

ENDOMETRIAL STROMAL TUMORS

Esther Oliva, M.D.

Pathology Department, Massachusetts General Hospital, Boston, USA

Endometrial stromal tumors (EST) of the uterus are the second most common pure mesenchymal tumor of the uterus even though they account for < 10% of all such tumors. In the latest 2003 WHO classification they are divided into:

- a) endometrial stromal nodule (ESN)
- b) low-grade endometrial stromal sarcoma (ESS)
- c) undifferentiated endometrial/uterine sarcoma (UES)

Endometrial stromal nodule and low-grade ESS fall in the lower end of the spectrum of this group of tumors. Both are typically composed of a diffuse growth of small blue cells with scant cytoplasm and oval to spindle nuclei that resemble the stromal cells of the proliferative-phase endometrium. At the other end of the spectrum is the UES, a very high-grade sarcoma which does not resemble the proliferative-phase endometrium. It is a diagnosis that should only be made after excluding other high-grade tumors with a sarcomatous component.

ENDOMETRIAL STROMAL NODULE AND LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

Clinical features

ESNs are very rare while low-grade ESSs account for approximately 0.2 % of all malignant uterine tumors and 10-15% of uterine malignancies with a mesenchymal component. Both tumors frequently occur in women between 40 and 55 years of age. Some low-grade ESSs have been reported in women with ovarian polycystic disease, estrogen use, or tamoxifen therapy. Patients commonly present with abnormal uterine bleeding, pelvic pain, and dysmenorrhea, but as many as 25% of patients are asymptomatic. Extrauterine pelvic extension at the time of presentation is found in up to 1/3 of the patients with low-grade ESS, most commonly involving the ovary. Thus, when evaluating an ovarian tumor with a microscopic appearance consistent with an EST, it is important to exclude a prior history of a uterine EST and to suggest inspection of the uterus, as the latter are far more common.

Gross features

The main differentiating feature between the two neoplasms is tumor circumscription.

ESN: Well circumscribed, although nonencapsulated neoplasm ranging in size from 0.5 to 22 (mean 7) cm. If centered in the endometrium, it is frequently polypoid; but it is often intramyometrial.

Low-grade ESS: Frequent irregular nodular growth involving the endometrium, myometrium, or both. The main mass is frequently associated with varying degrees of permeation of the myometrium, including worm-like plugs of tumor that fill and distend myometrial veins, frequently extending to parametrial veins. On rare occasions, low-grade ESSs may appear deceptively well circumscribed on gross examination. In these cases, extensive sampling of the tumor interface is extremely important.

ESN and Low-grade ESS: Uniform soft, tan to yellow cut surface which may be associated with cyst formation as well as hemorrhage and/or necrosis.

Microscopic features

Myometrial and vascular invasion are the two most important features in the distinction between ESN and low-grade ESS.

ESN: The most important single criterion is the finding of a non-infiltrative border of the tumor. Focal irregularities in the form of lobulated or finger-like projections into the adjacent myometrium that do not exceed 3 mm and do not exceed 3 in number may be seen. No vascular invasion should be present.

Low-grade ESS: The tumor typically permeates the myometrium as irregular tongues and frequently invades myometrial as well as extrauterine veins and lymphatics.

ESN and low-grade ESS: The tumors are typically hypercellular but they may be hypocellular secondary to a fibrous or myxoid background. They are composed of sheets of uniform small blue cells closely resembling the proliferative-phase endometrial stroma. The cells have scant cytoplasm and oval to round nuclei with inconspicuous nucleoli. Mitotic activity is typically <5/10 high power fields. Brisk mitotic activity is still compatible with the diagnosis of low-grade ESS if the architectural and cytologic features of the tumor are reminiscent of endometrial stroma. There is frequent whorling of the neoplastic stromal cells around arterioles (the latter may appear hyalinized), but the characteristic arborizing vasculature is not always striking. Sex cord differentiation, smooth and skeletal muscle differentiation, fibrous or myxoid change, glandular differentiation (as benign or malignant endometrioid-type glands), rhabdoid, epithelioid, or clear phenotype as well as fatty metaplasia and bizarre cells may also be seen. Collagen bands or plaques, diffuse areas of hyalinization, foamy histiocytes, cystic degeneration associated with cholesterol clefts, and necrosis may be present in both tumors and are not useful in the differential diagnosis.

In the majority of cases it is impossible to differentiate between ESN and low-grade ESS on curettage specimens. Thus distinction can only be confidently established in a hysterectomy specimen. This is an important issue when the patient is of reproductive age and desires to preserve her uterus. In these circumstances, a combination of diagnostic imaging and hysteroscopy may be used to monitor the growth of the tumor and occasionally local excision has been successful.

Immunohistochemistry

ESN and low-grade ESS are typically positive for vimentin, muscle-specific and smooth muscle actin, and frequently keratin. Most ESTs stain for CD10. However, smooth muscle tumors, mixed mullerian tumors (including adenosarcoma and malignant mixed mullerian tumor (MMMT)), and rhabdomyosarcomas may be CD10 positive. Thus, this antibody should not be used in isolation when evaluating the cell of origin in a uterine mesenchymal tumor. Desmin staining in ESTs varies among studies and it should not be used in isolation to differentiate ESTs from smooth muscle tumors. Other muscle markers including h-caldesmon, myosin and HDCA8 are also helpful in this differential diagnosis. Areas of smooth muscle differentiation are positive for all smooth muscle markers as well as for CD10. Areas of sex cord-like differentiation may be positive for inhibin, calretinin, CD99, WT-1 and Melan A. Endometrial stromal tumors frequently contain ER and PR, although its presence is not specific to these tumors and they also frequently express β -catenin.

Cytogenetics

Conventional ESTs as well as their variants show as most common translocation $t(7;17)$ with involvement of two zinc finger genes, JAZF1 and JJAZ1.

Differential diagnosis

Highly cellular leiomyoma most frequently causes problems in the differential diagnosis with either a pure ESN or low-grade ESS, as they share the following features: dense cellularity, prominent vascularity, and an irregular margin with the surrounding myometrium (in some). However, highly cellular leiomyoma has a fascicular growth at the periphery of the lesion, the tumor cells merge with the surrounding myometrium and the vessels are typically thick and large in contrast to the delicate arteriolar network present in ESTs. A cellular endometrial polyp may enter in the differential diagnosis when fragmented and present in a curettage. The inactive appearance of the stromal cells as well as the finding of large vessels and absence of the small arteriolar network will favor the diagnosis of polyp. A uterine tumor resembling a sex cord-stromal tumor (UTROSCT) may enter in the differential diagnosis of and ESN or low-grade ESS as ESTs may show extensive sex cord-like differentiation. A diagnosis of UTROSCT can only be made when no evident endometrial stromal component is seen. Thus, this is only achieved with the hysterectomy specimen. Low-grade ESS with gland differentiation should be distinguished from low-grade mullerian adenosarcoma and adenomyosis.

Prognosis and treatment

Patients with an ESN have an excellent prognosis and the treatment of choice is surgery. Patients with low-grade ESSs have a 5-year survival rate of approximately 60 to 80%. These tumors have a low malignant potential and are characterized by late recurrences even in patients with stage I disease, as one third or more develop recurrences, most commonly in the pelvis (occurring in up to one half of the patients) and abdomen, and

less frequently in lung and vagina. Thus, patients require long follow-up. Standard initial surgical treatment encompasses total abdominal hysterectomy and bilateral salpingo-oophorectomy as these tumors are often hormone sensitive and it has been shown that patients retaining their ovaries have a much higher risk of recurrence (up to 100%). Lymph node dissection does not seem to have a role in the treatment of these tumors. Patients may also receive adjuvant radiation or hormonal treatment with progestational agents or aromatase inhibitors. Clinicopathologic factors reported in the older literature to be of potential prognostic importance included age, race, size, FIGO stage, depth of myometrial invasion, tumor grade, mitotic activity, and DNA ploidy. However, in the largest study of low-grade ESS, mitotic activity and cytologic atypia were not predictive of tumor recurrence in stage I tumors (most common scenario), while size poorly correlated with outcome as tumors <4 cm also recurred. Endometrial stromal tumors with unusual types of differentiation should be reported as *ESN or low-grade ESS based on the margins, as this is the only discriminating prognostic factor*.

UNDIFFERENTIATED ENDOMETRIAL/UTERINE SARCOMA

These are extremely rare tumors and the lack of specific evidence of endometrial stromal cell origin in most cases precludes their placement in the endometrial stromal group of uterine tumors. Grossly, they show a fleshy, gray cut surface with common areas of hemorrhage and necrosis. On microscopic examination, there is destructive myometrial invasion while the intravascular worm-like plugs characteristic of low-grade ESS are typically absent. They have marked cellular pleomorphism and brisk mitotic activity. These tumors should be diagnosed only after extensive sampling has excluded smooth or skeletal muscle differentiation or even small foci of carcinoma, as this finding would result in a diagnosis of MMMT. Occasional tumors have a component of low-grade ESS indicating that the high-grade component is presumably of endometrial stromal derivation. In these cases, the designation of high-grade ESS arising from a low-grade ESS is indicated. A recent study has divided high-grade tumors in two categories based on nuclear uniformity. Undifferentiated tumors with nuclear uniformity shared some immunohistochemical and molecular features with low-grade ESS. Undifferentiated endometrial/uterine sarcomas carry a very poor prognosis and most patients die of disease within two years of the initial diagnosis. CD10 expression is not helpful in this differential as UES as well as leiomyosarcoma, rhabdomyosarcoma and MMMT express this marker. Smooth muscle markers and myogenin or myoD1 may be used to rule out leiomyosarcoma or rhabdomyosarcoma respectively, or to identify a rhabdomyosarcoma component in a MMMT.

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**Esther Oliva, M.D
Massachusetts General Hospital
eoliva@partners.org**



ENDOMETRIAL STROMAL TUMORS

WHO Classification

- Endometrial Stromal Nodule
 - Low-Grade Endometrial Stromal Sarcoma
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- 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)
- Staging following carcinoma FIGO staging
- 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

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

DIFFERENTIAL HISTOLOGIC FEATURES

Myometrial and/or vascular invasion

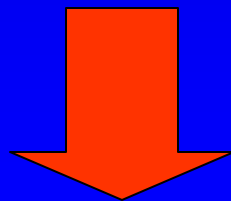
Endometrial Stromal Nodule

WHO definition

- **Unusual benign endometrial stromal tumor characterized by a well delineated expansile margin on microscopic examination**
- **Presence of focal irregularities in the form of lobulated or finger-like projections (< 3) into the adjacent myometrium that do not exceed 3 mm**
- **No vascular invasion**

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

Endometrial Stromal Sarcoma

Differential Diagnosis:

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

Features of Highly Cellular Leiomyomas that Cause Confusion with Endometrial Stromal Tumors

- Dense cellularity
- Prominent vascularity
- Irregular margin

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

Prognosis and treatment

- Hysterectomy and bilateral oophorectomy
- 80-90% 5-year survival rate and 70% 10-year survival
- 5-year survival close to 100% and 10-year survival of 80-90% for stage I (organ confined)
- Hormonal treatment, aromatase inhibitors or radiation as other options

Stage most powerful prognostic factor

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

Potential prognostic factors?

- Even though low-grade endometrial stromal sarcomas are considered low-grade malignant tumors, still a number of patients with stage I disease develop recurrences or even die of disease
- Are there any pathologic parameters that can help to predict which tumors will behave in a more aggressive manner?

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

- Potential prognostic factors:
 - Age
 - Race
 - Size
 - Cytologic atypia
 - Mitotic activity
 - Ploidy

PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

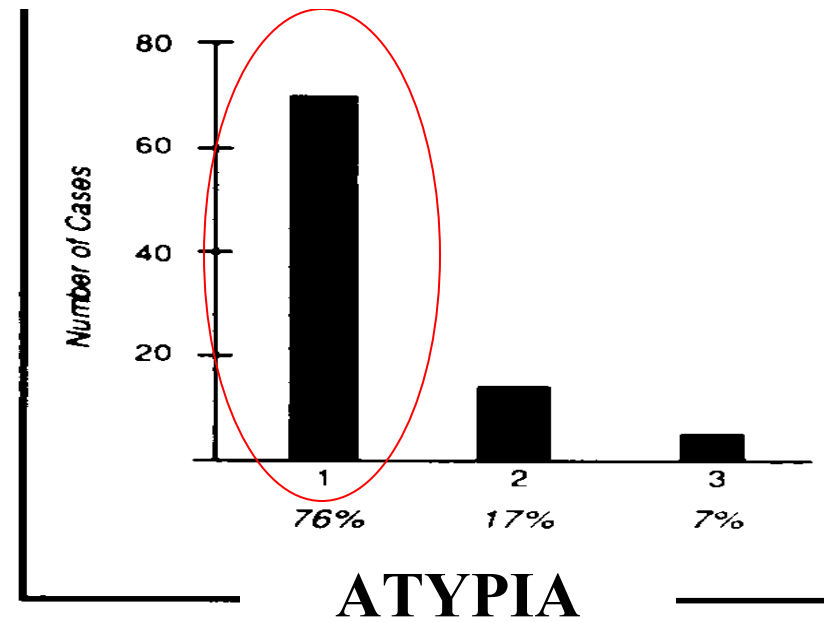
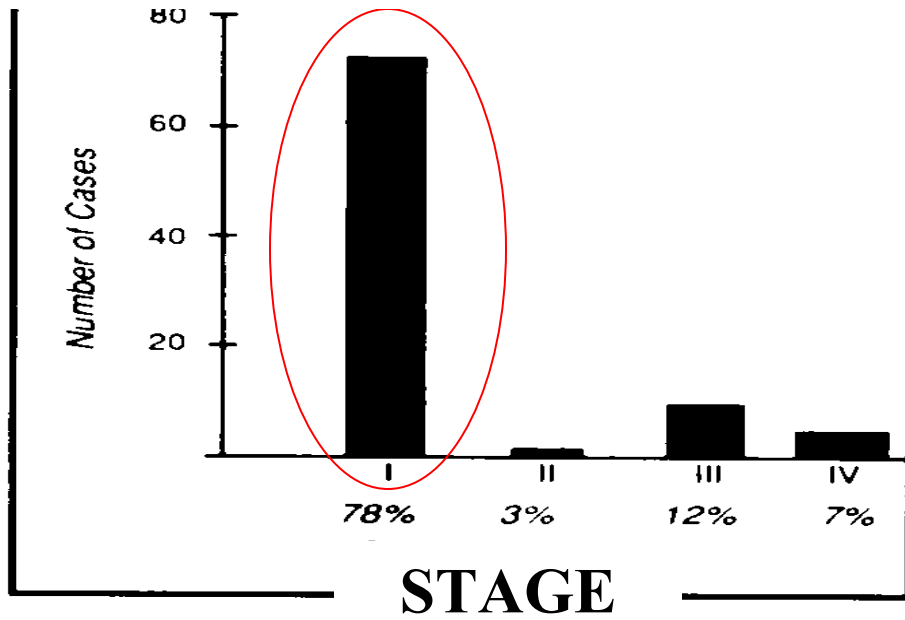
Chang KL et al, Am J Surg Pathol 1990;14:415

- 96 primary uterine corpus ESS
- 85 patients with stage I tumors
- 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

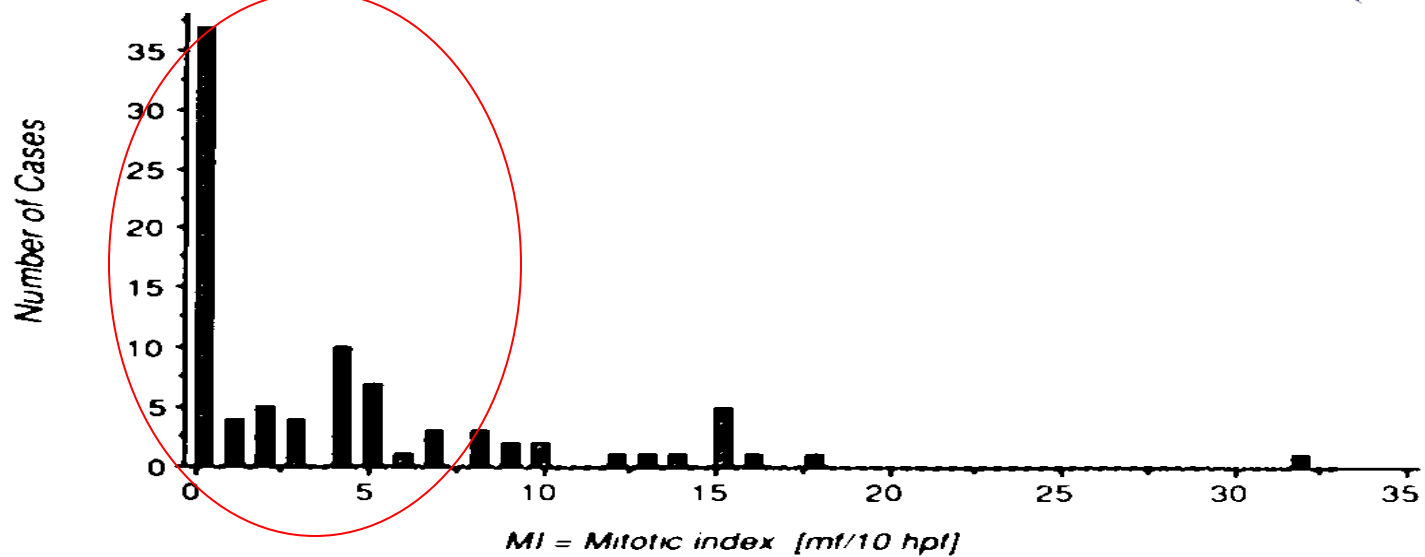
PRIMARY UTERINE ENDOMETRIAL STROMAL NEOPLASMS

Chang KL et 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

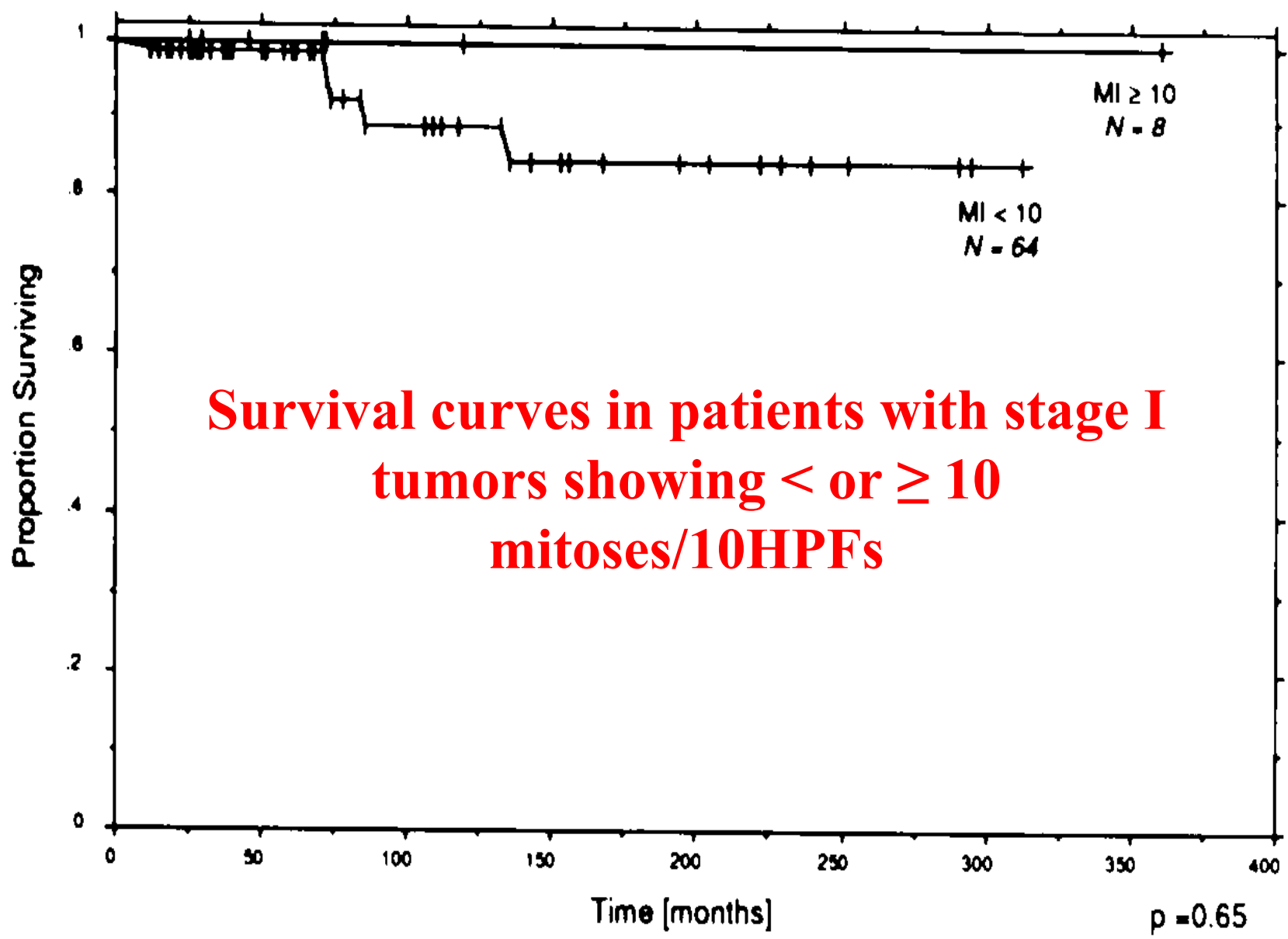


ENDOMETRIAL STROMAL SARCOMAS (93)



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

MITOSES



**Survival curves in patients with stage I
tumors showing $< \text{or } \geq 10$
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)
- 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

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**
- **DIAGNOSIS OF EXCLUSION**
- **Very aggressive behavior (most patients die within 2 years of diagnosis)**

**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 non-low grade ESS (“Undifferentiated endometrial sarcoma”)**
- **18 low-grade ESS, 7 UES-U (nuclear uniformity, but nucleomegaly, hyperchromatism and nucleoli), and 6 UES-P (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	3/7	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 fusion</i>	6/12	1/3	0/3
• p53 mutations	0/17	0/7	3/7

SUMMARY

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

