confirmed LMS. Lesion (b) had been imaged with MRI 12 months previously, when it had low *T*2W signal. Between the two MRIs, the female had become pregnant and given birth and the follow-up
MRI was for further management of her benign leiomyoma, which had undergone red degeneration during pregnancy. LMS, leiomyosarcoma.



SUMMARY

- it is vital to raise suspicion on pre-operative imaging to provide timely priority referral for appropriate surgical planning.
- MRI is the best modality for assessing uterine sarcomas with CT used for assessment of distant spread.
- Atypical leiomyomas which have undergone degeneration, are cellular, metastasizing or intravascular leiomyomas all have at least one key feature that can mimic diagnosis of LMS on MRI but combining MR imaging features and taking into account the clinical scenario are helpful.
- Identifying these key MR imaging features such as irregular Borders, heterogenous Enhancement with central poor enhancement, hyperintense *T*1W signal in keeping with haemorrhage, T2 dark areas from vascular signal voids and haemosiderin, Endometrial invasion and restricted diffusion together aids successful pre-operative suspicion for sarcoma with the combination increasing sensitivity, specificity and accuracy. These can be remembered as the acronym BET1T2ER check


THANK
YOU!