Leiomiosarcomas

Criterios diagnósticos y factores pronósticos

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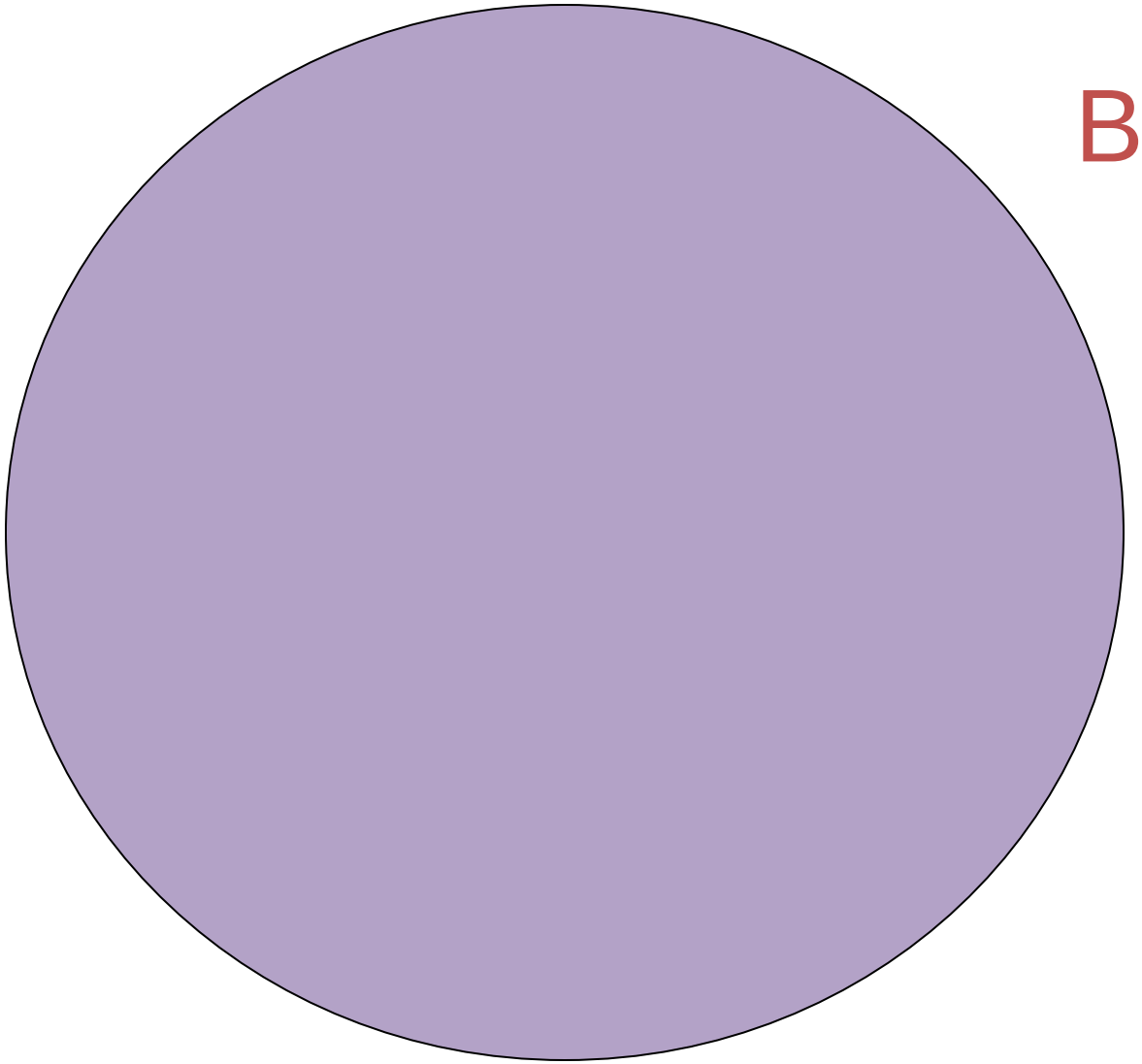
CONGRESO SEAP – SEC- SEPAF
Zaragoza, 20 de Mayo, 2011

Universitat Autònoma de Barcelona

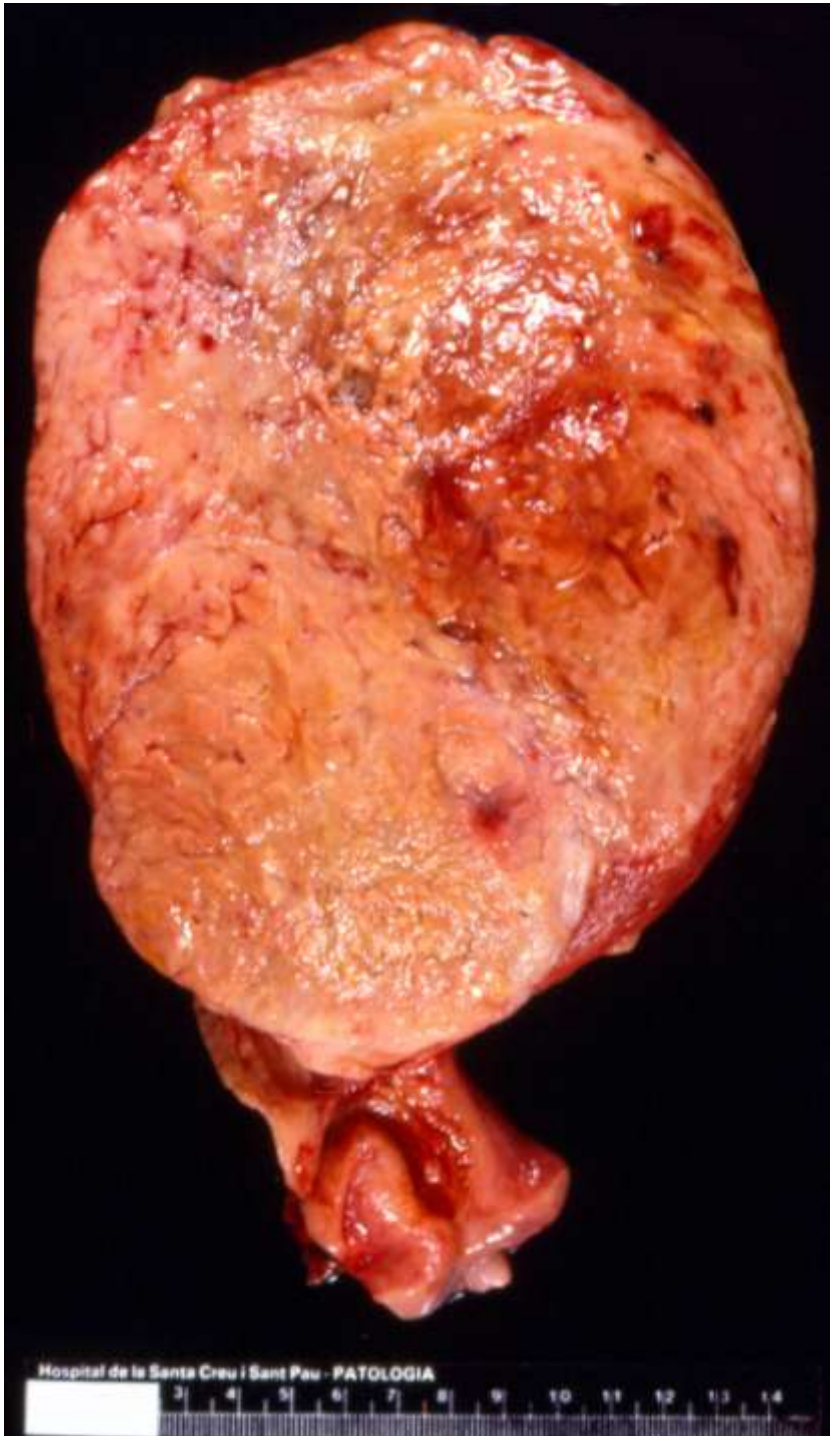
Smooth Muscle Tumors of the Uterus

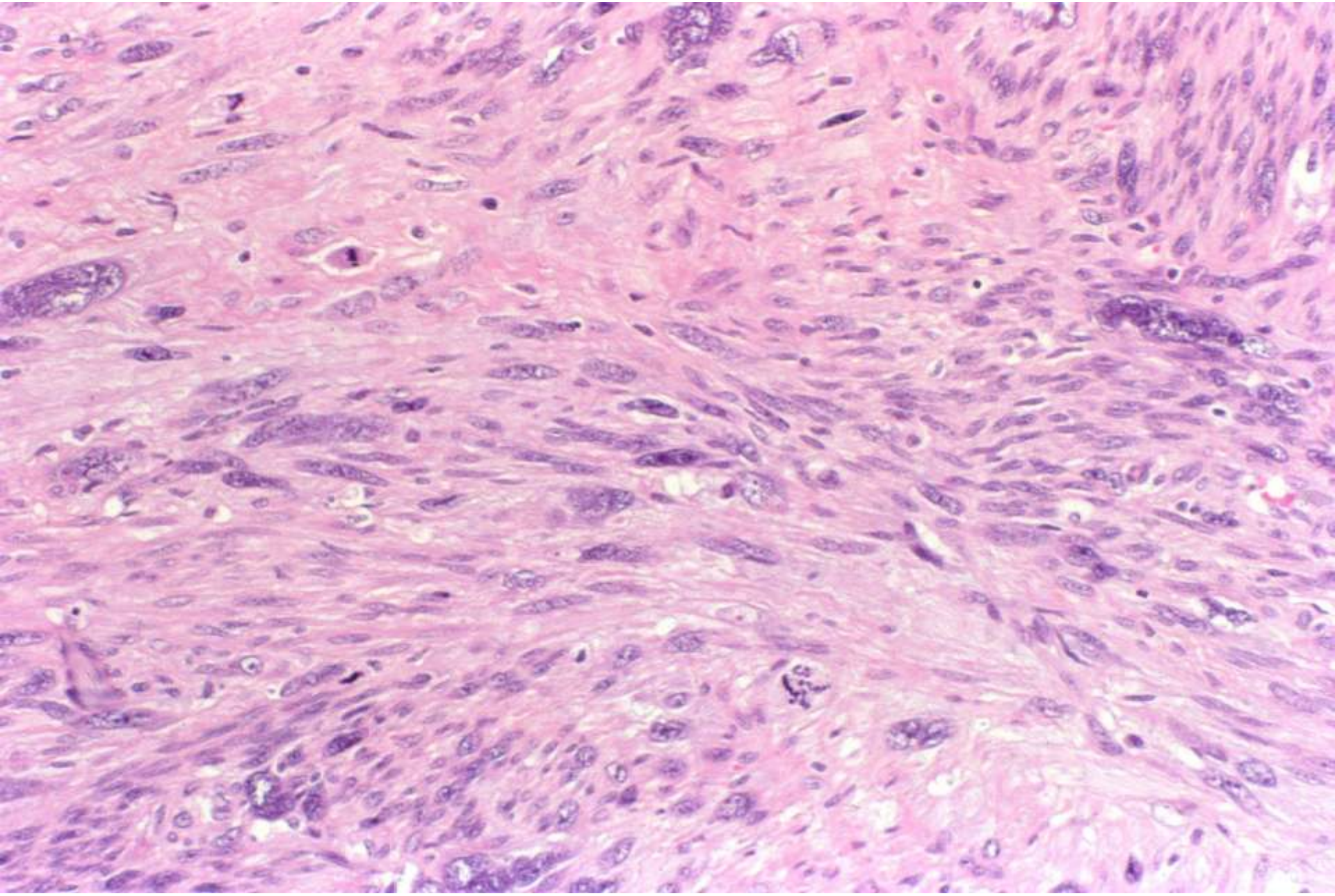


Benign

Clinically Malignant

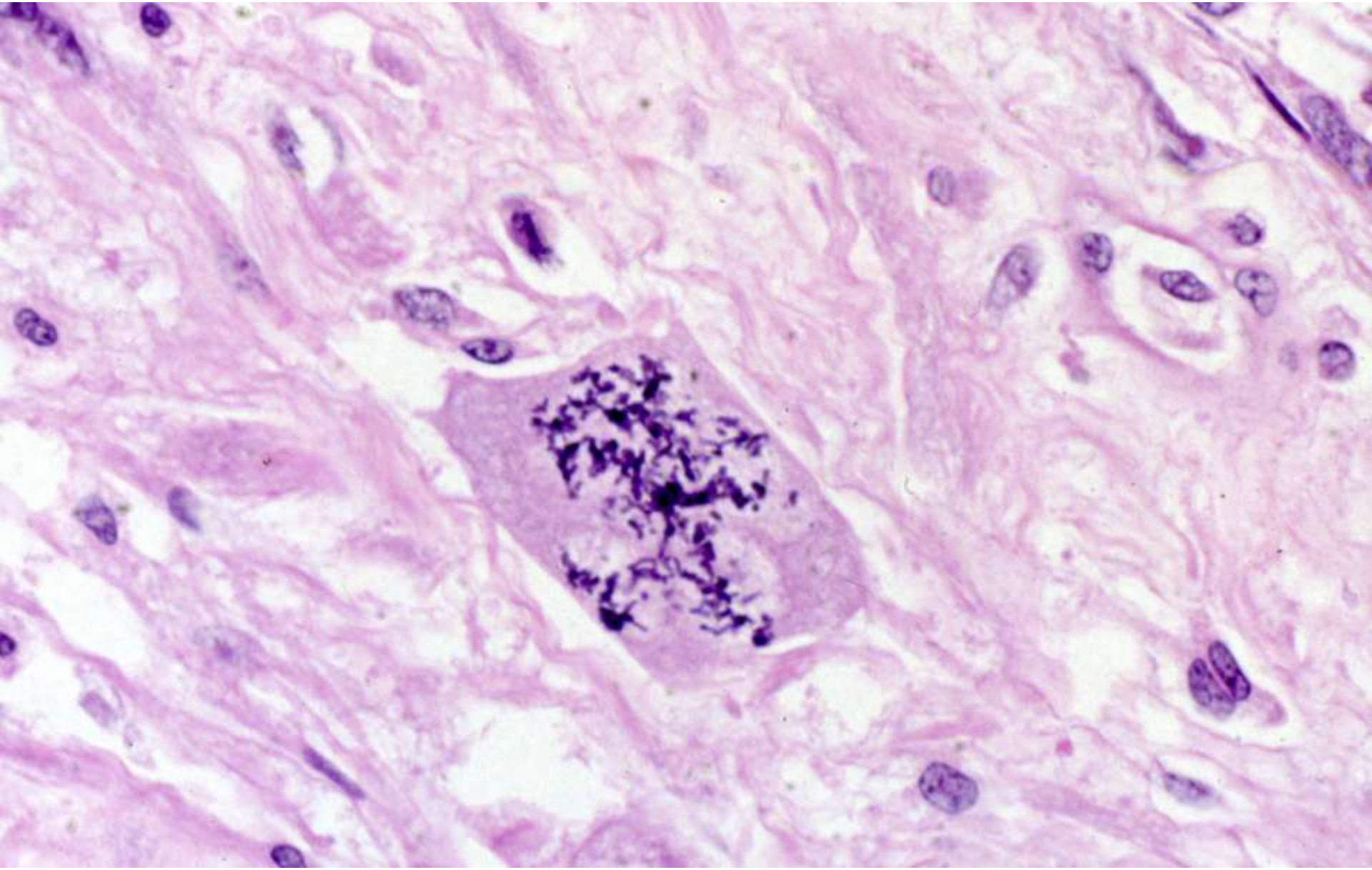
Malignant or atypical for the pathologist


Hospital de la Santa Creu i Sant Pau - PATOLOGIA



40 F

LMS - Atypia and mitoses (<5/10 HPF)



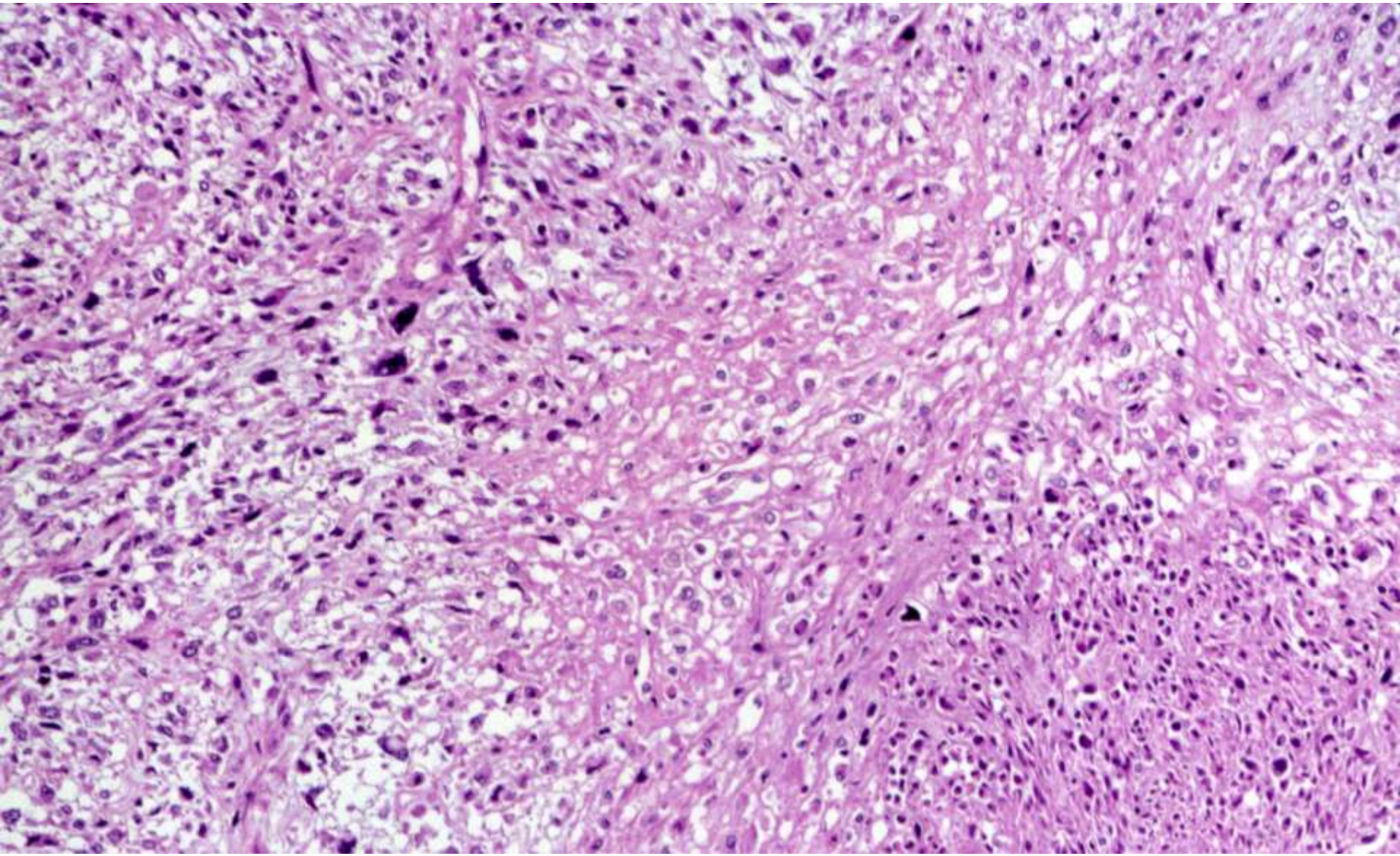
LMS - Atypical mitosis (5/10 HPF)

Cellular & Atypical Smooth Muscle Tumors of the Uterus

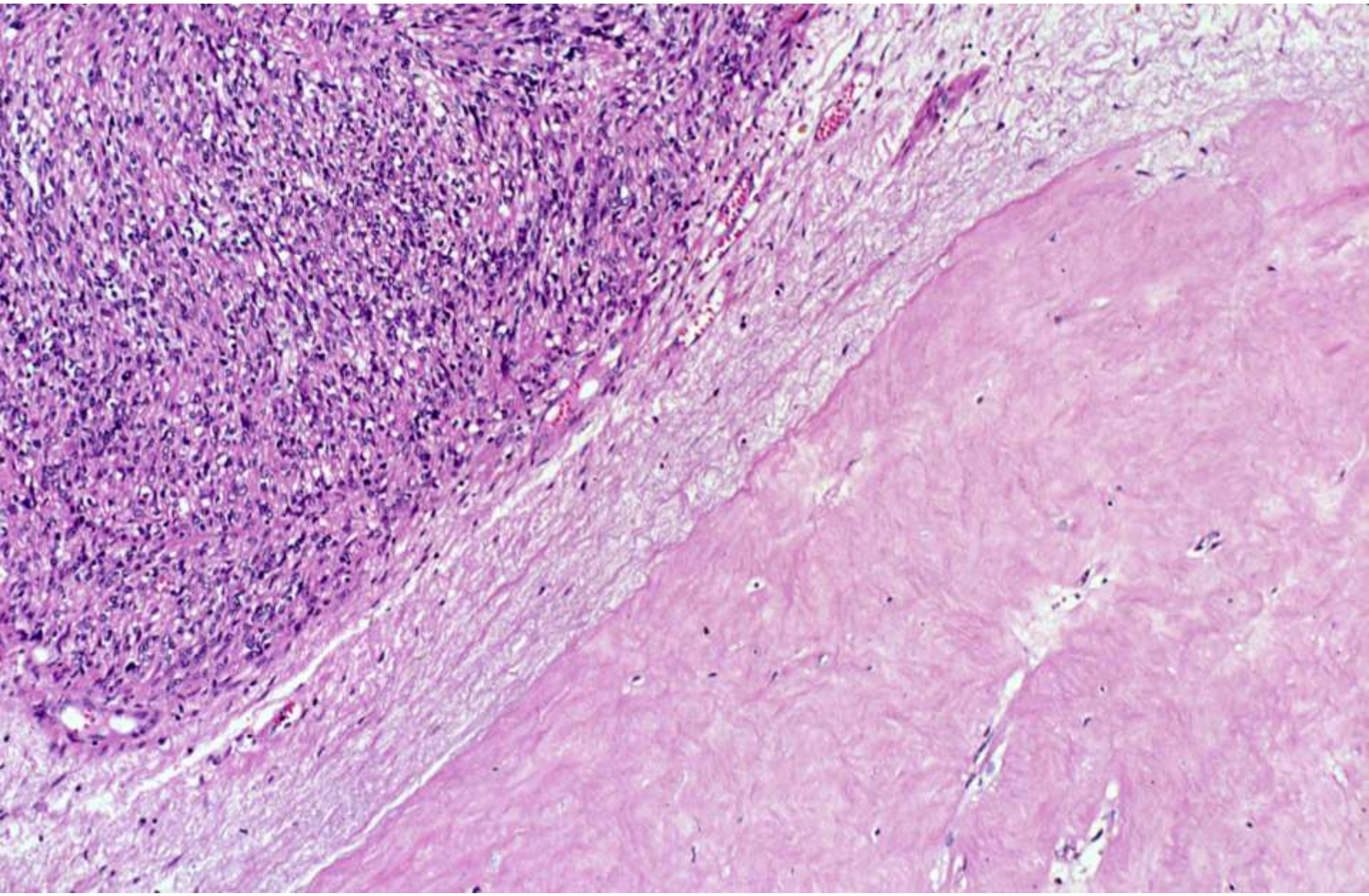
5+ Mit/10HPF Malignant (75%)

4- Mit/10HPF Benign

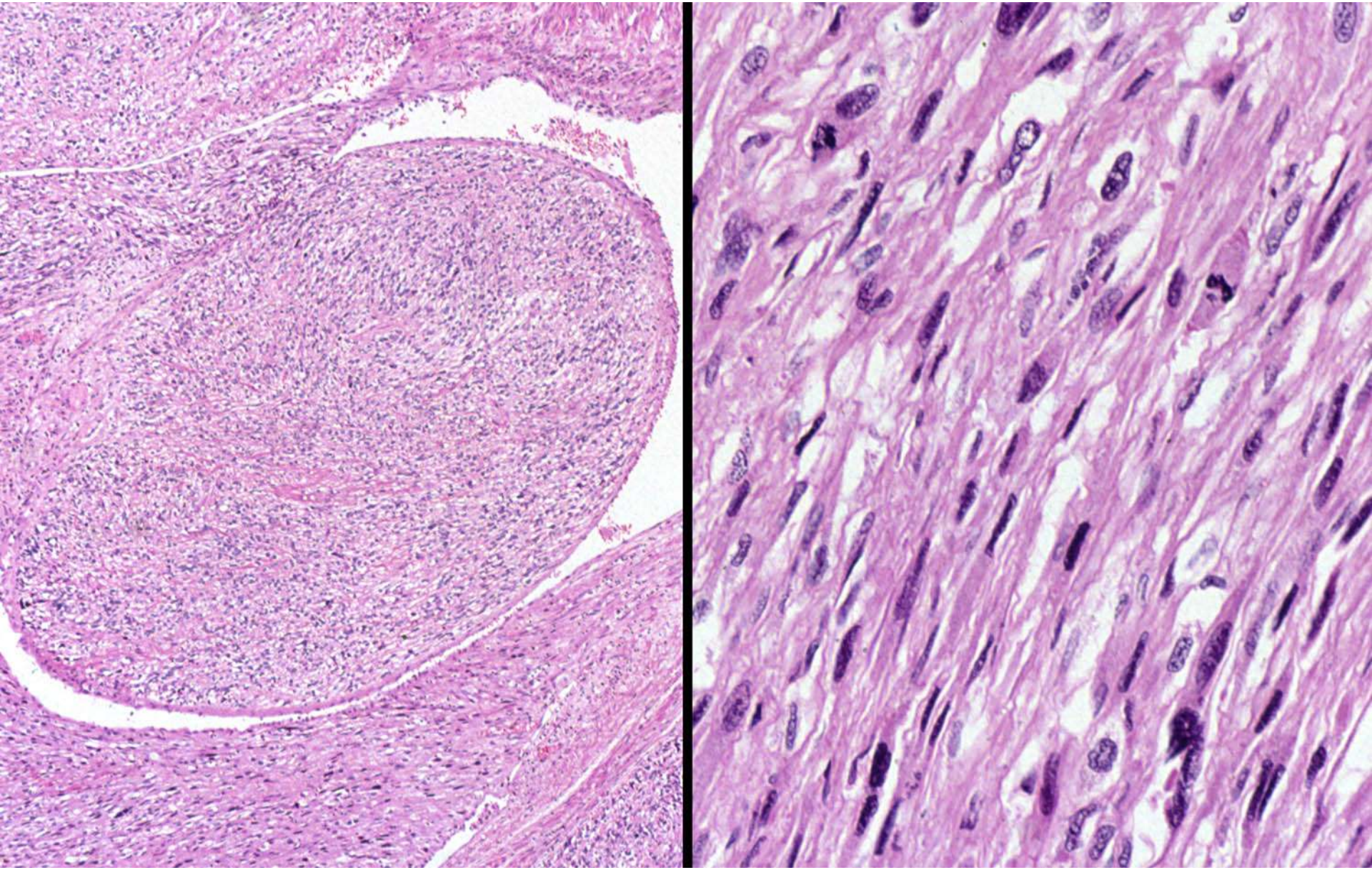
Zaloudek & Norris, 1981



Tumor necrosis



Infarct type necrosis



Vascular invasion

Leiomyosarcoma

- Diagnosis is usually straightforward
- Over 90% of cases:
    - Hypercellularity
    - Marked nuclear atypia
    - High mitotic rate (15 MF/10 HPF)

Leiomyosarcoma

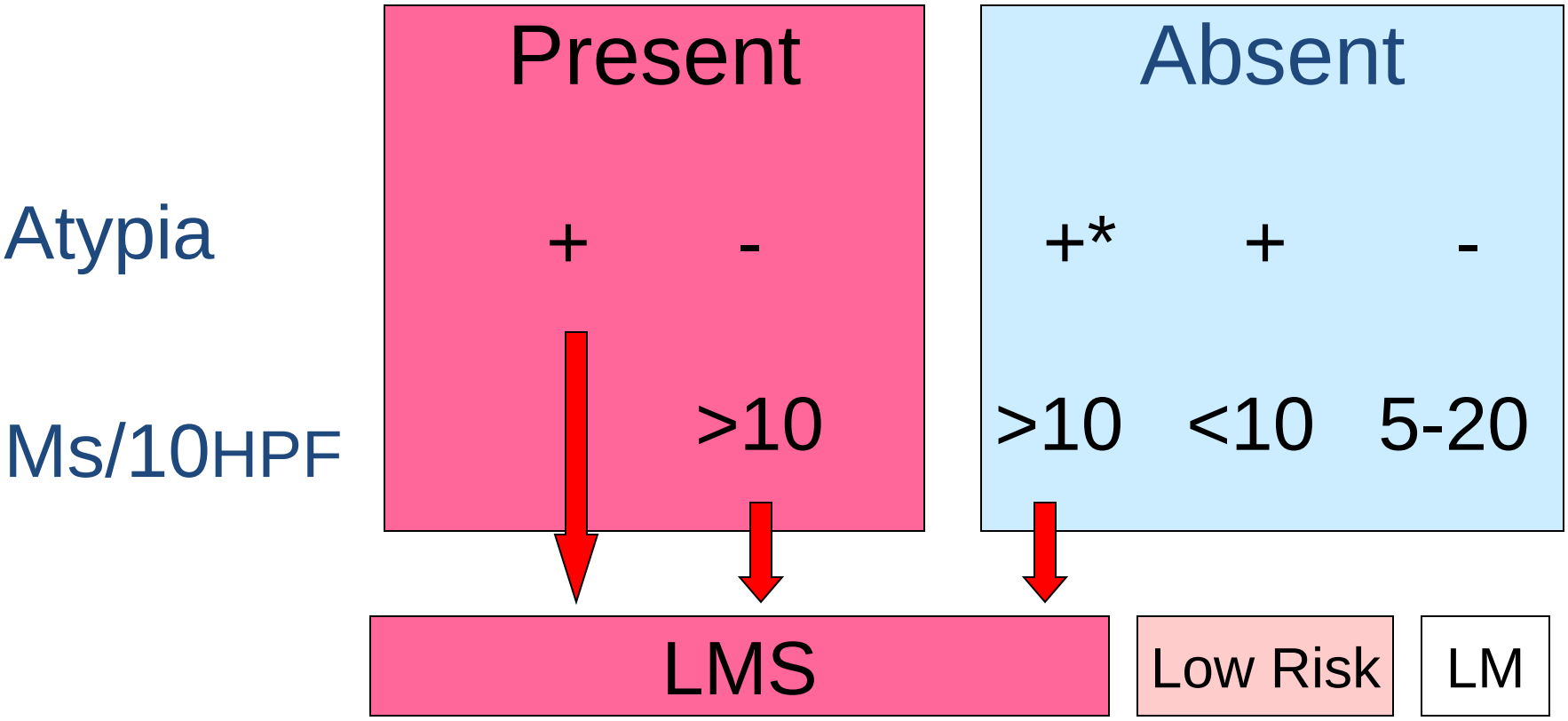
(Additional relevant findings)

- Peri- or postmenopausal age
- Extrauterine extension
- Diameter over 10 cm
- Infiltrating border
- Coagulative necrosis
- Atypical mitoses

Perrone T. Dehner LP
Am J Surg Pathol 1988; 12:1-8

Problematic Uterine Smooth Muscle Tumors

Tumor Necrosis



Bell SW et al., 1994

* diffuse or focal

Smooth Muscle Tumors of Uncertain Malignant Potential "STUMPS"

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

Bell SW et al.
Am J Surg Pathol 1994

Immunohistochemistry
(221 leiomyosarcomas)

- S M Actin 90%
- S M Actin+Desmin 96%
- S M Actin+Caldesmon 92%

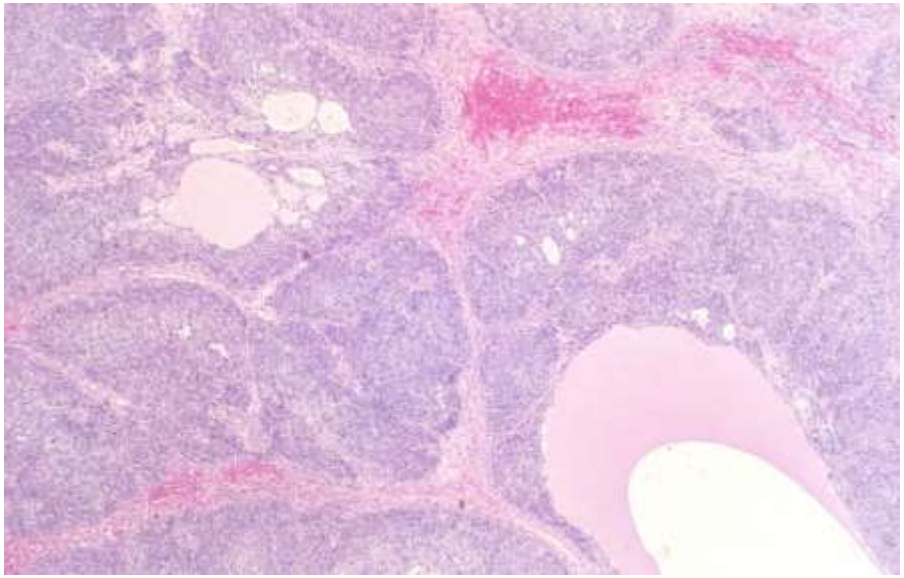
Abeler VM, et al. Int J Gynecol Pathol, May 2011

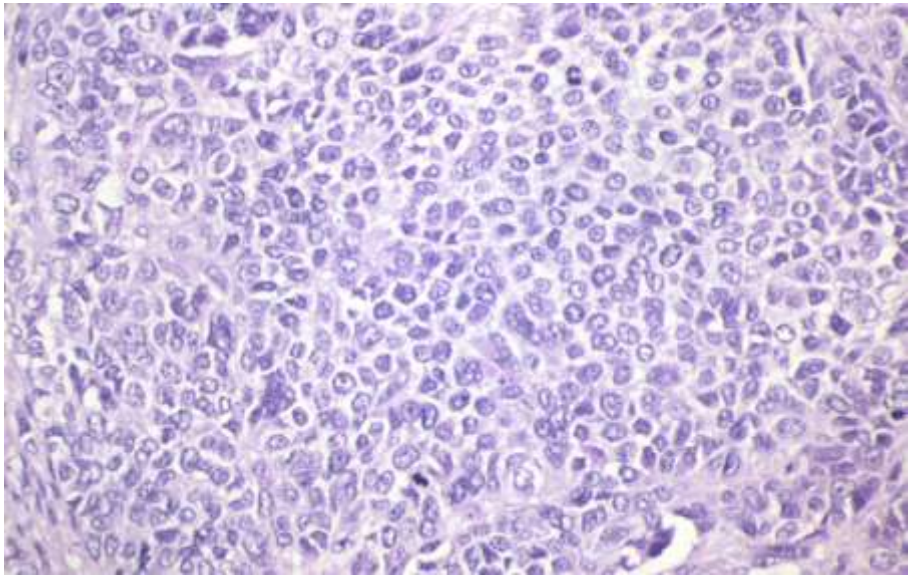
Leiomyosarcoma

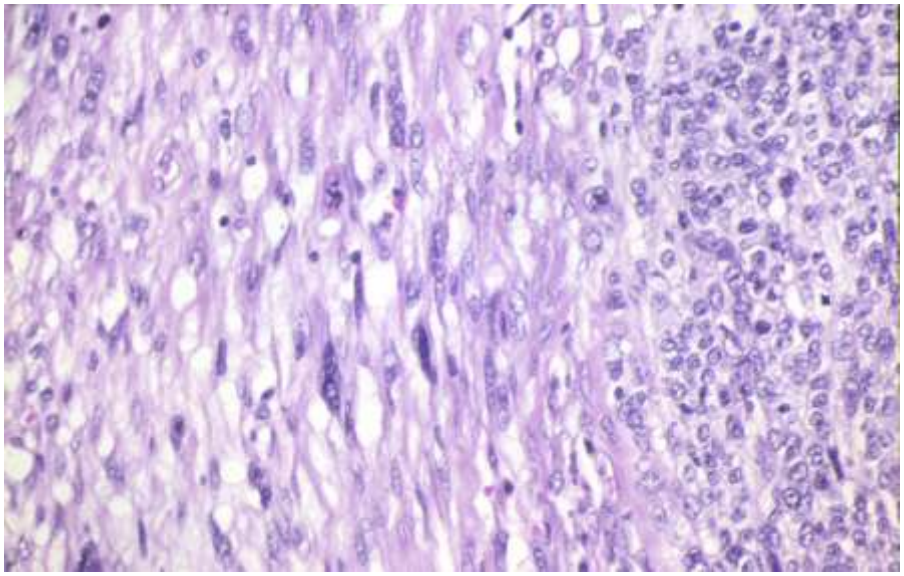
(Rare variants)

- Epithelioid LMS
- Myxoid LMS

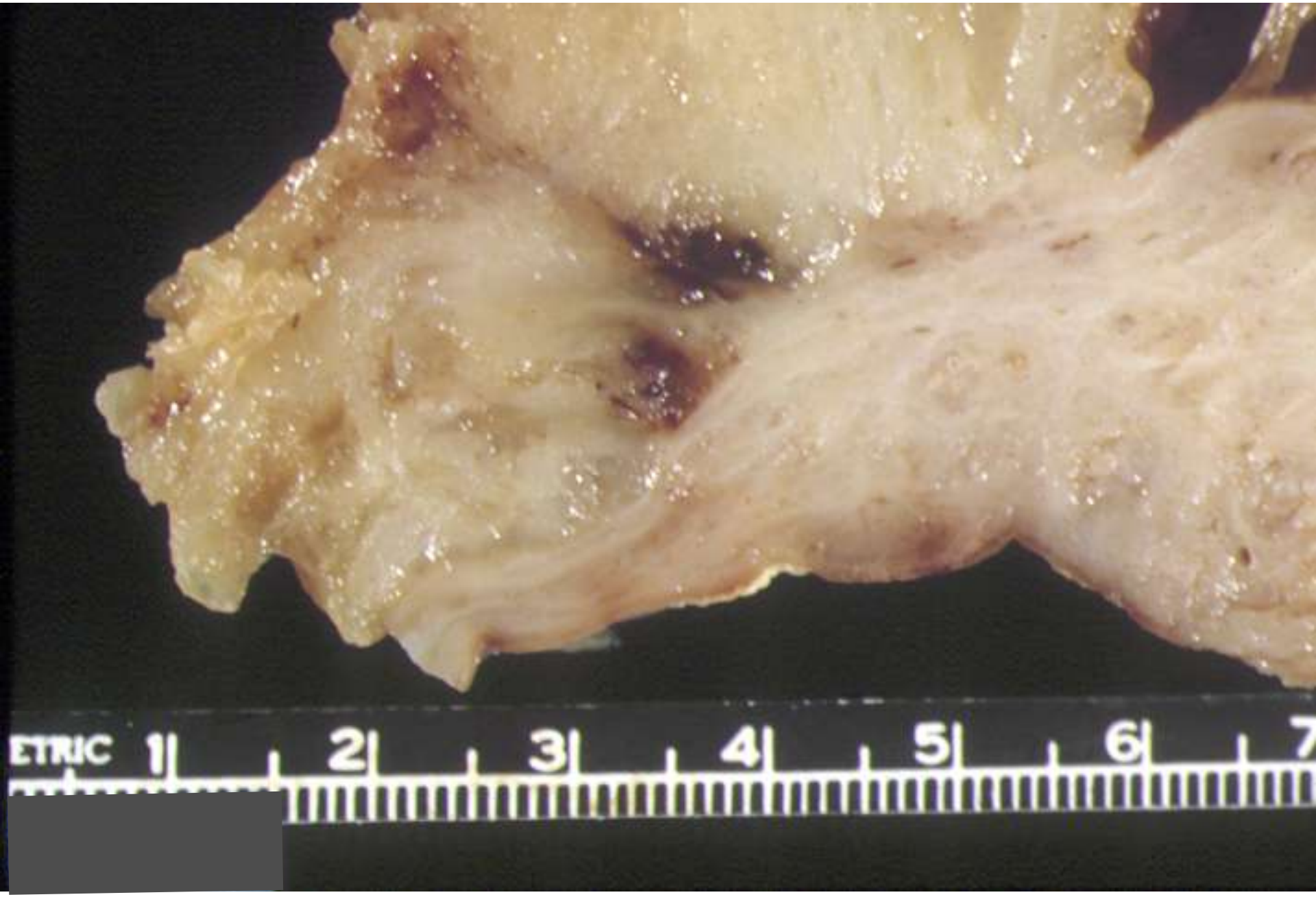
Epithelioid Leiomyosarcoma





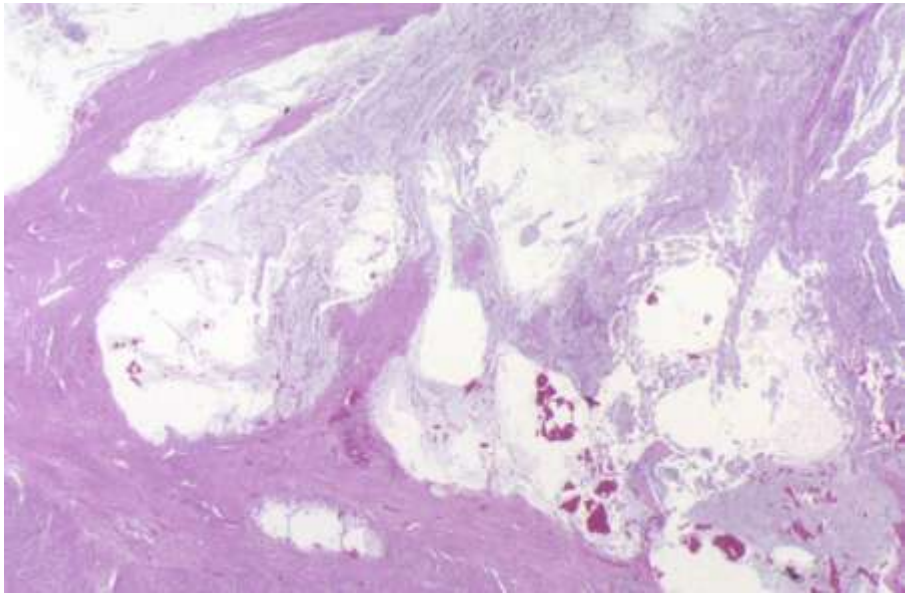


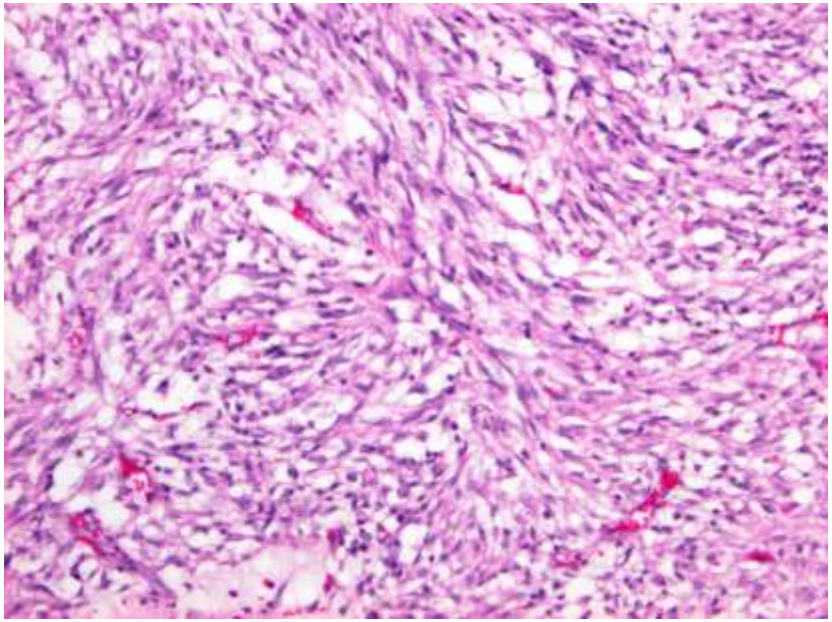
- Diameter > 6 cm
- Infiltrative margin
- 3-5 mitoses/10 HPF
- Necrosis +/-

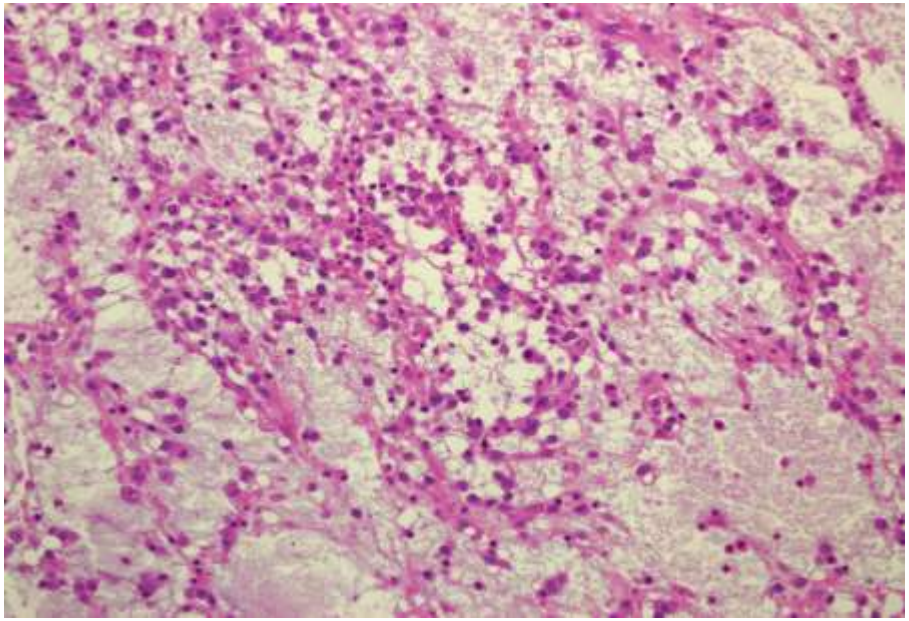


Myxoid LMS

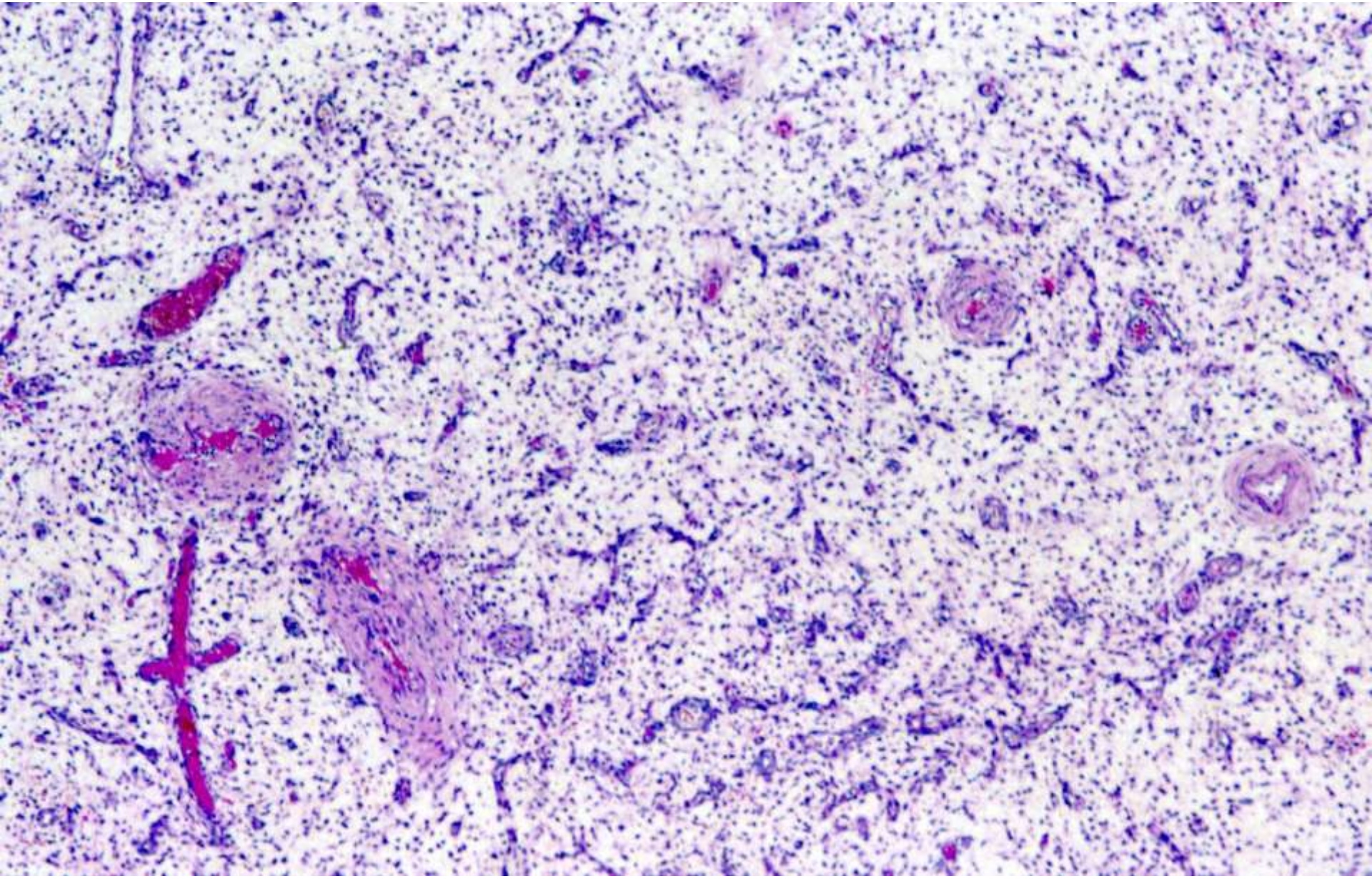
Myxoid Leiomyosarcomas







- Gelatinous/myxoid (>50%)
- Infiltrative borders
- Bland nuclear features
- 0-2 mitoses/10 HPF (40%)



LM with hydropic change

Histopathology 2009, **54**, 355–364. DOI: 10.1111/j.1365-2559.2009.03231.x

Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients

Vera M Abeler,[1] Odd Røyne,[2] Steinar Thoresen,[3] Håvard E Danielsen,[2,5] Jahn M Nesland[1,6] & Gunnar B Kristensen[2,4]

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(2009) *Histopathology* **54**, 355–364

Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients

Aims: To determine the frequency and survival of the various types of uterine sarcoma in the total population of Norway and evaluate histopathological prognostic factors in order to identify risk groups.

Methods and results: Histopathological review of all uterine sarcoma cases reported to the Norwegian

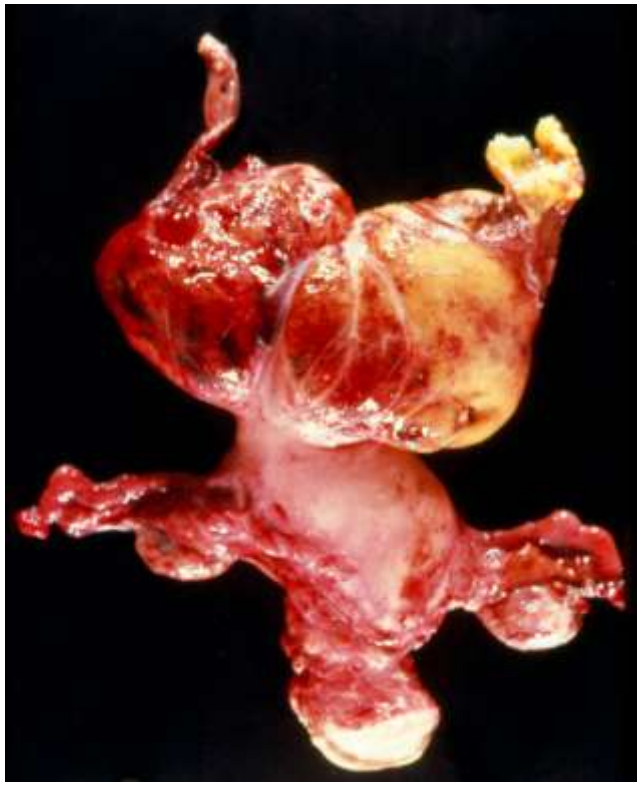
prognostic factors ($P < 0.0001$) in leiomyosarcomas confined to the uterus and allowed for separation into three risk groups with marked differences in prognosis. The prognosis of endometrial stromal sarcomas confined to the uterus was related to MI ($P < 0.0001$) and tumour cell necrosis ($P < 0.004$). Combining these

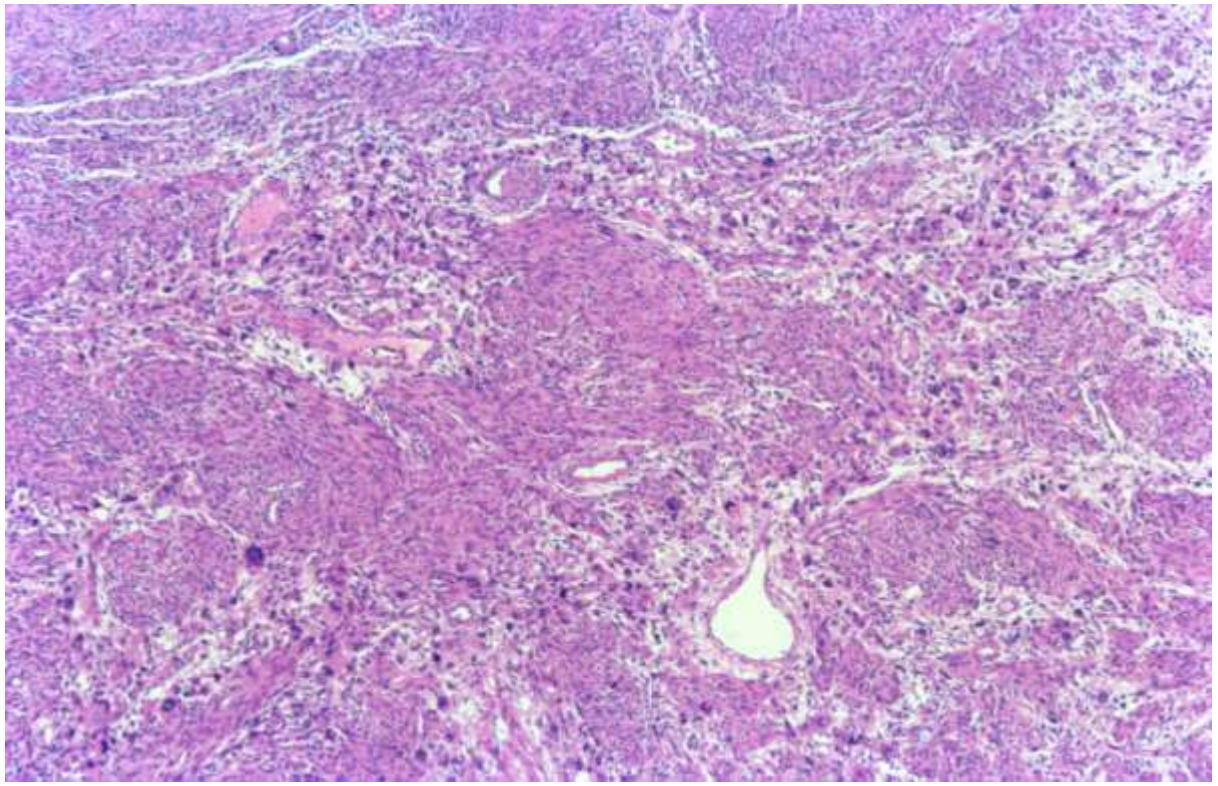
Leiomyosarcomas

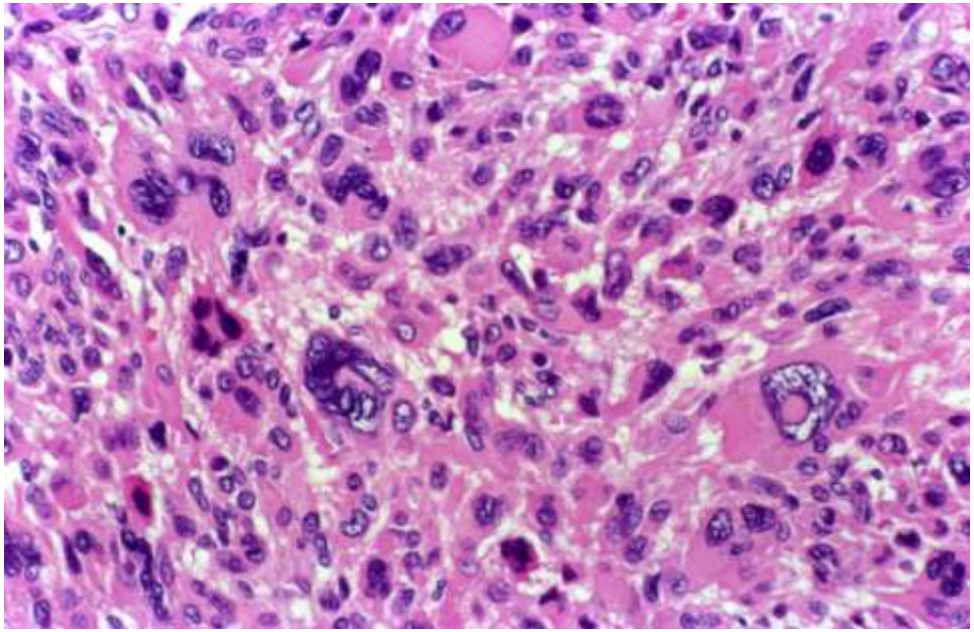
(245 patients)

- Application of 2003 WHO criteria
- Possibly, many so-called “low-grade” leiomyosarcomas may represent histologic variants of leiomyomas frequently misdiagnosed as leiomyosarcomas
- Most uterine sarcomas are leiomyosarcomas (after reclassification of carcinosarcomas)
- The vast majority of leiomyosarcomas are high-grade sarcomas associated with poor prognosis

Abeler V. et al
Histopathology 2009; 54:355-364







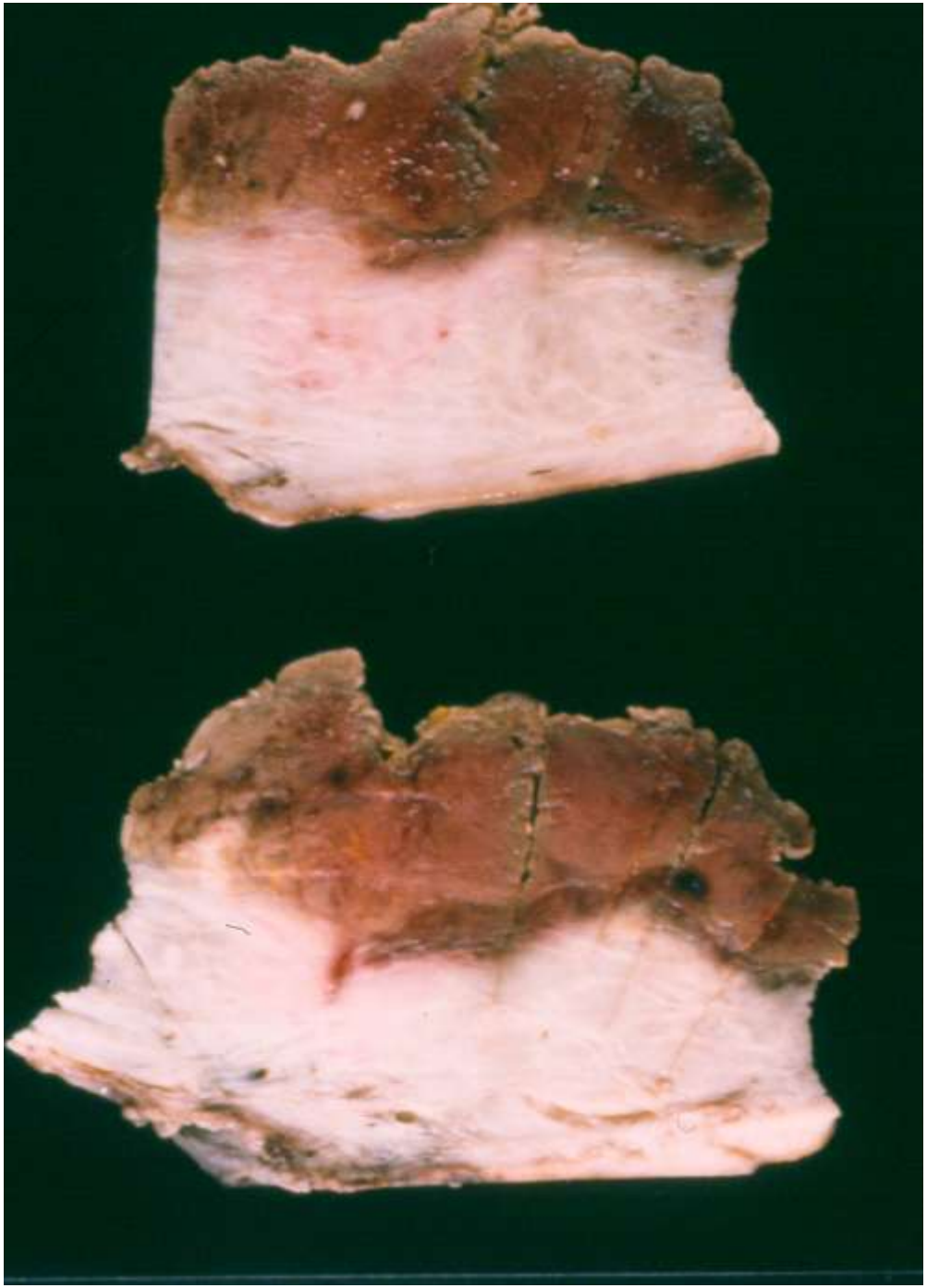
Atypical (bizarre) leiomyoma

49F (12 cm)

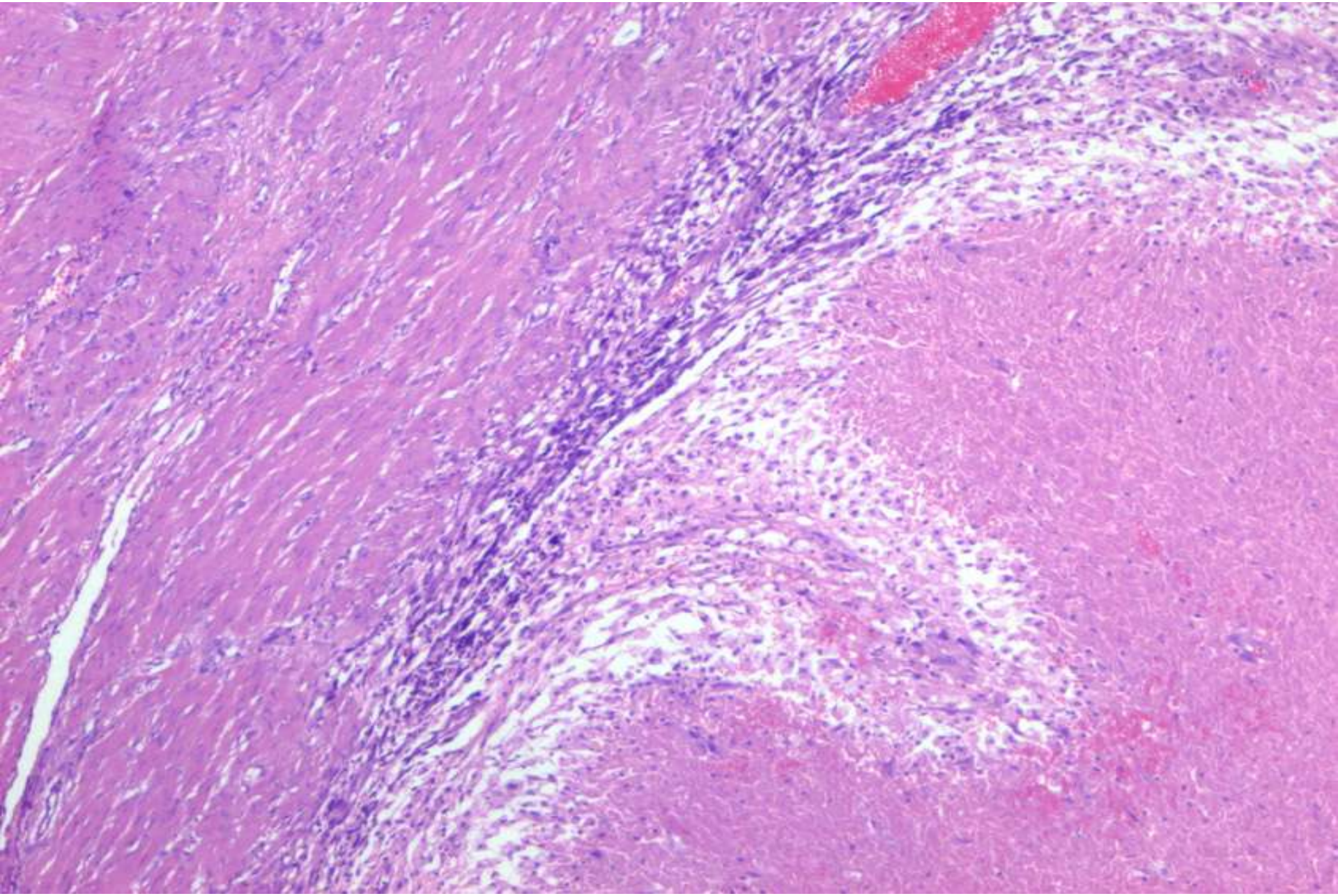
Bizarre Leiomyoma versus Leiomyosarcoma

	BL	LMS
Mitotic count	< 10	> 10
Tumor cell necrosis	-	+
DNA ploidy	Diploid	Aneuploid
MIB-1	Low	High
p53	-	+

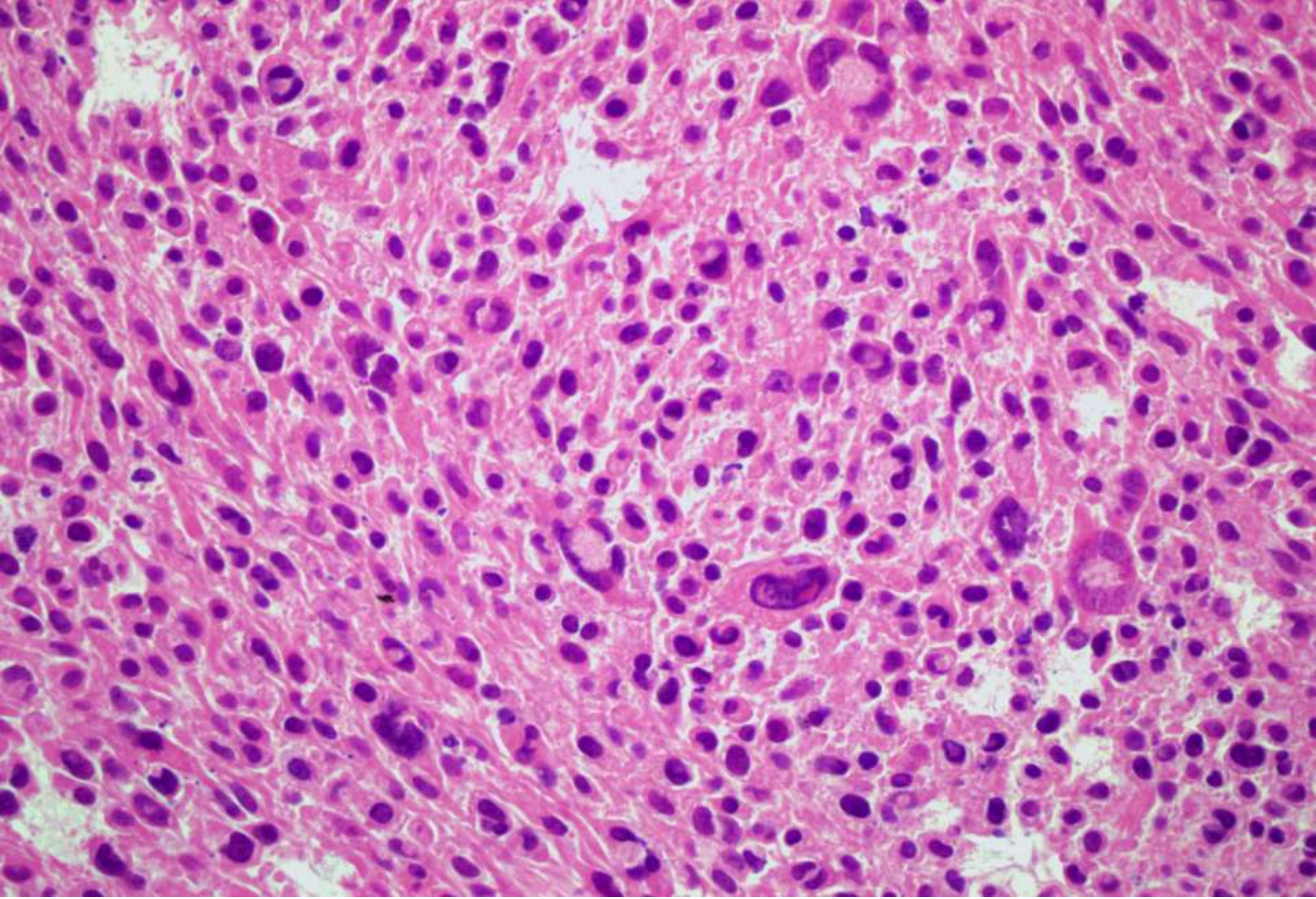
Downes KA and Hart WR, 1999



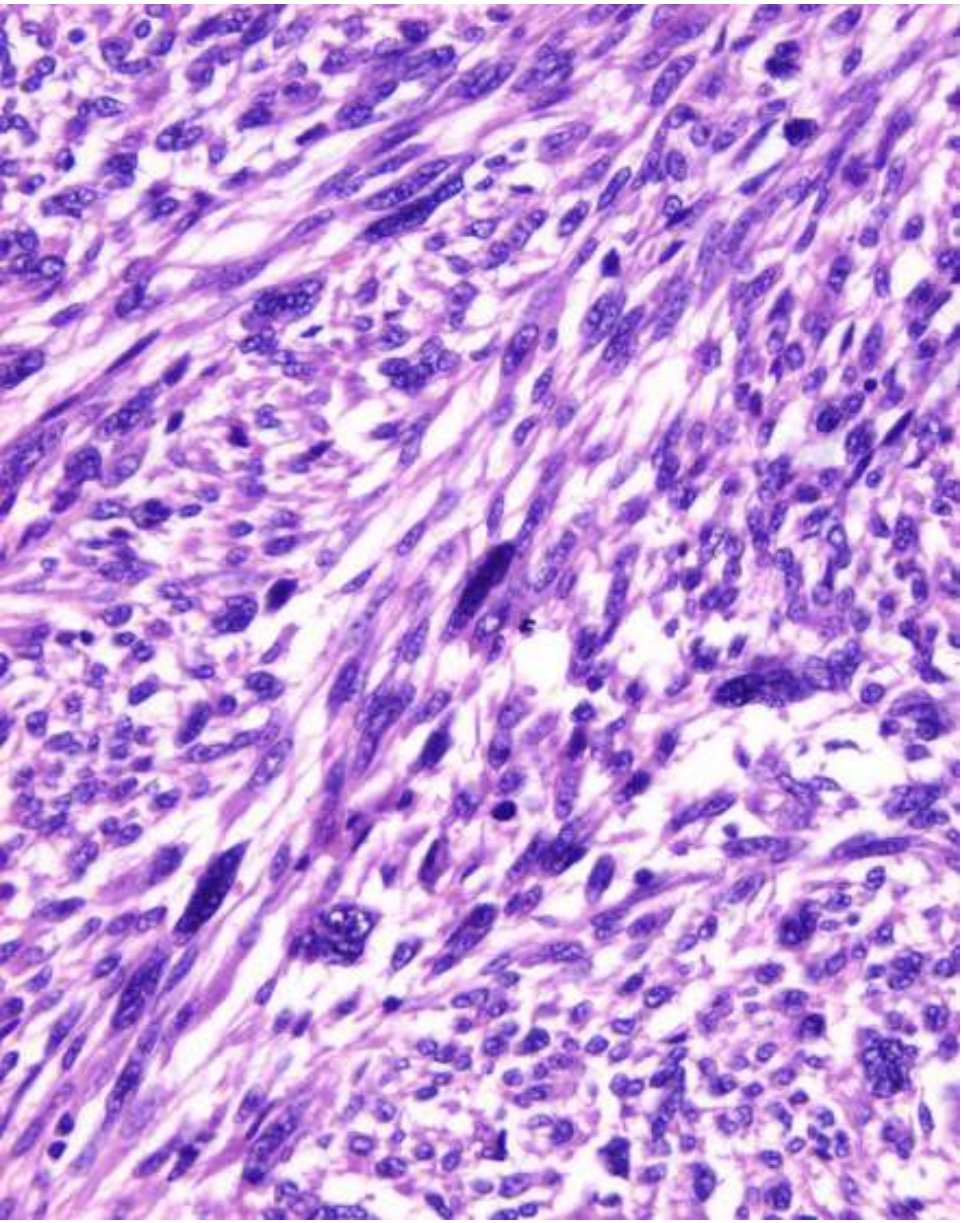
41 yr-old F
(12 cm)

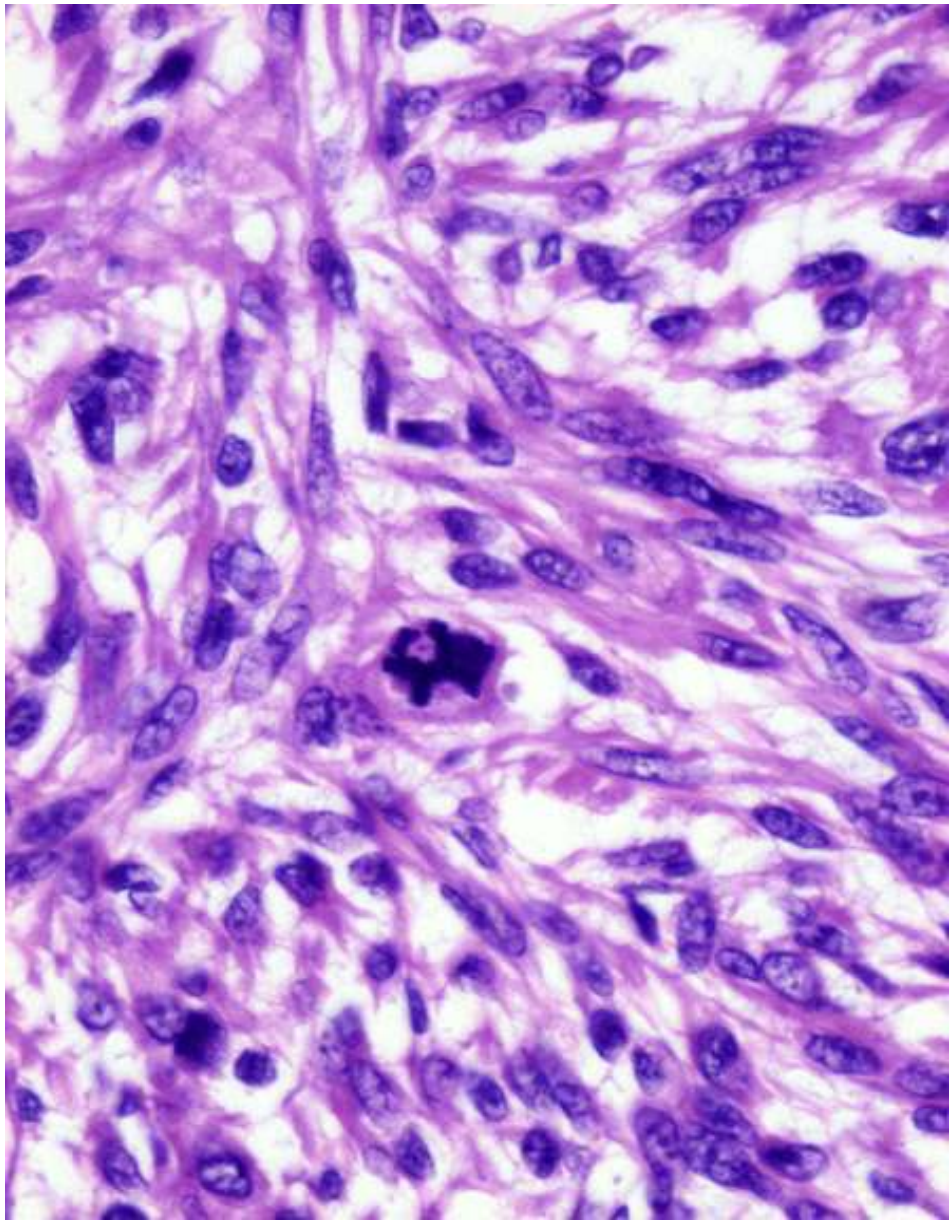


Infarct-type necrosis

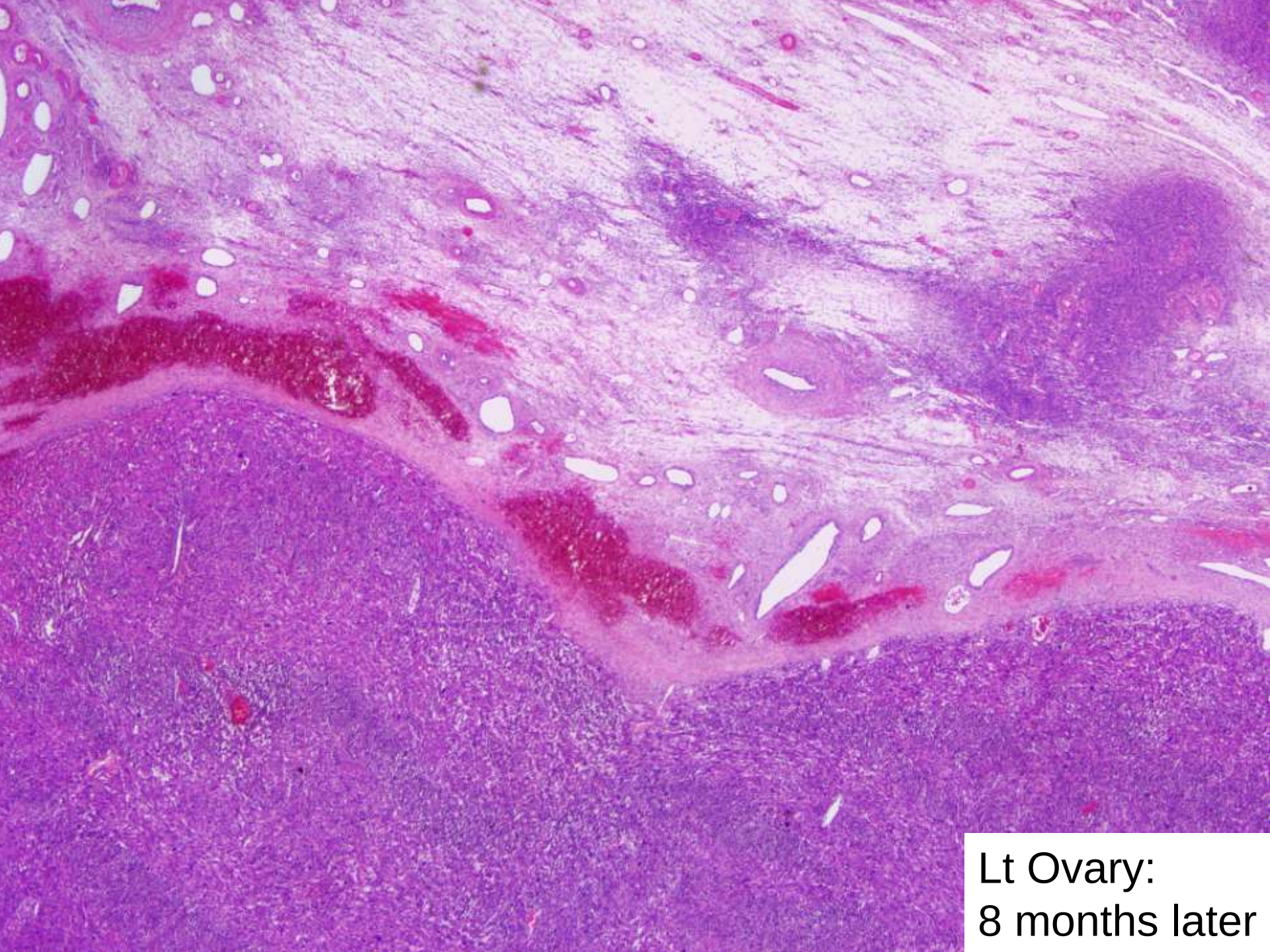


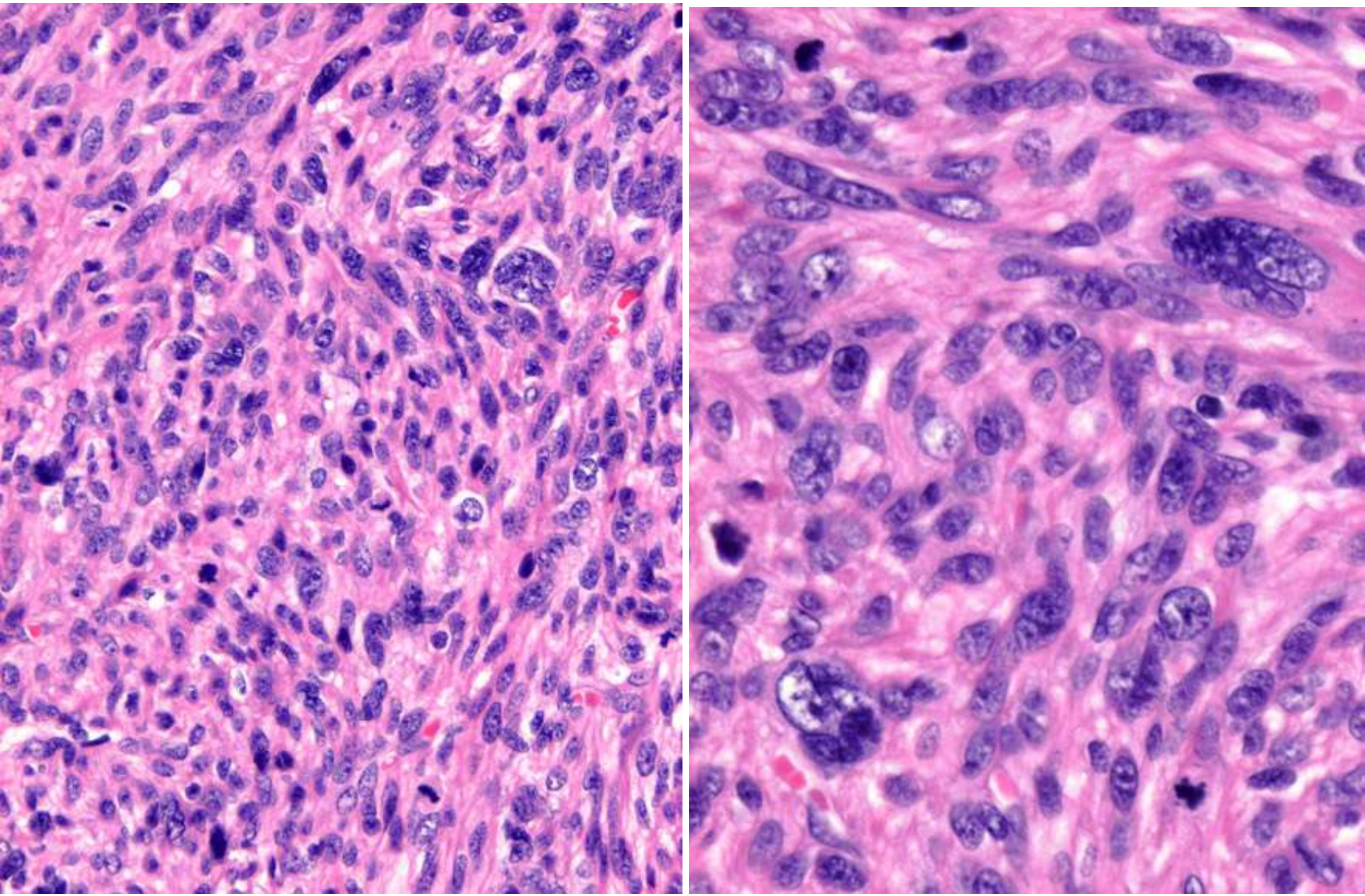
Atypical (bizarre) leiomyoma?





Leiomyosarcoma?


Lt Ovary:
8 months later



Leiomyosarcoma

A note of caution:

Leiomyosarcomas may show superimposed “bizarre” change!

Leiomyosarcomas are high-grade sarcomas associated with poor prognosis even if at Stage I

Uterine Leiomyosarcomas
(5 yr Surv)

Stage I 40-70%

Overall 15-25%

Leiomyosarcomas

(Inconsistent Prognostics Factors)

- Age
- Stage
- Size
- Border (pushing vs infiltrative)
- Necrosis
- Mitosis
- Nuclear atypia
- Vascular invasion

Leiomyosarcomas

Prognostics Factors

(245 cases)

	Tumor size		Mitotic index
Low risk	≤ 10 cm	&	≤ 10
Medium risk	> 10 cm	or	> 10
High risk	> 10 cm	&	> 10

Abeler V. et al.
Histopathology 2009; 54:355-364

Stage I Leiomyosarcomas

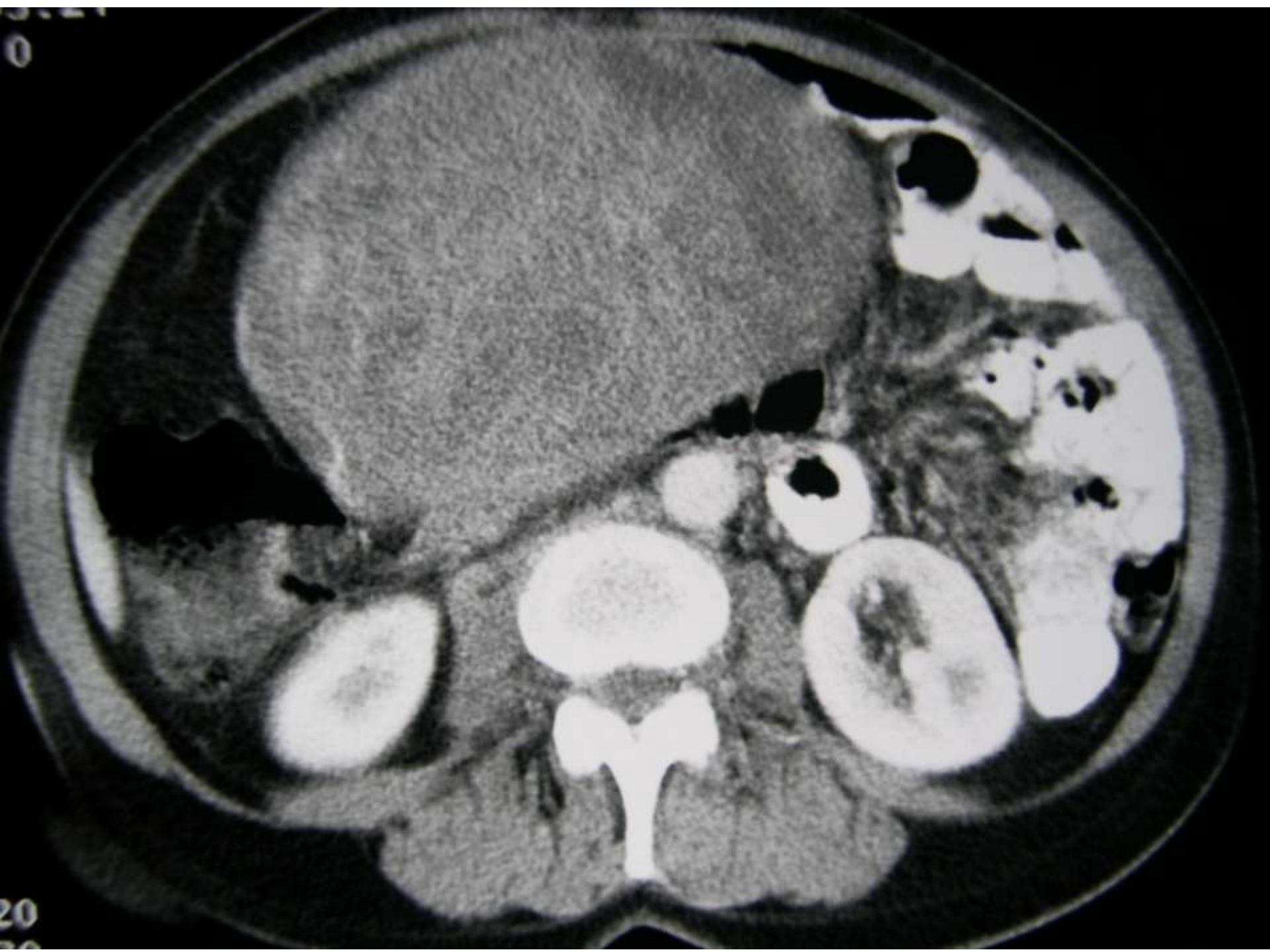
Prognostic Factors

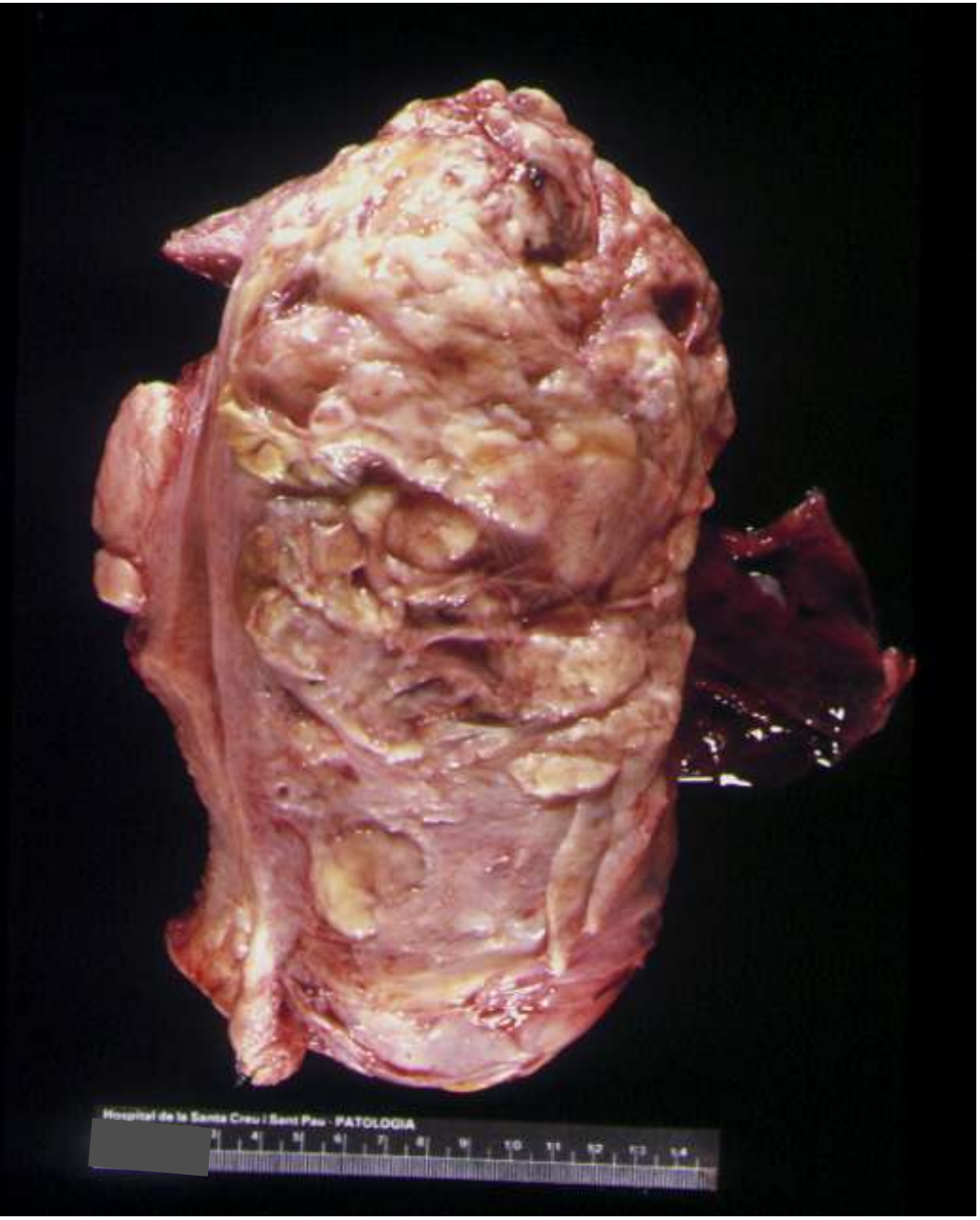
(27 cases)

Poor prognosis

- Spindle-cell morphology- better
- Diffuse high grade cytologic atypia- worse

Wang, et al. Am J Surg Pathol, April 2011

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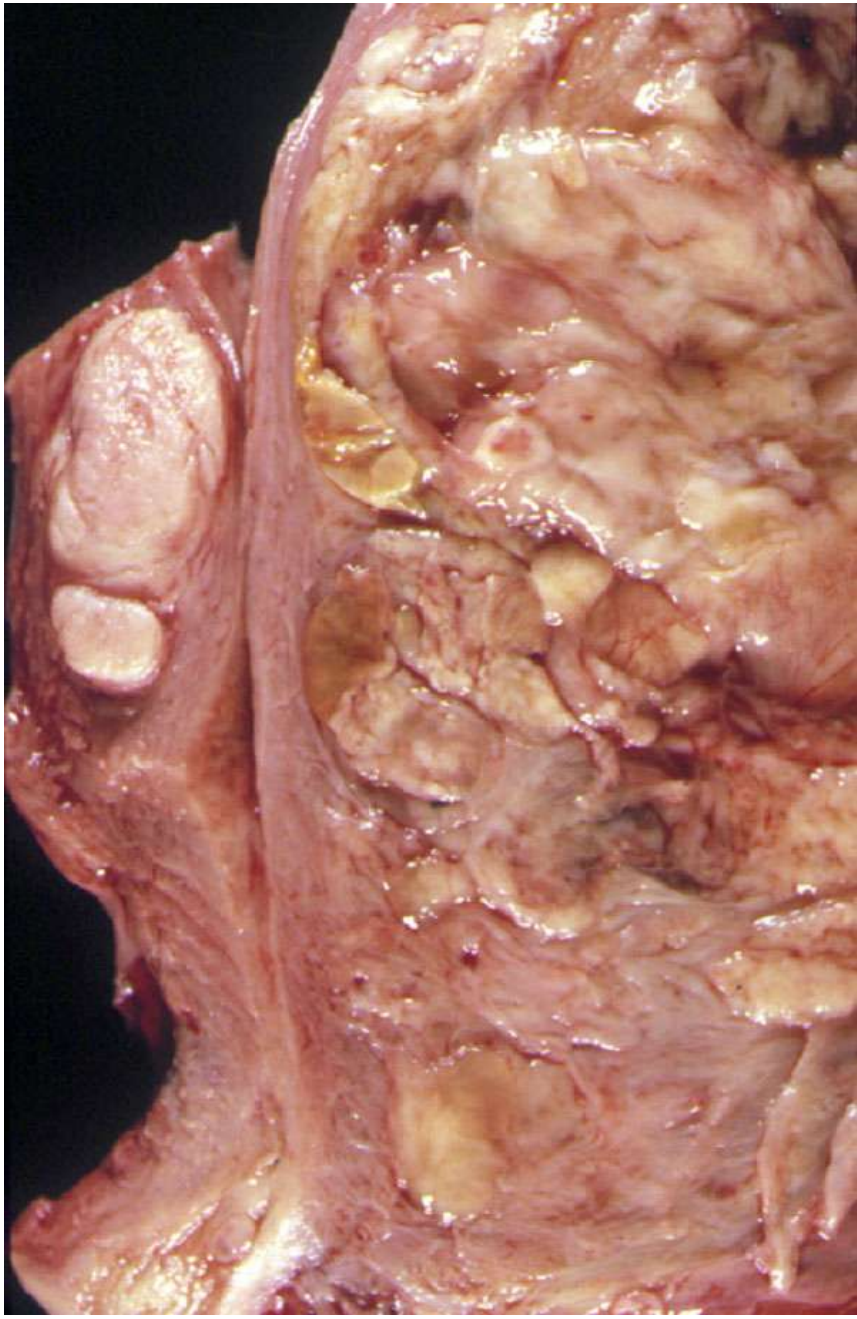
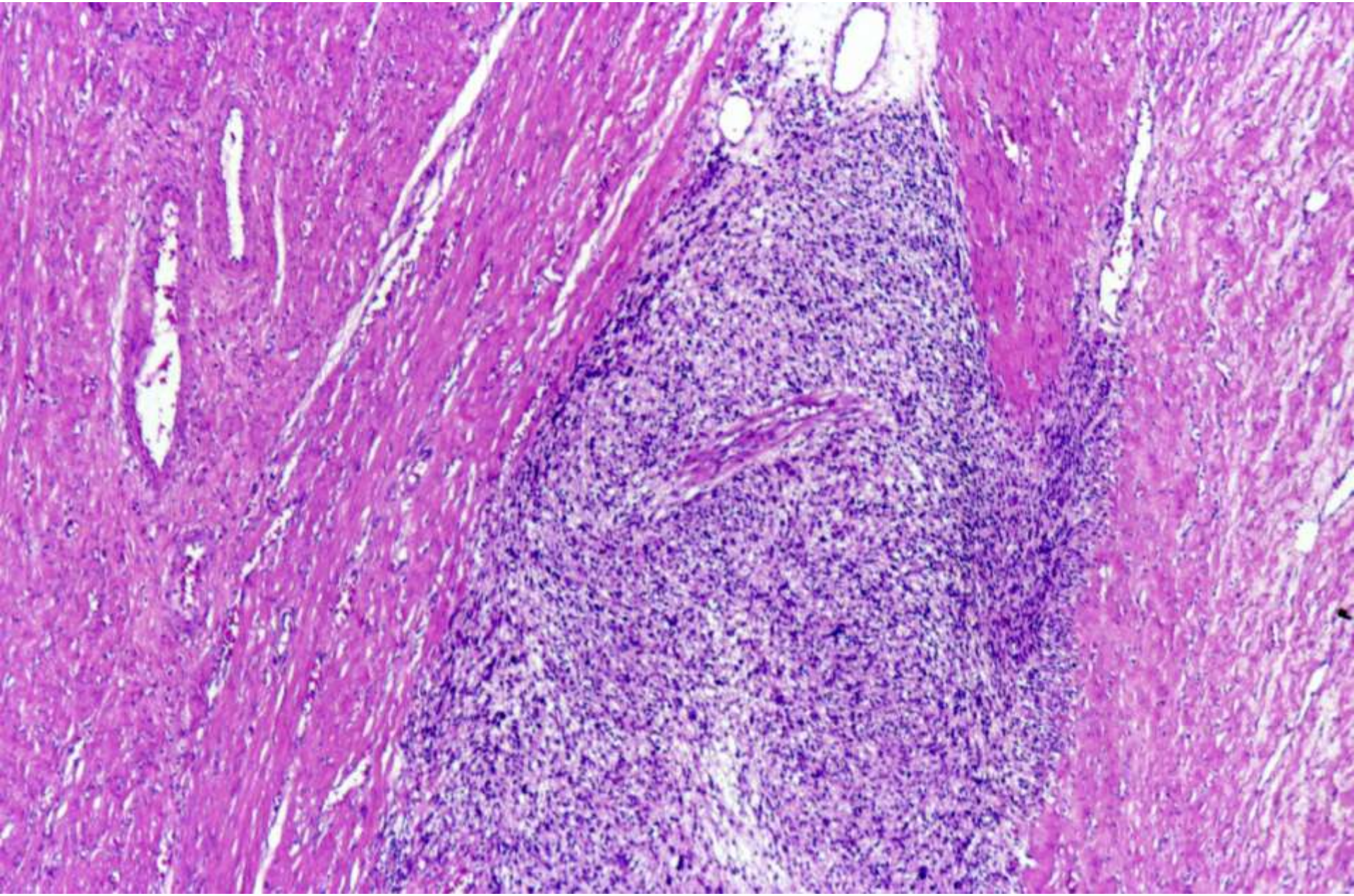
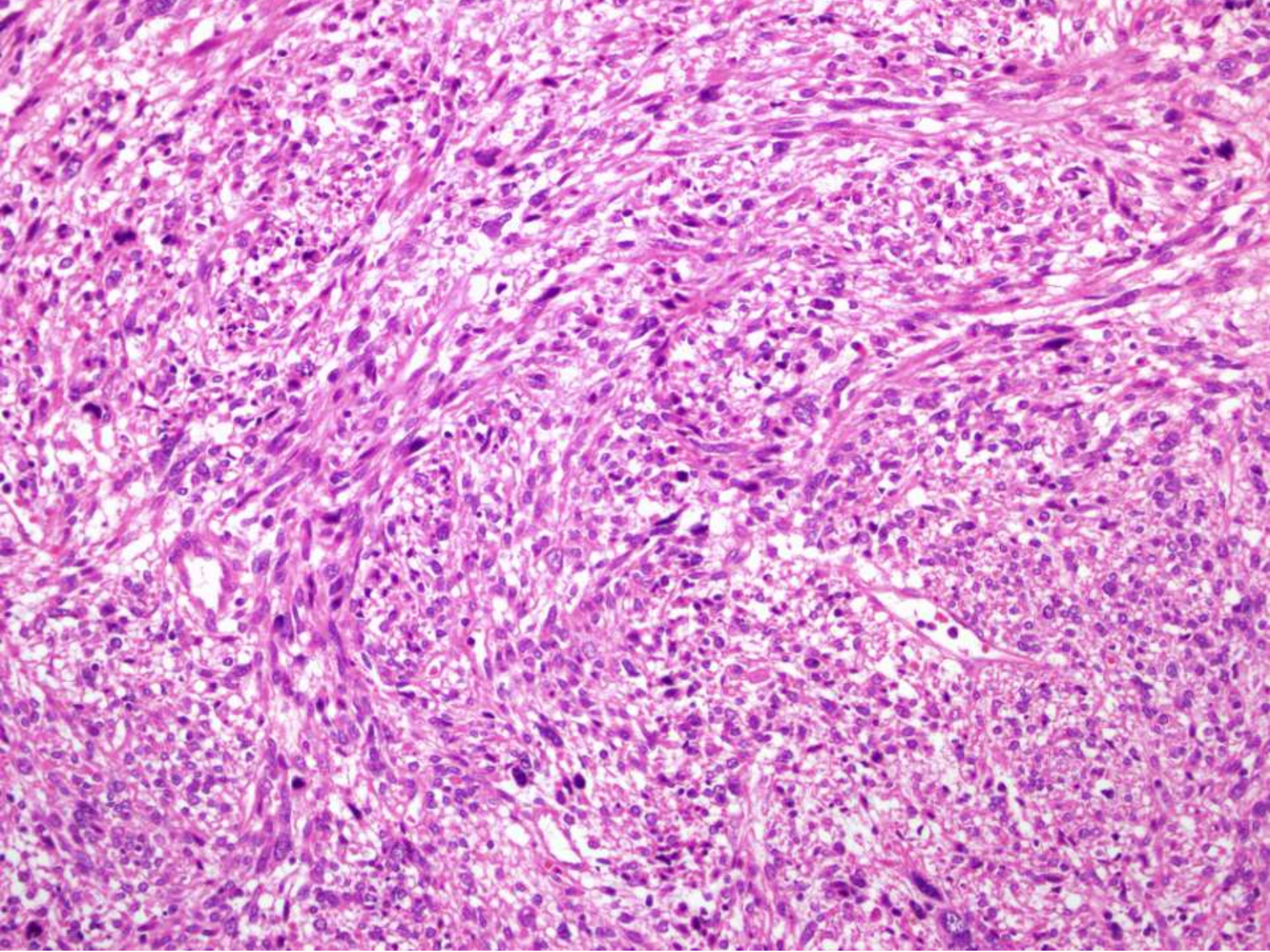
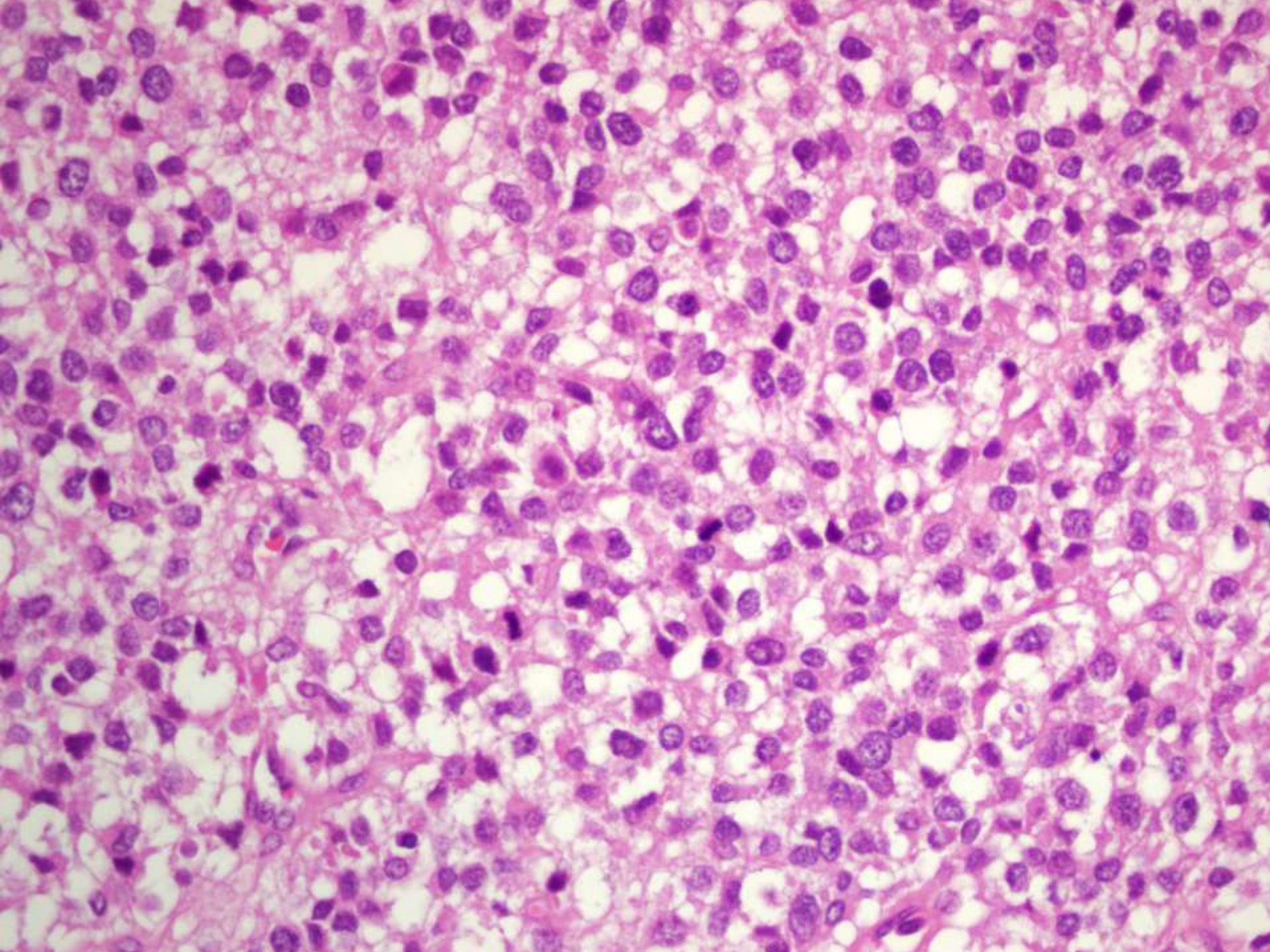




Myometrial invasion



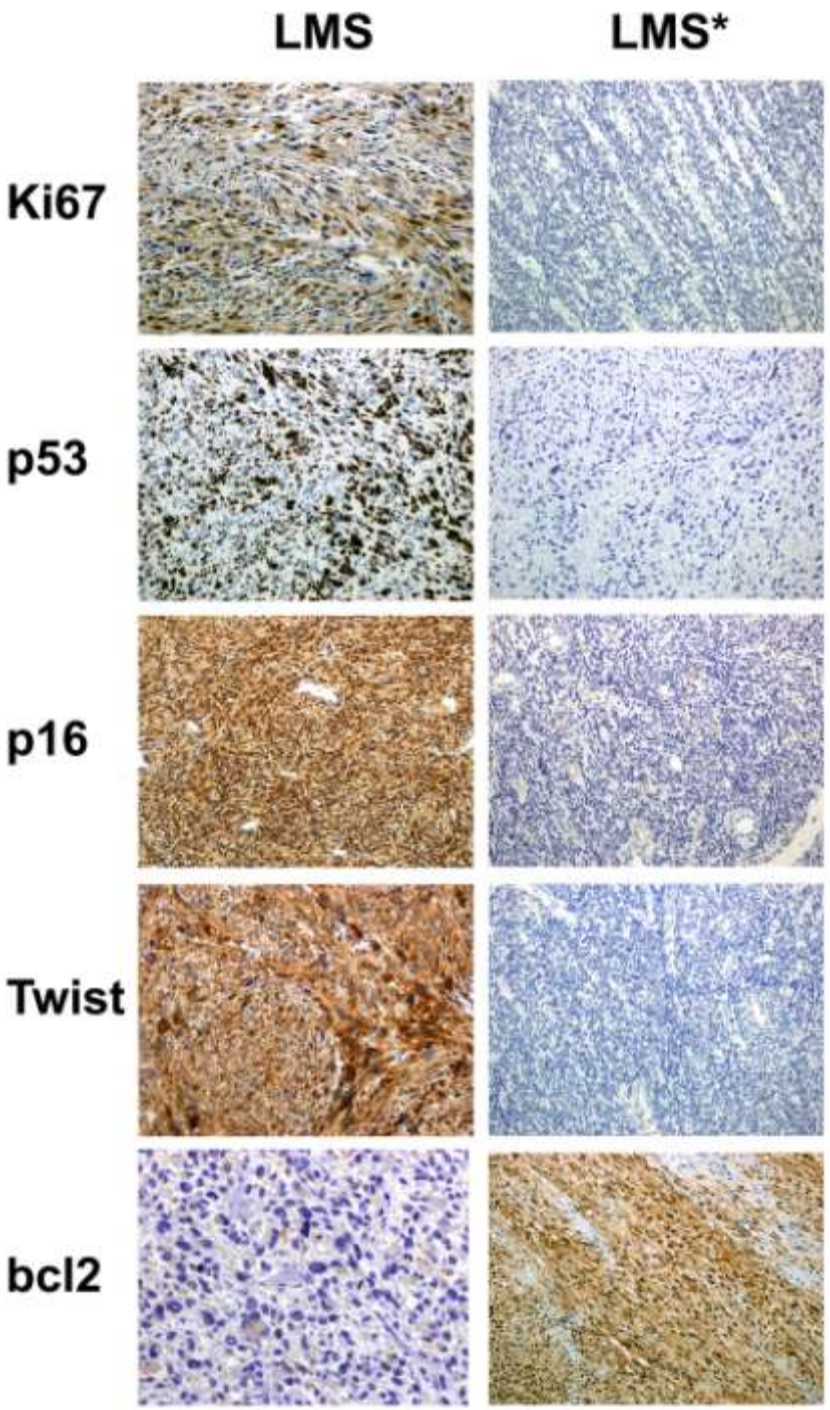


Clinicopathological Features and Follow-up

- 56 year-old female
- TAH-BSO
- Stage I LMS (22 cm)
  - 25 MF/10 HPF
  - Tumor necrosis
  - Vascular invasion
- Recurrences (2)
- NED at 11 yrs

Uterine Leiomyosarcomas

- FIGO Stage I includes highly heterogeneous group of patients
- Urgent need for a prognostic model
- Combination of conventional and molecular parameters



(*) NED @ 5-10 yrs

D'Angelo E, et al.,
Human Pathol 2009

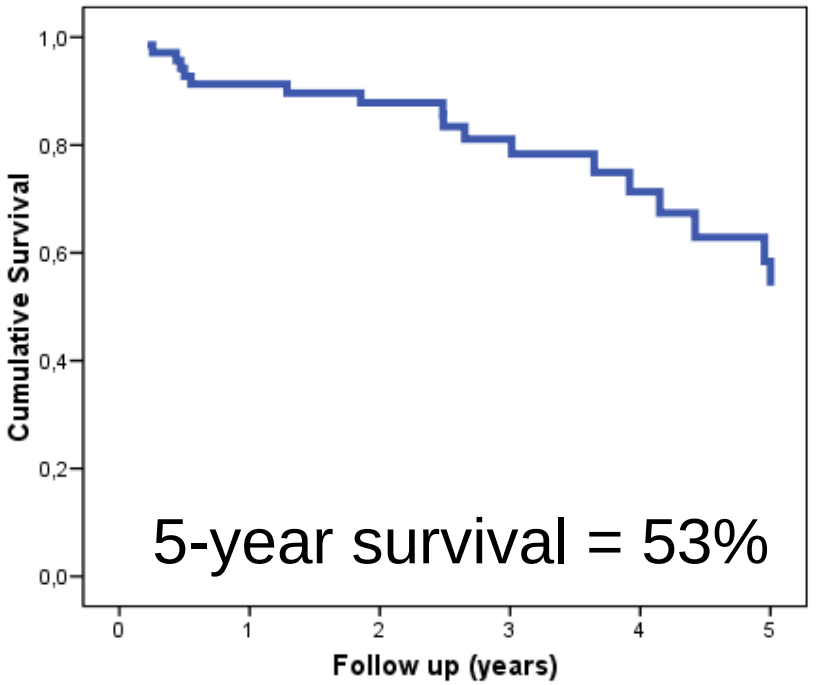
Stage (FIGO 2009)

I A	8/77	(10%)
I B	63/77	(82%)
III A	2/77	(2%)
III B	1/77	(1%)
IV A	1/77	(1%)
IV B	2/77	(3%)

71 (92%)

DOT 18 (25%)
AWT 29 (41%)
NED 24 (34%)

Stage I LMS



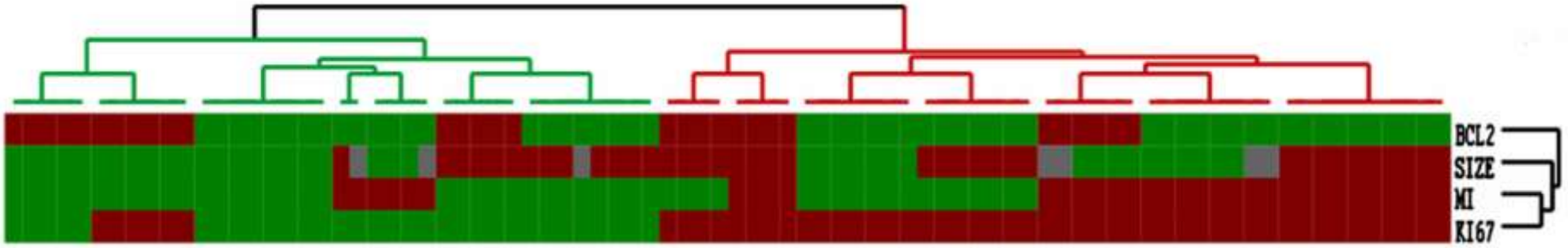
D'Angelo E, et al. Gynecol Oncol, May 2011

Prognostic model

84 leiomyosarcomas

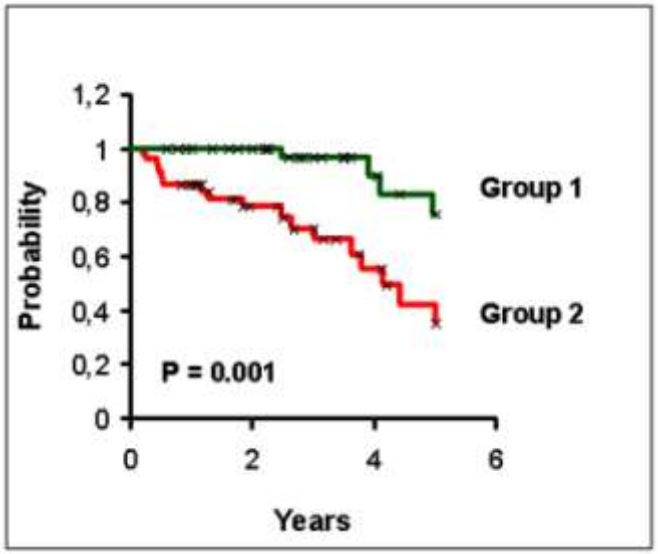
- Tumor size
- Mitotic index
- Ki-67
- Bcl-2

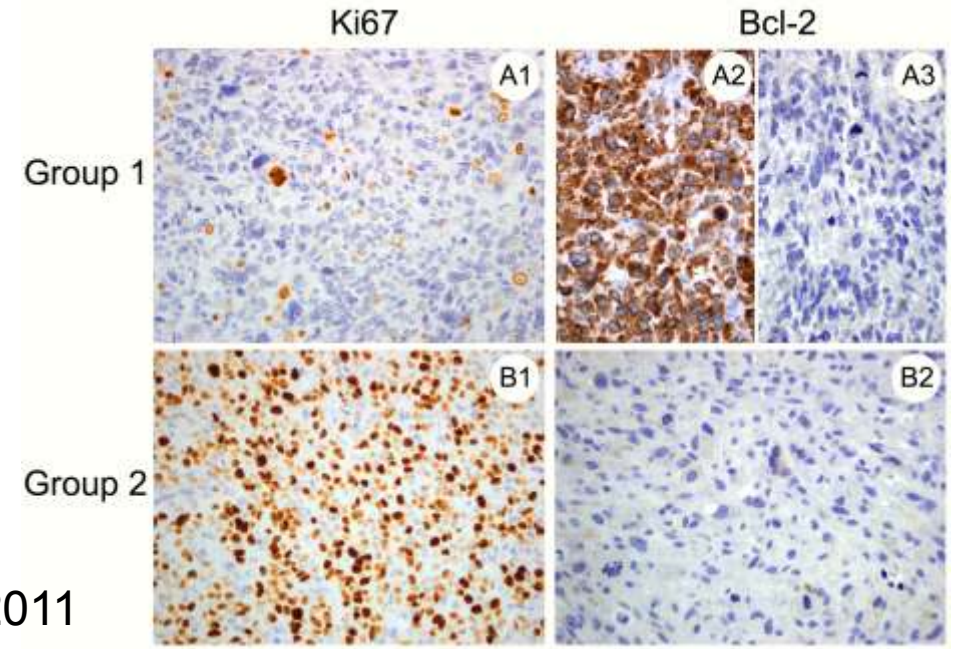
Leiomyosarcomas (n=82)



Group 1 (38 LMS)
< 10 cm
< 20 MF/10 HPF
Ki67 -
Bcl2 + or -

Group 2 (44 LMS)
≥ 10 cm
≥ 20 MF/10 HPF
Ki67 +
Bcl2 -





D'Angelo E, et al. Gynecol Oncol, May 2011

Leiomiosarcomas

- La estadificación de la FIGO agrupa la mayoría de pacientes en estadio I y sugiere erróneamente que tienen un pronóstico homogéneo.
- El tamaño del tumor y el índice mitótico son los parámetros morfológicos que predicen una conducta agresiva.
- El único biomarcador importante desde el punto de vista pronóstico es Ki67.
- La combinación del tamaño tumoral, el índice mitótico y las inmuno-reacciones de Ki67 y Bcl-2 ayudan a identificar leiomiosarcomas con distinto pronóstico.

Leiomiosarcomas Uterinos
(Resumen)

- Sarcomas de alto grado (1-2 % de los cánceres uterinos)
- Variantes de leiomioma (diagnóstico erróneo)
- Criterios diagnósticos mínimos: las mitosis son necesarias pero no suficientes (tamaño, atipia, necrosis)
- Falta de factores prognosticos (biomarcadores)
- Estadio I FIGO (grupo heterogéneo)

Leiomiosarcomas Uterinos
(Resumen)

- Tumores epitelioides y Mixoides (¡atención!)
- Potencial de malignidad incierto (sólo seguimiento)
- La mayoría de leiomiosarcomas son de alto grado y tienen mal pronóstico (incluso tumores en estadio I).
- Algunos casos se asocian a supervivencia prolongada y hace falta identificarlos (biomarcadores).