More then a Fibroid?
Red Flags for the Diagnosis of Leiomyosarcoma and STUMP

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Disclosures

- None
- An AI search engine was utilized to identify references

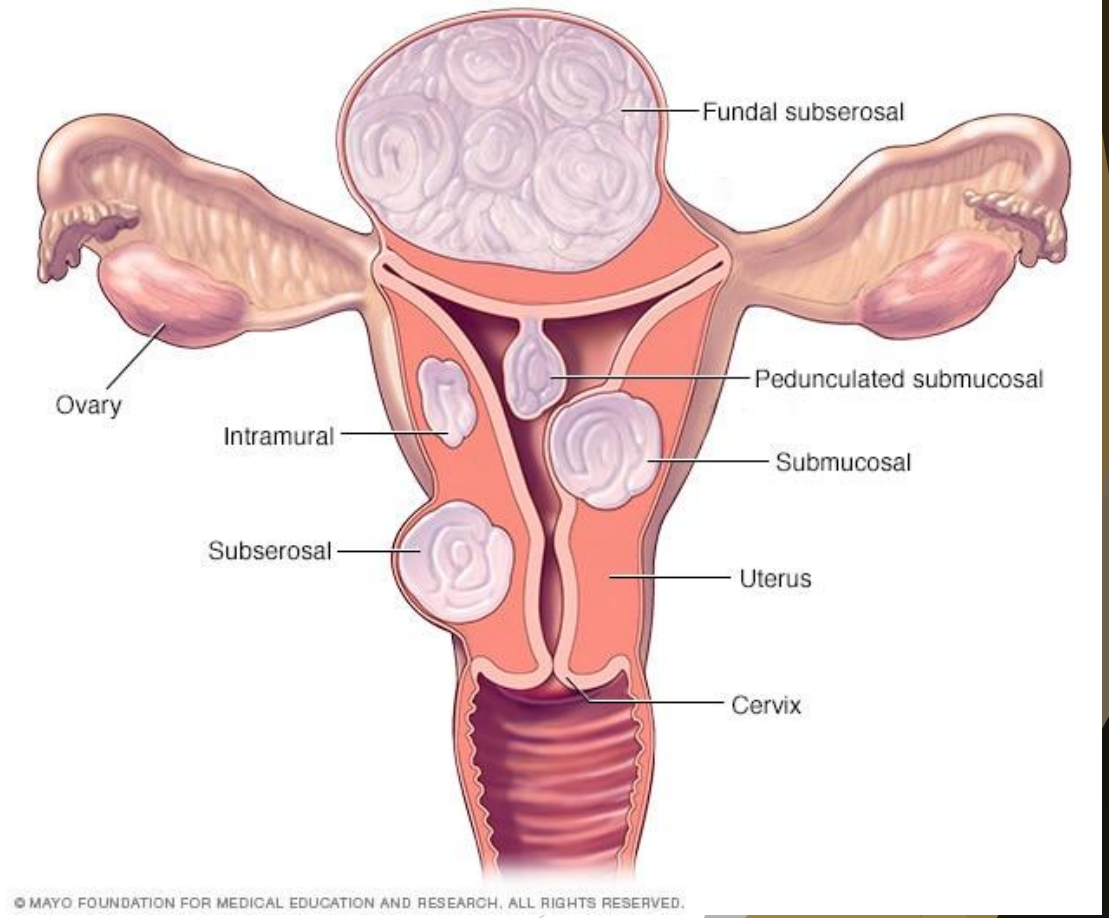
Objectives

- Define the diagnostic criteria for leiomyosarcoma, STUMP and other atypical leiomyomas
- Identify key clinical and radiologic features that differentiate a leiomyosarcoma from a benign uterine leiomyoma
- Outline the essential components of initial surgical management of a leiomyosarcoma or STUMP tumor

Epidemiology and Definitions

The Clinical Dilemma:
The prevalence of leiomyomas vs the rarity of leiomyosarcomas

- Fibroids affect 70 to 80% of women with a uterus during their lifetime
  - Prevalence is higher among black women than white women
  - Up to 50% of women with fibroids have symptoms
  - Only ~25% of cases are clinically significant enough to require intervention
- Uterine leiomyosarcoma (LMS) represents 1-2% of uterine malignancies
  - incidence is approximately 0.8 per 100,000 persons
  - 1 in 800 smooth muscle tumors of the uterus



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The Clinical Dilemma:

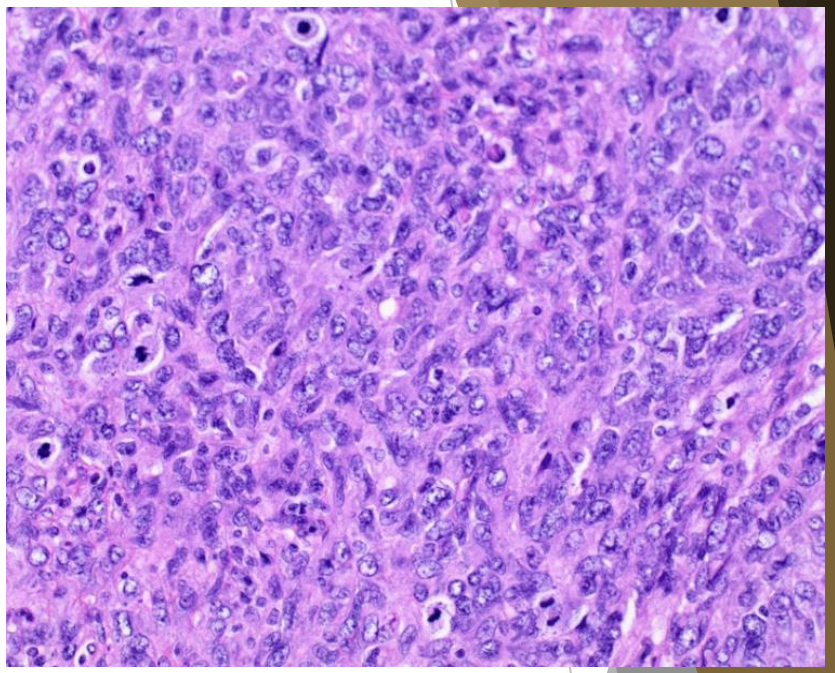
Among women undergoing surgery for presumed benign leiomyomas, the prevalence of occult leiomyosarcoma is low

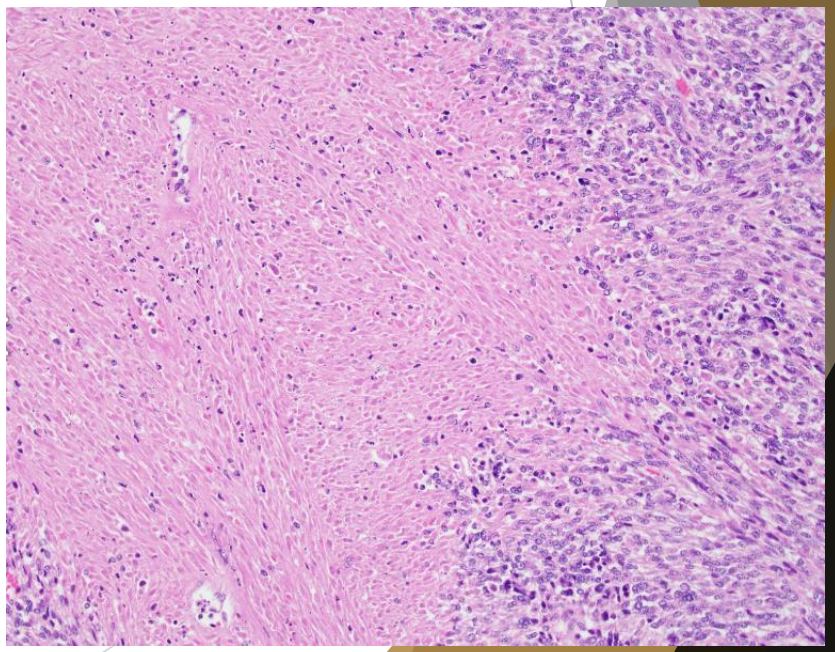
- A systematic review by the FDA included 23 studies published from 2015 to 2017 and found that among patients undergoing surgery for presumed benign fibroids the rate of:
  - unsuspected uterine sarcoma (any histologic type): 0 to 1.48%
  - Leiomyosarcoma: 0 to 0.51%.
- The risk increased with age, and for any uterine sarcoma, approximate rates were:
  - 40 to 50 years (0.15 to 0.22 percent)
  - 50 to 60 years (0.58 percent)
  - 60 years or older (1.5 to 2.8 percent).

Pathologic Diagnosis of LMS:
The Stanford Criteria

- The Stanford Criteria for diagnosis uterine leiomyosarcoma, established by Bell et al, require two of the following 3 histologic features:
  - Cytologic atypia
    - Diffuse, moderate-to-severe
  - High mitotic activity
    - >10 mitotic figures per 10 high-power fields
  - Tumor cell necrosis
    - Abrupt transition from viable tumor cells to necrosis

- This criteria differentiates LMS from benign leiomyomas or intermediate smooth muscle tumors of the uterus





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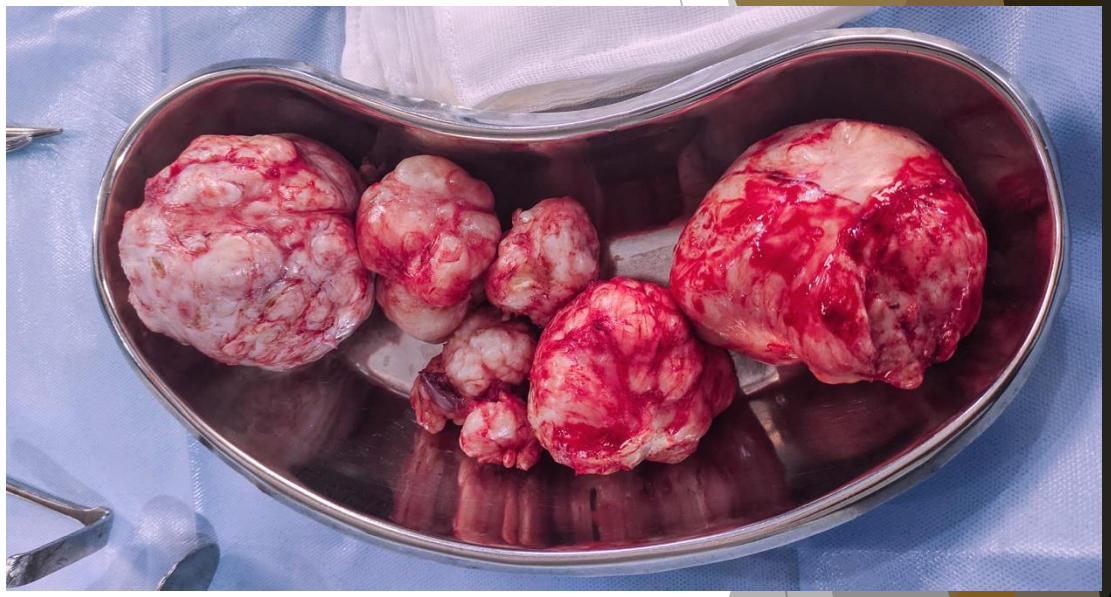
Defining the Spectrum:
From benign leiomyoma to malignant LMS



- Benign Leiomyoma
- Lipoleiomyoma
- Intermediate Leiomyomas
  - Cellular/Highly Cellular Leiomyoma
  - Leiomyoma with Bizarre Nuclei (LBN)
  - Mitotically Active Leiomyoma
    - leiomyoma with >5 and <19 mitotic figures per 10hpf
- Smooth Muscle Tumor of Undetermined Malignant Potential (STUMP)
- Leiomyosarcoma

STUMPed?
Further defining Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP)

- Do not meet criteria of leiomyoma or leiomyosarcoma
  - Diagnosis of Exclusion
- Some tumors do not fall neatly into the LMS vs leiomyoma definitions (Stanford criteria). Examples:
  - Necrosis of uncertain type (not tumor necrosis) with high mitotic activity
  - Marked atypia and borderline mitotic counts (no necrosis)
  - Marked atypia with difficult determining mitotic counts (no necrosis)
  - High mitotic activity (>15-20/10hpf) but no atypia or necrosis
  - Tumors with early necrosis that is difficult to define
  - Tumor necrosis, lower mitotic activity (<10/10hpf)
- Pathologic features raise concern for malignant behavior, but only outcomes will determine if tumor is malignant or benign
  - Recurrence rate up to 36% based on multiple studies, mean value of 12%, Guntupalli et al 7%
  - Can recur as leiomyoma, STUMP or LMS

Gadducci A, Zannoni GF. Uterine smooth muscle tumors of unknown malignant potential: A challenging question. Gynecol Oncol. 2019 Sep;154(3):631-637.

Clinical Presentation

What to watch for:
Risk Factors for LMS

- Most patients have no risk factors
- African American race
  - 2x the incidence among black persons
  - Incidence is increasing
- Tamoxifen use
  - >5 years
  - 17 per 100,000
- History of pelvic radiation
- Hereditary cancer syndromes
  - Hereditary Retinoblastoma Syndrome
  - Li-Fraumeni Syndrome
- Age
  - Peri- and Post-menopausal

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2. Felix AS, et al. The etiology of uterine sarcomas: a pooled analysis of the epidemiology of endometrial cancer consortium. Br J Cancer. 2013 Feb 19;108(3):727-34.
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Is it or Isn't it?

Rapid Growth as a Controversial Risk Factor for LMS

- Rapidly growing mass is defined as increase in 6cm in 6-12 months
- Contradictory evidence as to whether rapid growth is associated with risk of LMS
  - Both leiomyomas and LMS have the propensity to grow rapidly
    - In large retrospective studies, incidence of sarcomas is similar among uterine masses that are rapidly growing and those that are not
    - Leiomyomas can grow up to 138% within six months
    - A prospective study evaluated 101 fibroids in 36 patients with MRI every 3 months for 1 year. 37 fibroids had an increase in volume of ≥30% in a three-month period. Rapid growth was more likely in tumors that were ≤5 cm in diameter.
  - Many tumors present at a large size and do not allow for surveillance over time
  - Rapid growth is more concerning in the postmenopausal state

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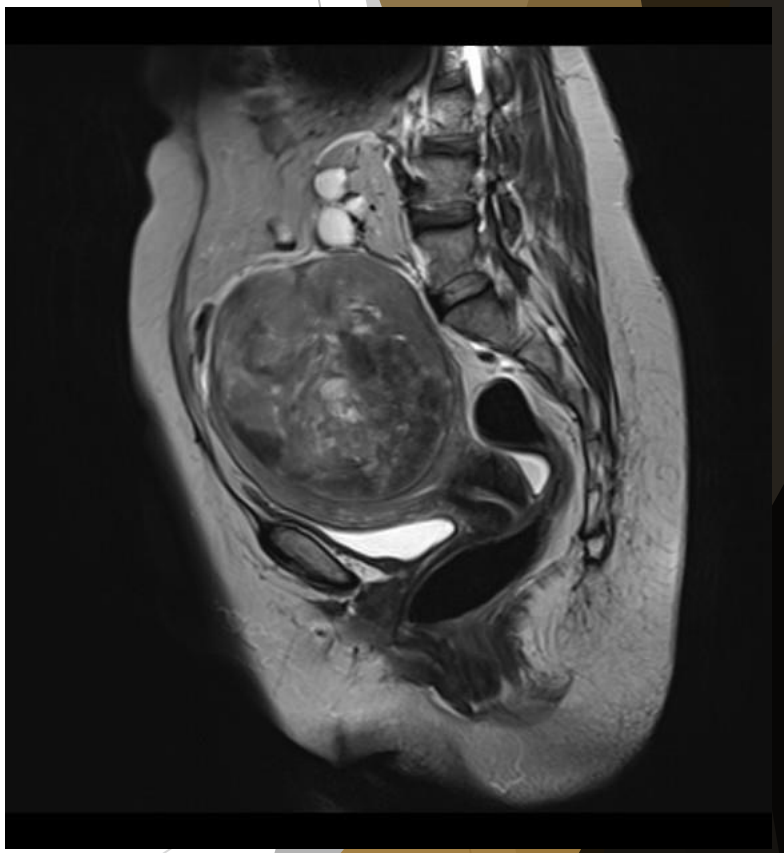
Is it or Isn't it?

Large Solitary Mass as a Controversial Risk Factor for LMS

- Evidence for large solitary mass being a risk factor for LMS:
  - In some cohort studies, sarcomas have been reported as the largest (or the only) mass within a uterus, averaging 7 to 9 cm in diameter
  - In a retrospective study of 190 patients undergoing hysterectomy for symptomatic fibroids, mass size of ≥10 cm compared with <10 cm on preoperative imaging was associated with a higher risk of leiomyosarcoma
- Evidence against large solitary mass being a risk factor for LMS:
  - In two retrospective studies, large uterine size (in excess of 20 gestational weeks) was not associated with sarcoma risk



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Not Very Specific:
Clinical Presentation of LMS

- Most often diagnosed in women between ages 35 – 75
  - Spike in incidence during the perimenopausal years
  - Median age of diagnosis = 54
- Most common symptoms **For BOTH Leiomyomas and LMS**
  - Abnormal uterine bleeding (56%)
  - Palpable pelvic mass or enlarged uterus (54%)
  - Pelvic pressure or pain (22%)

Pre-operative Evaluation

Check List:
Standard Pre-op Evaluation

- Pelvic Exam
  - Compare to prior exams
  - Mobile vs immobile
- Evaluation and Screening for more common gynecologic malignancies
  - Cervical screening up to date
  - Endometrial biopsy

Is Pre-op Pathology Possible?
The Role of Endometrial Sampling

- Endometrial sampling yields a preoperative diagnosis in 33-68% of patients with uterine sarcomas
  - A study done with the Canadian Task Force III database showed that among patients with leiomyosarcoma who underwent endometrial sampling before surgery (n = 68), the sensitivity of sampling for a diagnosis of features of a malignant smooth muscle neoplasms was 52 percent%
    - no significant difference between office endometrial biopsy and dilation and curettage.
- Significant limitations:
  - have limited access to these mesenchymal tumors
  - Small sample is unlikely to provide enough tissue to fully evaluate for malignant features of a smooth muscle neoplasm
- Therefore, a negative endometrial sampling does NOT rule out LMS
- Recommend endometrial sampling for:
  - Abnormal bleeding
  - Any concern for malignancy, including LMS
  - Planning Morcellation

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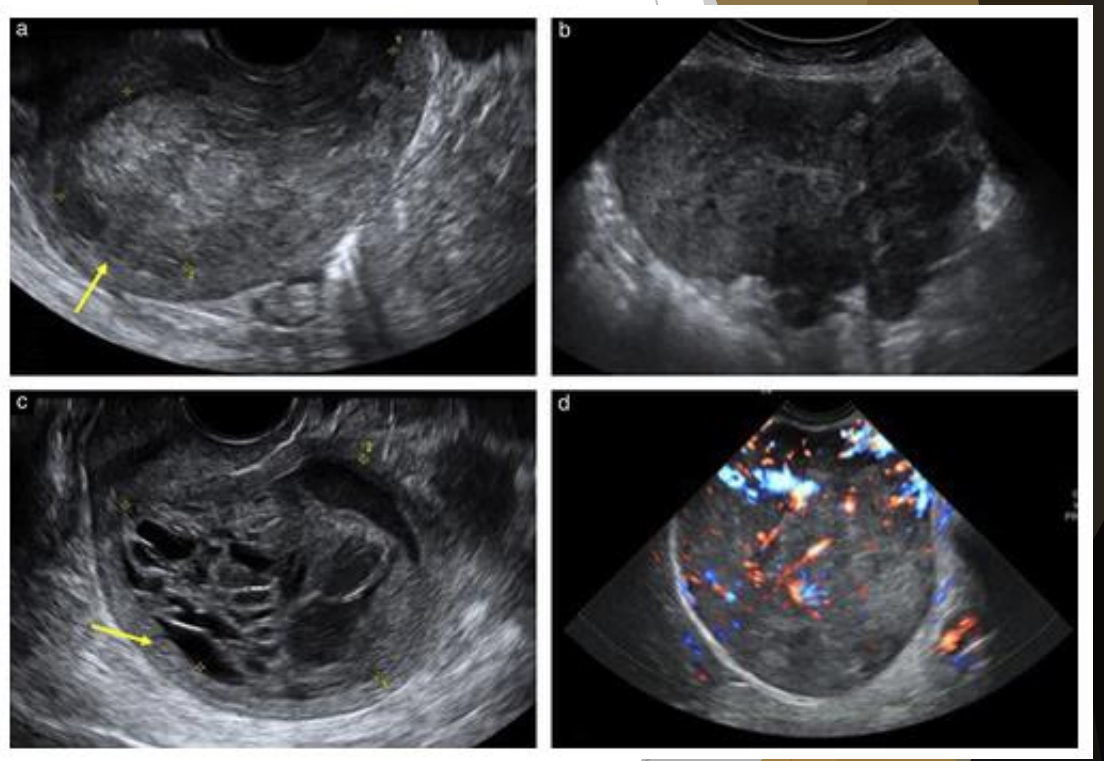
Check List:
Standard Pre-op Evaluation

- Pelvic Exam
  - Compare to prior exams
  - Mobile vs immobile
- Evaluation and Screening for more common gynecologic malignancies
  - Cervical screening up to date
  - Endometrial biopsy
- Imaging
  - Pelvic Ultrasound
  - CT Chest/Abdomen/Pelvis
  - Pelvic MRI

Imaging Modalities:
Role of Ultrasound

- Recommended as first imaging evaluation
- Features suggestive of sarcoma include:
  - inhomogeneous echogenicity of the solid tissue
  - Irregular borders
  - Cystic areas
  - color Doppler findings of irregular and moderate-rich vessel distribution
  - central necrosis
- In a meta-analysis of three observational studies, in diagnosing uterine sarcomas, ultrasound was found to have:
  - Sensitivity of 0.76 (95% CI, 0.70-0.81)
  - Specificity of 0.89 (95% CI, 0.87-0.92)



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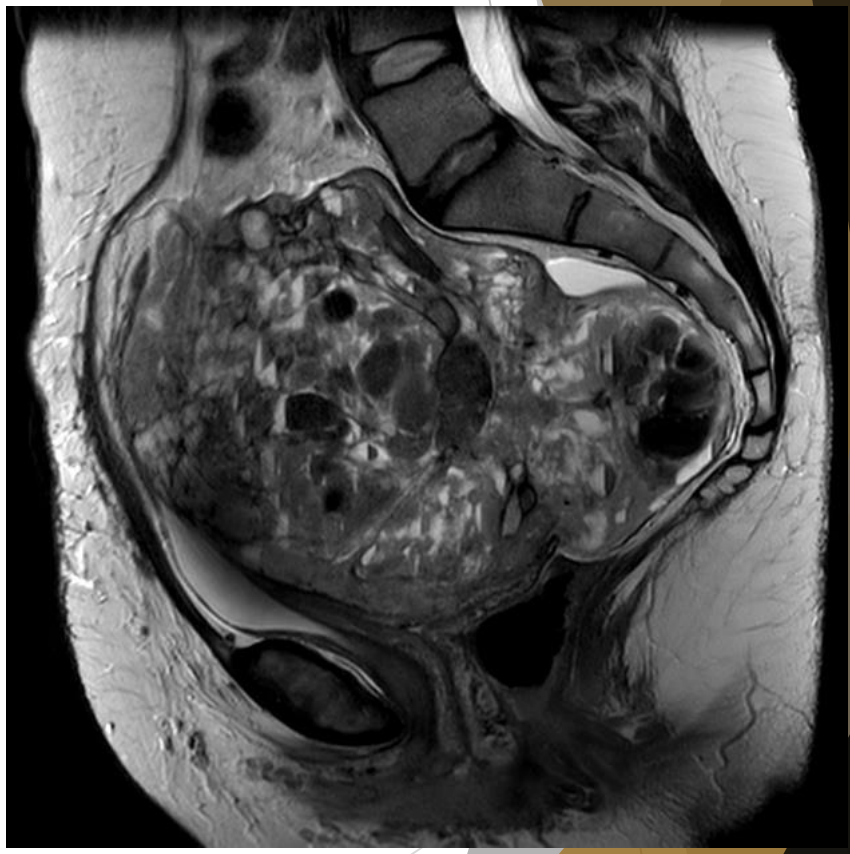
Focusing in with MRI:
MRI increases sensitivity, specificity in evaluating for LMS

- A meta-analysis of 8 observational studies with 2253 uterine leiomyomas and 179 uterine sarcomas showed that in differentiating between leiomyomas and sarcomas, MRI had:
  - Sensitivity = 90%
  - Specificity = 96%
- Diffusion-weighted imaging (DWI) MRI appears to assist in differentiating between leiomyomas and sarcomas
  - A retrospective study evaluating the added value of DWI found that DWI-based quantitative parameters improved the diagnostic performance over that of routine MRI
    - AUC 0.92 versus 0.78
- An MRI that shows a typical fibroid (dark and homogenous in T2-weighted images) has a high negative predictive value



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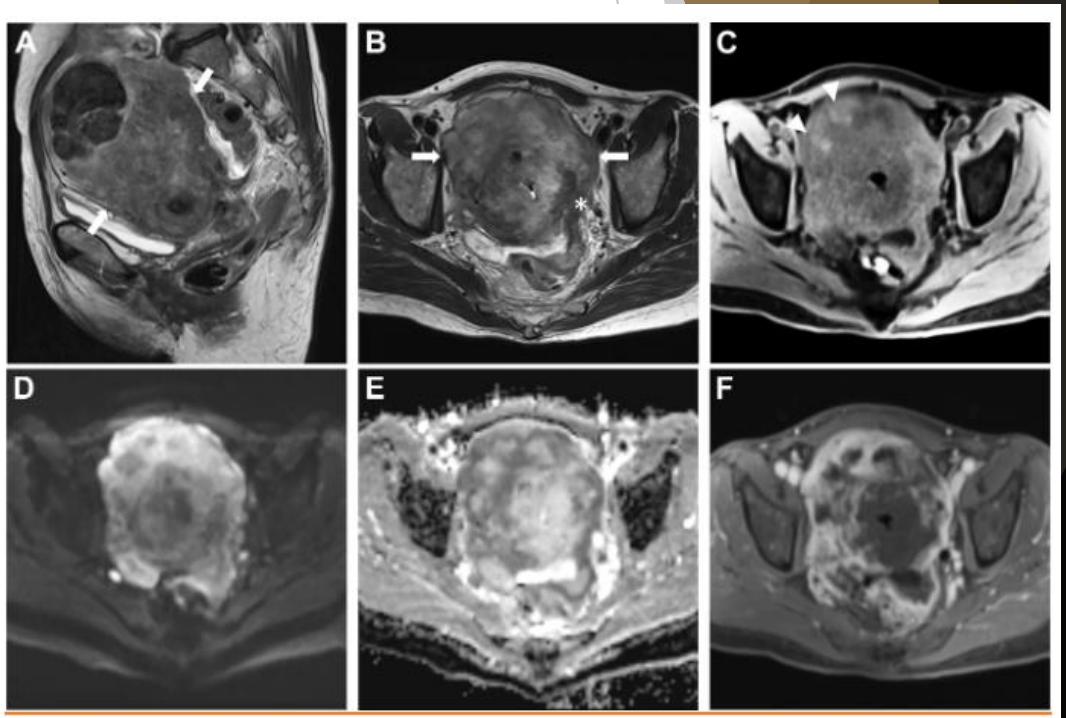
Focusing in with MRI:
Features Suggestive of LMS

- Solitary mass
- Irregular, infiltrating borders
- Heterogenous T2 signal with areas within the solid component showing intermediate or hyperintense T2 signal intensity
- Absence of calcifications/presence of necrosis
- Presence of intralesional hemorrhage



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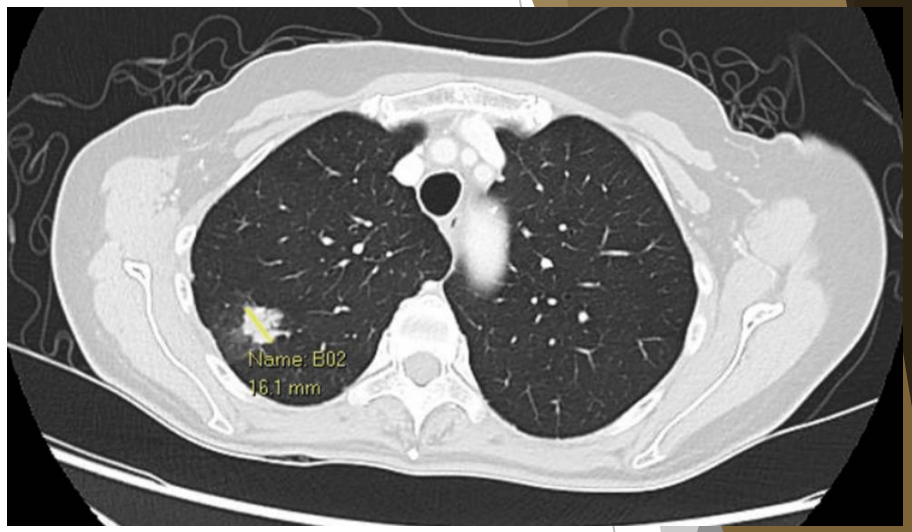
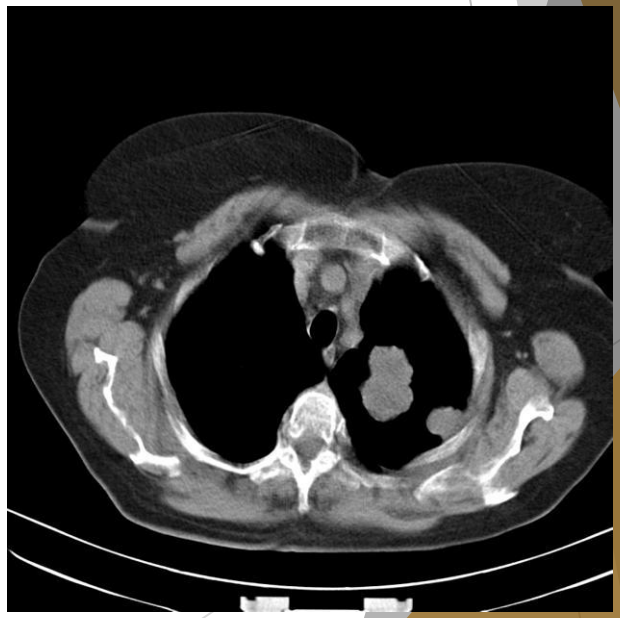
Imaging Modalities:
Role of CT

- Evaluation for metastatic disease
  - CT Chest, Abdomen, Pelvis with contrast
- Among patients with metastatic LMS, up to 80% have metastases to the lung
- In a study of 130 women with metastatic leiomyosarcoma the following metastatic locations were identified:
  - Lungs 67.7%
  - Cranial/intracranial 16.2%
  - Skin/soft tissues: 15.3%
  - Bone 13.8%





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Surgical Considerations

Surgical Route:
The Do Not Morcellate Warning

- Intact removal of uterine LMS has improved outcomes with lower recurrence rates and less tumor dissemination
  - In a study of 25 women with uterine LMS who underwent morcellation compared to 31 patients with intact tumor removal:
    - rate of abdominopelvic dissemination was 44% vs. 12.9% (p =0.032)
    - Poorer overall survival on multivariate analysis was observed in the morcellated cohort.
  - Another study compared 19 women with fragmented uterine removal and 39 with intact removal anf found >3x risk of recurrence in the morcellation cohort
- FDA guidance is that morcellation should not be used in peri- and post-menopausal patients with a uterine tumor
  - Based off large database study showing that the presence of malignant neoplasm was associated with increasing age. The risk of occult uterine cancer stratified by age was:
    - <40 years 1 in 2337
    - 40 to 49 years 1 in 702
    - 50 to 59 years 1 in 154
    - ≥60 years 1 in 31
- Imaging findings suspicious for malignancy should preclude morcellation

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2. Uterine Morcellation for Presumed Leiomyomas: ACOG Committee Opinion, Number 822. Obstet Gynecol. 2021 Mar 1;137(3):e63-e74.

Surgical Route:
Carving out a place for Myomectomy?

- There is a lack of data about the risk of tumor dissemination and prognosis with myomectomy.
- No studies have examined patients who underwent myomectomy without morcellation.

Let it Go:
Limitations of Intraoperative Frozen Section

- "Smooth muscle neoplasm, can not rule out malignancy"
- Frozen section analysis is not reliable for excluding uterine sarcoma
- Frozen section analysis utilizes one or a small number of small representative samples, where as larger evaluation of smooth muscle neoplasms is needed to evaluate for features of LMS.
  - High likelihood of a false-negative result even if a sarcoma is present.

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Management of the Ovaries:
Is Ovarian Preservation an Option for LMS?

- Metastases of LMS to the ovary is rare, 3-4%
- Multiple large retrospective reviews have demonstrated no benefit in survival for BSO
  - Large National Cancer Database (NCD) study of over 7000 patients with LMS demonstrated no survival impact when omitting oophorectomy under the age of 51
- Common practice: leave ovaries in place in pre-menopausal patients with LMS and normal appearing ovaries

Leitao MM, Sonoda Y, Brennan MF, Barakat RR, Chi DS. Incidence of lymph node and ovarian metastases in leiomyosarcoma of the uterus. Gynecol Oncol. 2003 Oct;91(1):209-12.
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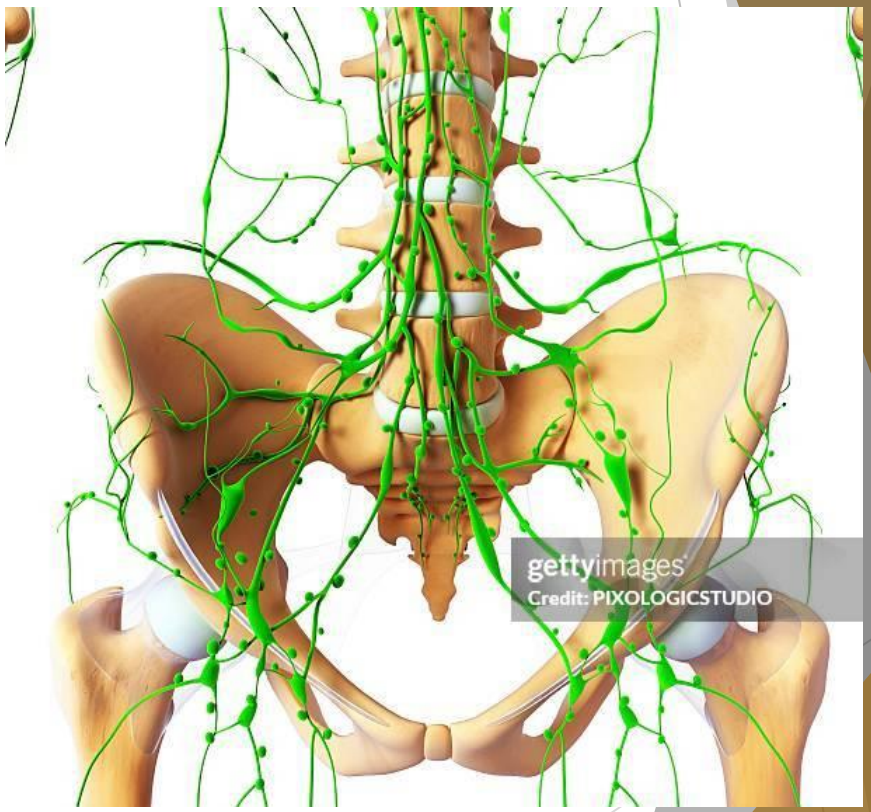
Lymphadenectomy:
Should routine lymph node dissection be performed?

- Rate of lymph node involvement in LMS is 5-11%
- Rate of occult lymph node involvement is up to 3%
  - One study found no lymph node involvement in Stage I/II LMS
- Contradictory evidence of whether lymph node dissection has any impact on survival outcomes
  - NCD Study demonstrated no impact on survival when omitting lymphadenectomy
- Common practice: if not enlarged, do not perform dissection



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Post-Operative Management

Management of Incidental Diagnosis of LMS:
What to do if LMS is diagnosed after myomectomy or hysterectomy?

- Expert pathology review
- Refer to Gynecologic Oncologist
- CT Chest/Abdomen/Pelvis with Contrast to evaluate for metastases

Still STUMPed?
Post-Operative Management for STUMP tumors

- Expert pathology review
- Referral to Gyn Onc
- No role for chemotherapy or hormonal therapy
- Surveillance
  - CT Chest/Abdomen/Pelvis with contrast following diagnosis to rule-out disease elsewhere (if not previously performed)
  - Clinical surveillance every 6 months for 5 years
    - If hysterectomy
      - Pelvic exam and ultrasound every 6 months
      - CT annually
    - If no hysterectomy (myomectomy)
      - Pelvic exam and ultrasound every 6 months
      - MRI and Chest Xray annually

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Highlights:

- There is no pelvic imaging modality that can reliably diagnose uterine sarcomas
  - If concern for LMS, get an MRI in order to increase sensitivity and specificity.
    - Helpful in ruling out LMS
  - CT CAP with contrast to evaluate for metastatic disease
- Have increased suspicion in post-menopausal patients
- Imaging findings suspicious for malignancy should preclude morcellation and myomectomy
- Surgical management does not require expert oncologic procedures if confined to uterus
- When to refer to Gynecologic Oncologist
  - Metastatic disease
  - Expedite surgery
  - Surgical complexities
  - Pathologic diagnosis

Thank You and Questions?

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