The Strange Pathology of Uterine Sarcomas

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Disclosure slide

No conflicts of interests to declare

Uterine Sarcomas

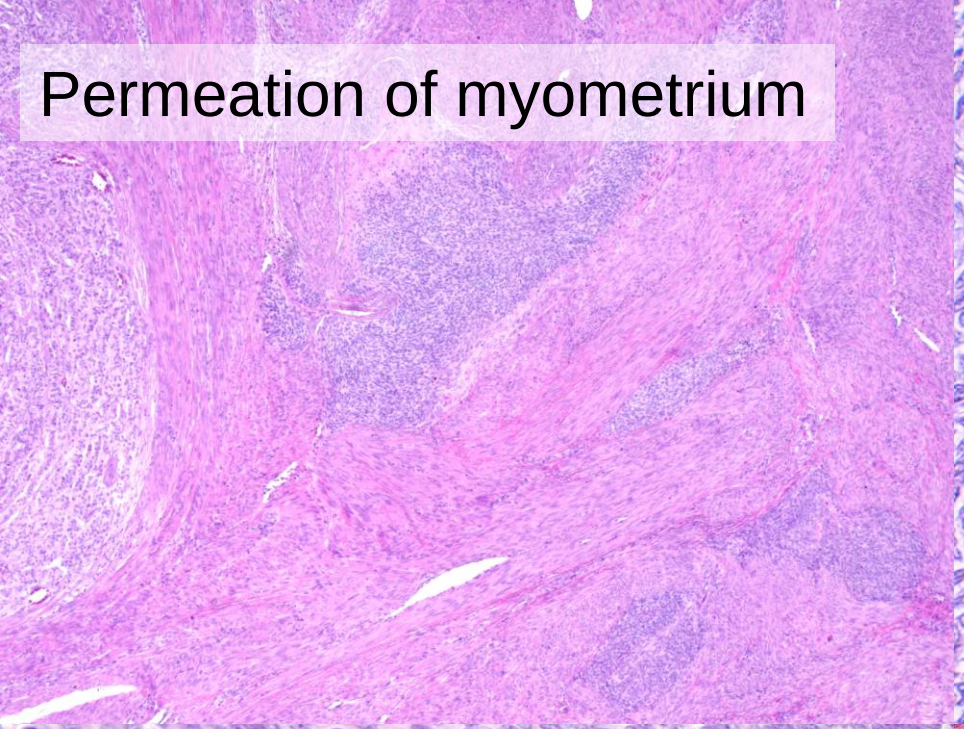
- Endometrial Stromal Tumors
  - Endometrial stromal nodule
  - Endometrial stromal sarcoma
  - Undifferentiated endometrial sarcoma
- Smooth muscle tumors
  - Leiomyoma and variants
  - STUMP
  - Leiomyosarcoma
- Mixed epithelial/mesenchymal tumors
  - Adenosarcoma
  - Carcinosarcoma (MMMT)

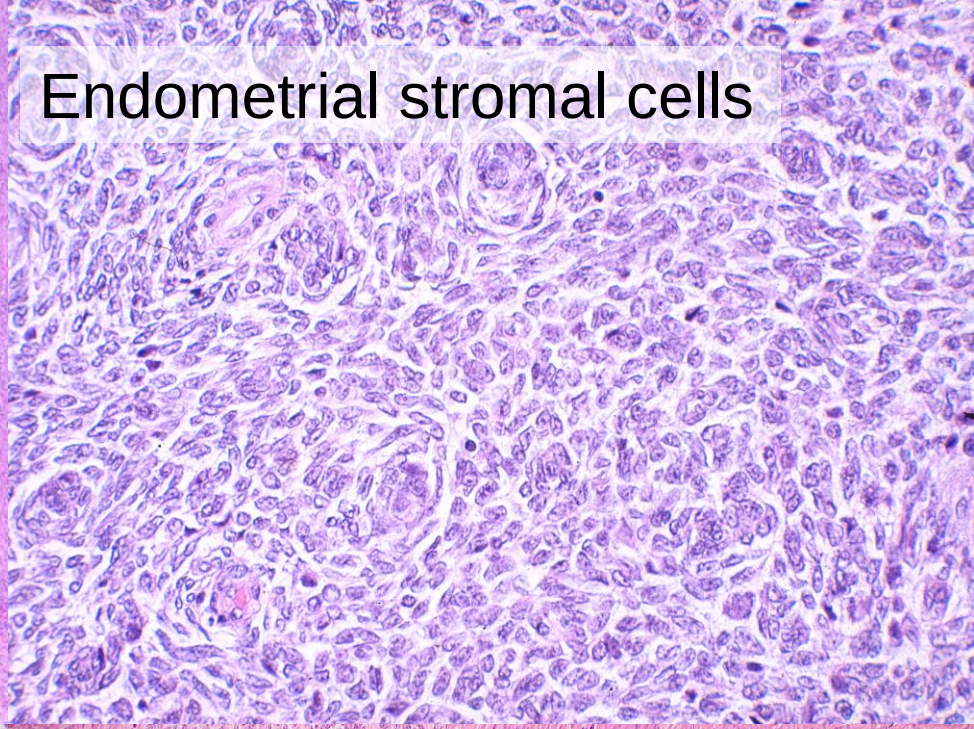
Endometrial stromal sarcoma

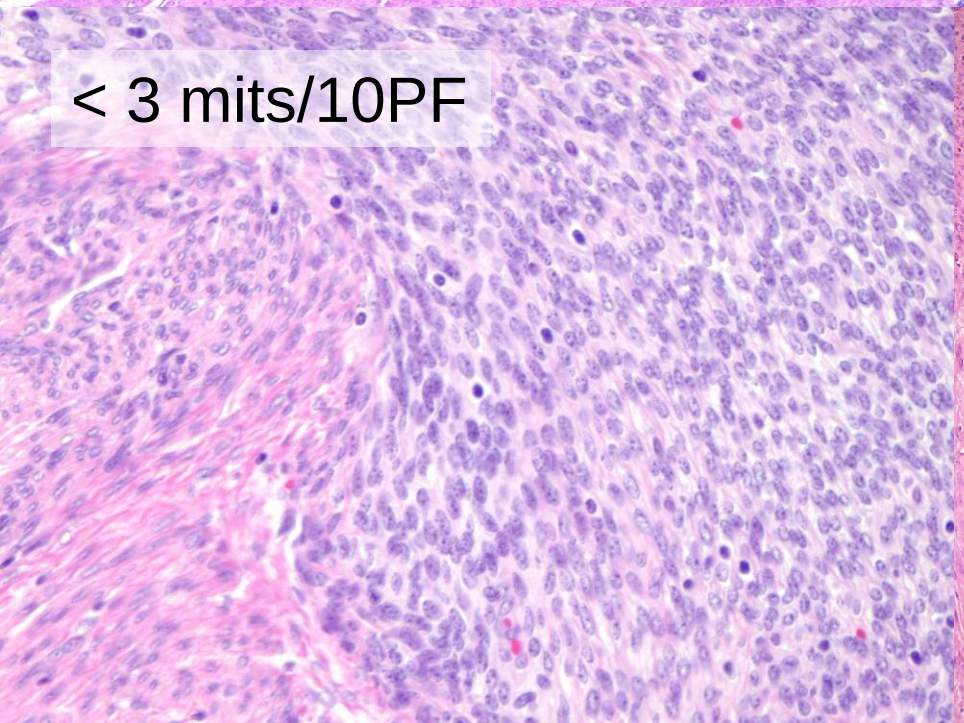
- “Low grade” disappeared from label
- Middle-aged women complaining vaginal bleeding or abdominal pain
- Intracavitary fleshy polyp or intramural mass
- Nodular or diffuse; neoplastic plugs in myometrial or parametryal veins

Endometrial stromal sarcoma

- 1/3 ⇒ extrauterine pelvic extension at diagnosis
- Rarely presentation at metastatic sites (usually ovary)
- Occasionally association with prolonged estrogenic stimulation, tamoxifen treatment, or prior pelvic irradiation


Permeation of myometrium


Endometrial stromal cells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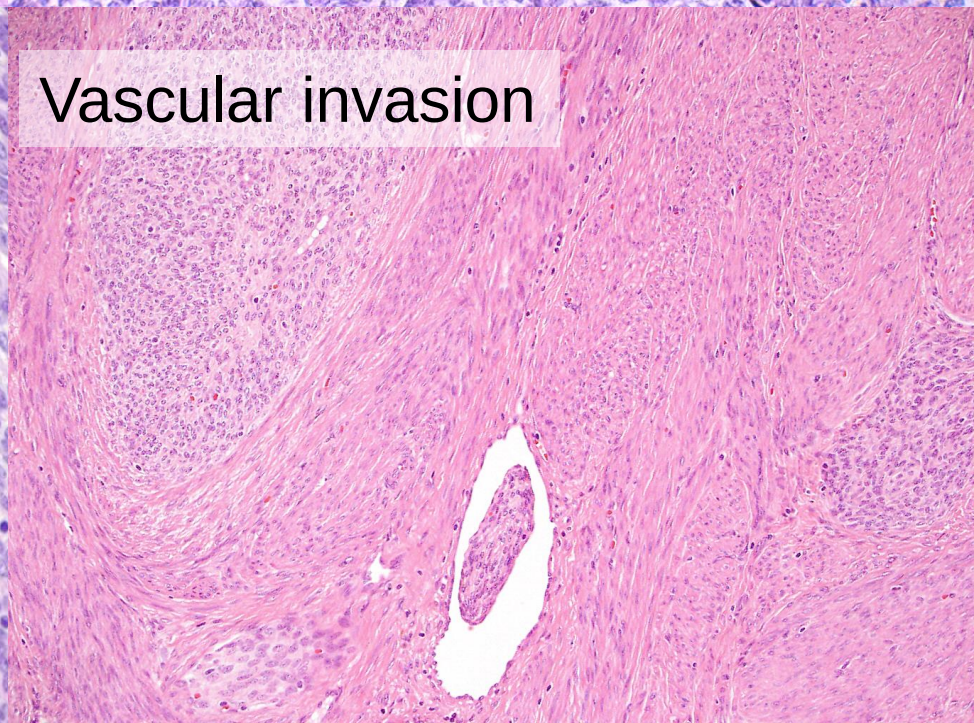
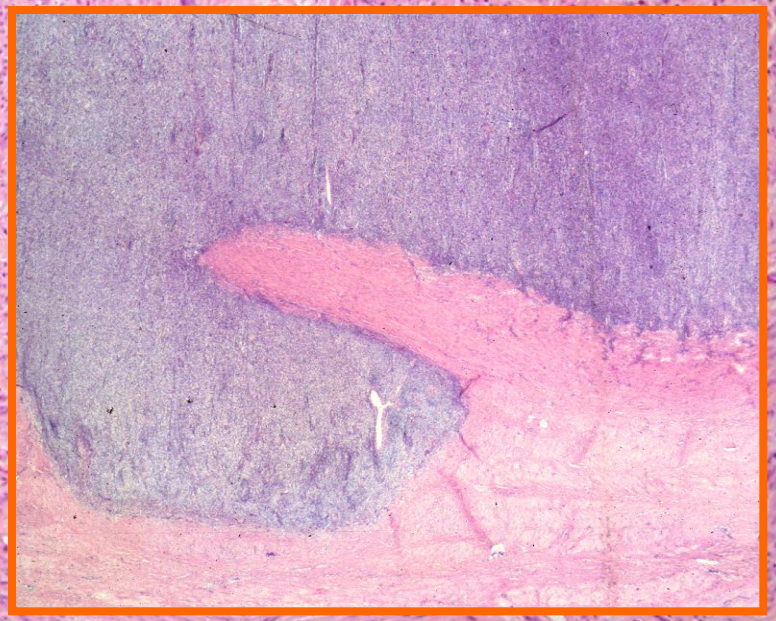

Vascular invasion

Endometrial stromal sarcoma

- OS at 5 years (Stage I) approx 95%
- Local recurrence up to 25%
- Lung mets > 10 years
- No predictive morphological parameters
- Mitotic activity not used as a prognostic tool

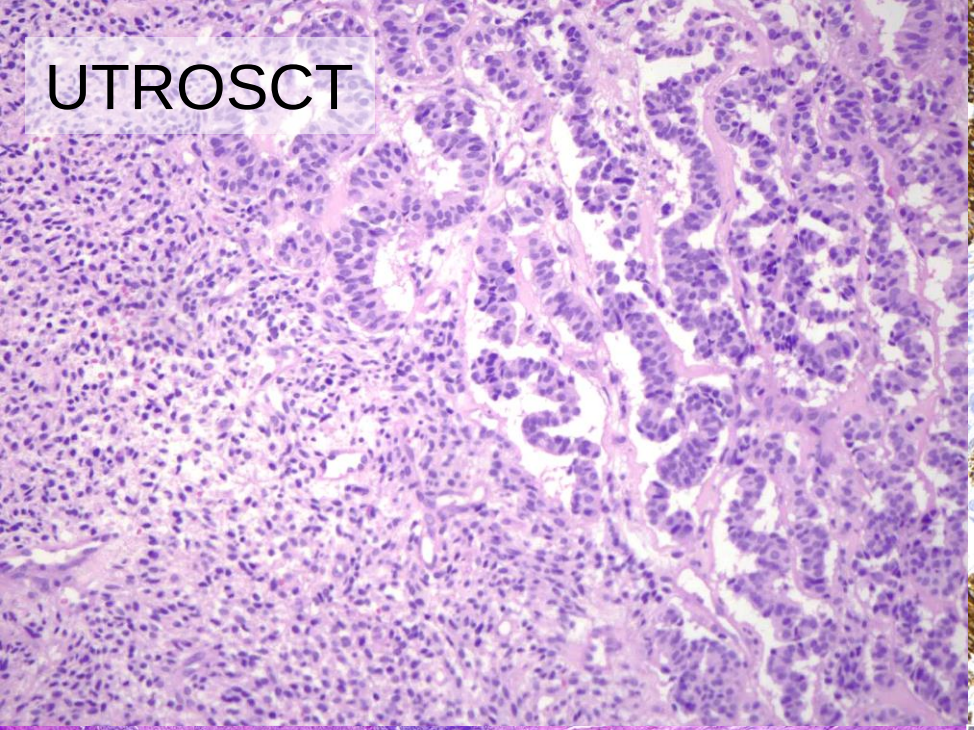
Endometrial Stromal Nodule

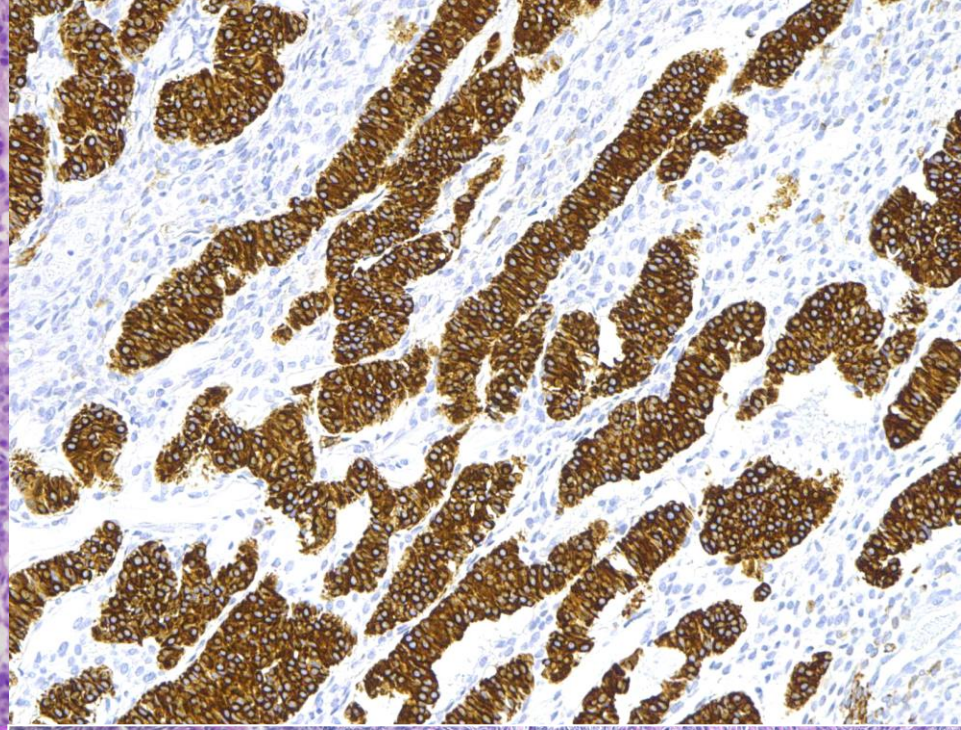
- Benign
- Well circumscribed not encapsulated
- Finger-like projections into myometrium not exceeding 3 mm allowed
- No vascular invasion
- Diagnosis not possible in curettage specimen
- Presence of infiltrative margins or vascular permeation are mostly found in the hysterectomy specimen

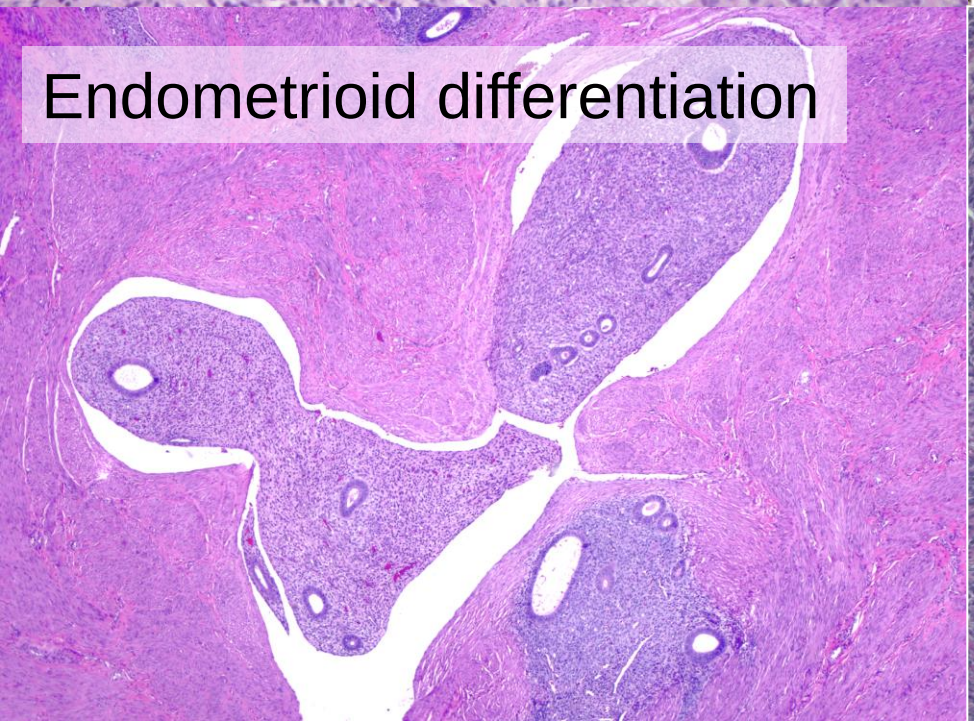


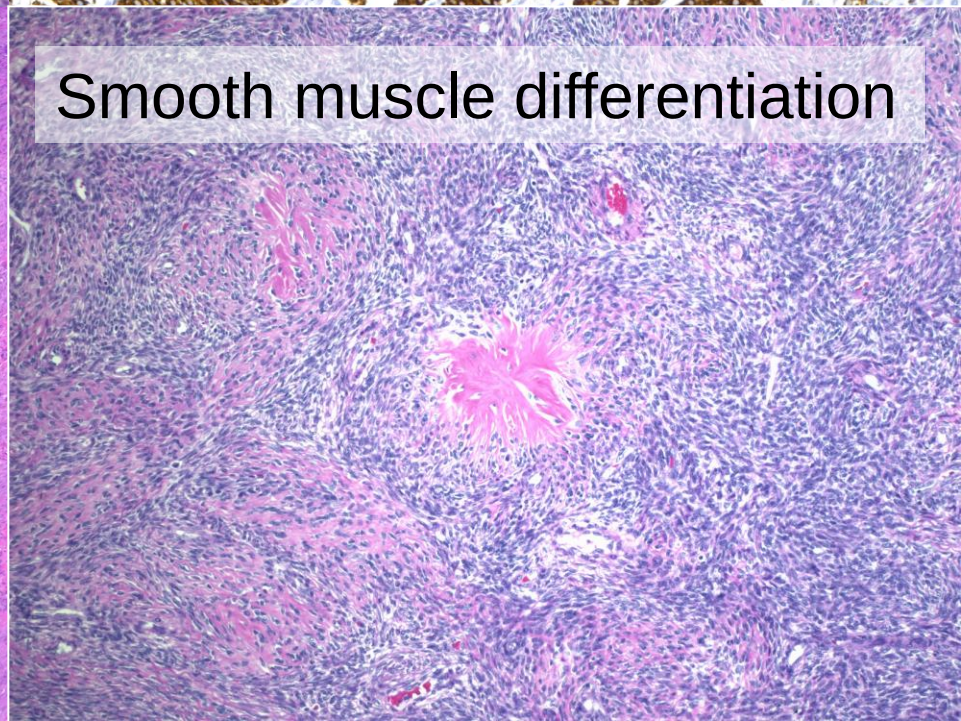
EST with sex cord-like differentiation

- Type I (ESS with sex cord component):
  - Sex cord component = no prognostic significance
- Type II (UTROSCT)
  - solid, well circumscribed myometrial masses
  - variety of epithelial and stromal patterns resembling granulosa cell and Sertoli cell tumors :
  - Very good prognosis
  - Distinct neoplasm? (lack JAZF1-JJAZ1 fusion)


UTROSCT

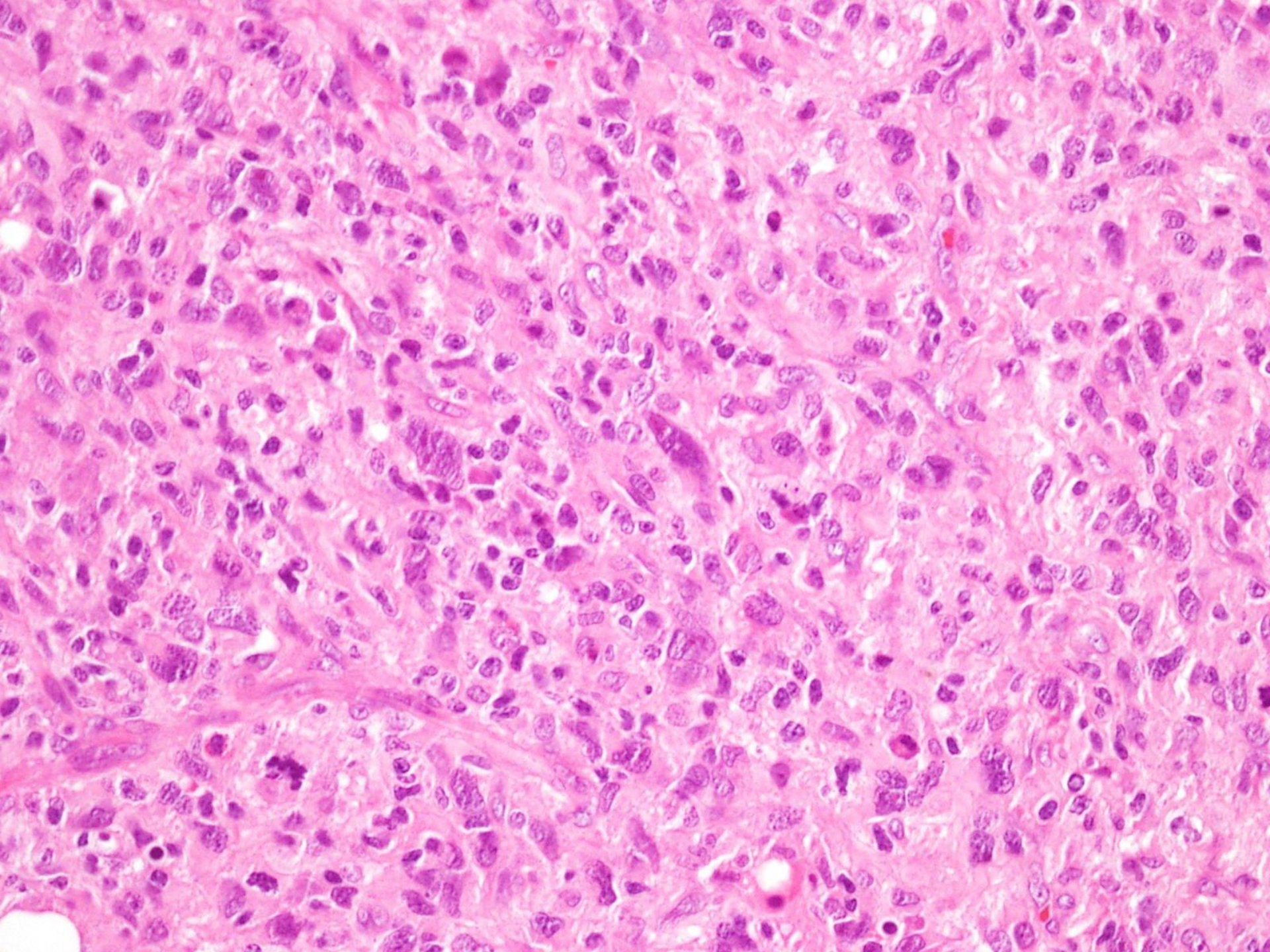



Endometrioid differentiation


Smooth muscle differentiation

Undifferentiated Endometrial Sarcoma

- Postmenopausal women
- Fleshy masses with hemorrhage and necrosis
- High grade morphology
- Destructive but not permeative (ESS)
- No endometrial stromal differentiation
- Very aggressive behavior
- Diagnosis of exclusion
  - No distinctive line of differentiation



LG vs. HG ESS

- The diagnosis of HIGH-GRADE ESS can only be established if areas of LOW-GRADE ESS are identified
- Mitotic activity SHOULD NOT BE USED to separate between low-grade and high-grade ESS

Cytogenetic alterations in EST

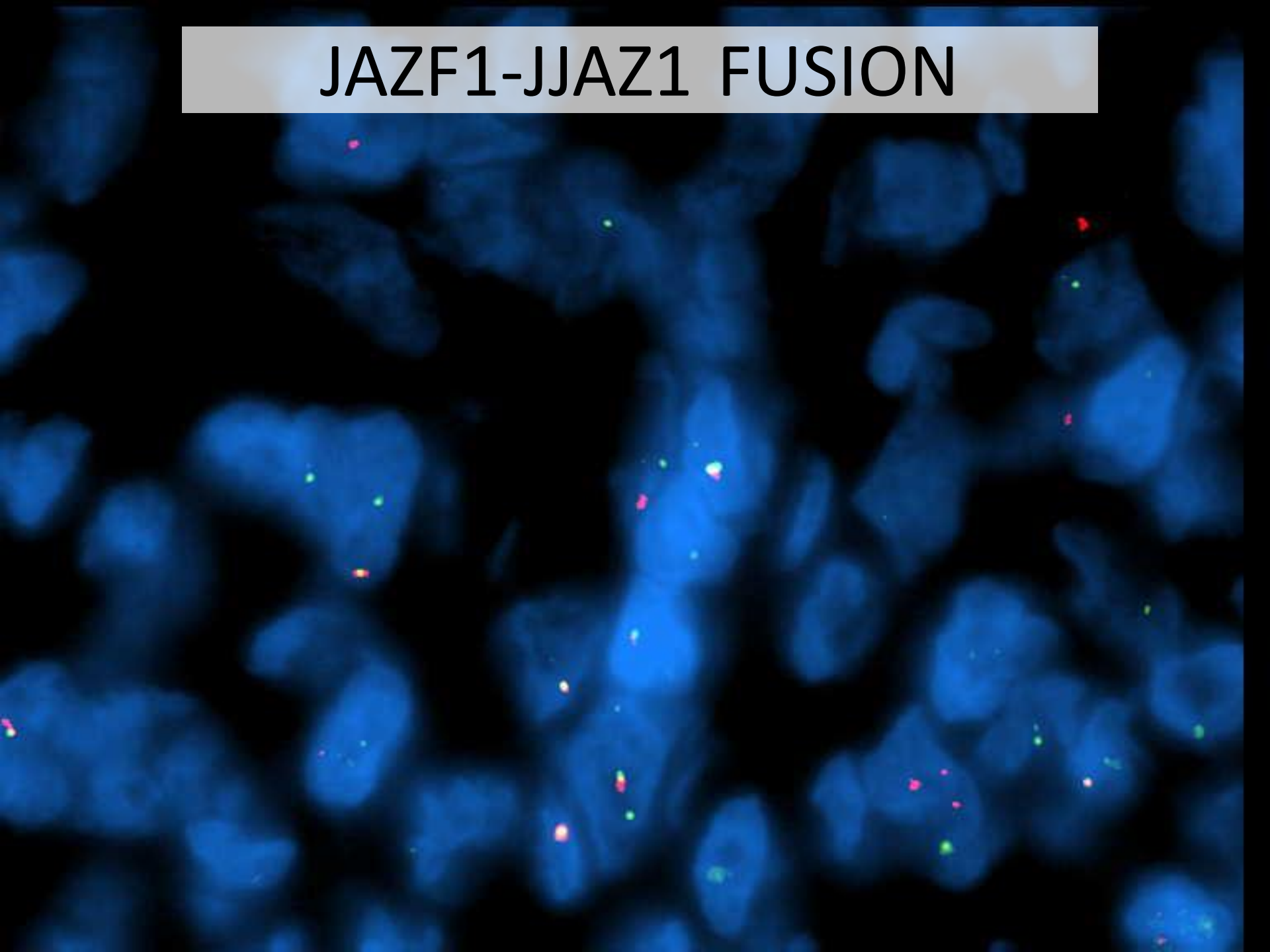
in 1973. After plastic surgery on the external genitalia a good result was obtained. She delivered two healthy children in 1979 and in 1981. Since 1989 abdominal complaints gradually increased and an enlarged uterus was found. In April 1991 a hysterectomy was performed and the diagnosis of endometrial stromal sarcoma was made. At laparotomy, performed in November 1991 because of subobstruction, extensive peritoneal and lymphatic metastases were found and a partial resection of the small bowel was done.

from collagenase-disaggregated tumor cells, according to the procedures previously described [4, 5].

Only one of 11 G-banded metaphases analyzed showed a normal female karyotype. The remaining ten cells were abnormal. A balanced translocation between chromosomes 7 and 17, at bands p15–21 and q12–21, respectively, was always found, and it was the only chromosome change in three cells. In five cells, the second chromosome 7 was replaced by a marker chromosome containing almost all the long arm of a chromosome 7, and the remaining three abnormal metaphases displayed a third abnormality such as a dicentric chromosome replacing two normal chromo-

- Recurrent translocation t(7;17)(p15;q21)
  - JAZF1- JJAZ1
- t(10;17) (q22;p13) identified in ESS with high grade features or clinically aggressive behavior
  - YWHAE-FAM22A/B

JAZF1-JJAZ1 FUSION



PNAS

14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma

Cheng-Han Lee[a,b,1], Wen-Bin Ou[a,1], Adrian Mariño-Enriquez[a], Meijun Zhu[a], Mark Mayeda[a], Yuexiang Wang[a], Xiangqian Guo[c], Alayne L. Brunner[c], Frédéric Amant[d], Christopher A. French[a], Robert B. West[c], Jessica N. McAlpine[e], C. Blake Gilks[b], Michael B. Yaffe[f], Leah M. Prentice[g], Andrew McPherson[g], Steven J. M. Jones[h], Marco A. Marra[h], Sohrab P. Shah[g], Matt van de Rijn[c], David G. Huntsman[g], Paola Dal Cin[a], Maria Debiec-Rychter[d], Marisa R. Nucci[a], and Jonathan A. Fletcher[a,2]

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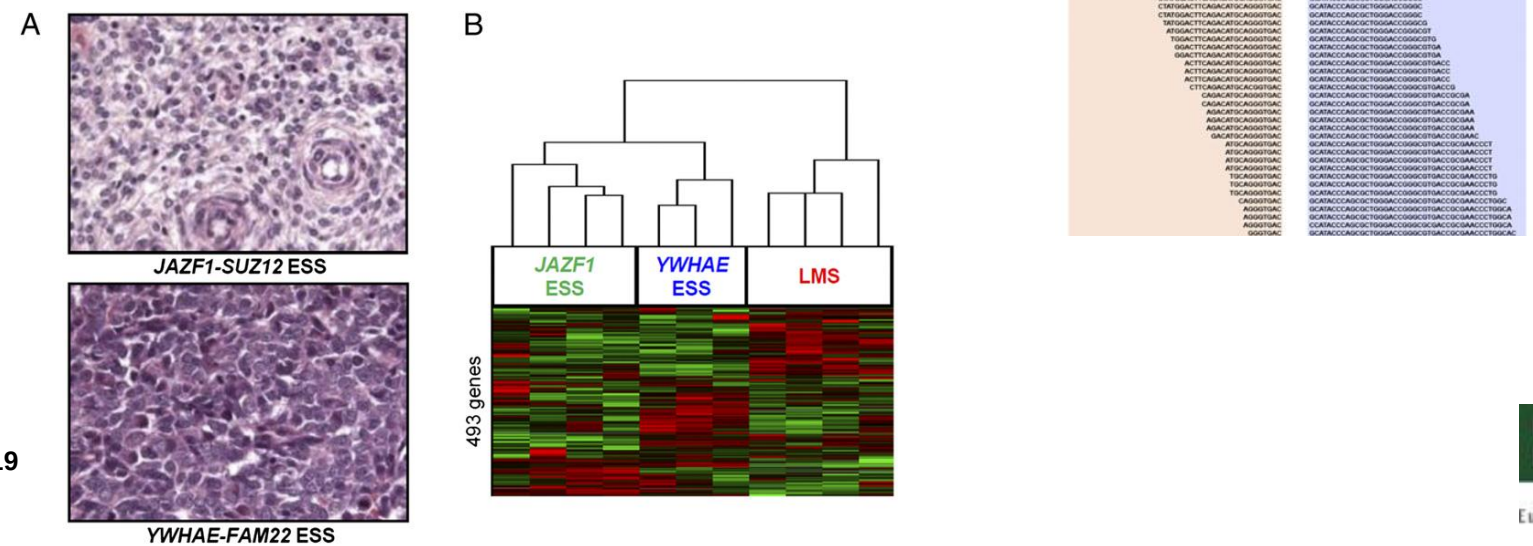
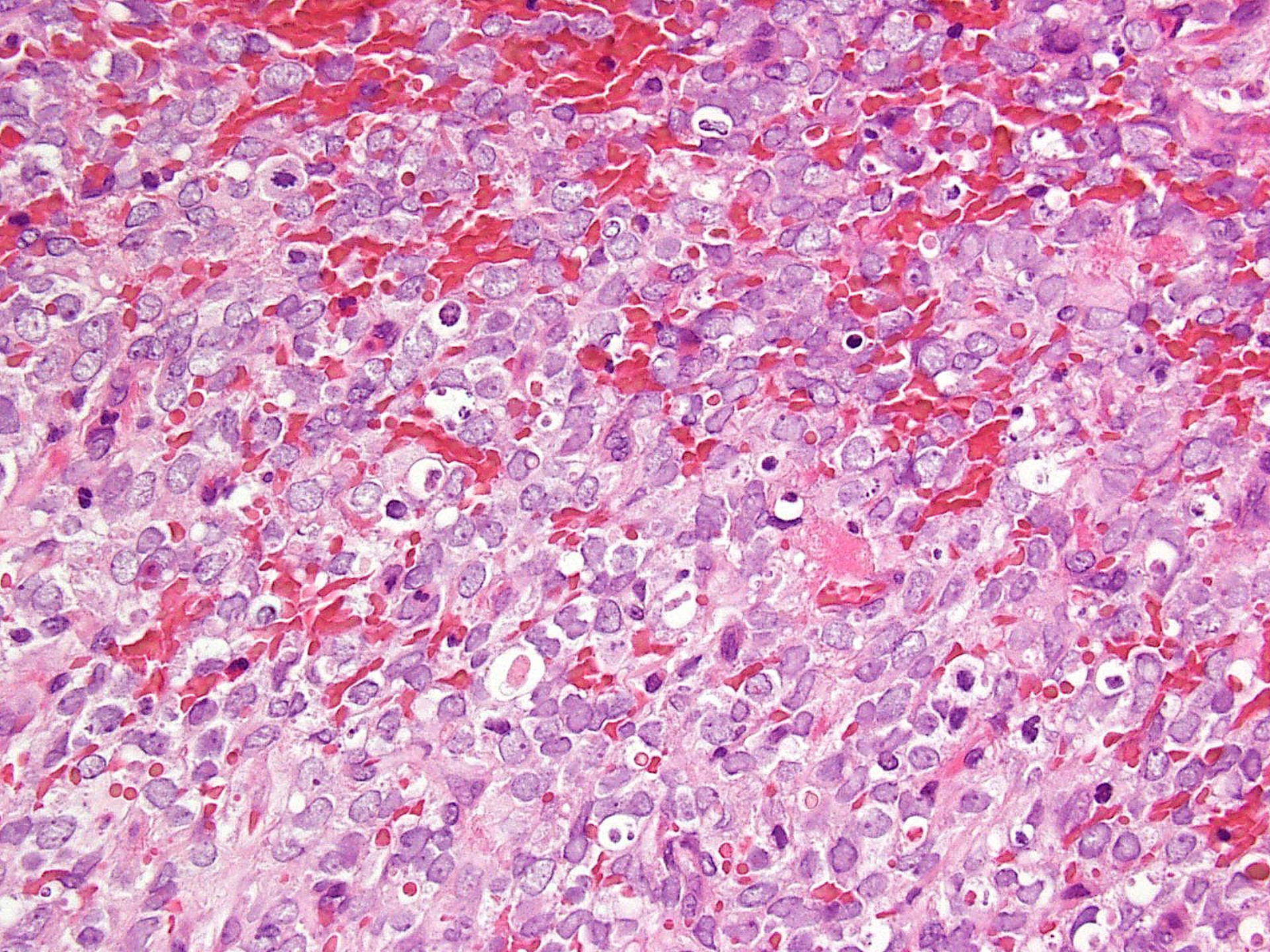


Sarcoma and GIST Conference 2014

The Clinicopathologic Features of *YWHAE-FAM22* Endometrial Stromal Sarcomas: A Histologically High-grade and Clinically Aggressive Tumor

Cheng-Han Lee, MD, PhD,† Adrian Mariño-Enriquez, MD,* Wenbin Ou, PhD,* Meijun Zhu, PhD,* Rola H. Ali, MD,† Sarah Chiang, MD,‡ Frédéric Amant, MD,§ C. Blake Gilks, MD,† Matt van de Rijn, MD, PhD,‖ Esther Oliva, MD,‡ Maria Debiec-Rychter, MD,¶ Paola Dal Cin, PhD,* Jonathan A. Fletcher, MD,* and Marisa R. Nucci, MD**

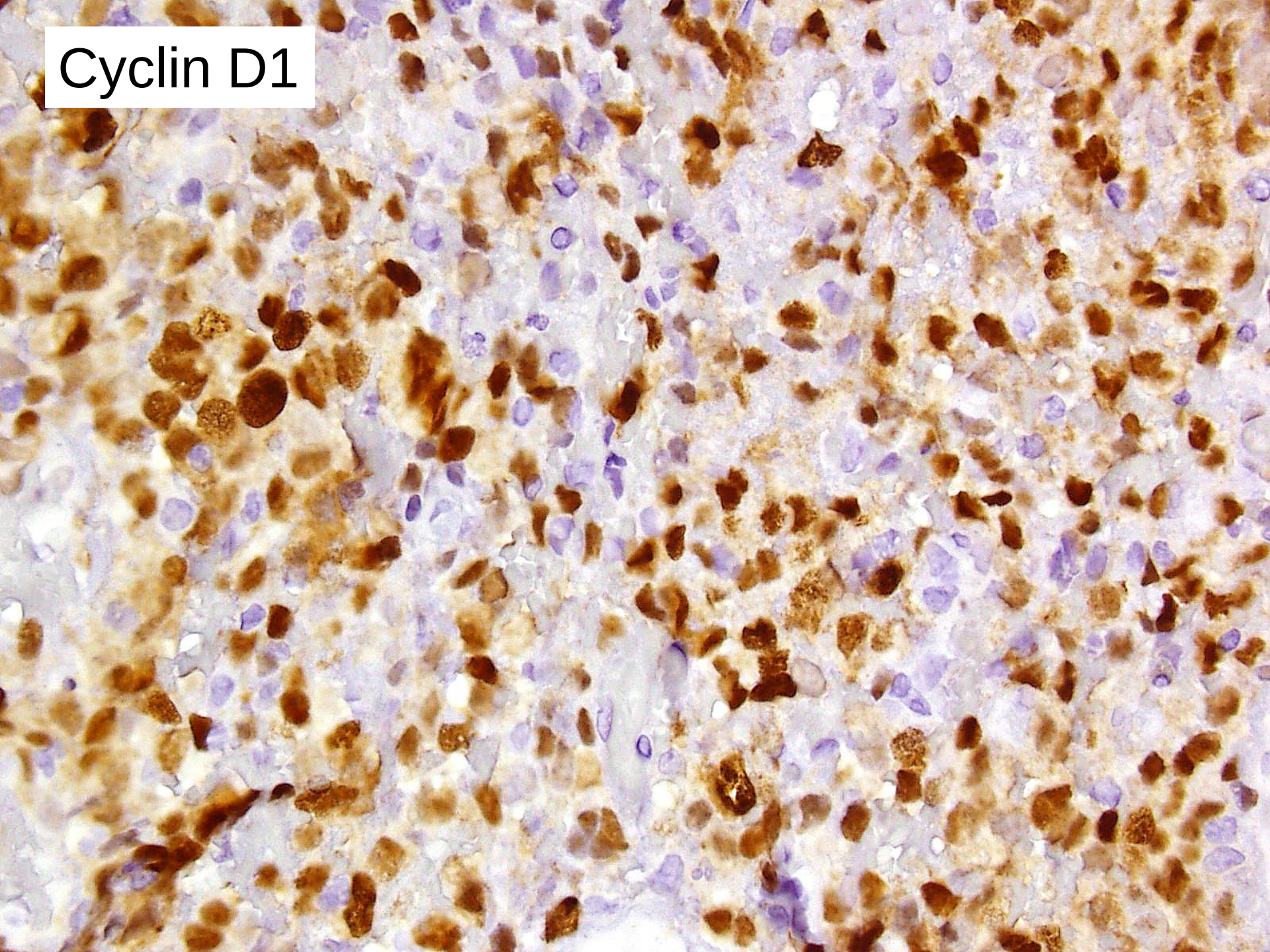


ORIGINAL ARTICLE

Cyclin D1 as a Diagnostic Immunomarker for Endometrial Stromal Sarcoma With *YWHAE-FAM22* Rearrangement

Cheng-Han Lee, MD, PhD,† Rola H. Ali, MD,*† Marjan Rouzbahman, MD,‡ Adrian Marino-Enriquez, MD,§ Meijun Zhu, PhD,§ Xiangqian Guo, PhD,‖ Alayne L. Brunner, PhD,‖ Sarah Chiang, MD,¶ Samuel Leung, MSc,*† Nataliya Nelnyk, MSc,# David G. Huntsman, MD,# C. Blake Gilks, MD,*† Torsten O. Nielsen, MD, PhD,*† Paola Dal Cin, PhD,§ Matt van de Rijn, MD, PhD,‖ Esther Oliva, MD,¶ Jonathan A. Fletcher, MD,§ and Marisa R. Nucci, MD,§*

(*Am J Surg Pathol* 2012;36:1562–1570)

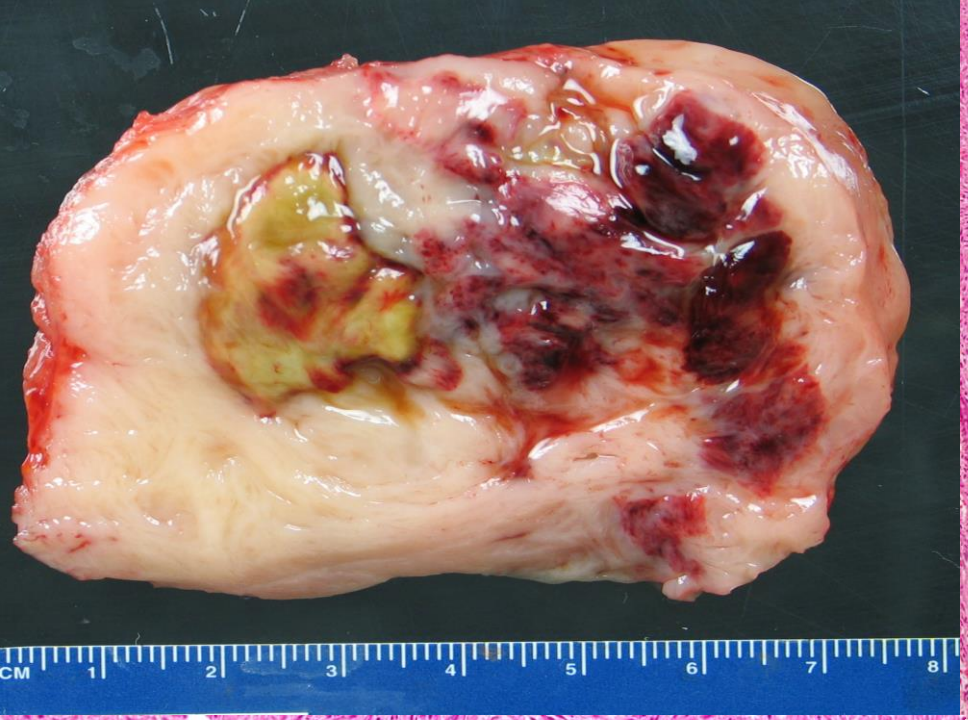

Cyclin D1

EST Classification

- LG ESS
  - Mostly associated with JAZF1-JJAZ1
  - CD10 +; ER/PR +
- HG ESS
  - Mostly associated with YWHAE-FAM22A/B
- Undifferentiated endometrial sarcoma

Uterine Leiomyosarcoma

- Most common sarcoma among young women
  - 25% of all uterine malignancies
- Five-year survival: 25 to 75%
- Risk of recurrence: 45-73%
- Patients with tumors initially confined to the uterus may be clinically aggressive
- Unclear role of adjuvant therapy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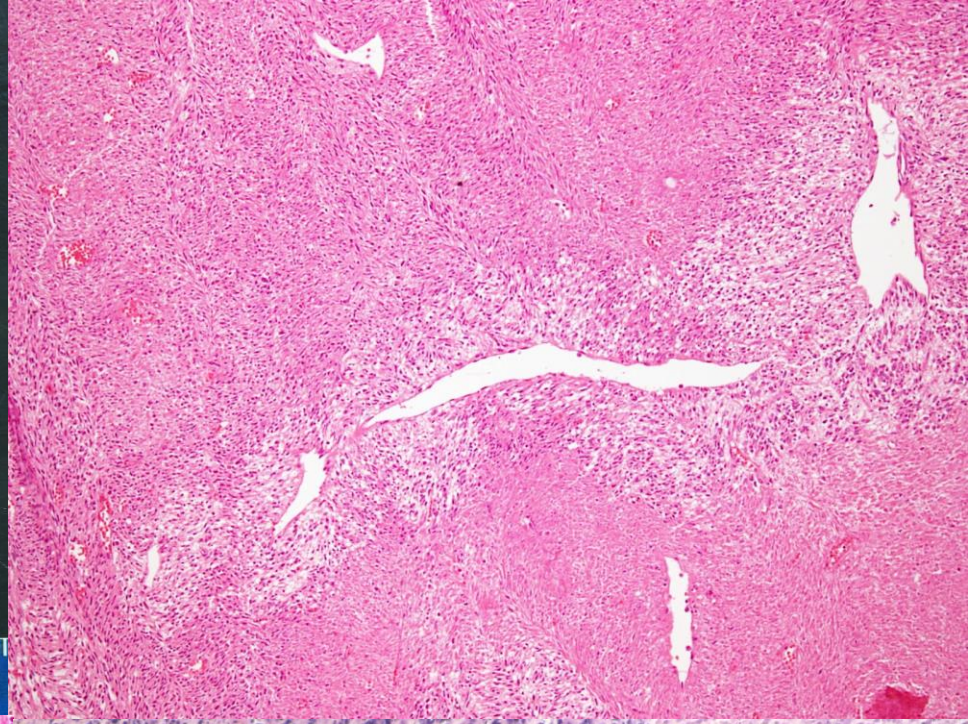
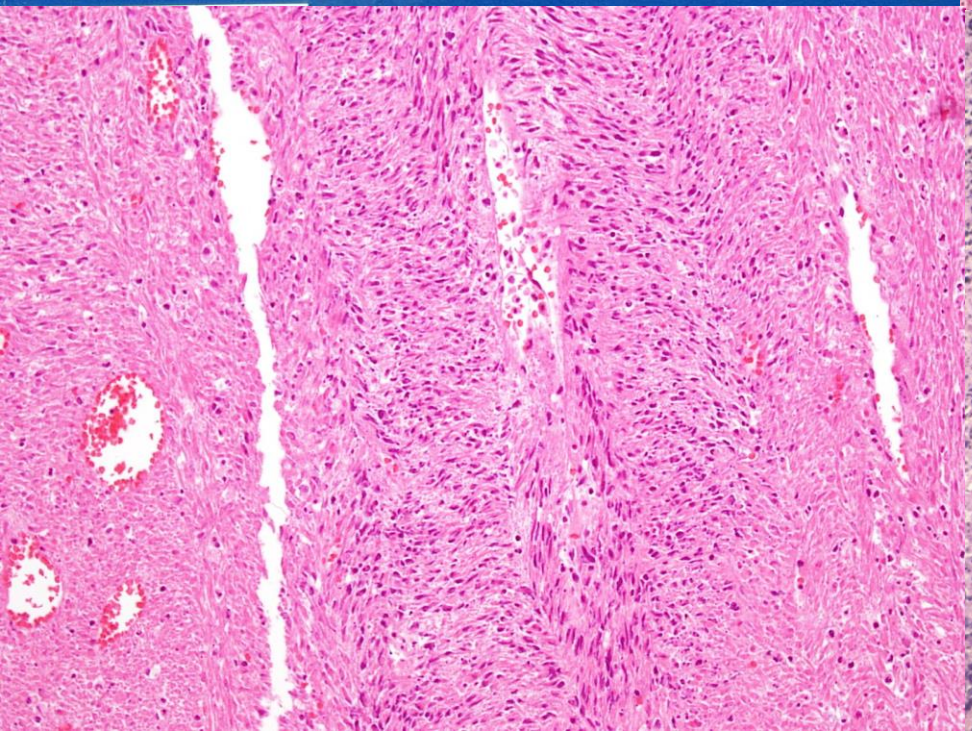
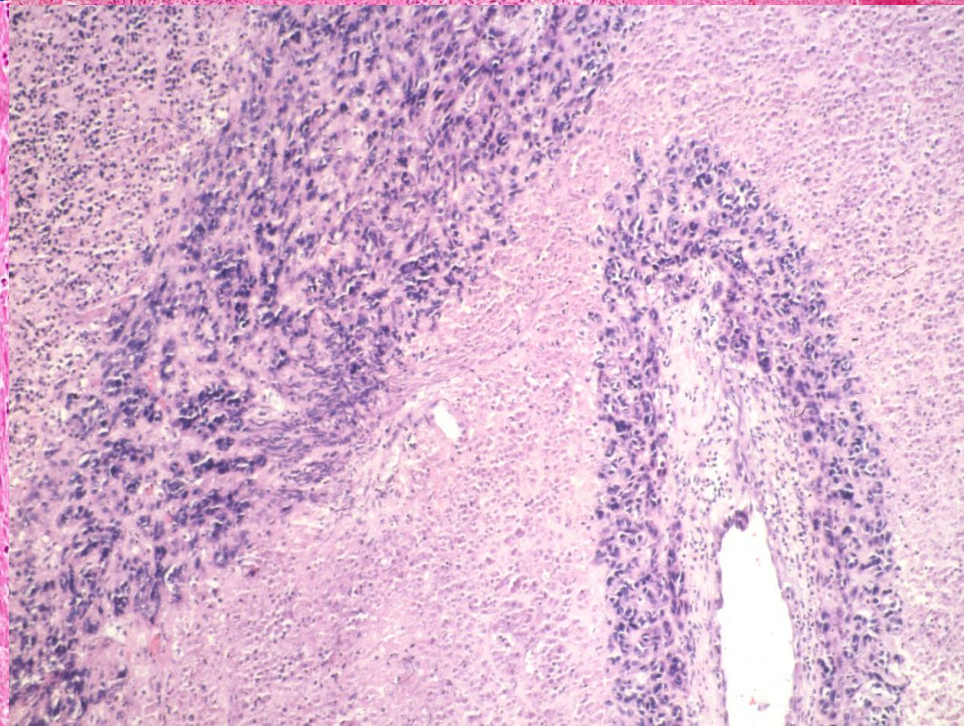






Diagnostic Criteria

- Coagulative tumor cell necrosis*
- Diffuse moderate to marked atypia*
  - Visible at low power
- High mitotic rate (>10MFs/10HPFs)*
- Diffuse hypercellularity
  - Any two of these criteria (*) diagnostic of leiomyosarcoma

Bell et al, Am J Surg Pathol 1994;18:535

Diagnostic Criteria

Diagnosis	Tumor Necrosis	Mitotic Rate	Atypia
Leiomyosarcoma	Present	Any Rate	Present or absent
	Absent	≥ 10	Diffuse
STUMP	Questionable	Any Rate	Present or absent
	Absent	> 15	None
	Absent	< 10	Diffuse
Atypical LM	Absent	≤ 10	Diffuse
LM with increases mitotic activity	Absent	≤ 15	Absent

Uterine Smooth Muscle Tumors

Current Challenges

- Definition of necrosis
- Atypical/Bizarre leiomyoma
- Cellular/mitotically active leiomyoma
- Myxoid smooth muscle tumors
- Epithelioid smooth muscle tumors
- STUMP
- Intravenous leiomyomatosis
- Disseminated peritoneal leiomyomatosis
- Benign metastasizing leiomyoma

ORIGINAL ARTICLE

Interobserver Variability in the Interpretation of Tumor Cell Necrosis in Uterine Leiomyosarcoma

Diana Lim, MBBS, FRCPath, FRCPA, Teresa Alvarez, MD,† Marisa R. Nucci, MD,‡ Blake Gilks, MD,§ Teri Longacre, MD,‖ Robert A. Soslow, MD,¶ and Esther Oliva, MD#*

(*Am J Surg Pathol* 2013;37:650–658)

Tumor cell necrosis

- 34 cases
- 6 GYN pathologists
- TCN defined as: abrupt transition from viable to necrotic tumor, with tumor ghost cells. Hemorrhage and inflammation uncommon.

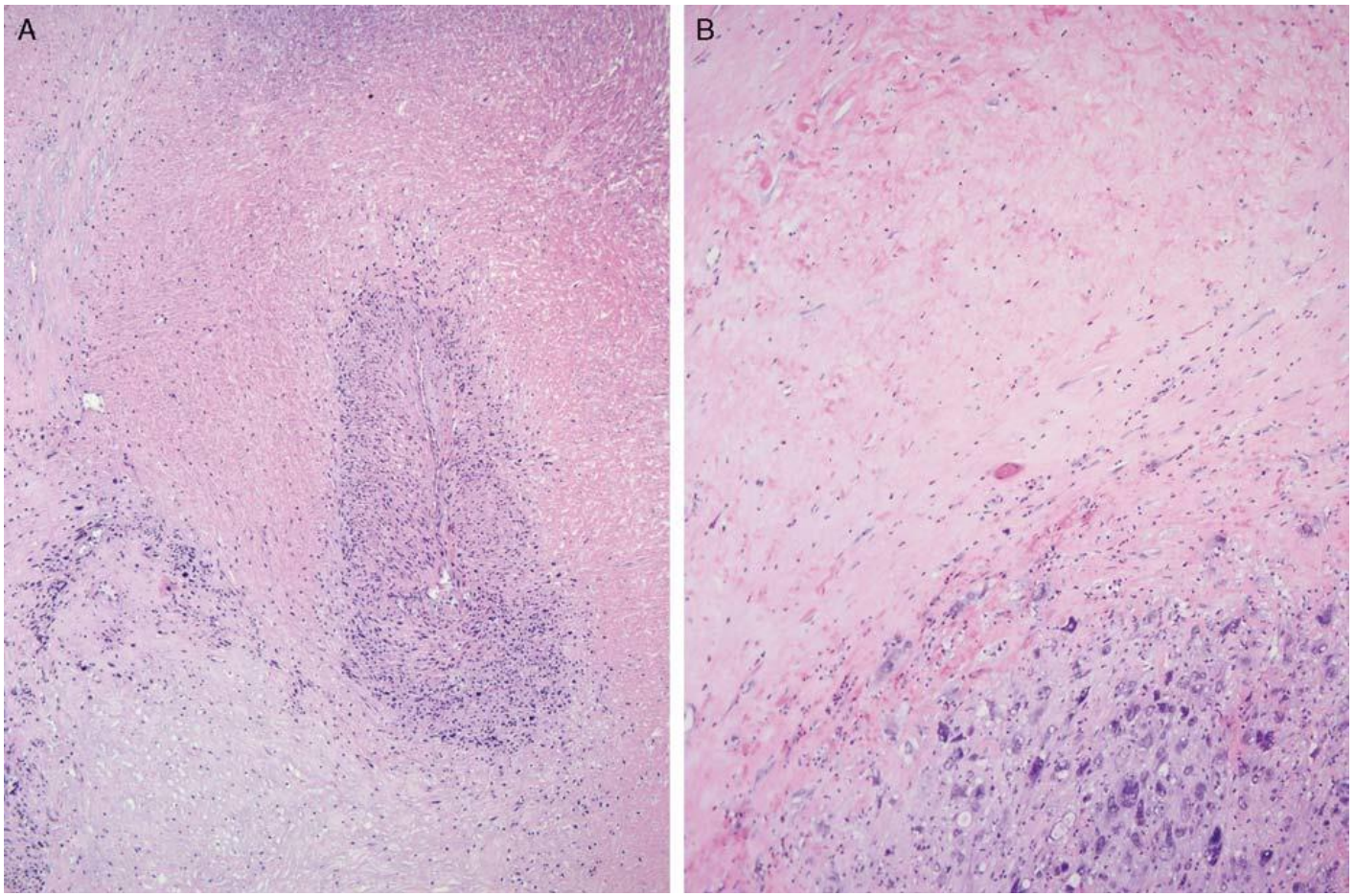


FIGURE 1. Full agreement in the diagnosis of TCN represented by cases 2 (A) and 27 (B). An abrupt transition from viable to nonviable tumor without interposed granulation or fibrocollagenous tissue. A residual perivascular rim of viable tumor cells is seen (A). Hyalinized tissue with scattered inflammatory cells, adjacent to viable tumor is present (B).

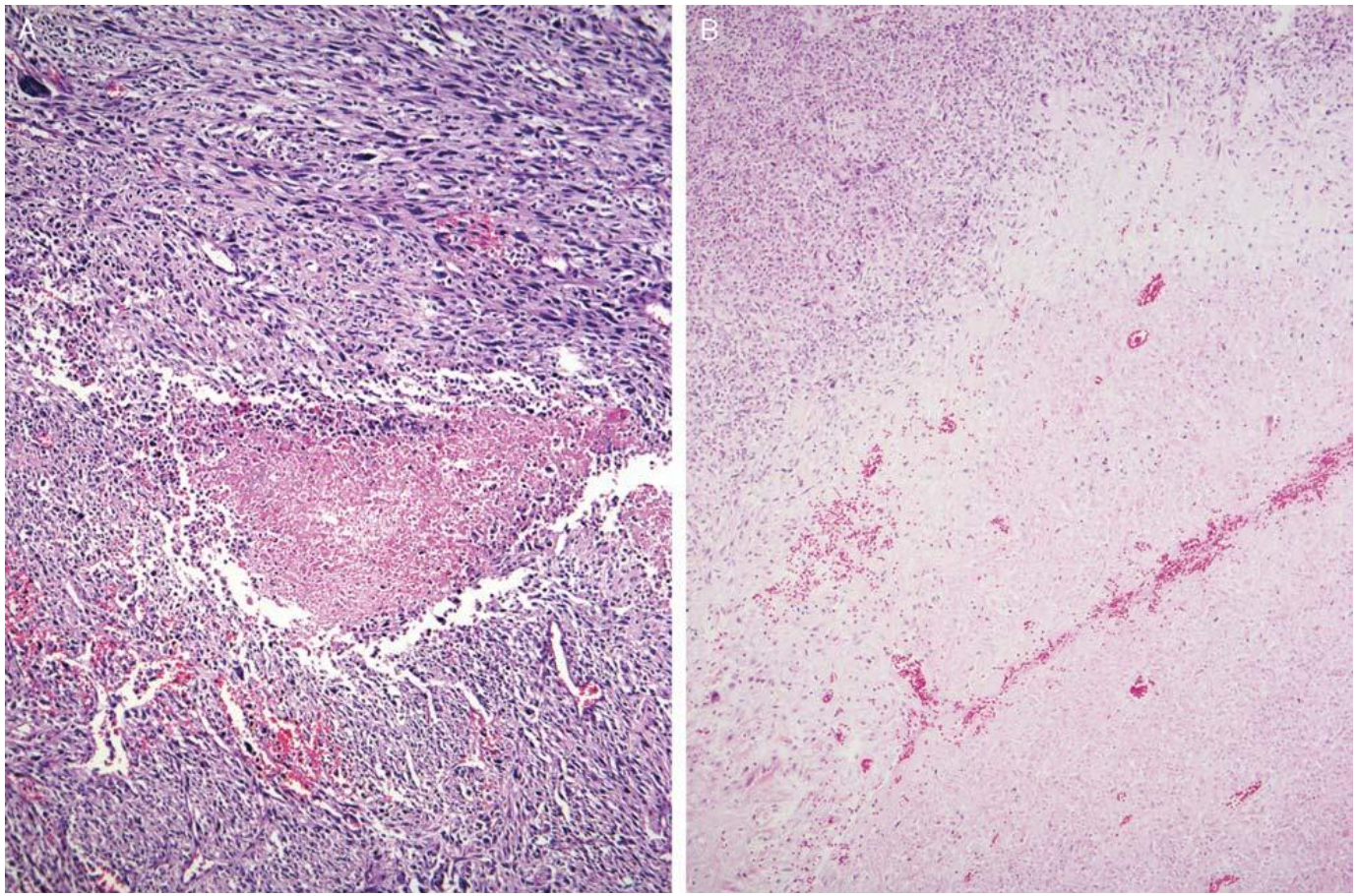


FIGURE 2. Partial agreement in the diagnosis of TCN represented by cases 21 (A) and 25 (B). A necrotic area with an abrupt transition from viable to nonviable tumor is seen which is also associated with hemorrhage and inflammation (A). Focus of necrosis in which "ghost" outlines of tumor cells are seen. However, an intervening rim of fibrocollagenous tissue with foci of hemorrhage separates the viable and nonviable areas (B).

Tumor cell necrosis

- Full agreement: 35% of cases
- Partial agreement: 47% of cases
- No agreement: 18% of cases
- Necrosis called “indeterminate” by at least one pathologist in 60% of cases

Smooth Muscle Tumors of Uncertain Malignant Potential "STUMPS"

- Tumor cell necrosis in ordinary leiomyoma
- Necrosis of uncertain type with 10 or more MFs/10 HPFs or marked diffuse atypia
- Marked diffuse atypia with uncertain or borderline mitotic counts
- Focal marked atypia and 10 or more MFs/10HPFs

"Low-Grade Leiomyosarcoma" and Late-Recurring Smooth Muscle Tumors of the Uterus: A Heterogenous Collection of Frequently Misdiagnosed Tumors Associated With an Overall Favorable Prognosis Relative to Conventional Uterine Leiomyosarcomas

Emanuela Veras, Oliver Zivanovic,† Lindsay Jacks,‡ Daniel Chiappetta,* Martee Hensley,§ and Robert Soslow, MD**

(*Am J Surg Pathol* 2011;35:1626–1637)

Low Grade Leiomyosarcoma

- Local recurrences
- Histologic progression in recurrences
- LMS with indolent behavior

Low Grade Leiomyosarcoma

- 9% of LMS
- Heterogeneous group of lesions
- Atypical leiomyomas
- EES with smooth muscle differentiation
- Leiomyosarcomas
- Unrelated mesenchymal neoplasms
- Existence of low grade LMS regarded at best as debatable

Original Article

A Nomogram to Predict Postresection 5-Year Overall Survival for Patients With Uterine Leiomyosarcoma

Oliver Zivanovic, MD[1]; Lindsay M. Jacks, MS[2]; Alexia Iasonos, PhD[2]; Mario M. Leitao, Jr., MD[1]; Robert A. Soslow, MD[3]; Emanuela Veras, MD[3]; Dennis S. Chi, MD[1]; Nadeem R. Abu-Rustum, MD[1]; Richard R. Barakat, MD[1]; Murray F. Brennan, MD[4]; and Martee L. Hensley, MD[5]

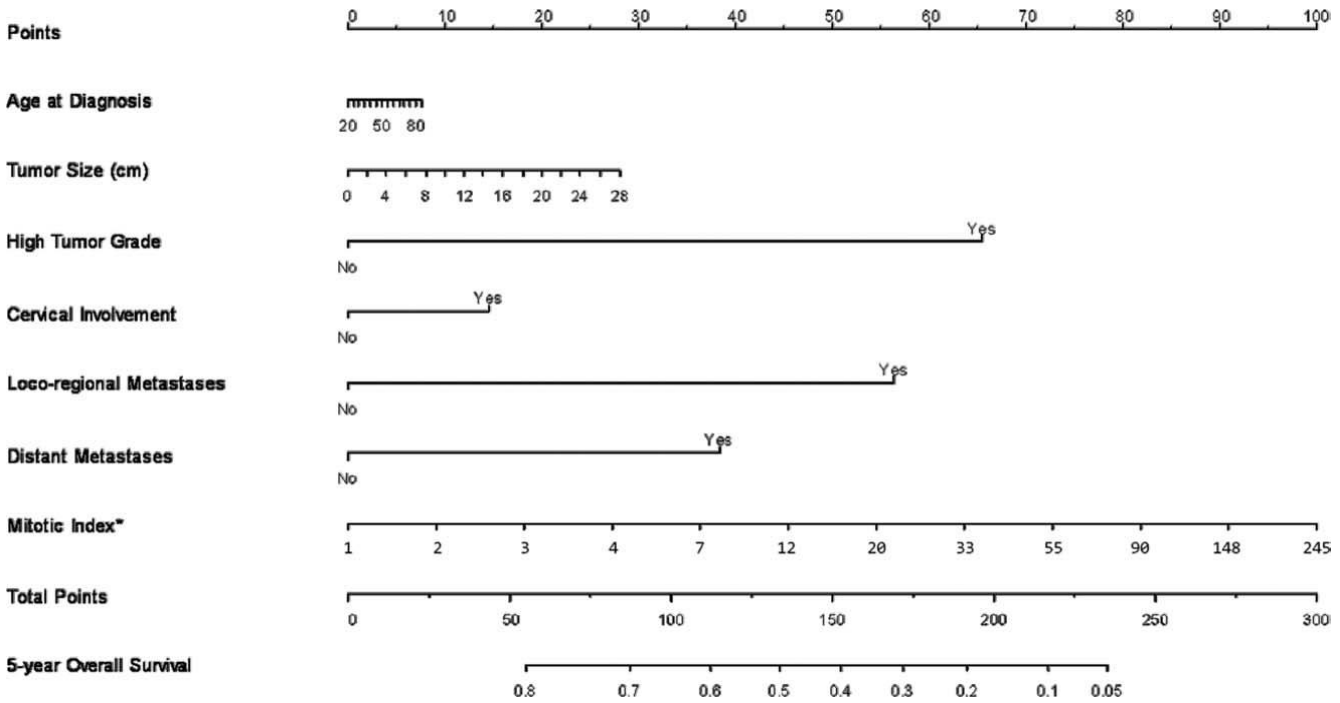


Figure 2. This is the uterine leiomyosarcoma nomogram for 5-year overall survival. The mitotic index (asterisk) was modeled using log transformation; for display purposes, values were converted back to original scale (exponential; concordance probability [CP], 0.671; bootstrap-validated CP, 0.651).

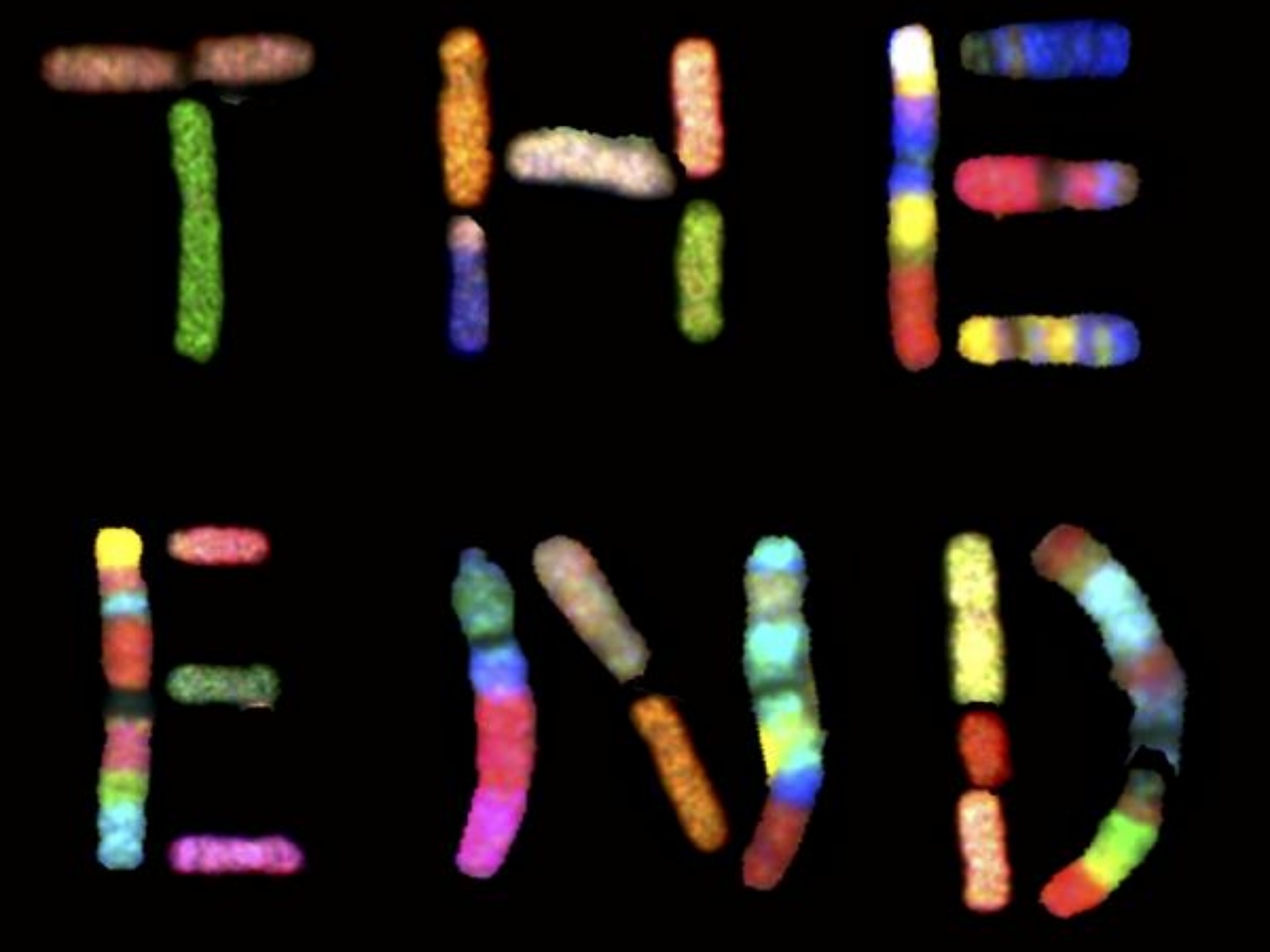
Diagnostic Criteria

- Coagulative tumor cell necrosis*
- Diffuse moderate to marked atypia*
  - Visible at low power
- High mitotic rate (>10MFs/10HPFs)*
- Diffuse hypercellularity
  - Any two of these criteria (*) diagnostic of leiomyosarcoma

Bell et al, Am J Surg Pathol 1994;18:535

Pending Issues

- Uterine smooth muscle tumors poorly defined
- STUMP concept leads to significant uncertainty
- Low grade LMS need to be defined
- LGESS vs. HGESS need reappraisal on the basis of genetics
  - ESS (JAZF1-JJAZ1)
  - HG-ESS (YWHAE-FAM22A/B)
  - UES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