

**SOCIEDAD ESPAÑOLA DE ANATOMIA PATOLOGICA
ZARAGOZA, 2011**

**SARCOMAS DEL ESTROMA ENDOMETRIAL
Y SARCOMAS INDIFERENCIADOS:
CRITERIOS DIAGNOSTICOS,
DIAGNOSTICO DIFERENCIAL
Y FACTORES PRONOSTICOS**

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ENDOMETRIAL STROMAL TUMORS

WHO Classification

- Endometrial Stromal Nodule
 - Low-Grade Endometrial Stromal Sarcoma
-
- Undifferentiated Endometrial Sarcoma

ENDOMETRIAL STROMAL NODULE AND LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

- Shared clinical features:
 - Frequently diagnosed between 40-55 years
 - 1/3 of patients are postmenopausal
 - Abnormal uterine bleeding or pelvic
/abdominal pain common presentations
 - May be asymptomatic

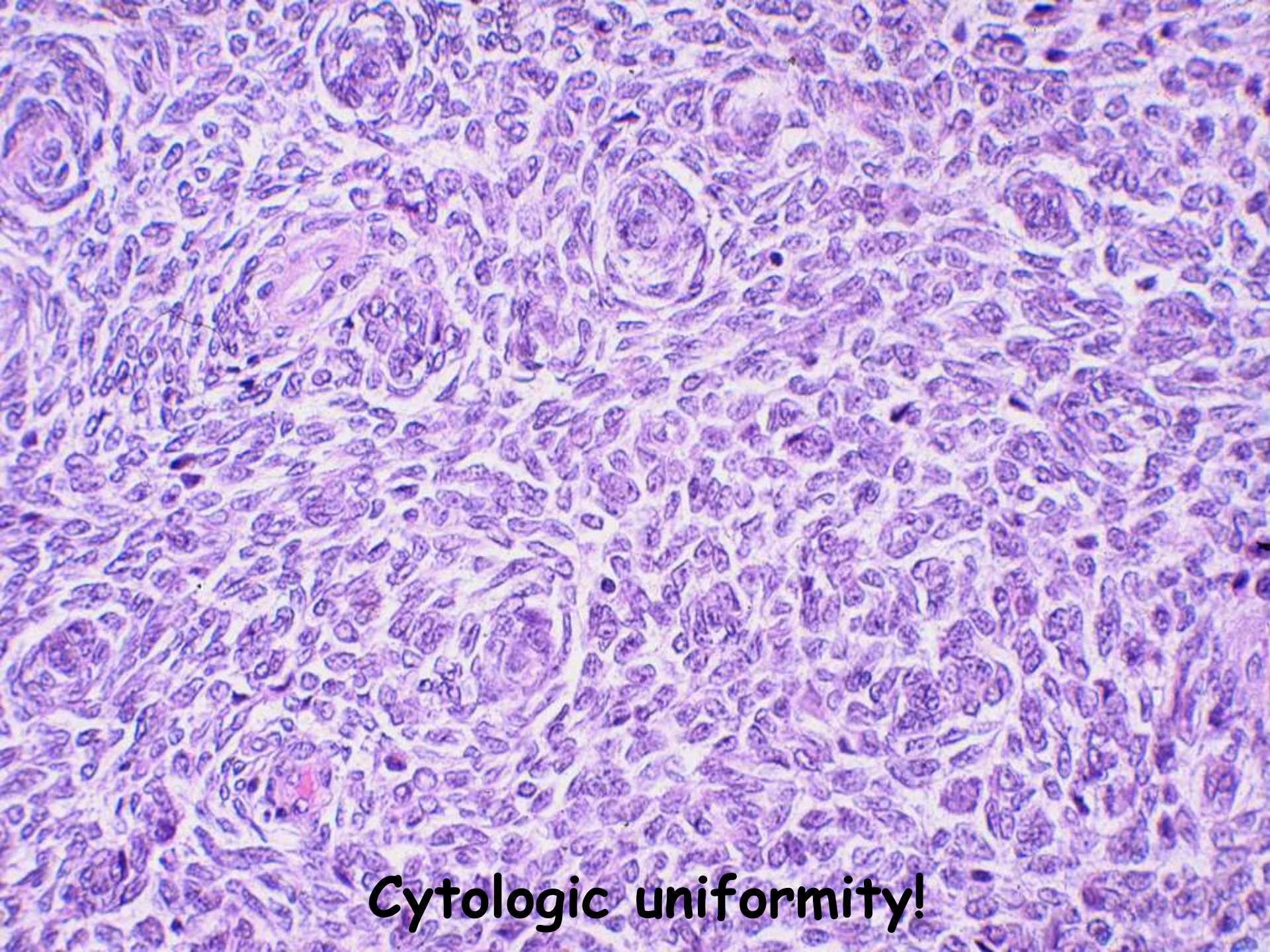
LG Endometrial Stromal Sarcoma

- **10-15% of uterine malignancies with a mesenchymal component**
- **1/3 extrauterine pelvic extension at diagnosis**
- **Rarely presentation at metastatic site (often ovary)**
- **Occasionally association with prolonged estrogenic stimulation, tamoxifen treatment, or prior pelvic irradiation**

ENDOMETRIAL STROMAL NODULE AND LOW-GRADE ENDOMETRIAL STROMAL SARCOMA (WHO)

SHARED HISTOLOGIC APPEARANCE

Tumors composed of cells resembling those of the proliferative-phase endometrial stroma. Numerous thin-walled small arteriolar-type vessels are characteristically present

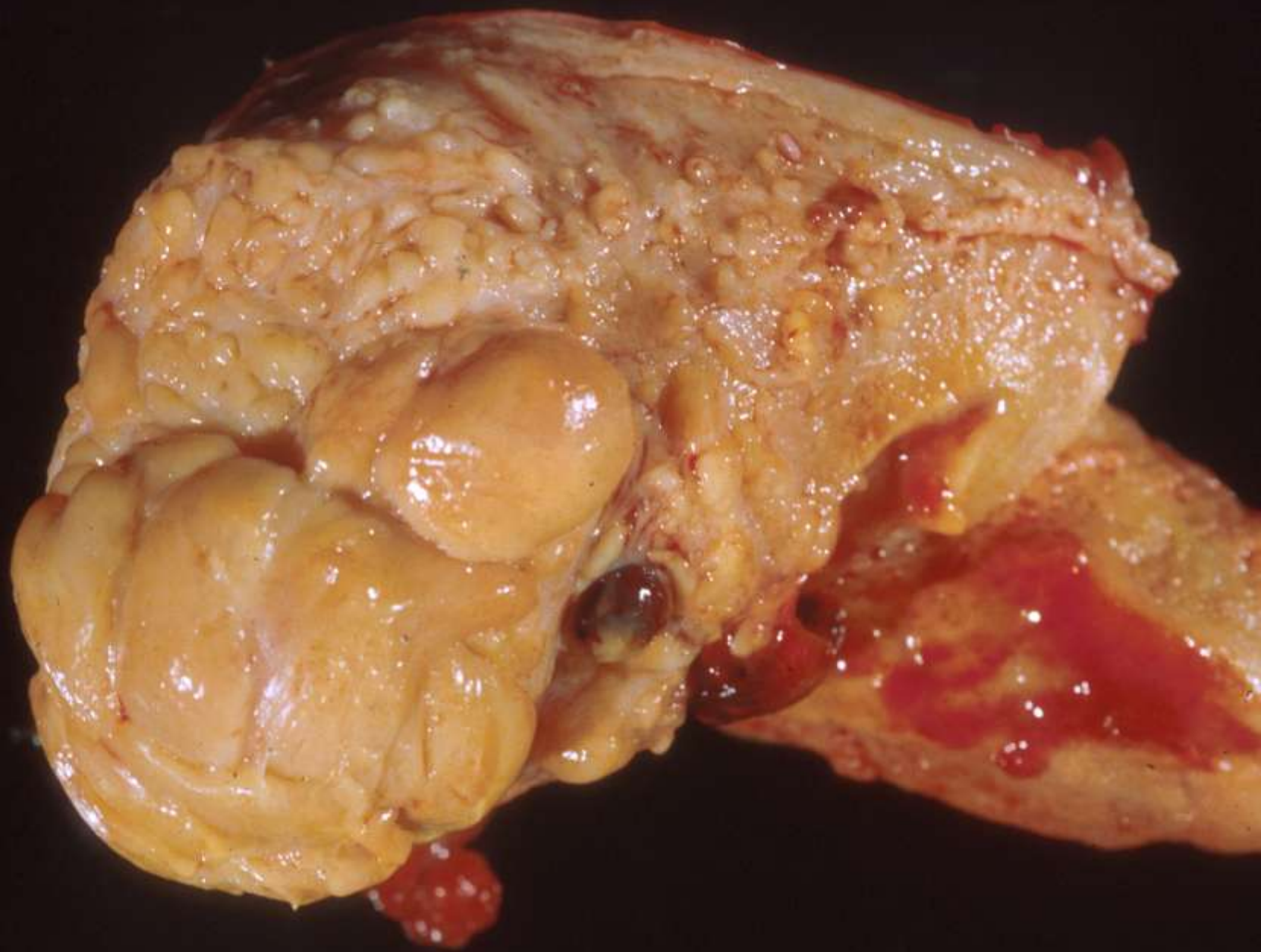


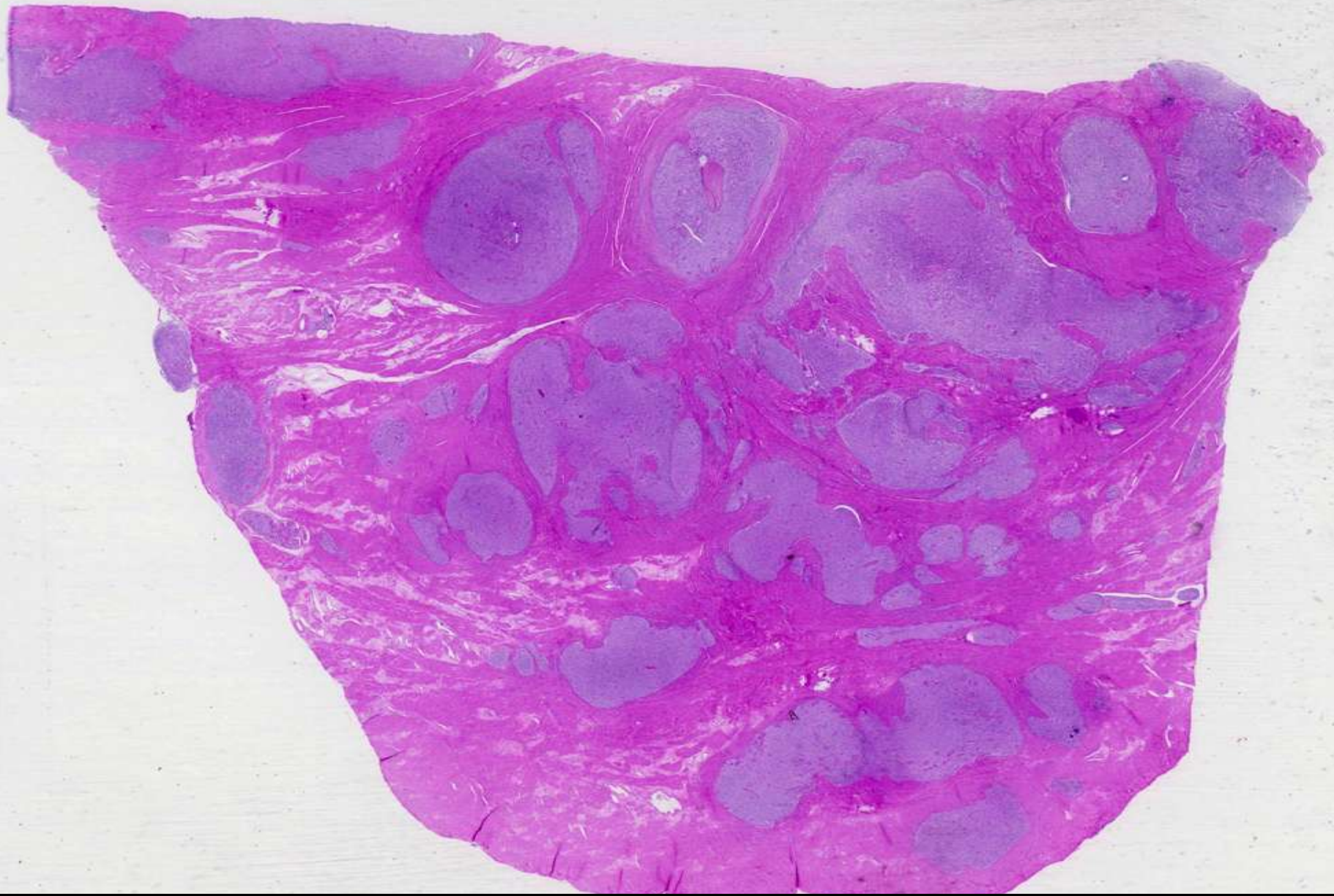
Cytologic uniformity!

ENDOMETRIAL STROMAL NODULE *vs* LOW-GRADE ENDOMETRIAL STROMAL SARCOMA (WHO)

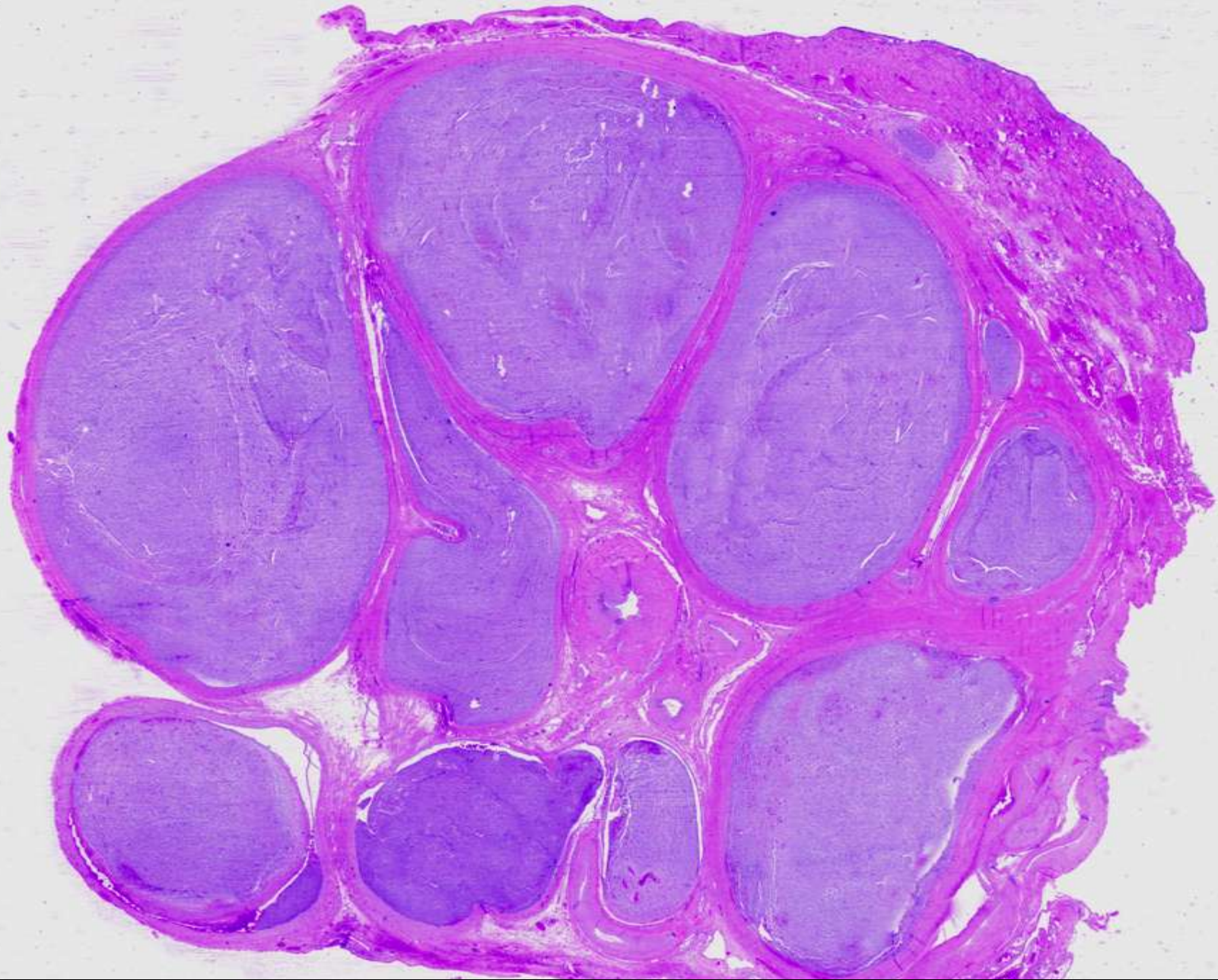
DIFFERENTIAL HISTOLOGIC FEATURES:

Myometrial and/or vascular invasion



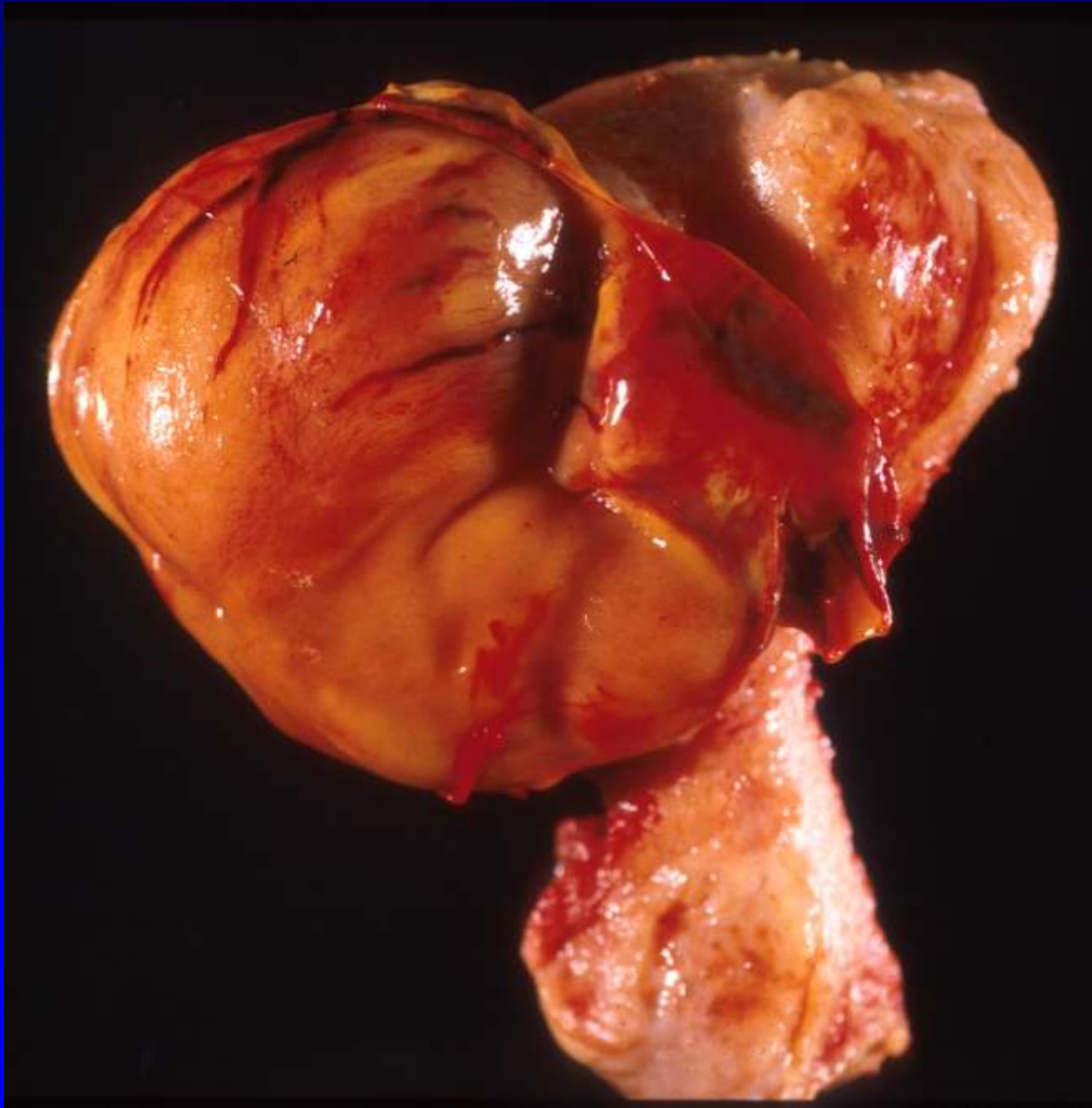


Permeative, not destructive, growth in myometrium



Not infrequently associated with vascular invasion

Endometrial Stromal Nodule



ENDOMETRIAL STROMAL NODULE

WHO

Well delineated,
expansile margin on
microscopic exam

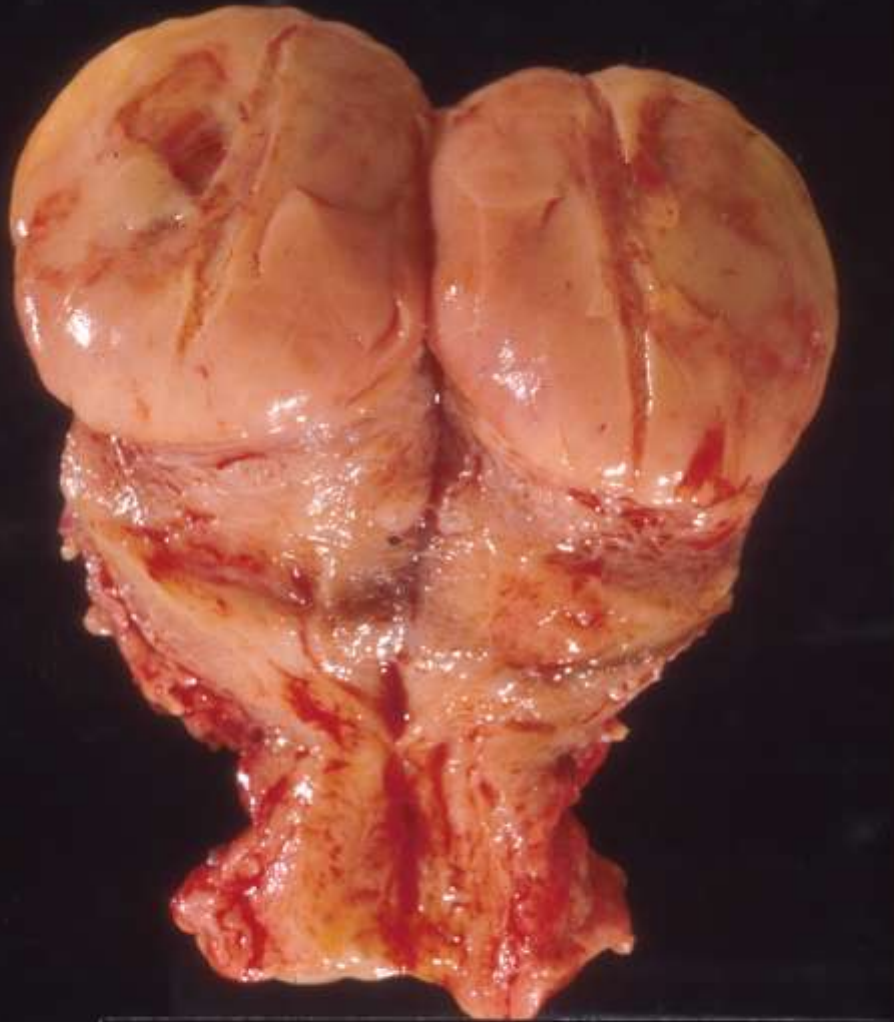
Focal irregularities:
lobulated or finger-
like projections (< 3)
into myometrium
(≤ 3 mm) allowed

No vascular invasion



**LOW-GRADE
ENDOMETRIAL
STROMAL SARCOMA
WITH APPARENTLY
WELL-CIRCUMSCRIBED
MARGINS**

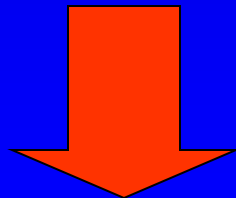
**SAMPLING OF
TUMOR-INTERFACE
VERY IMPORTANT**



MASS. GENERAL HOSPITAL PATHOLOGY DEPT.
METRIC 1 2 3 4 5 6 7

REPORTING ENDOMETRIAL STROMAL TUMORS IN CURETTAGE SPECIMENS

- Adequate sampling of the tumor-myometrial interface is necessary in order to:
 - 1- evaluate the degree of infiltration of the tumor into the myometrium
 - 2- correctly classify the tumor
 - 3- properly treat the patient
- In 99.9% of cases, margins cannot be completely assessed in endometrial curettage



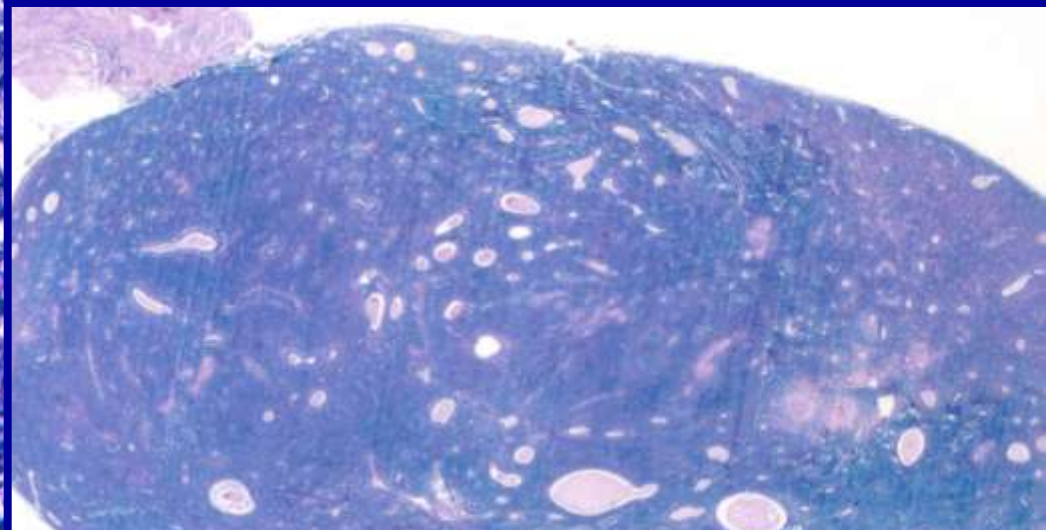
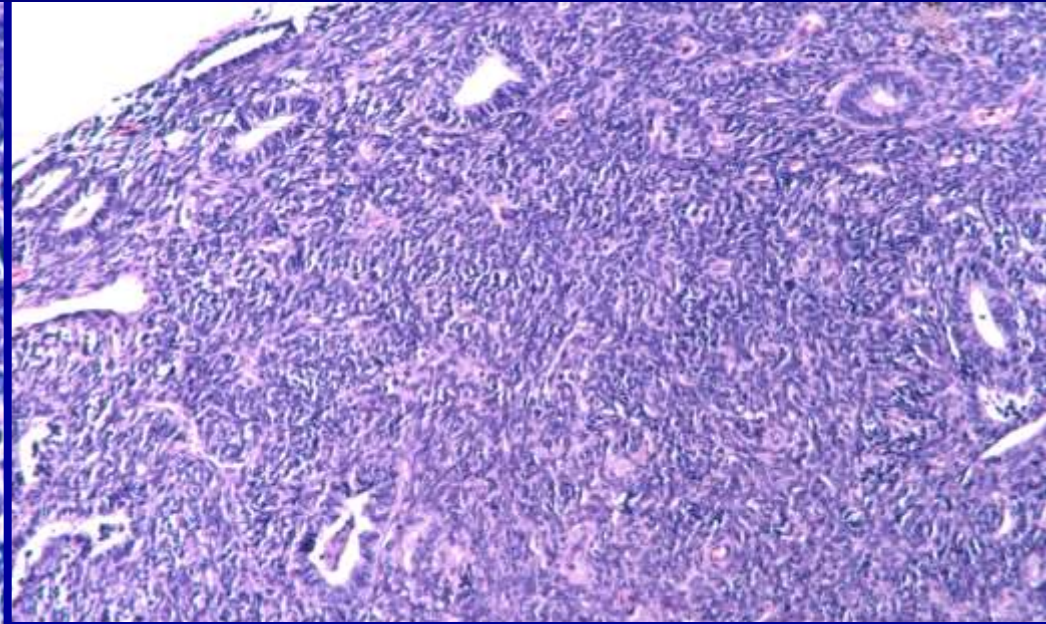
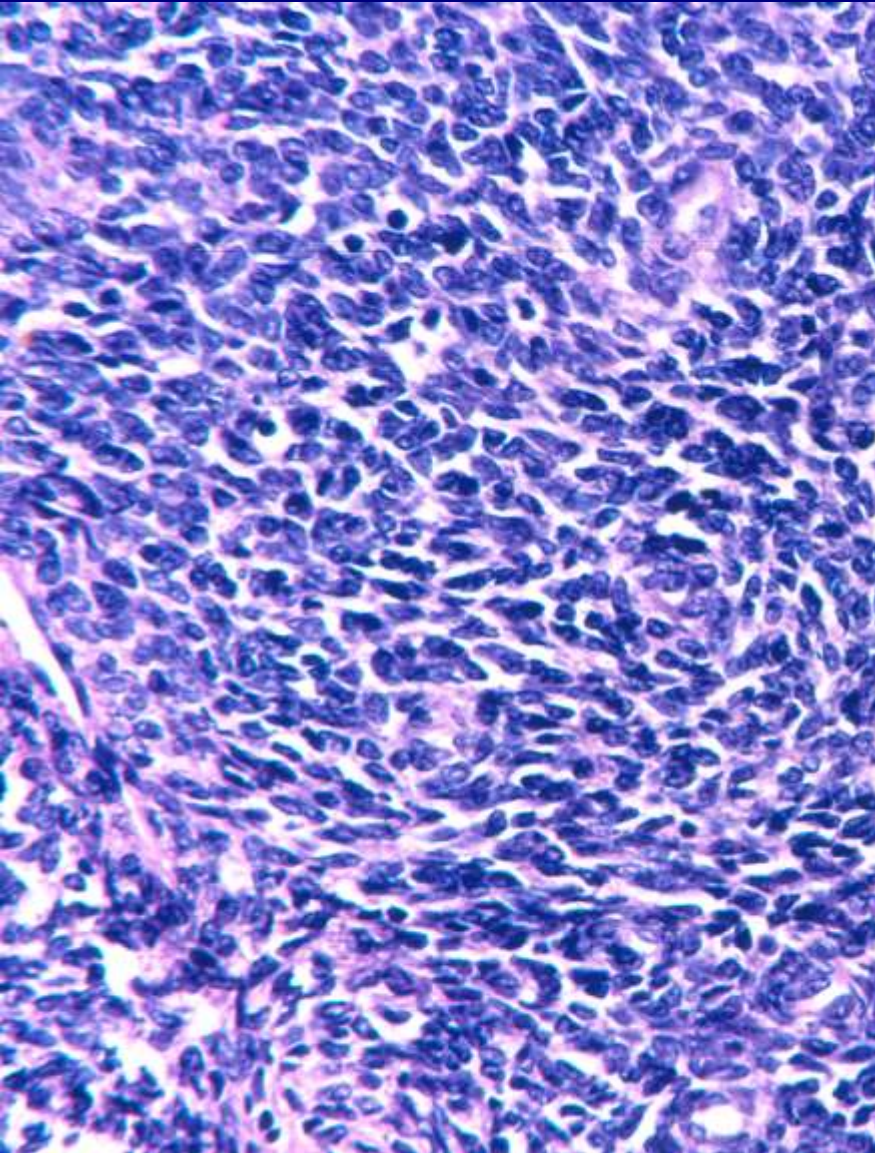
working diagnosis should be EST

LG Endometrial Stromal Sarcoma

Differential Diagnosis:

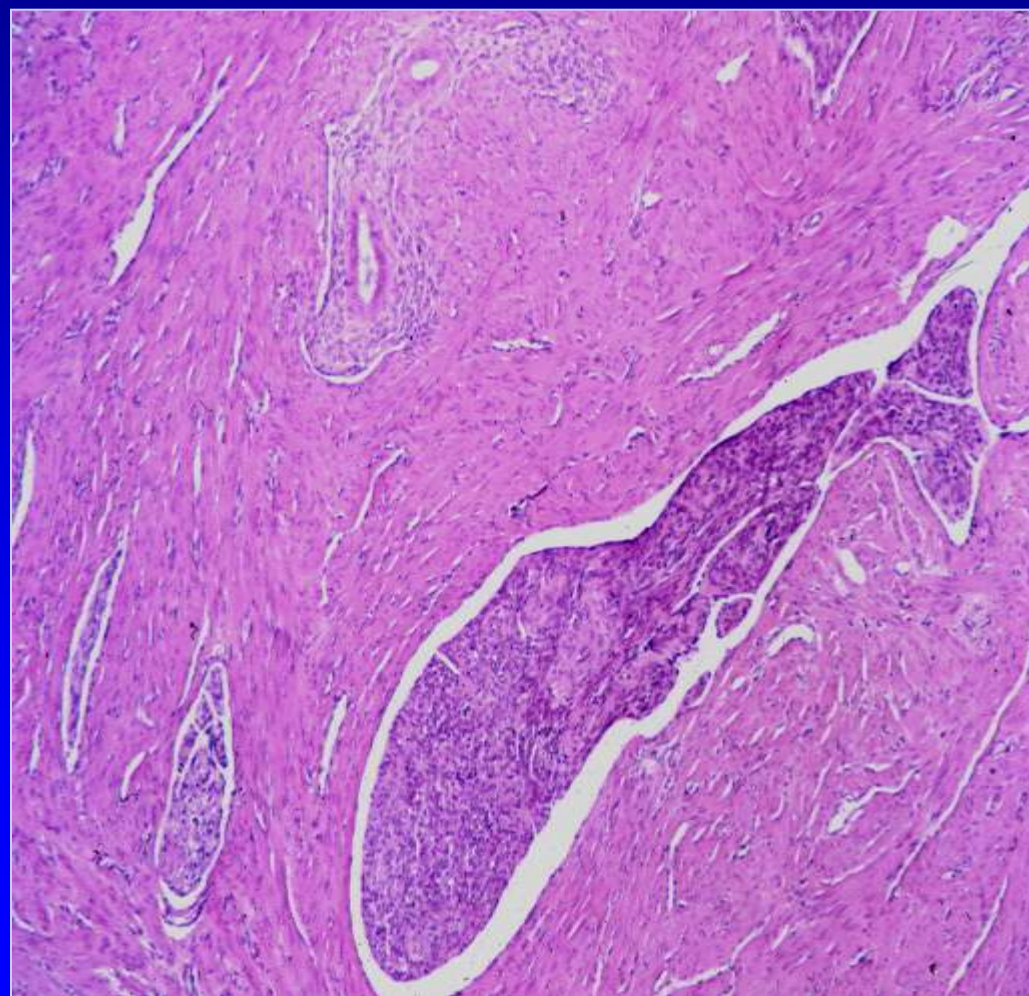
- Cellular endometrial polyp
- Adenomyosis
 - with sparse glands / intravascular
- Highly cellular leiomyoma
- Highly cellular variant of intravenous leiomyomatosis

CELLULAR ENDOMETRIAL POLYP



Tips: Compact inactive stroma and thick-walled blood vessels

GLAND POOR ADENOMYOSIS AND INTRAVASCULAR GLAND POOR ADENOMYOSIS



- Postmenopausal age
- Incidental finding in uteri removed for other reason
- Ill defined nodularity or asymmetric thickening but no mass
- Atrophic stromal nests
- Typical adenomyosis
- Absence of other features of ESS

Most Common Dilemma:

**Smooth muscle tumor
(typically highly cellular leiomyoma)**

VS

**Endometrial stromal tumor
(typically endometrial stromal sarcoma)**

HIGHLY CELLULAR LEIOMYOMA

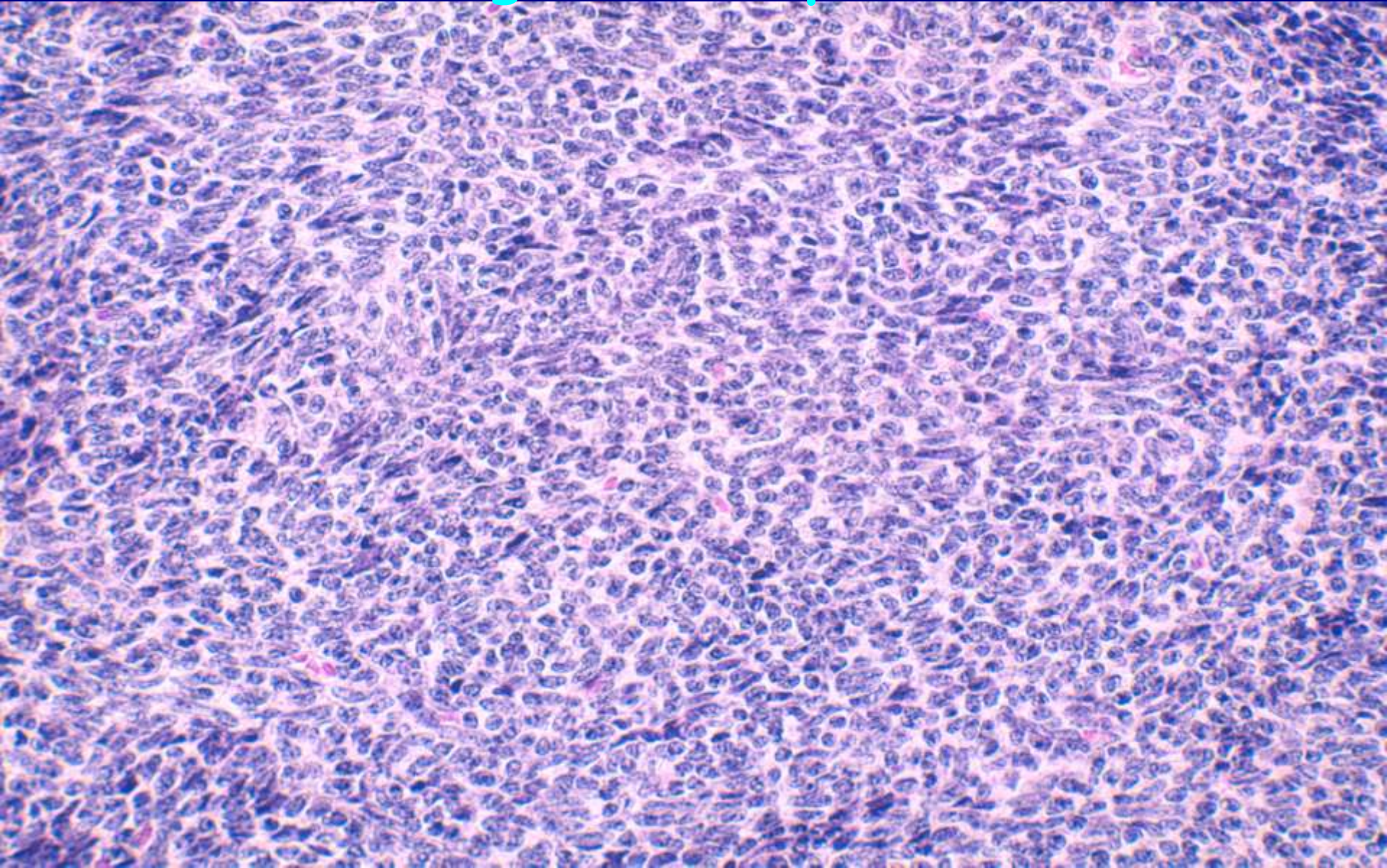


Highly Cellular Leiomyoma vs Endometrial Stromal Tumor

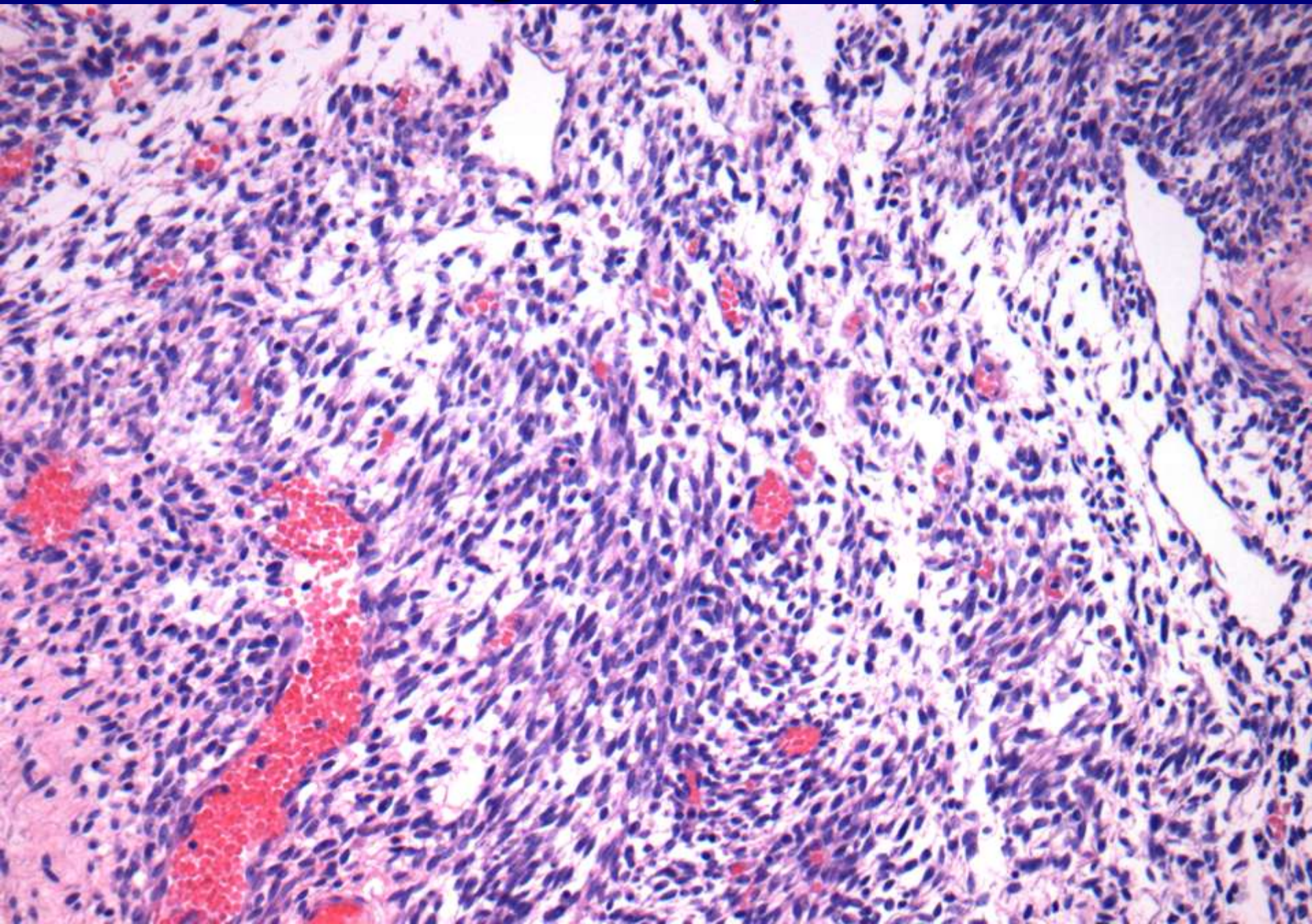
Shared features

- Dense cellularity
- Prominent vascularity
- Irregular margin

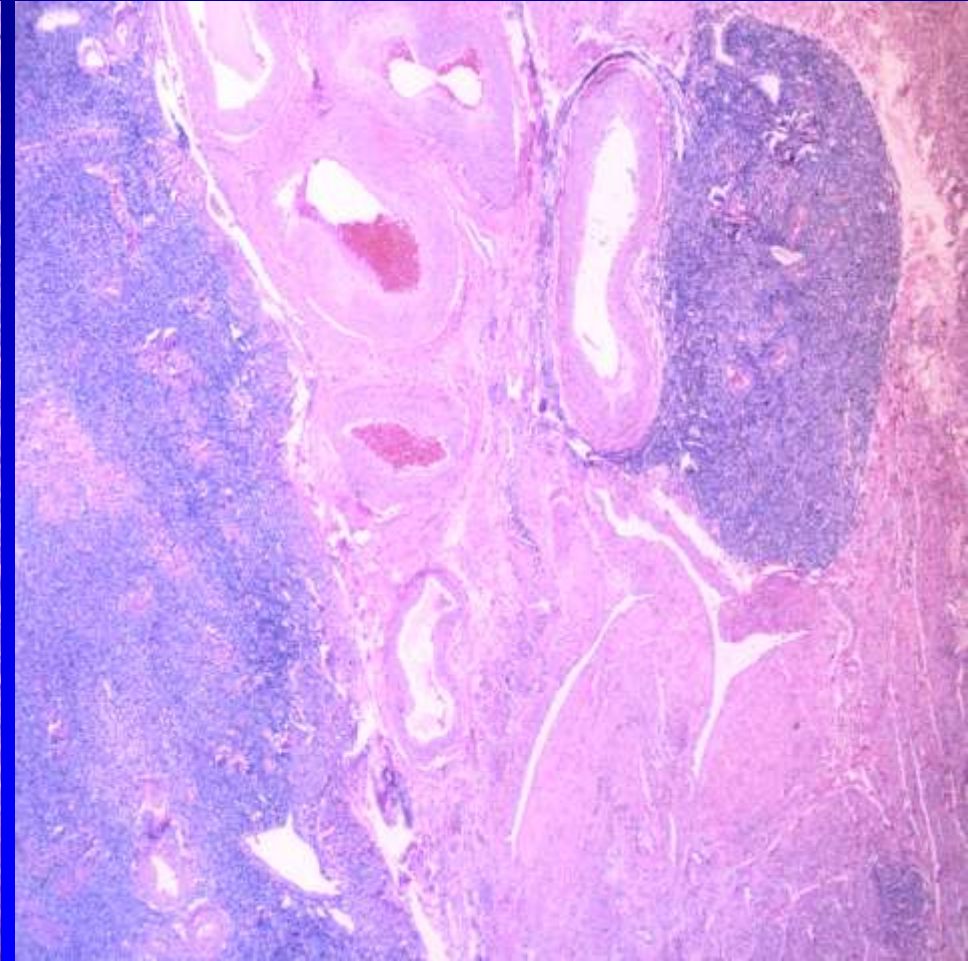
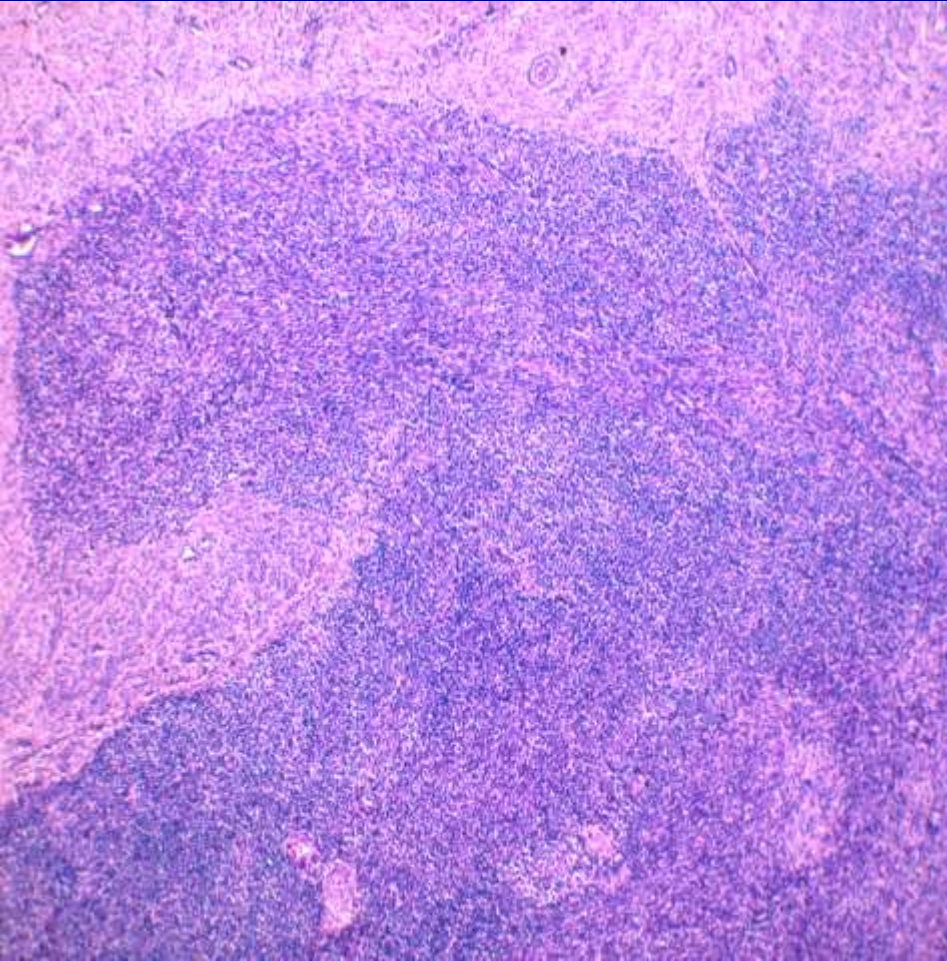
HIGHLY CELLULAR LEIOMYOMA: Misleading microscopic features



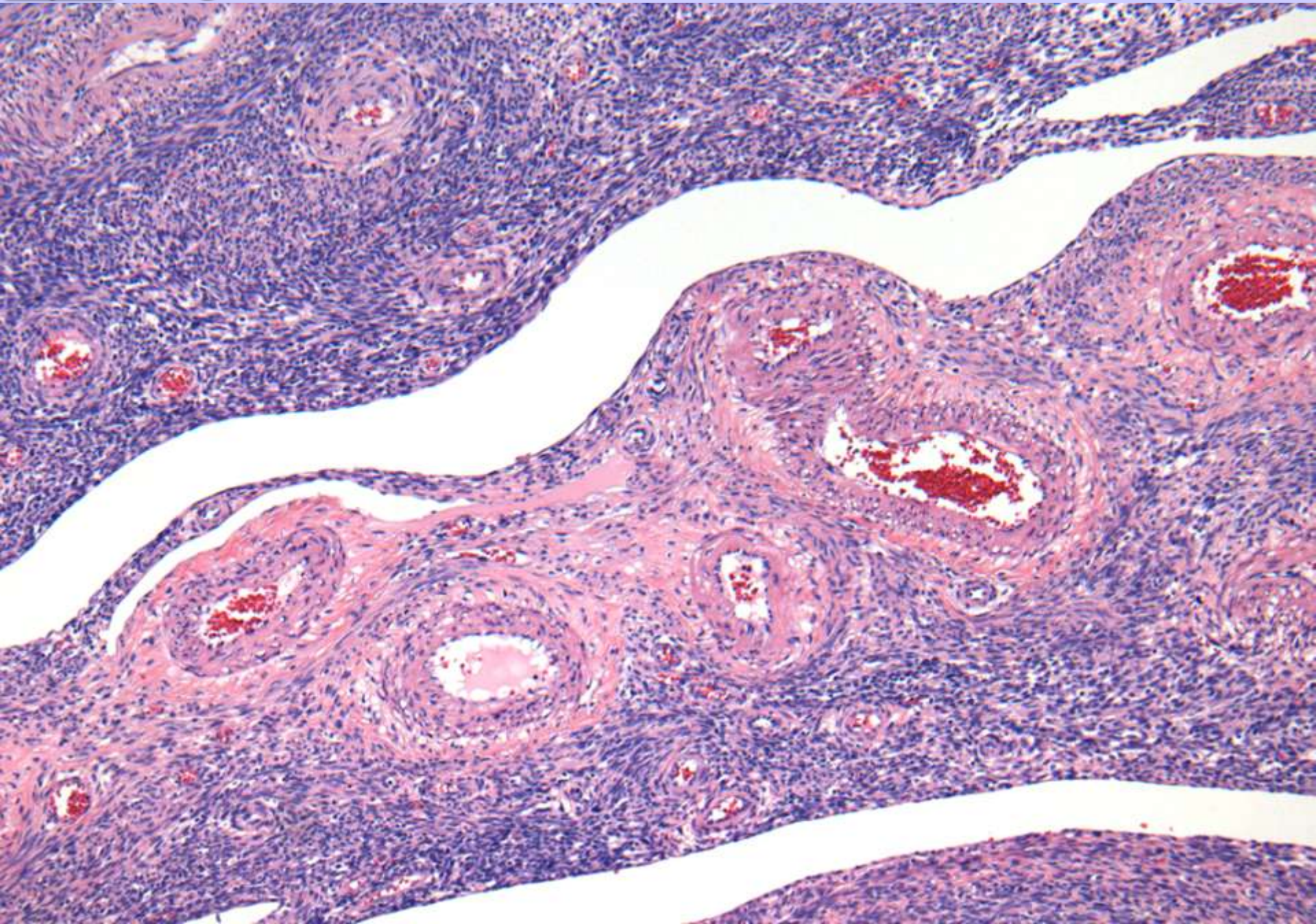
Misleading microscopic features

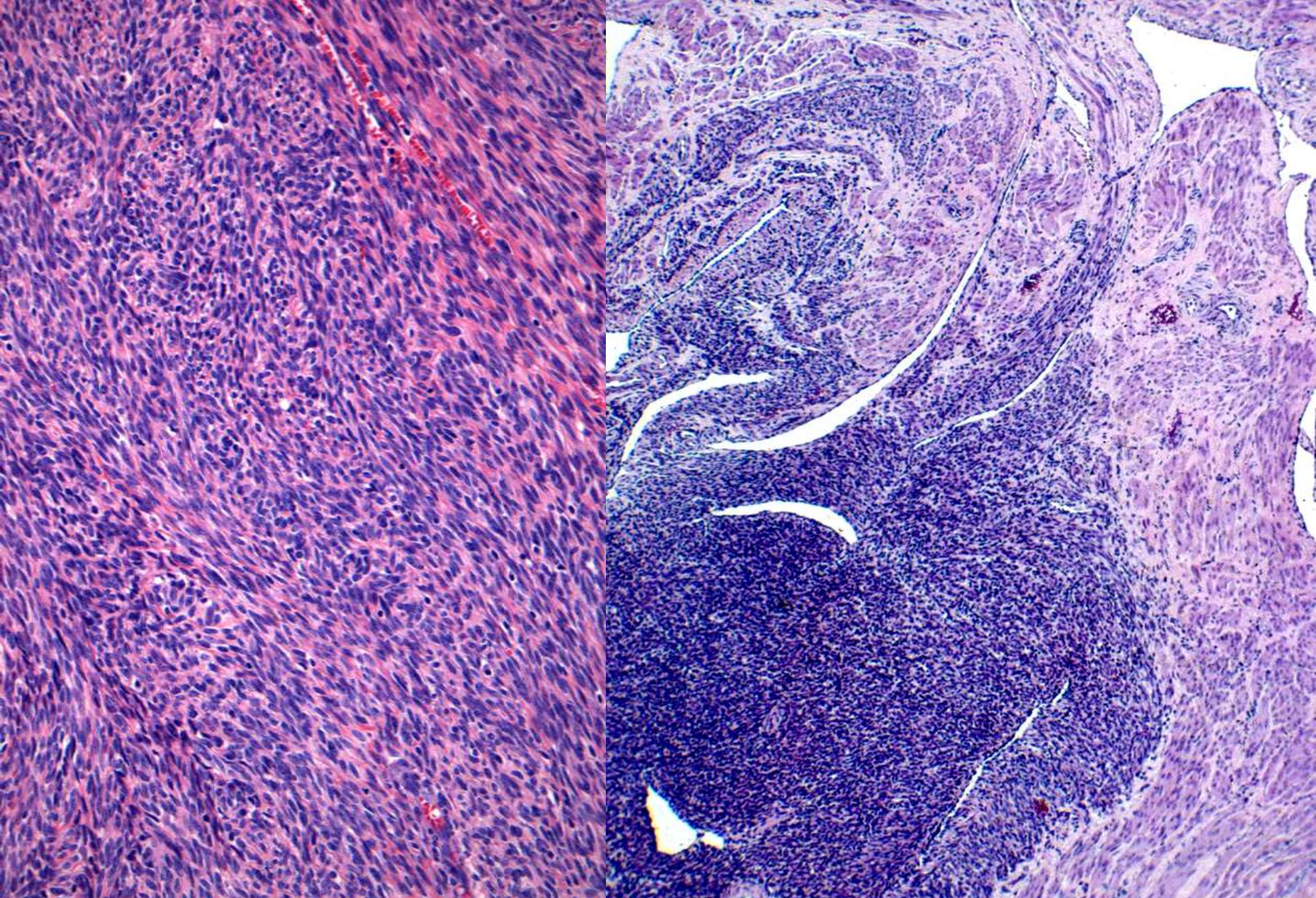


HIGHLY CELLULAR LEIOMYOMA: Misleading Microscopic Features



Tips: Large thick-walled blood vessels and cleft-like spaces



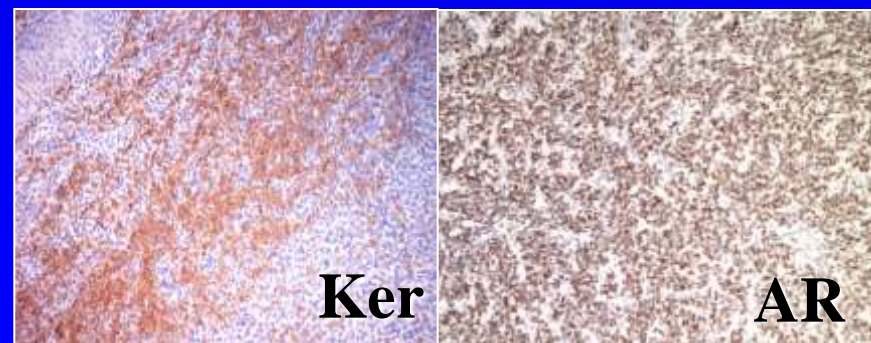
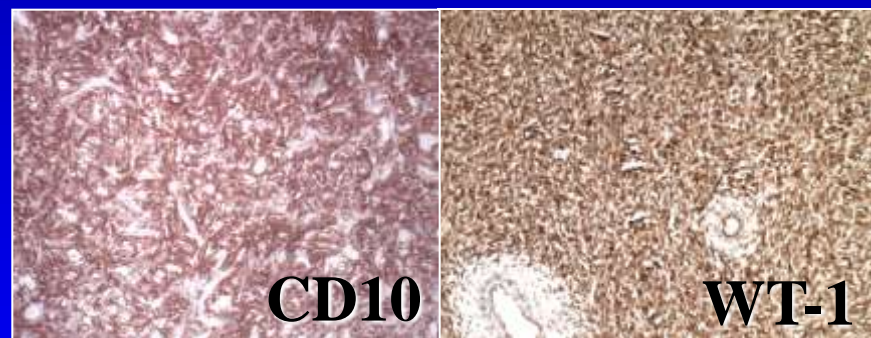
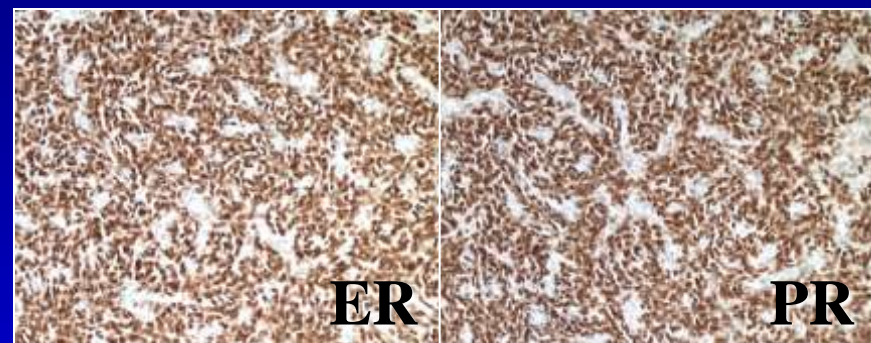


TIPS: Fascicular growth and transition to myometrium

ENDOMETRIAL STROMAL TUMORS

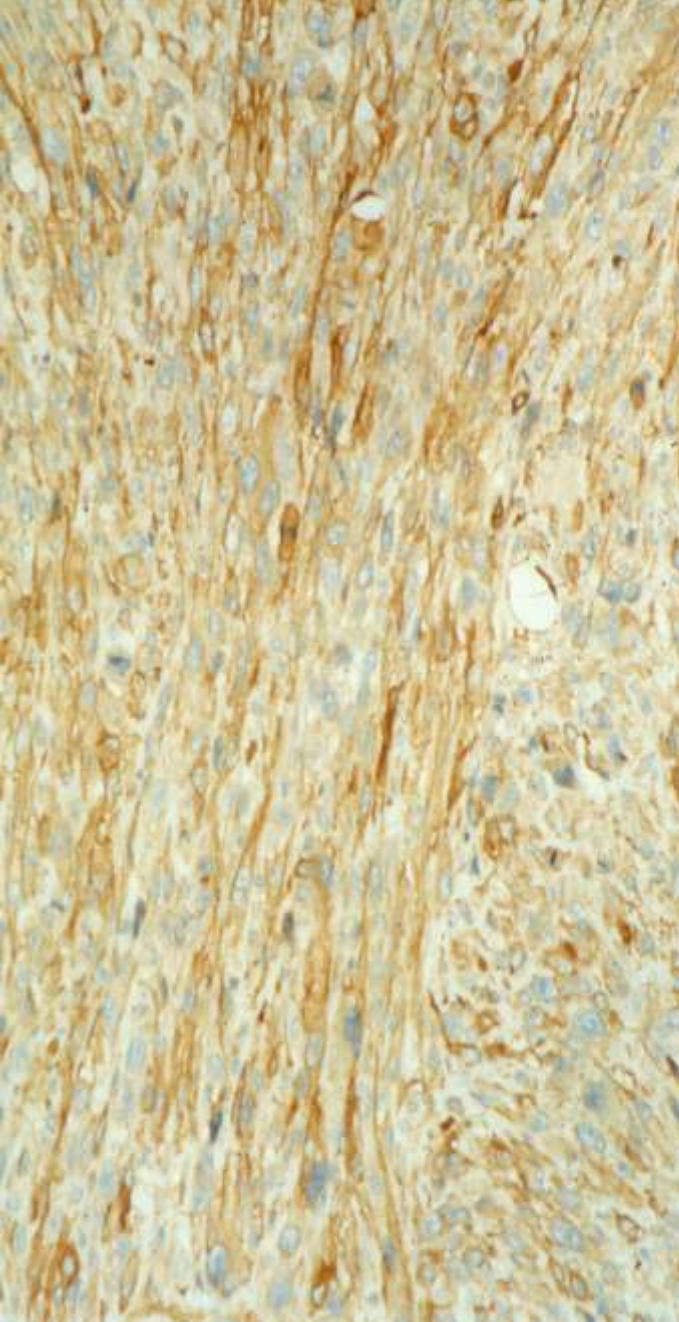
Immunohistochemical profile

Vim	+
ER/PR	+
CD10	+
SMA	+
WT1	+
AR	+/-
Keratin	+/-
B-catenin	-/+
Desmin	-/+
H-caldesmon	-
Calretinin	-
CD99	-

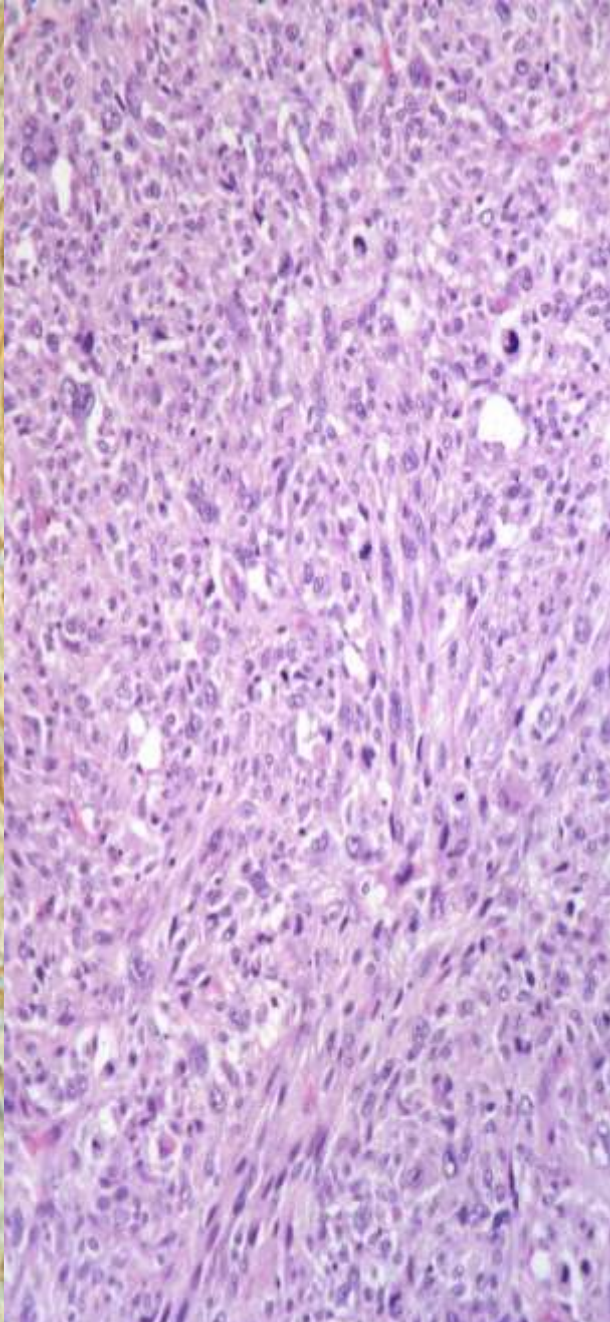


CD10- CAVEATS

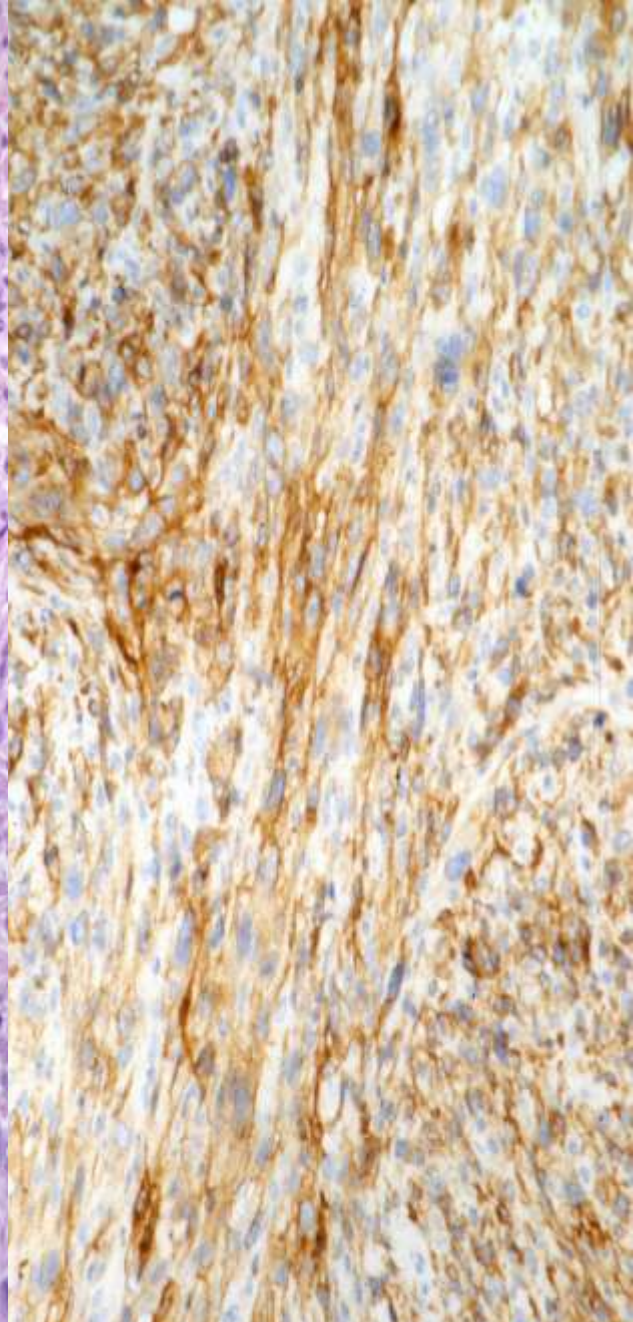
- **Up to 40% of low-grade ESS may only show focal and weak positivity and rare tumors are completely negative**
- **Smooth muscle tumors, more commonly leiomyosarcoma and highly cellular leiomyoma, are also positive**



h-caldesmon



Leiomyosarcoma



CD10

SMOOTH MUSCLE TUMOR *vs* ENDOMETRIAL STROMAL TUMOR

MOST HELPFUL PANEL:

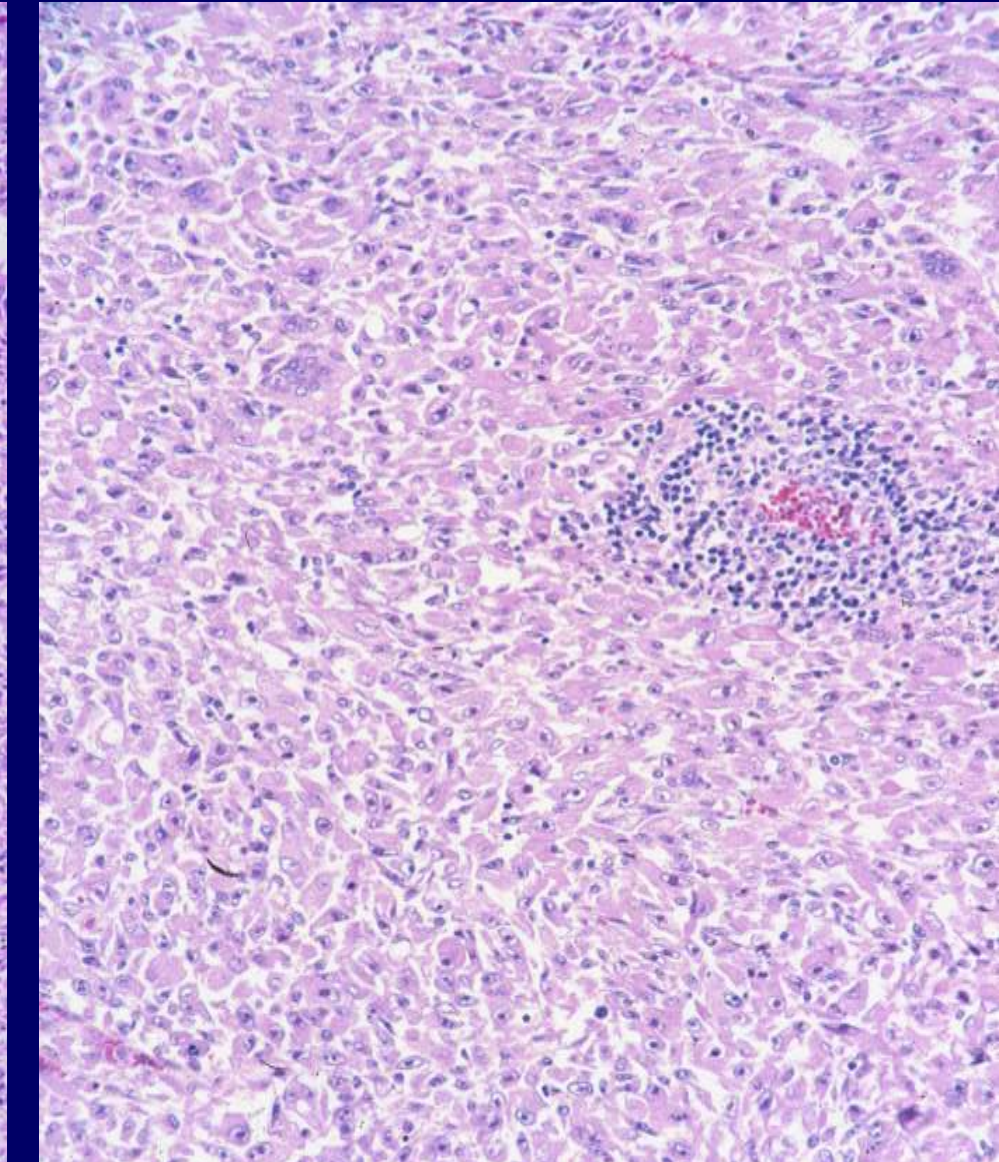
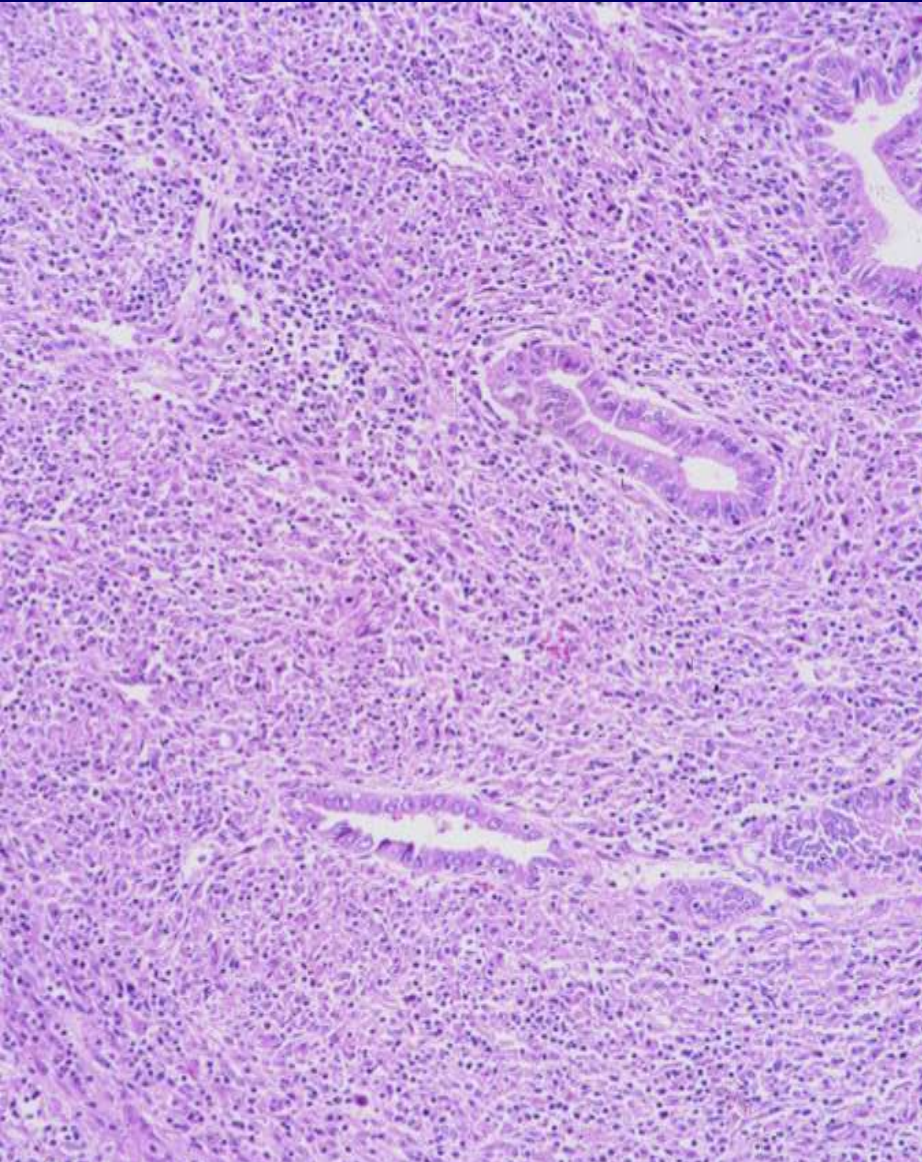
CD10 + DESMIN + h-CALDESMON

UNDIFFERENTIATED ENDOMETRIAL SARCOMA

- Postmenopausal women
- Fleshy masses with hemorrhage and necrosis
- Frequent myometrial invasion, destructive but not permeative as seen in low-grade ESS
- Highly pleomorphic
- **NO** histologic evidence of endometrial stromal differentiation
- Very aggressive behavior (most patients die within 2 years of diagnosis)

-
- **MITOTIC ACTIVITY SHOULD NOT BE USED TO SEPARATE LOW-GRADE FROM HIGH-GRADE TUMORS**

UNDIFFERENTIATED ENDOMETRIAL SARCOMA



DIAGNOSIS OF EXCLUSION

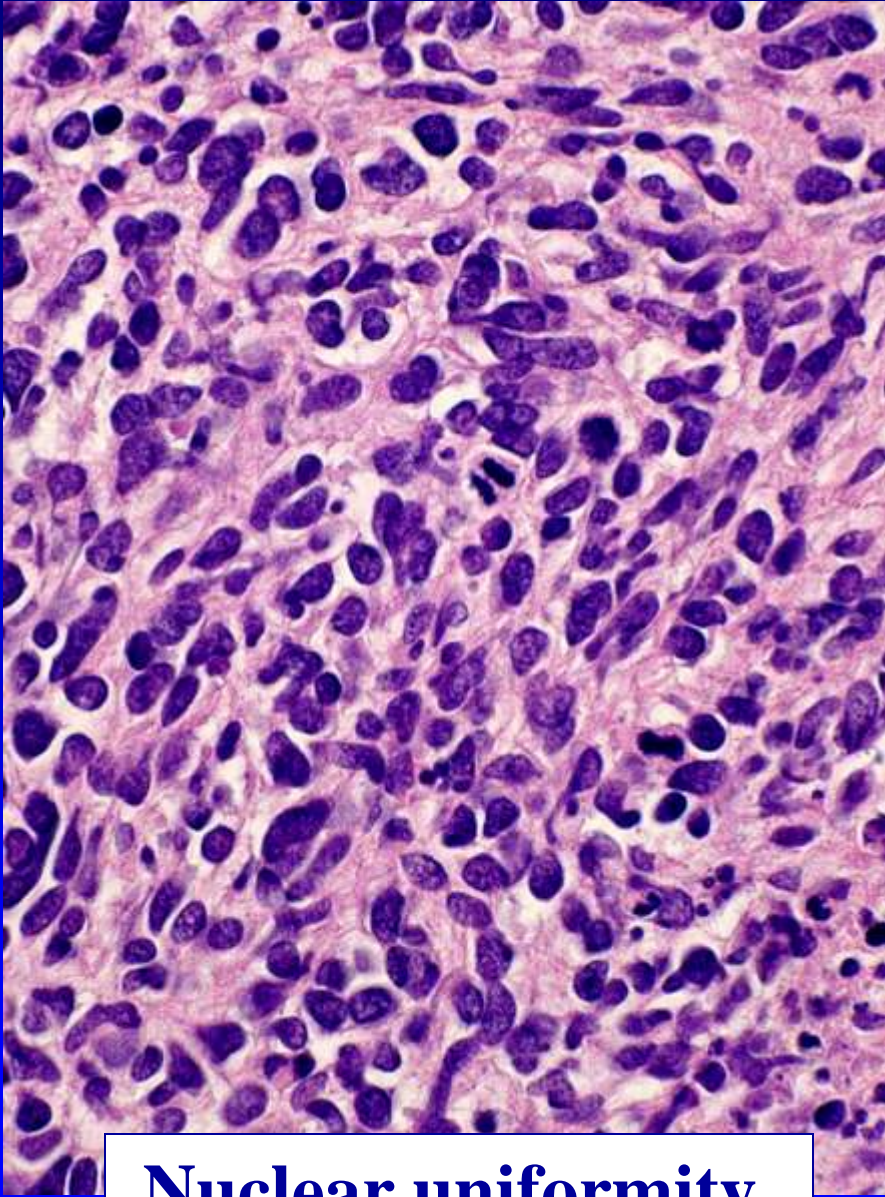
ENDOMETRIAL STROMAL SARCOMAS AND RELATED HIGH-GRADE SARCOMAS: IMMUNOHISTOCHEMICAL AND MOLECULAR GENETIC STUDY OF 31 CASES

Kurihara S et al, Am J Surg Pathol 2008;32:1228

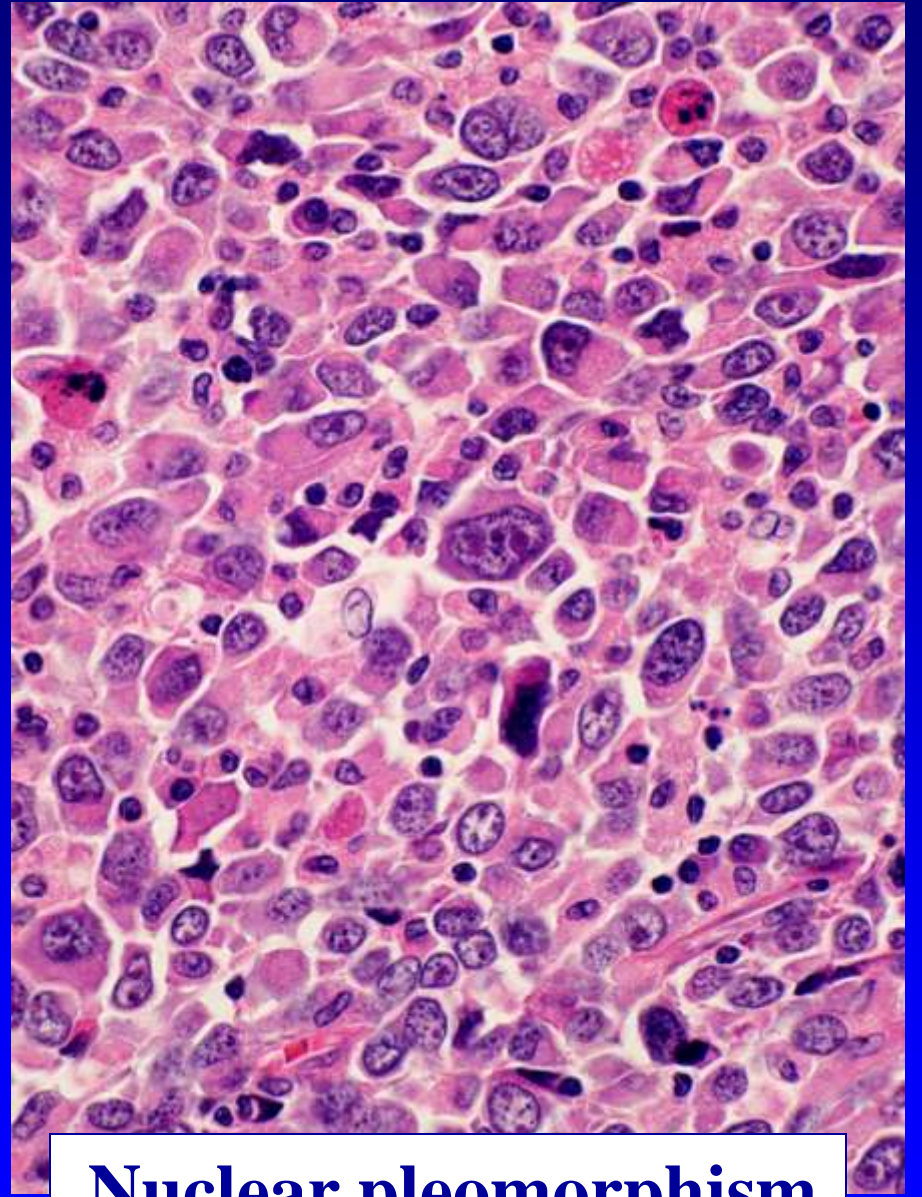
- Objective: Address the controversial nomenclature of “Undifferentiated endometrial sarcoma”

-
- 18 low-grade ESS
 - 7 UES-U (monotonous cytologic uniformity reminiscent of LG-ESS with nucleomegaly, hyperchromatism and nucleoli)
 - 6 UES-P (nuclear pleomorphism with no resemblance to endometrial stroma)

UNDIFFERENTIATED ENDOMETRIAL SARCOMA



Nuclear uniformity



Nuclear pleomorphism

ENDOMETRIAL STROMAL SARCOMAS AND RELATED HIGH-GRADE SARCOMAS: IMMUNOHISTOCHEMICAL AND MOLECULAR GENETIC STUDY OF 31 CASES

Kurihara S et al, Am J Surg Pathol 2008;32:1228

	<u>LG-ESS</u>	<u>UES-U</u>	<u>UES-P</u>
• Stage I	13/17	2/7	2/6
• DOD	0/13	4/7	3/5
• ER	17/17	4/7	0/5
• PR	17/17	4/7	0/5
• β -catenin	8/17	6/7	2/6
• <i>JAZF1-JJAZ1</i> fusion	6/12	1/3	0/3
• p53 mutations	0/17	0/7	3/7

ENDOMETRIAL STROMAL SARCOMAS AND RELATED HIGH-GRADE SARCOMAS: IMMUNOHISTOCHEMICAL AND MOLECULAR GENETIC STUDY OF 31 CASES

Kurihara S et al, Am J Surg Pathol 2008;32:1228

Conclusions:

- Besides nuclear atypia, the finding of <10 mitoses/10 HPFs and typical whorling of cells around arterioles help to separate LG-ESS from UES-U**
- Some UES-U may originate from low-grade ESS as they show low-grade ESS areas and share immunohistochemical/molecular abnormalities**
- However, UES-U is biologically closer to UES-P**

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

Prognosis and treatment

- **Hysterectomy and bilateral salpingo-oophorectomy**
- **Overall 80-90% 5-year and 70% 10-year survival rates**
- **5- and 10-year survival close to 100% and 80-90% for patients with stage I tumors**
- **Hormonal treatment, aromatase inhibitors or radiation as alternative options**

STAGE MOST IMPORTANT PARAMETER

ENDOMETRIAL STROMAL SARCOMAS

Potential prognostic factors:

Clinical Factors

Age
Race
Parity
Menopausal status

Pathologic Factors

Stage
Tumor size
Nuclear atypia
Mitotic index
Tumor necrosis
Lymphatic space invasion
Status of surgical resection margins
DNA ploidy/proliferation index
ER, PR, and AR expression

PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

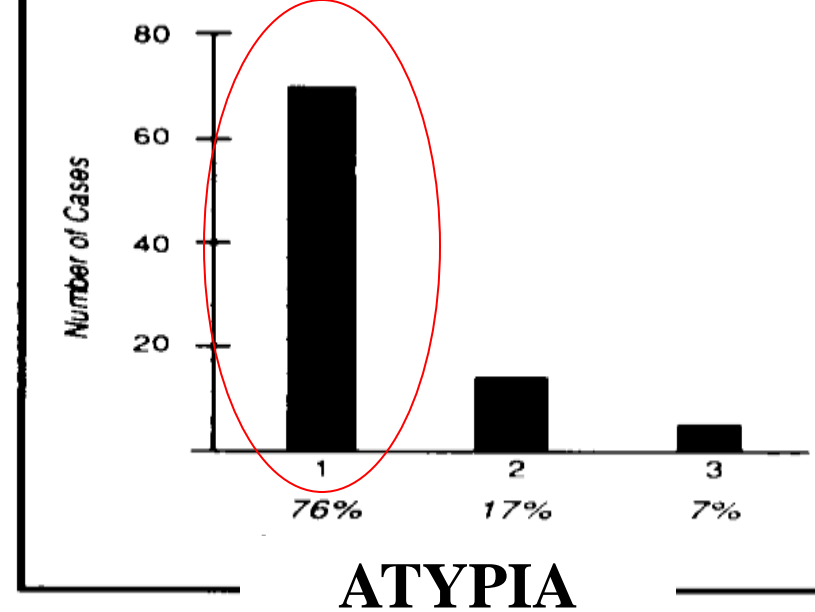
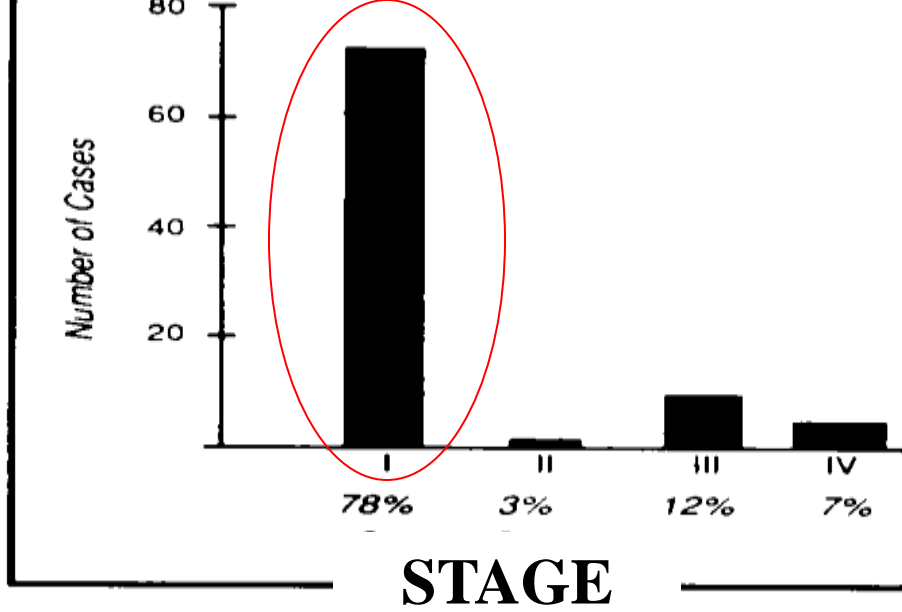
Chang KL et al, Am J Surg Pathol 1990;14:415

- 85 patients with stage I tumors (73 with FU)
- Analysis of size, stage, and morphologic features including **mitotic activity, degree of cytologic atypia**, tumor cell necrosis, hemorrhage, inflammation, calcification, foam cells, cells with decidual features, epithelioid, glandular, or smooth muscle areas

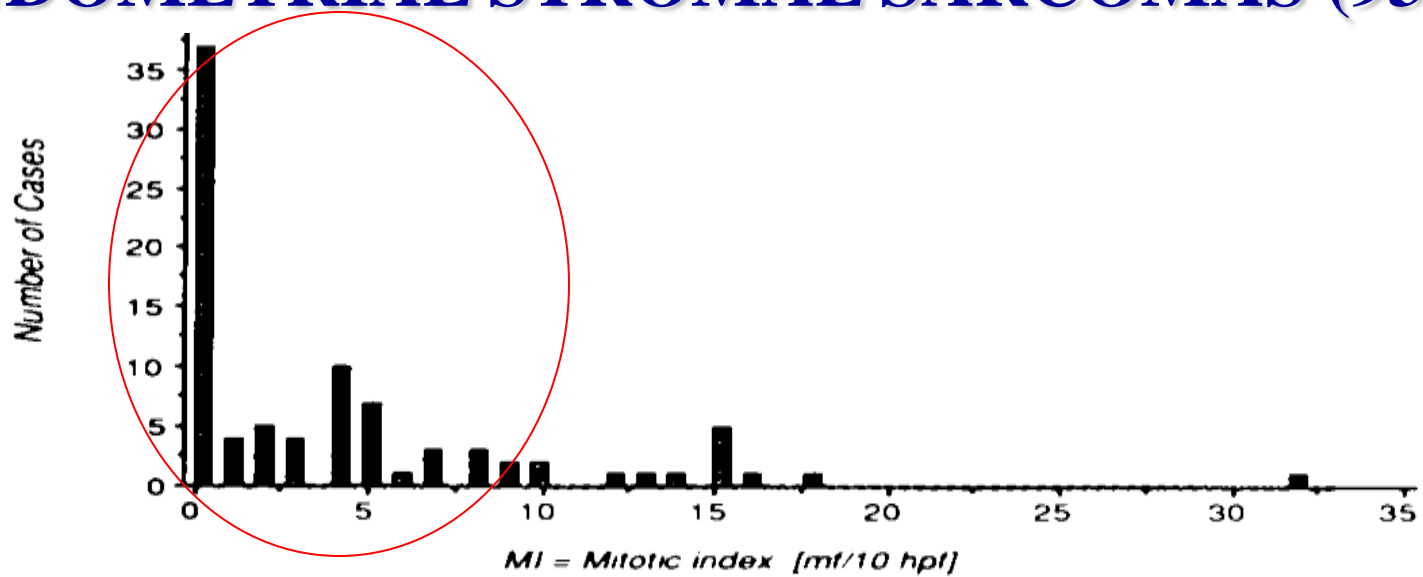
PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

Chang KL at al, Am J Surg Pathol 1990;14:415

- When evaluating mitotic activity they followed Norris and Taylor guidelines who divided ESS into low and high grade on the basis of finding $<$ or ≥ 10 mitoses/10 high-power fields
- When evaluating cytologic atypia, all tumors with significant pleomorphism were excluded (following Evans work = tumors should show evidence of endometrial stromal differentiation)
- Nucleomegaly could not be greater than moderate, but still gave three grades



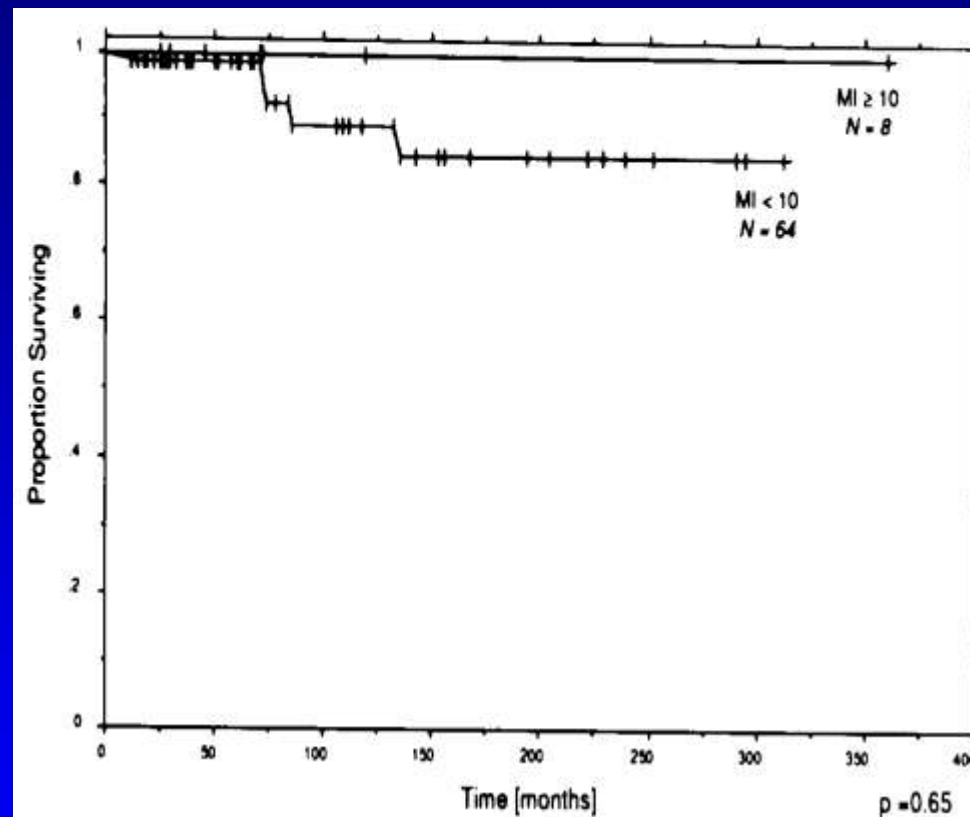
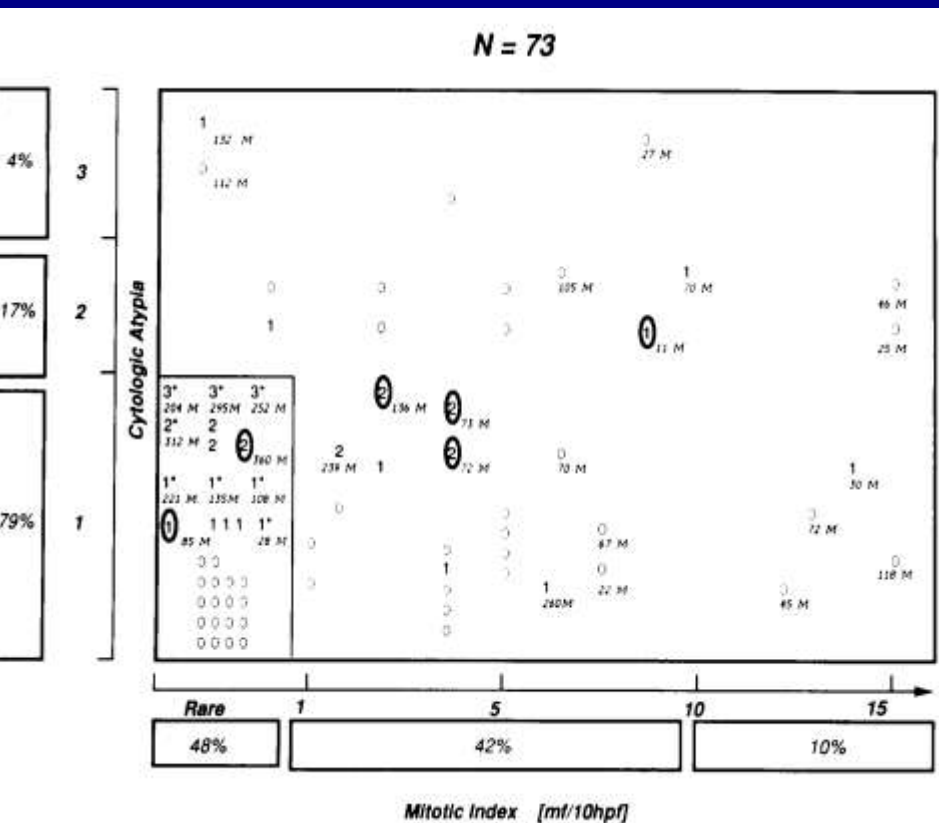
ENDOMETRIAL STROMAL SARCOMAS (93)



41%	45%	14%
<i>MI = 0 'Rare'</i>	$1 \leq MI \leq 9$	$MI < 10$

MITOSES

STAGE I ENDOMETRIAL STROMAL SARCOMAS (73)



0: Patients that DOD
Numeral: N° of recurrences

**Patients with < or \geq 10
mitoses/10HPFs**

PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

Chang KL et al, Am J Surg Pathol 1990;14:415

Conclusions:

- By univariate analysis and including all stages:
 - Patients with tumors showing ≥ 10 mitoses/10 HPFs had significantly less favorable survival
 - Increasing atypia was associated with an increasing relapse rate
- By multivariate analysis only stage was a significant predictor of recurrence and survival
 - Mitotic index and cytologic atypia lost predictive value in stage I tumors

PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

Chang KL at al, Am J Surg Pathol 1990;14:415

- Pleomorphic undifferentiated sarcoma is a different clinicopathologic entity (as described by Evans) = UES-P
- The main strategy for separating mitotically active, cytologically atypical endometrial stromal sarcomas that lack the arborizing stromal vasculature from undifferentiated sarcoma involves an assessment of nuclear pleomorphism = UES-U

SUMMARY

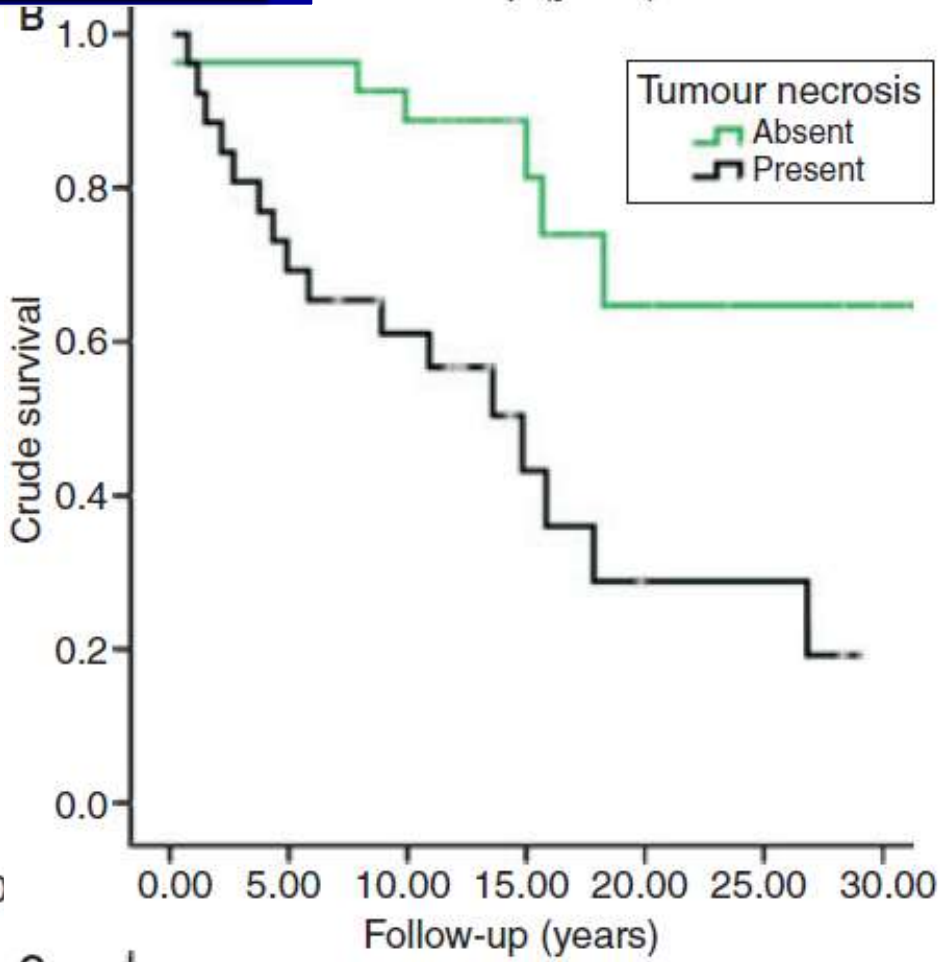
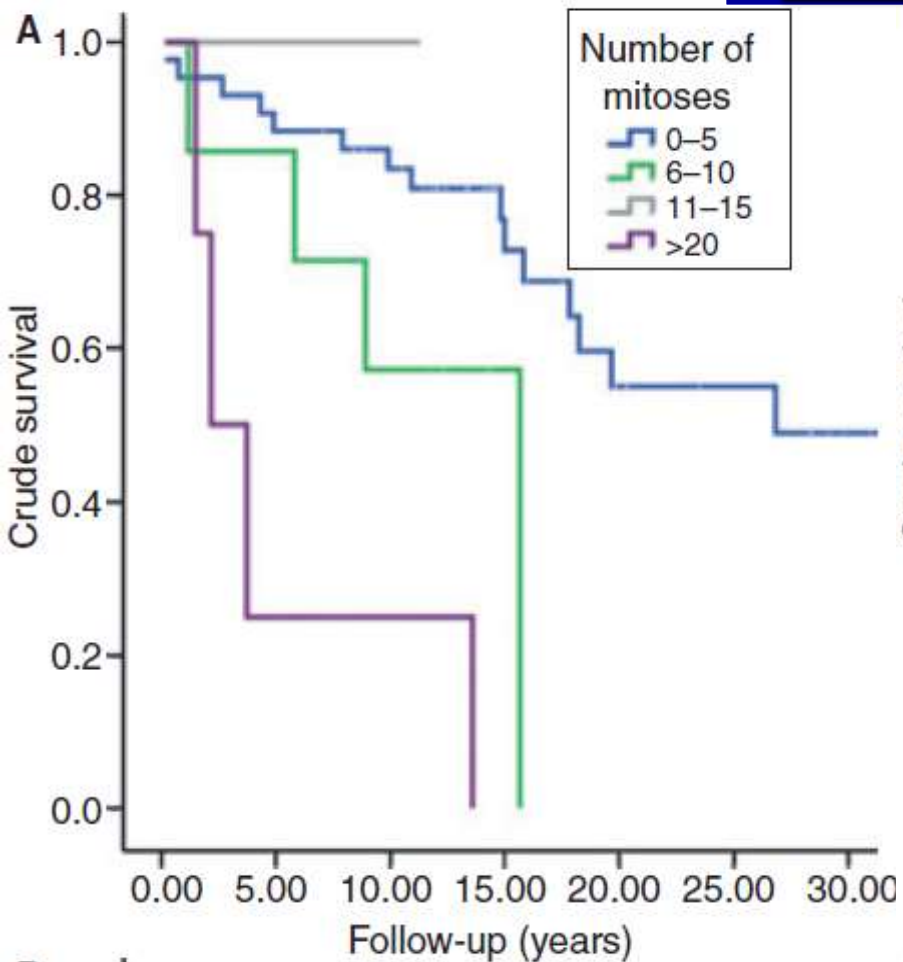
- Stage most important prognostic factor in low-grade ESS
- No other proved pathologic factors to predict recurrence in stage I low-grade ESS



ENDOMETRIAL STROMAL SARCOMAS

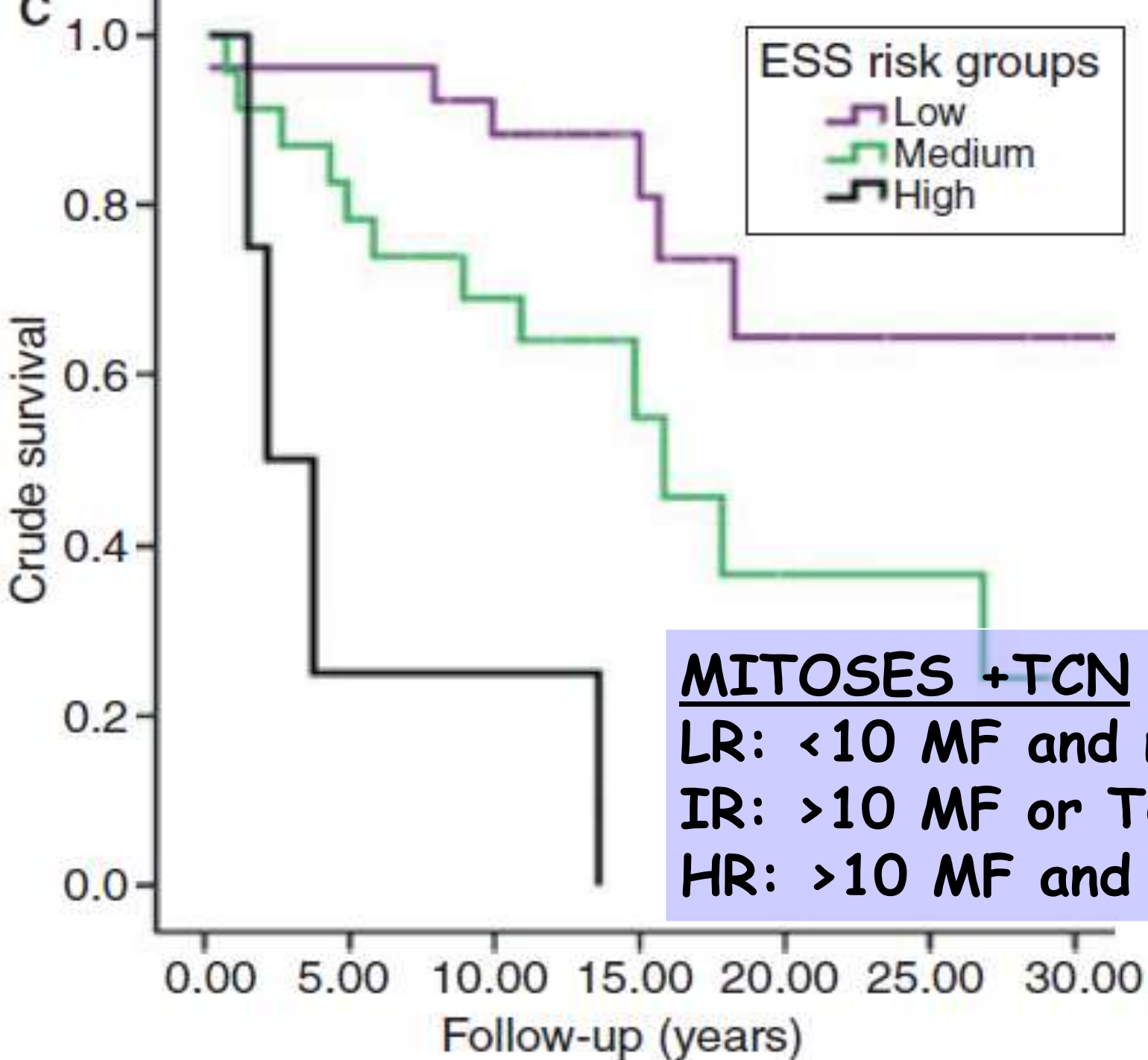
Abeler et al, Histopathology 2009, 54:355

STAGE I



MITOSES

TUMOR NECROSIS



MITOSES + TCN

LR: <10 MF and no TCN

IR: >10 MF or TCN

HR: >10 MF and TCN

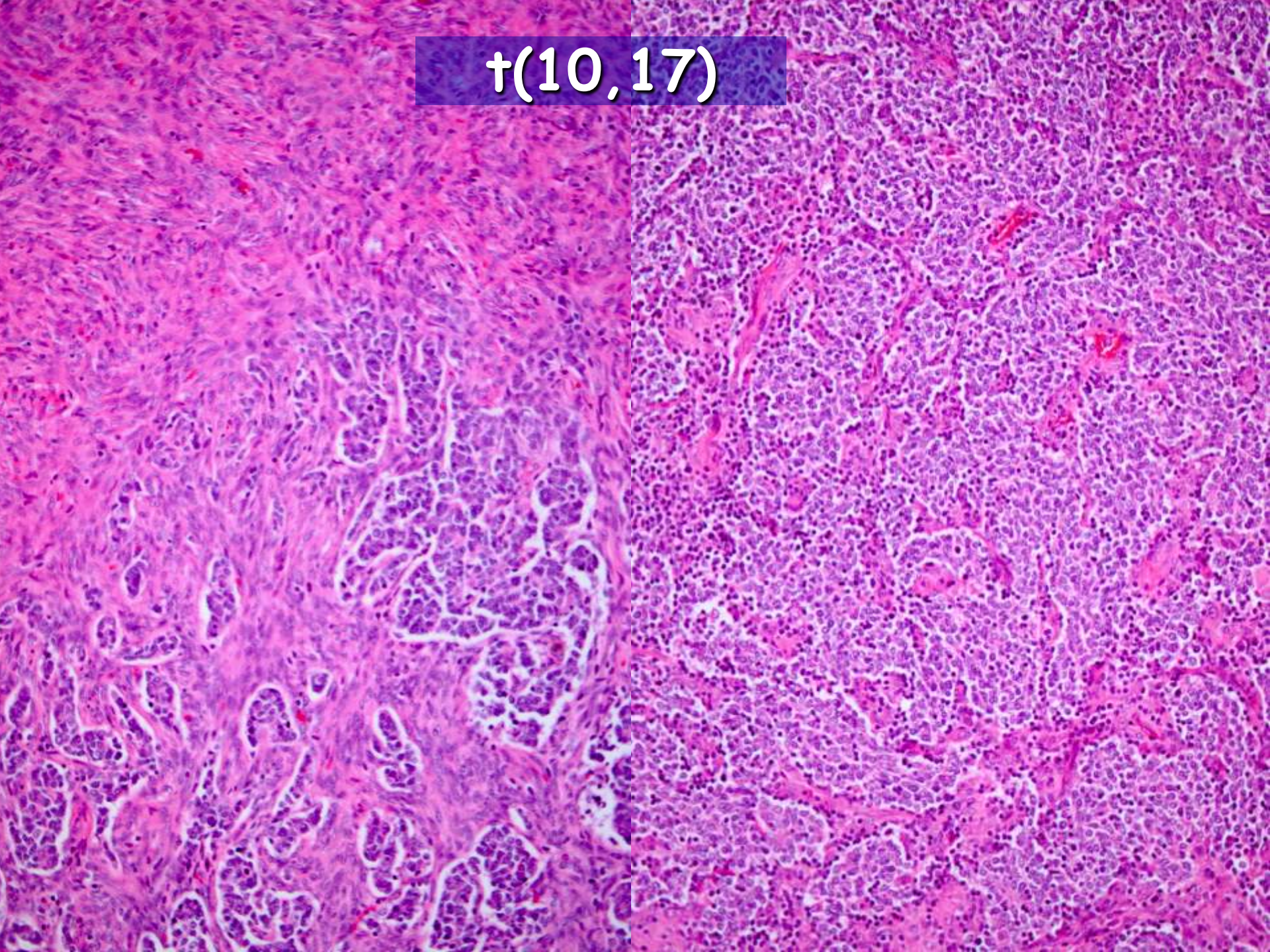
Histologic Features of ESS Characterized by YWHAE Rearrangement-Distinction from Usual LG-ESS with JAZF1 Rearrangement

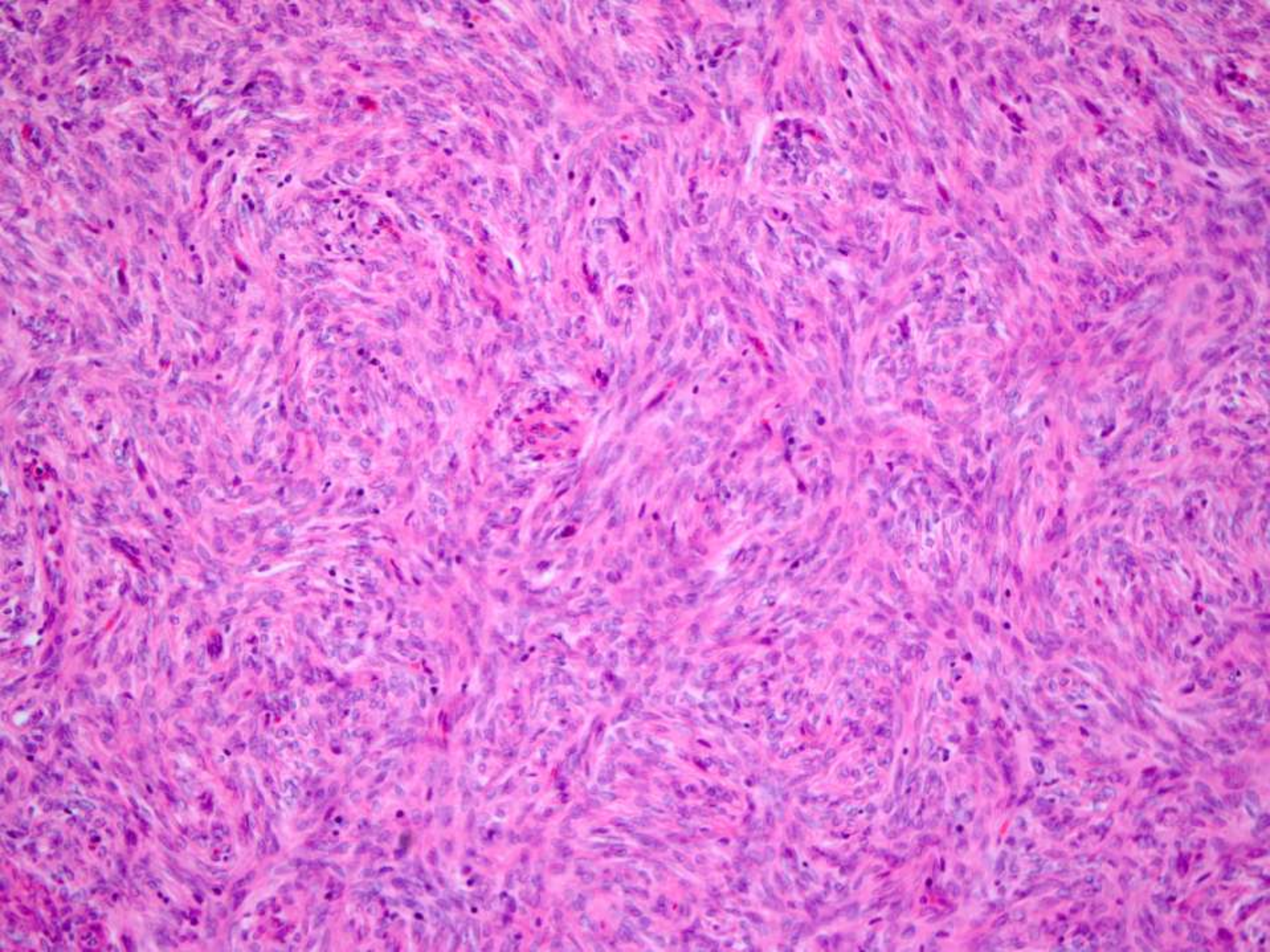
Cheng-Han Lee et al, Modern Pathol, 2011, A

11 tumors:

- **Epithelioid areas with cells arranged in nests**
- **Cells with moderate amount of cytoplasm, large nuclei (when compared to conventional ESS) with irregular contours, and increased mitotic activity**
- **Tumor cell necrosis**
- **Associated fibromyxoid areas in some tumors**

$t(10,17)$





ENDOMETRIAL STROMAL SARCOMA

Summary Prognostic Factors

- **Stage most important**
- **In stage I tumors, mitotic activity and tumor cell necrosis may be important**
- **Tumors with epithelioid morphology associated with a fibromyxoid background and t(10;17) may behave in a more aggressive manner**



Gracias !