Uterine sarcomas
(mesenchimal tumors)

מיחאי מאירוביץ

היחידה לגינקולוגיה אונקולוגית

המרכז הרפואי האוניברסיטאי סורוקה
SOROKA UNIVERSITY MEDICAL CENTER
www.soroka.co.il

The Israeli Society of Gynecologic Oncology
החברה הישראלית לגינקולוגיה אונקולוגית

- rare tumors
- 1% of female genital tract malignancies
- 3%–7% of uterine cancers
- their rarity and histopathologic diversity have contributed to the lack of consensus on
  - risk factors for poor outcome
  - optimal treatment

WHO histological classification of tumours of the uterine corpus - 2014

- Uterine mesenchymal tumours are derived from the mesenchyme of the corpus consisting of ***endometrial stroma, smooth muscle and blood vessels*** or admixtures of these.
  - Rarely, these tumours may show mesenchymal differentiation that is foreign to the uterus.

- Uterine sarcomas have been classified into three main histological types:
  - leiomyosarcomas (LMS),
  - endometrial stromal sarcomas (ESS)
  - mixed tumours
    - adenosarcomas
    - carcinosarcomas
      - now regarded as metaplastic carcinoma

WHO histological classification of tumours of the uterine corpus - 2014

- **Mesenchymal tumours**

- Endometrial stromal and related tumours
  - Endometrial stromal sarcoma, low grade
  - Endometrial stromal nodule
  - Undifferentiated endometrial sarcoma
  - Smooth muscle tumours

- Leiomyosarcoma
  - Epithelioid variant
  - Myxoid variant

- **Mixed epithelial and mesenchymal tumours**
- Carcinosarcoma (malignant müllerian mixed tumour, metaplastic carcinoma)
- Adenosarcoma

UTERINE SARCOMA CLASSIFICATION

- **Endometrial stromal sarcoma (ESS)[1]**
- **High-grade (undifferentiated) endometrial sarcoma[2]**
- **Uterine leiomyosarcoma (uLMS)[3]**

[1]Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index. By definition, ESS is low-grade histology.
[2]High-grade sarcomas showing pleomorphism or anaplasia greater than that seen in proliferative phase endometrial stroma or completely lacking recognizable stromal differentiation; mitotic index is almost always >10 mf/10 hpf.
[3]Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis; management in individual cases may be modified based on clinicopathologic prognostic factors, such as size (< or > 5 cm), mitotic activity (< or > 10 mf/10 hpf), age (< or > 50 years), and presence or absence of vascular invasion.

(1) Leiomyosarcomas and endometrial stromal sarcomas (ESS)*

Stage		Definition
I		Tumor limited to uterus
	IA	≤5 cm
	IB	>5 cm
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	>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

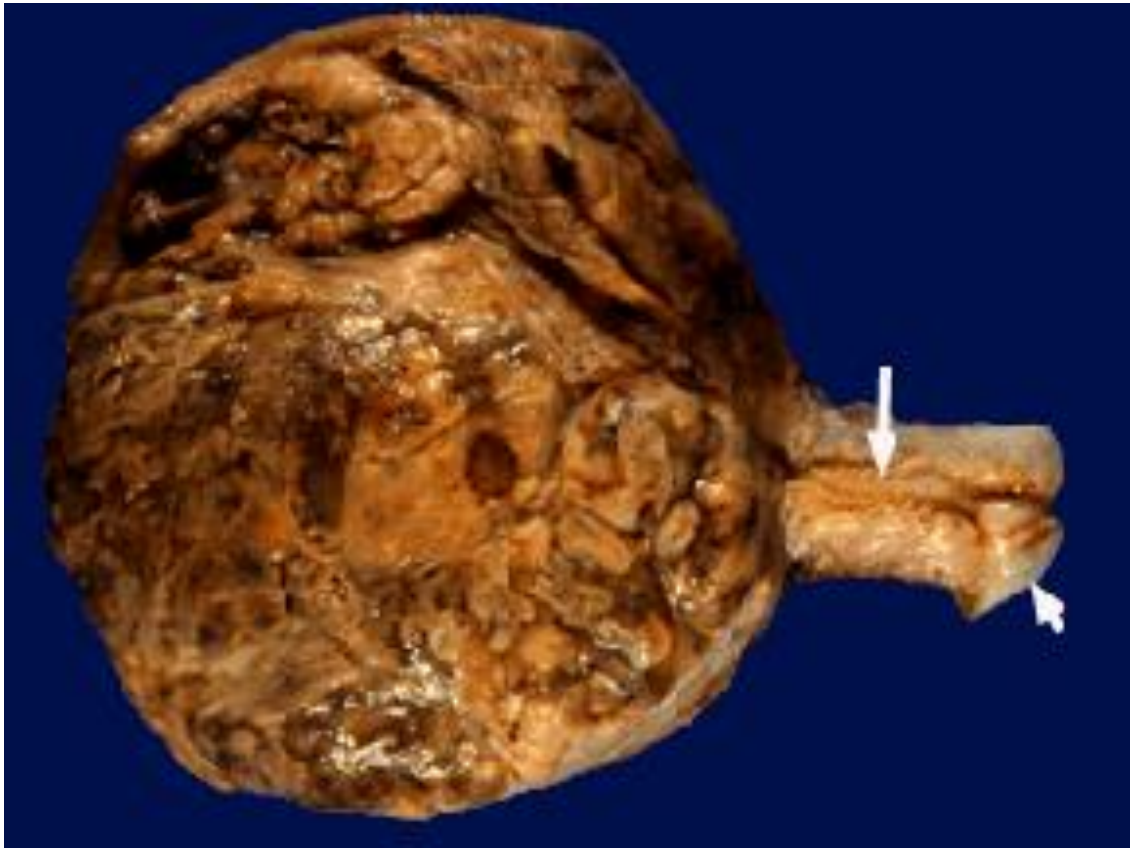
Stage		Definition
I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	>one site
	IIIC	Metastasis to pelvic 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.

*Note:
Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

Leiomyosarcomas



Leiomyosarcomas (LMS)

- Uterine tumors exhibiting smooth muscle differentiation are diagnosed as leiomyosarcomas based on the presence of at least two of the following three features:
  - moderate to severe nuclear atypia;
  - mitotic index ≥10 mitotic figures (MFs) per 10 high-power-fields (HPFs);
  - and/or tumor cell necrosis.

- Occasionally, the histologic features are insufficient to allow classification into benign or malignant categories and, in such cases, the designation “smooth muscle tumors of uncertain malignant potential” (STUMP) is recommended

- No single driving mutation has been identified in uterine LMS.
  - Most tumors show multiple somatic chromosomal abnormalities

LMS

- Most patients with uterine LMS have no identifiable risk factors
  - History of pelvic radiotherapy?
  - Patients who carry a germ line p53 gene mutation (Li Fraumeni syndrome) have an increased risk for soft tissue sarcoma, including uterine LMS, as well as other cancers
  - Patients with Rb mutations who are survivors of childhood retinoblastoma, and survivors of childhood rhabdomyosarcoma or other childhood cancers whose treatment involves radiation, have an increased risk for secondary cancers, including uterine LMS

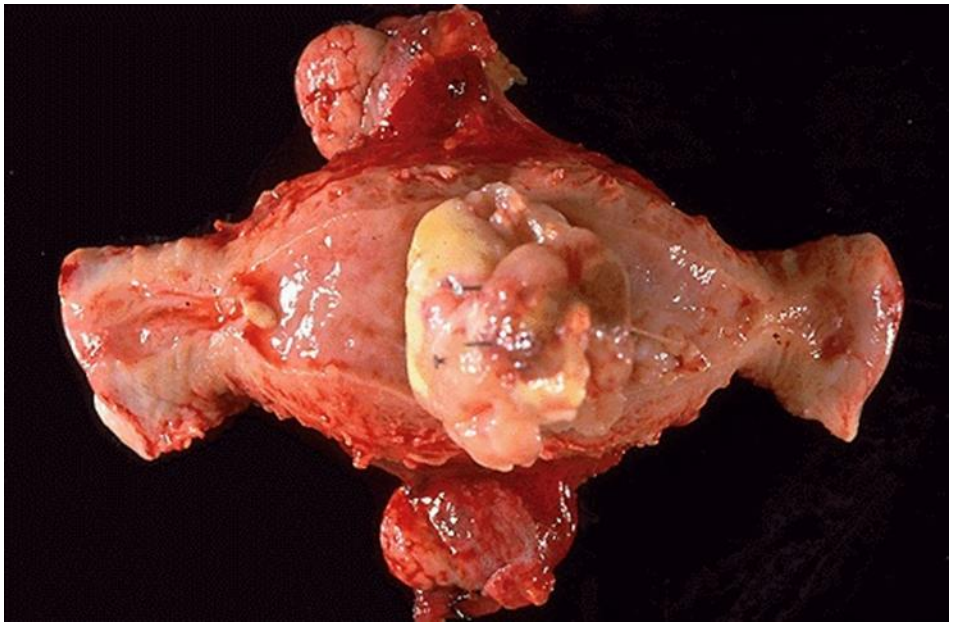
LMS

- Presenting symptoms may include
  - pelvic pain or pressure
  - abnormal vaginal bleeding.
- No single imaging modality can reliably distinguish a benign uterine tumor from a malignant one
  - US , CT , MRI may reveal a uterine mass.
- Intrauterine tumors that continue to increase in size after menopause should raise suspicion for malignancy.
- **In most patients, the diagnosis of uterine LMS is made at the time of myomectomy or hysterectomy for presumed benign disease**

FIGO 2009

Stage	Definition
I	Tumor limited to uterus
IA	≤5 cm
IB	>5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic 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 metastases

LMS apparently limited to the uterus



LMS – initial treatment

- For patients whose disease seems limited to the uterus, hysterectomy is recommended.
  - Routine lymph node dissection is not generally required
    - it is recommended that lymph nodes that appear enlarged/suspicious for malignant involvement should be resected
  - Bilateral salpingo-oophorectomy (BSO) is reasonable in perimenopausal and postmenopausal women
    - **there are no data to show that oophorectomy improves survival outcomes**.
    - estrogen receptors and/or progesterone receptors have been reported to be positive in 40% to 70% of uterine LMS and may have prognostic significance suggesting that oophorectomy may be reasonable even in premenopausal women.
    - however, **retrospective data have not shown survival differences** among women younger than 50 with uterus-limited disease who did or did not undergo BSO

Postresection Management of Uterus-Limited Disease

- the risk for recurrence after resection of uterus-limited high-grade LMS exceeds 50%

- no adjuvant intervention has been shown to improve progression-free survival (PFS) or overall survival outcomes (OS).

- **standard management after complete resection of uterus limited disease is observation**.

- Nearly one third of patients who are found at time of hysterectomy to have uterine LMS will have evidence of metastatic disease on postresection imaging
  - CT and/or PET/CT and/or MRI is recommended to rule out distant metastases.

Locally advanced disease

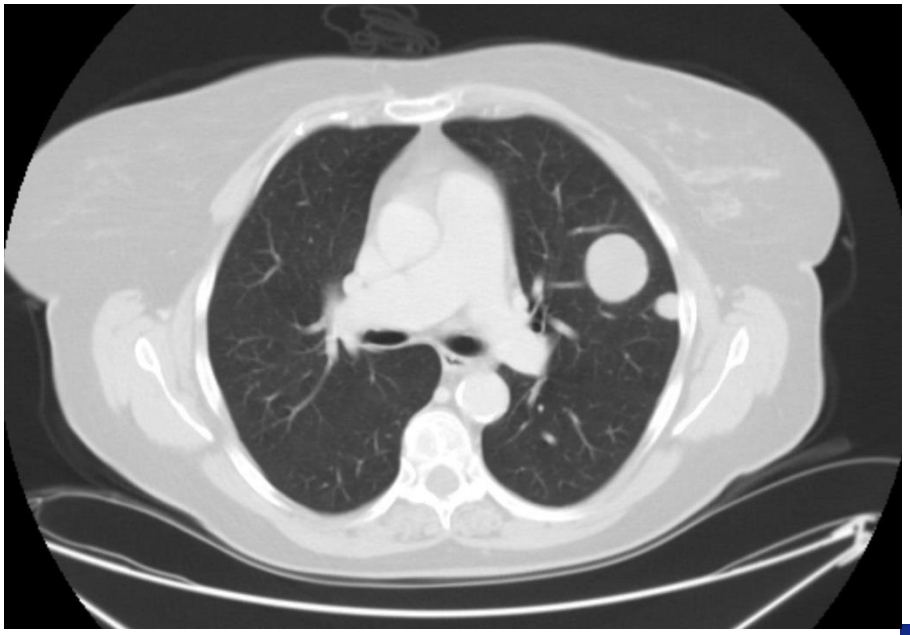
- For patients with locally advanced, completely resected uterine LMS, there are no prospective data on which to base management recommendations.
  - Choices may include
    - Observation
    - adjuvant radiation
    - adjuvant hormone blockade
    - adjuvant chemotherapy.
  - The location of the disease, histologic grade, estrogen receptor (ER) and progesterone receptor (PR) status, patients' preferences, organ function, and comorbidities should be incorporated into the decision.

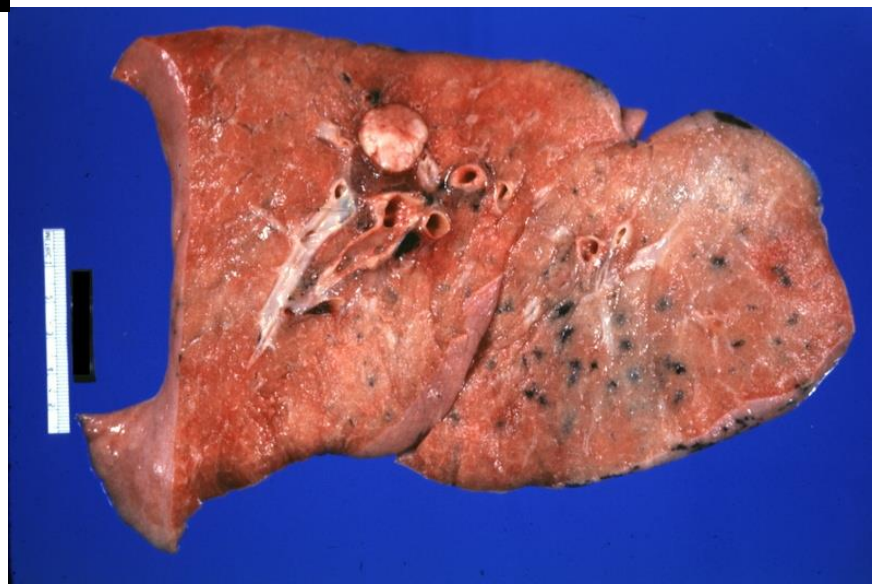
LMS – initial treatment

- For disease that appears locally advanced but potentially completely resectable, an attempt to resect all disease is reasonable.
  - Retrospective data have shown longer overall survival among women whose disease is completely resected compared to those with residual disease at end of the resection attempt.

- For women who present with multisite metastatic, unresectable disease, there is not generally a role for hysterectomy.
  - Palliative hysterectomy may be appropriate for patients with metastatic disease who have poorly controlled uterine bleeding.

LMS - resectable metastases

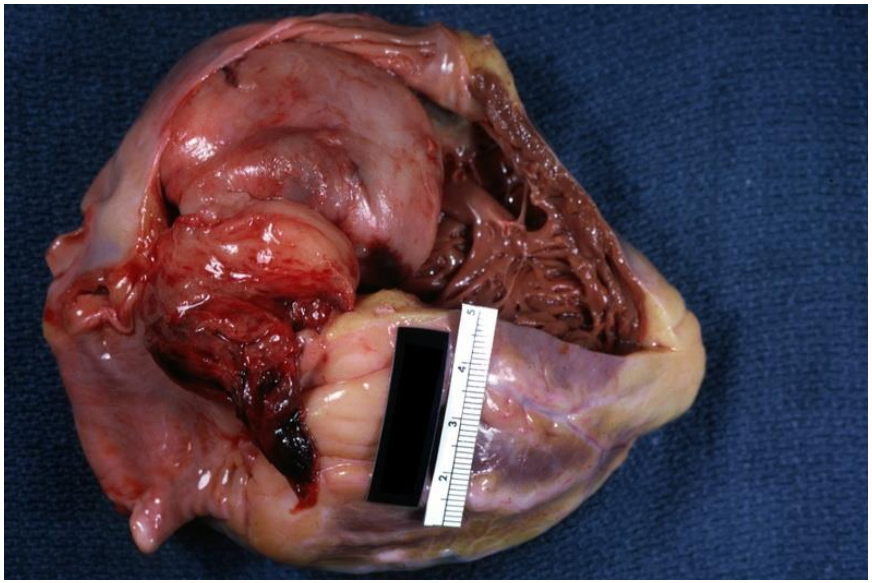


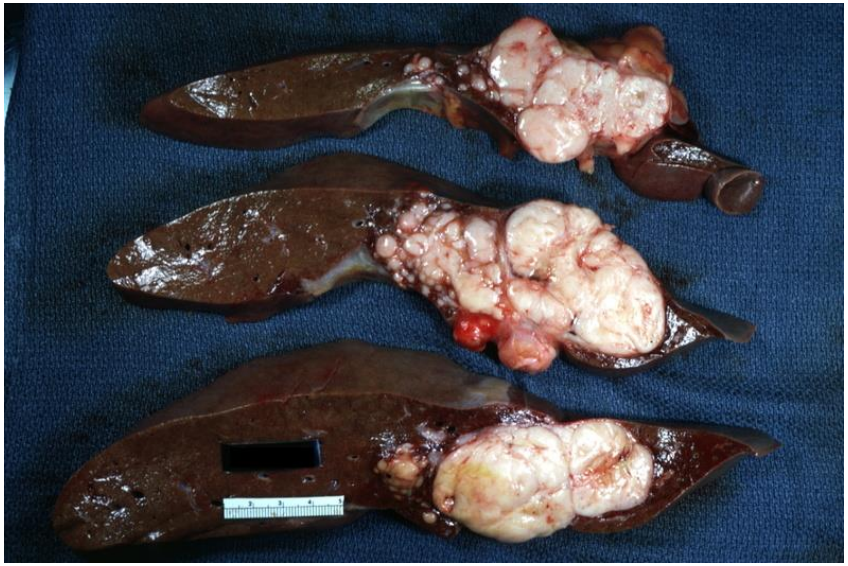


LMS – metastatic disease

- Potentially Resectable Metastatic Disease:
  - Retrospective data show that survival may be prolonged among patients who undergo resection of metastatic disease
    - Outcomes are more favorable for the patients with
      - a long disease-free interval
      - paucity of metastatic sites
      - for whom the resection is likely to render them measurably disease free
- nonsurgical, interventional radiology techniques may be appropriate for certain patients
  - radiofrequency ablation
  - tumor chemoembolization

LMS – unresectable metastases





LMS – metastatic disease

- Unresectable Metastatic Disease
  - objective response rates can be achieved with systemic treatment for metastatic uterine LMS
  - in patients with symptomatic disease, chemotherapy may provide palliation of symptoms.
  - no established superior first-line chemotherapy regimen.
  - treatment recommendations for an individual patient should take into consideration the patient's preferences for the treatment schedule, adverse effects of drugs, venous access, comorbidities, disease burden, and organ function

- Reasonable regimens to consider for first-line therapy include doxorubicin, doxorubicin plus ifosfamide, gemcitabine, and **gemcitabine plus docetaxel.**

- Other treatment options, used as second-line therapy include
  - pazopanib, trabectedin, dacarbazine, or temozolomide

Endometrial stromal tumors

- The term endometrial stromal tumor is applied to neoplasms typically composed of cells that resemble endometrial stromal cells of the proliferative endometrium
- They are classified into
  - noninvasive (stromal nodules)
  - invasive (endometrial stromal sarcomas).
- Endometrial stromal sarcomas (ESS) have been traditionally divided into low and high grade types based on mitotic count.
- However, since high grade endometrial sarcomas lack specific differentiation and bear no histological resemblance to endometrial stroma, it has been proposed that they be designated undifferentiated endometrial or uterine sarcoma
- In this classification the distinction between low grade ESS and undifferentiated endometrial sarcoma is not made on the basis of mitotic count but on features such as nuclear pleomorphism and necrosis
- Endometrial stromal sarcomas exhibit
  - only mild nuclear atypia
  - characteristically invade the myometrium and lymphovascular spaces.
  - Tumor cell necrosis is rarely seen.
- The diagnosis of undifferentiated endometrial sarcoma is applied to cases that lack smooth muscle or endometrial stromal differentiation and exhibit
  - myometrial invasion,
  - severe nuclear pleomorphism,
  - high mitotic activity
  - tumor cell necrosis.
  - the histologic appearance of this tumor is more like the mesenchymal elements of a carcinosarcoma than a typical endometrial stromal tumor

EST - WHO 2014 Classification

- Endometrial stromal tumours are subdivided into benign and malignant groups based on the type of tumour margin.
  - those with pushing margins are benign stromal nodules
  - those with infiltrating margins qualify as stromal sarcomas.

- low grade ESS
  - a clinically indolent neoplasm
  - plexiform vasculature
  - minimal cytological atypia and infrequent mitotic figures.

- Undifferentiated sarcoma
  - a highly aggressive neoplasm
  - lacks a plexiform vasculature
  - substantial cytological atypia and has frequent and often atypical mitotic figures.
  -
- However, there is no valid evidence that the isolated finding of a mitotic index of 10 or more per 10 high power fields is an adverse prognostic finding in a neoplasm that is otherwise a typical low grade ESS.

ESS – genetic changes

- the majority of LGESSs, including conventional and variant tumours, harbour **chromosomal rearrangements**
  - at present there seems to be no correlation between the histological variant and the underlying genotype.
  - the most common rearrangement, t(7;17)(p15;q21), results in JAZF1-SUZ12 gene fusion

- molecular testing is not routinely performed
  - may be helpful when dealing with cases of unusual location or morphology.

- Recently, a new fusion protein (YWHAE-FAM22) has been identified
  - In contrast to classic ESS, harboring JAZF1 genetic fusions, YWHAE-FAM22 ESS displays high-grade histologic features, a distinct gene expression profile, and a more aggressive clinical course
  - Fluorescence in situ hybridization analysis demonstrated absolute specificity of YWHAEFAM22A/B genetic rearrangement for high-grade ESS, with no fusions detected in other uterine and nonuterine mesenchymal tumors

ESS

- endometrial stromal sarcoma accounts for approximately 20% of all uterine sarcomas
  - incidence of one third of that of uterine leiomyosarcoma
  - mean age around 50 years
- obesity, diabetes, and younger age at menarche have been associated with increased risk of ESS
  - the molecular mechanisms involved are yet to be elucidated
- most cases (60%) present with FIGO stage I disease, with only 20% presenting with stage IV metastatic disease
- tamoxifen intake is associated with ESS development

Low Grade ESS

- the second most common malignant mesenchymal tumour of the uterus
- slow-growing tumour with an indolent clinical course
- multiple and/or late relapses, some occurring as late as 20 years after hysterectomy
- the majority of LGESSs, including conventional and variant tumours, harbour **chromosomal rearrangements**
  - at present there seems to be no correlation between the histological variant and the underlying genotype.
  - the most common rearrangement, t(7;17)(p15;q21), results in JAZF1-SUZ12 gene fusion
- molecular testing is not routinely performed
  - may be helpful when dealing with cases of unusual location or morphology.

LGESS treatment

- stage is the most important prognostic factor

- stage I-II LGESS
  - total hysterectomy and bilateral salpingooophorectomy,with or without adjuvant therapy, are the mainstay of treatment
  - lymph node metastasis can occur, however, lymphadenectomy is unlikely to improve survival
- routine lymphadenectomy is not indicated unless lymph nodes are pathologically enlarged on preoperative imaging studies and as part of a cytoreductive procedure

- Traditionally, the ovaries were removed
  - ESS typically expresses estrogen and progesterone receptors,
  - it appears in small and large series that leaving the ovaries in situ does not worsen survival
  - Premenopausal women?

- advanced-stage (III–IV) disease
  - cytoreductive surgery
  - adjuvant hormonal therapy usually in the form of progestins or aromatase inhibitors

FIGO 2009

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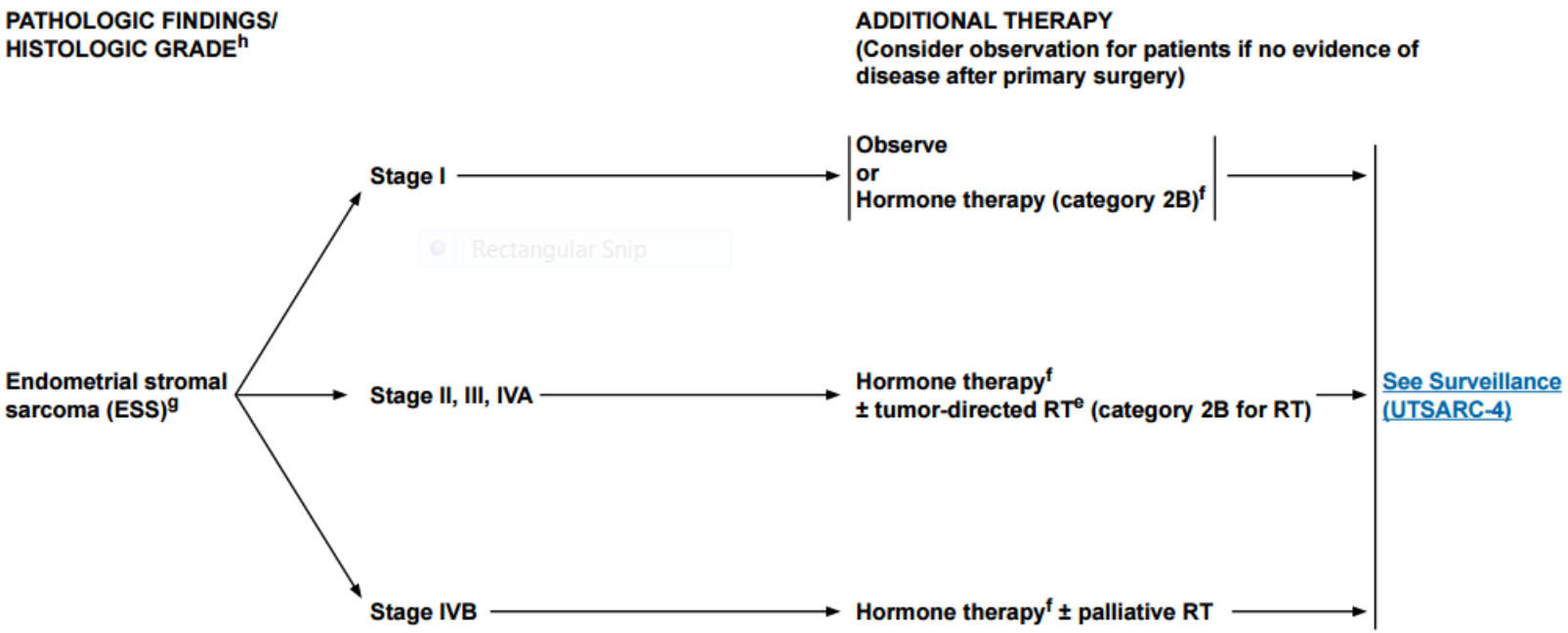
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV IVA	Tumor invades bladder and/or rectum
IVB	Distant metastases

LGESS adjuvant treatment

- There is a very high rate of hormone receptor positivity in ESS
  - up to 100% in some series
  - High response rates to hormonal blockade
    - progestins
    - aromatase inhibitors



[e] See Principles of Radiation Therapy (UN-A).
[f] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[g] By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined.
[h] See Uterine Sarcoma Classification (UTSARC-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Undifferentiated uterine sarcoma - USS

- a high grade endometrial sarcoma that lacks specific differentiation and bears no histological resemblance to endometrial stroma

- In contrast to ESS, which demonstrates a good prognosis and an indolent clinical course, HGUSs are characterized by aggressive behavior and poor prognosis
  - These differences might be related to a distinct genetic background
    - YWHAE-FAM22 ESS displays high-grade histologic features, a distinct gene expression profile, and a more aggressive clinical course
    - Specific for HGUUS

- marked cellular atypia and abundant mitotic activity

- UUS lack the typical growth pattern and vascularity of low grade ESS.
  - destructive rather than permeative infiltration of the myometrium.

- aggressive behavior and poor prognosis
  - median progression free survival (PFS) : 7 to 10 months
  - median overall survival (OS) : 11 to 23 months
  - 5-year survival of 51.4% for stage IA

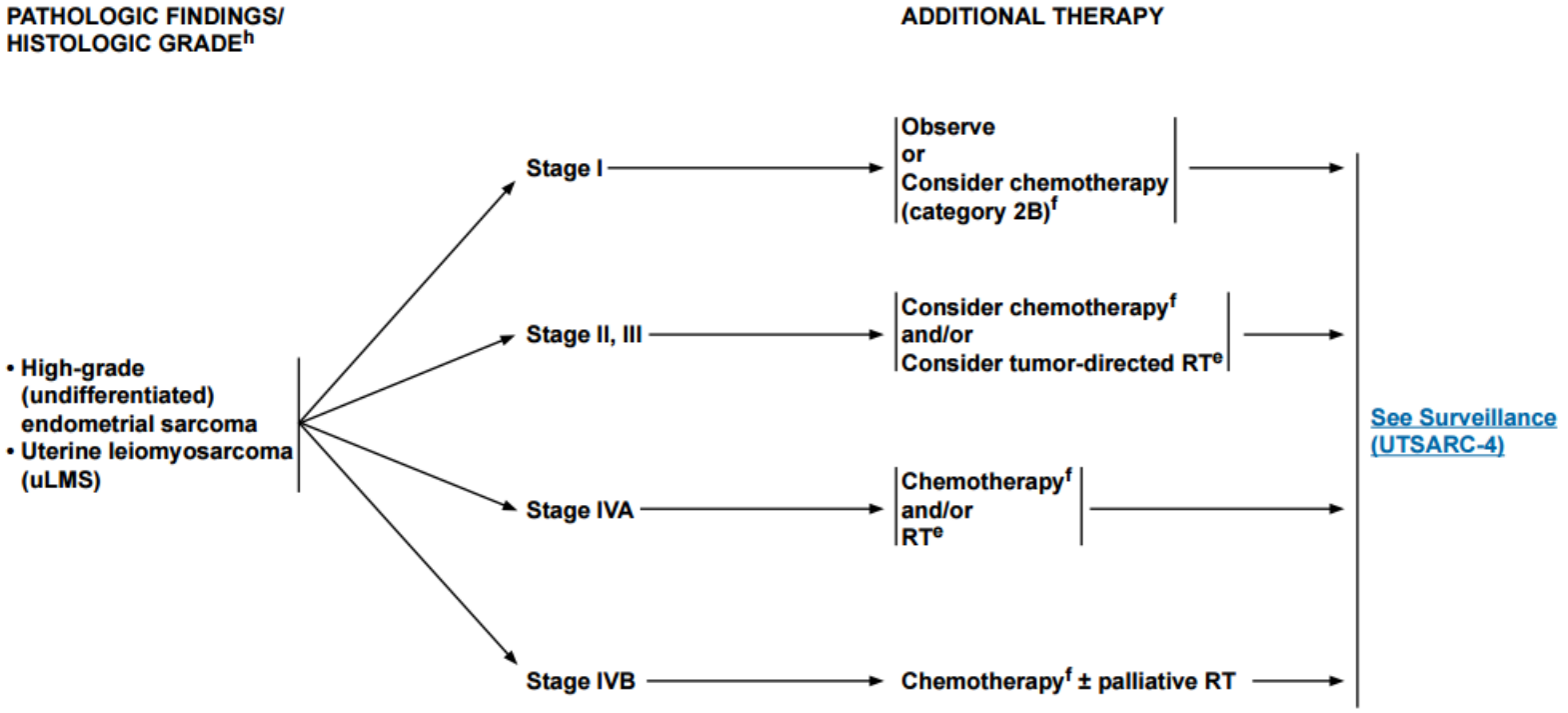
HG UUS

- Median age of patients : 55 and 60 years
- the most common symptoms are :
  - vaginal bleeding
  - abdominal pain
  - increasing abdominal girth
- HGUSs are often diagnosed histologically after surgery for presumed uterine fibroids.
- High-grade undifferentiated sarcomas are staged using the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification
- At diagnosis, disease is usually advanced
  - approximately 70% of patients staged FIGO III to IV
- Preferential metastatic locations include
  - peritoneum
  - lungs
  - intra-abdominal lymph nodes
  - bone

HG UUS treatment

- early stage HGUS :
  - TAH + BSO
    - The role of surgical regional lymphadenectomy remains unknown
    - Most relapses in patients with complete resection are visceral
    - Thus, systematic lymphadenectomy is not recommended unless there is a clinical or radiological suspicion of nodal involvement.
  - adjuvant therapy in patients with localized tumors may have a role
    - external pelvic irradiation has been widely used as adjuvant treatment an approach reported to decrease local recurrence but no benefit proven for OS.
    - chemotherapy with adriamycine, ifosfamide , cisplatin may increase DFS
- extensive disease:
  - surgical debulking if feasible
  - chemotherapy
    - Ifosfamide + Adriamycine
    - Gemcitabine+ Docetaxel

NCCN Guidelines Version 2.2015
Uterine Sarcoma



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Adenosarcoma

- 5% of uterine sarcomas
- tend to occur in postmenopausal women
- benign epithelial component with a malignant mesenchymal component
  - typically a low-grade endometrial stromal sarcoma but can also be a high-grade sarcoma
- usually low malignant potential
  - tumors that exhibit a high-grade sarcomatous overgrowth have a worse outcome

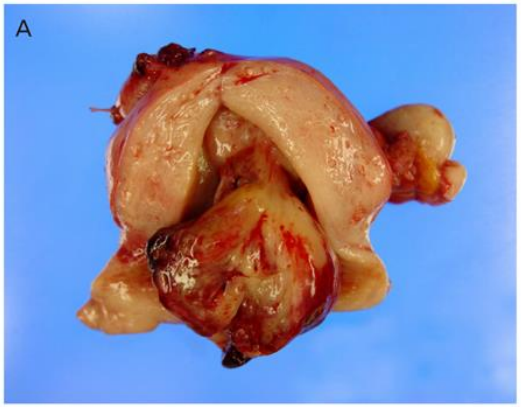
Adenosarcoma

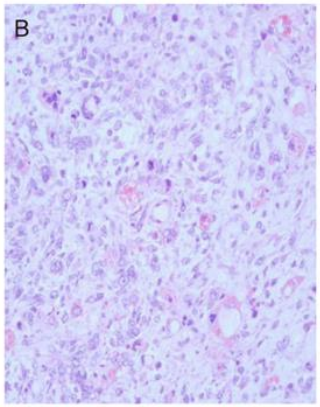
- polypoid tumors that arise from the endometrium and can protrude through the cervical os

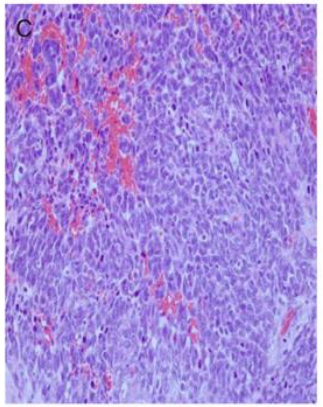
- a biphasic cellular differentiation
  - a benign appearing epithelial component
  - a (definitionally) malignant mesenchymal component
    - WHO requires the stromal mitotic rate to be in excess of 1 per 10 high power fields for a diagnosis of adenosarcoma

- adenosarcomas with more than 25% of the tumor composed of pure high-grade sarcoma are designated as adenosarcomas with sarcomatous overgrowth
  - They typically are composed of poorly differentiated sarcoma and may be associated with deep myometrial and vascular invasion

- the most common symptoms:
  - vaginal bleeding
  - pelvic pain
  - uterine enlargement







Uterine adenosarcoma
FIGO staging 2009

- **Stage I**, tumor limited to uterus
  - IA, tumor limited to endometrium/endocervix with no myometrial invasion
  - IB, less than or equal to half myometrial invasion
  - IC, more-than-half myometrial invasion
- **Stage II**, tumor extends beyond uterus, within the pelvis
  - IIA, adnexal involvement
  - IIB, involvement of other pelvic tissues
- **Stage III**, tumor invades abdominal tissues
  - IIIA, 1 site
  - IIIB, >1 site
  - IIIC, metastases to pelvic/and or para-aortic lymph nodes
- **Stage IV**
  - IVA, tumor invades bladder and/or rectum
  - IVB, distant metastases

Uterine adenosarcoma
Treatment

- Hysterectomy and bilateral salpingo-oophorectomy
  - Ovarian metastases seem to be very uncommon
    - possibility of not removing the ovaries in premenopausal women
  - The incidence of lymph node involvement is reported to be low in stage 1 uterine adenosarcomas
    - lymphadenectomy is not required for most patients

Endometrial stromal nodule (ESN)

- ESNs are rare **benign** tumours of the uterus.
  - well-circumscribed
  - intramural mass or as a polypoid tumour protruding into the endometrial cavity.
  - no myometrial invasion
  - the two largest series published to date showed no recurrences after a follow-up period of up to 16 years and 17.8 years, respectively

- A definitive diagnosis of ESN can only be made after careful sampling and examination of the tumour border, which is only possible on **hysterectomy** specimens

Selective bibliography

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Thank you

Tri & live better