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MMMT (Carcinosarcoma)

Carcinosarcoma, also referred to as “malignant mixed Mullerian tumor” or “MMMT” is a neoplasm composed of malignant-appearing epithelial and mesenchymal elements (1). Although they can arise in any genital organ, they are found most frequently in the uterus where they represent less than 5% of malignant neoplasms. These tumors are increasingly thought of as carcinomas that demonstrate sarcomatoid differentiation (2-5), although many gynecologists persist in classifying them as sarcomas. Regardless, they are extraordinarily heterogeneous, clinically aggressive neoplasms. Their morphologic heterogeneity is responsible for difficulties in accurate diagnosis. A particular problem is the imprecise nature of the entity’s current definition. As will be discussed subsequently, there is a group of biphasic uterine neoplasms that have been historically considered carcinosarcomas. With the advent of carcinoma-style staging surgeries for CS, treatment with effective chemotherapeutic agents for high-risk and high-grade uterine malignancies, specific treatment protocols for CS, increased use of immunohistochemistry and advances in our understanding of the interplay of genetics, tumor biology and epidemiology, it has become clear that only a subset of lesions historically considered CS conform to most of the commonly held assumptions about what the typical CS should be: CSs, as a group, should be highly aggressive tumors, more clinically aggressive than carcinomas, and composed of malignant epithelial and mesenchymal elements. These are the guidelines that will be used to define CS in this presentation

Clinical Features

The mean age of patients with endometrial carcinosarcoma is in the 7th decade, but the age range spans from the 4th through 9th decades. The disease tends to present like other endometrial cancers, with vaginal bleeding being common. Another typical presentation of carcinosarcoma is a polypoid mass that protrudes through the cervical os.

The 5-year survival for carcinosarcoma is around 30% and the 5 year survival in surgical stage I disease (confined to uterus) is approximately 50% (6-9). This very aggressive profile contrasts with that of other high grade endometrial cancers where 5 year survivals in stage I disease are approximately 80% or better (10, 10a). This has led to toxic treatment protocols that usually include ifosfamide and cisplatin along with whole pelvic irradiation. There are no data that suggest that treating the predominant tumor component (i.e. rhabdomyosarcoma, when present) is preferable to standard therapy.

There have been numerous studies that have sought to define prognostic factors in carcinosarcoma, but many are compromised by including at least 2 groups of patients,

some of whom were clinically staged and others who were comprehensively (i.e. surgically staged) (6-9). Pathologically determined prognostic features in *clinically staged* CS patients are generally the same as for patients with suboptimally staged endometrial carcinoma (grade, depth of invasion, presence of lymphovascular invasion). There is general agreement that surgical stage is the most important prognostic indicator regardless of how the patient was staged. In common with some of the older literature, our group has also recently found that the presence of heterologous elements is a statistically significant poor prognostic factor in comprehensively staged, FIGO stage I patients (11). 30% of patients with heterologous elements survive 5 years as compared to 80% of patients with homologous elements. Other factors that have been proposed include the grade of the carcinomatous and sarcomatous elements, the percentage of tumor demonstrating sarcomatous differentiation, the depth of myometrial invasion and the presence of lymphovascular invasion (6-9).

Morphology

The cardinal rule of carcinosarcoma is that it is a biphasic tumor, composed of distinctive and separate, but admixed, malignant-appearing epithelial and mesenchymal elements. The epithelial and mesenchymal elements should not merge with one another. This definition essentially excludes from consideration all monophasic tumors such as undifferentiated carcinomas and undifferentiated sarcomas and tumors that display *either* malignant-appearing epithelial elements (endometrioid adenocarcinoma with spindle cell features) *or* malignant-appearing mesenchymal elements (Mullerian adenosarcoma).

Carcinomatous and sarcomatous elements are generally easy to find, but occasional cases show sarcoma or carcinoma almost exclusively. About one-third of carcinosarcomas harbor a carcinoma with endometrioid differentiation and two-thirds contain carcinomas that are serous or high grade, not otherwise specified (11). The former tumors may be associated with complex atypical hyperplasia and endometrial intraepithelial carcinoma may be found in the latter tumors. Clear cell, mucinous and squamous carcinomas have also been described. In our series (11), 10% of the carcinomatous components were FIGO grade 1, 10% were grade 2 and 80% were grade 3. The sarcomatous components were heterogeneous. The homologous components of carcinosarcoma are usually spindle cell tumors without obvious differentiation; many resemble fibrosarcomas or pleomorphic sarcomas. In our experience, it is uncommon to find a carcinosarcoma containing areas that closely resemble leiomyosarcoma or endometrial stromal sarcoma. Almost all are histologically high grade. The most common heterologous elements are chondroid or rhabdomyoid (constituting something that resembles either pleomorphic rhabdomyosarcoma or embryonal rhabdomyosarcoma). Occasional cases showing lipoblastoid, osteoid, neural/neuroectodermal and angiomatoid elements have been described.

Most carcinosarcoma metastases are epithelial only or, less commonly, epithelial predominant. It is very uncommon to find sarcoma-only metastases from carcinosarcoma.

Immunohistochemistry

The immunophenotype of carcinosarcoma should closely follow that of the individual elements present in the tumor. For example, the serous component should express keratins and p53, while the rhabdomyoblastic component should express desmin and myogenin. It is a well known diagnostic pitfall that the sarcomatous component of carcinosarcoma can express keratins, but the same is true of leiomyosarcoma, in particular. Given this and the adherence to the cardinal rule of carcinosarcoma (see above), immunohistochemistry should not be needed for diagnosis and should only be used in exceptional circumstances. I essentially restrict the use of immunohistochemistry to cases where I want to support my impression of a heterologous element, particularly rhabdomyosarcoma. I will rarely perform immunohistochemistry to support my impression of a malignant epithelial component (p53 in epithelium that looks neoplastic and probably malignant) or to support a morphologically distinct epithelial component where the overwhelming impression is that of a monophasic undifferentiated tumor. Pleomorphic, monophasic neoplasms with patchy keratin expression should not necessarily be diagnosed as carcinosarcomas.

Differential Diagnosis

As mentioned earlier, most monophasic tumors should not be considered candidates for a carcinosarcoma diagnosis, although many pathologists believe that uterine pleomorphic rhabdomyosarcomas represent carcinosarcomas in which the epithelial component has not been sampled or has been overgrown by sarcoma. This leaves the biphasic tumors. The four most important biphasic tumors to consider in the differential diagnosis are adenosarcoma, endometrioid adenocarcinoma with spindle cell elements (12, 13), so-called dedifferentiated endometrial carcinoma (14, 15), and composite or collision tumors.

Endometrioid adenocarcinoma with spindle cell elements versus carcinosarcoma

Endometrioid adenocarcinoma with spindle cell elements has long been recognized, although it was only recently given a name and an in-depth description (12, 13). In this tumor, the endometrioid elements, frequently showing squamous metaplasia, fuse imperceptibly with spindle cell elements that are never histologically high grade. In most cases, the endometrioid component is no more than FIGO grade 2 and the spindle cell component is cellular and sometimes mitotically active, but not markedly atypical. If there is confusion between this entity and carcinosarcoma, use the tumor grade and the presence or absence of “element fusion” to inform the decision. Carcinosarcoma contains easily separable, high grade epithelial and mesenchymal elements whereas this type of endometrioid adenocarcinoma shows seamless fusion of two histologically low grade components (i.e. element fusion). Be aware here as well that endometrioid adenocarcinomas can contain chondroid and osteoid elements. Heterologous elements by themselves do not signify carcinosarcoma. FIGO grade 1 and 2 endometrioid carcinomas with spindle cell elements are thought to be clinically similar to low grade endometrioid carcinomas that lack spindle cell elements.

“Dedifferentiated” endometrial carcinoma vs carcinosarcoma

“Dedifferentiated” endometrial carcinoma is a recently described entity that includes a well or moderately differentiated endometrioid adenocarcinoma juxtaposed with an undifferentiated carcinoma (14, 15). In contrast to carcinosarcoma, the endometrioid component is usually well-differentiated; the undifferentiated component is made of sheets of small rounded cells of uniform size instead of spindle shaped or obviously pleomorphic cells. Glandular, nested and trabecular architecture are not encountered in the undifferentiated component. Squamous, mucinous and neuroendocrine differentiation are also lacking. The undifferentiated cells frequently have a rhabdoid appearance and may be deposited in a myxoid matrix (Altrabulsi, Malpica et al. 2005). The undifferentiated component may resemble lymphoma, plasmacytoma, myxoid chondrosarcoma, small cell carcinoma or even metastatic lobular carcinoma of the breast. These cells fail to express muscle-specific markers, including markers of skeletal muscle differentiation. The undifferentiated component characteristically shows only focal keratin expression, but nearly every case exhibits strong EMA (15) and cytokeratin 18 expression in a minority of cells. From a clinical standpoint, these tumors are probably even more aggressive than carcinosarcomas, with almost universal recurrences and deaths due to disease (14). Emerging data also suggest that, unlike CS, de-differentiated carcinomas frequently demonstrate an abnormal DNA mismatch repair gene expression profile that places some of them within the spectrum of tumors encountered among patients with Lynch Syndrome/Hereditary Non-polyposis Colorectal Carcinoma Syndrome (18).

MMMT (Carcinosarcoma) references

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Carcinosarcoma/MMMT

International Society of Gynecological Pathologists
USCAP Companion Meeting 2009

Boston, MA

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Carcinosarcoma

- WHO definition:
 - Neoplasm composed of an admixture of malignant epithelial and mesenchymal components

CS, as diagnosed historically, is an extremely heterogeneous entity

Carcinosarcoma

- WHO definition:
 - Neoplasm composed of an admixture of malignant epithelial and mesenchymal components
- Sarcoma vs carcinoma
 - How do we know when we're right?
 - Do we really need to choose?
 - Precedents: breast cancer; melanoma

Carcinosarcoma

- <5% of all uterine tumors
- Median age--65 years
- Symptoms/signs: bleeding, abdominal pain, polyp
- Diagnosis: bx/curettage, hysterectomy
- Staging: like endometrial cancer
- Epidemiology: may occur following pelvic irradiation, tamoxifen

Carcinosarcoma

- Overall survival is ~35%--adjuvant therapy
 - ~50% survival stage I
 - 0-25% survival >stage II

Stage is the most important prognostic factor

Carcinosarcoma

– Clinical versus surgical staging

– Other prognostic features:

- Depth of invasion
- Lymphovascular invasion
- Tumor size
- Sarcoma histology
- Carcinoma histology and grade

Stage I carcinosarcoma study

- WHO criteria, excluding:
 - Monophasic tumors with an epithelial/mesenchymal immunophenotype

Stage I carcinosarcoma study

- WHO criteria, excluding:
 - Monophasic tumors
 - Biphasic tumors containing carcinoma without a definitive mesenchymal component

Stage I carcinosarcoma study

- WHO criteria, excluding:
 - Monophasic tumors
 - Biphasic tumors without a mesenchymal component
 - Biphasic tumors other than CS

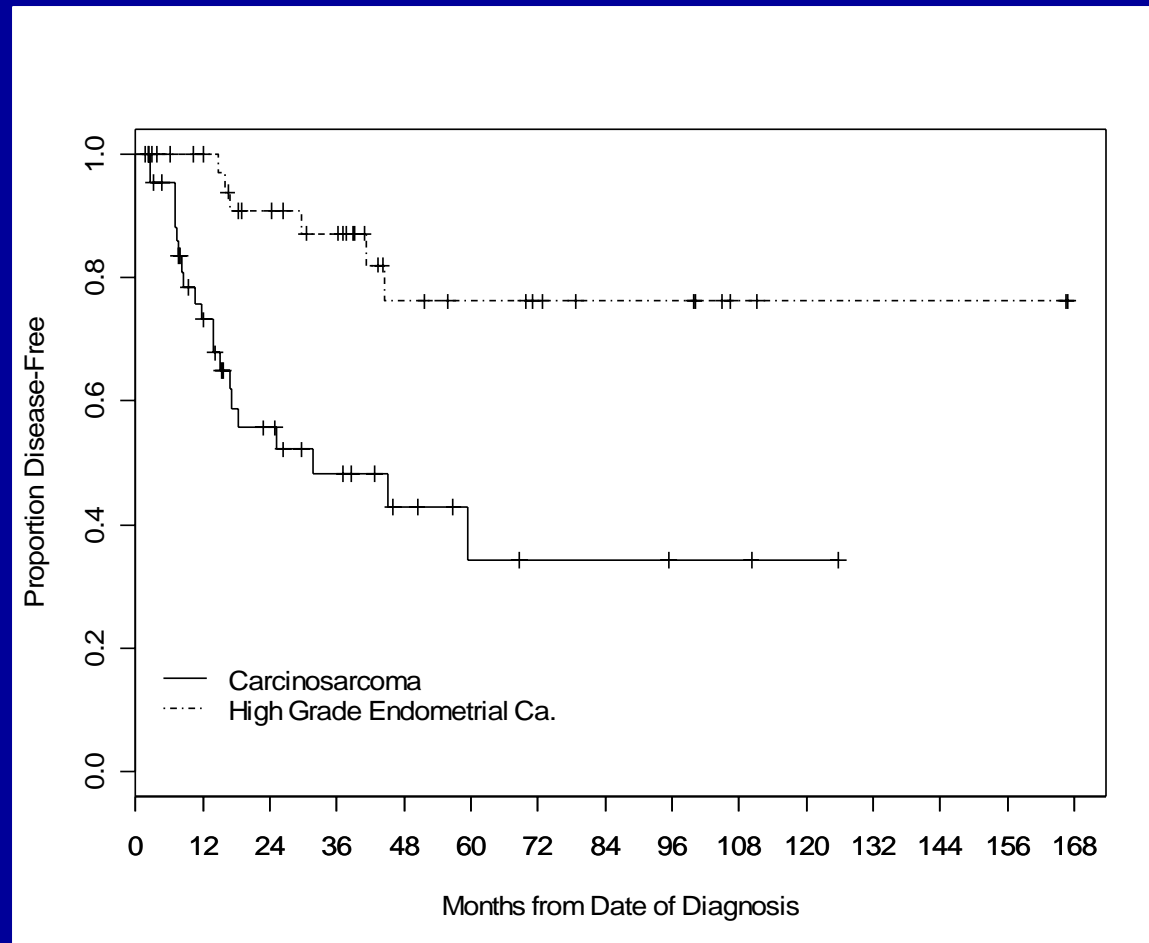
Stage I carcinosarcoma study

- WHO criteria, excluding:
 - Monophasic tumors
 - Biphasic tumors without a mesenchymal component
 - Biphasic tumors other than CS
 - Biphasic tumors that are reportedly less aggressive than CS

Stage I carcinosarcoma study

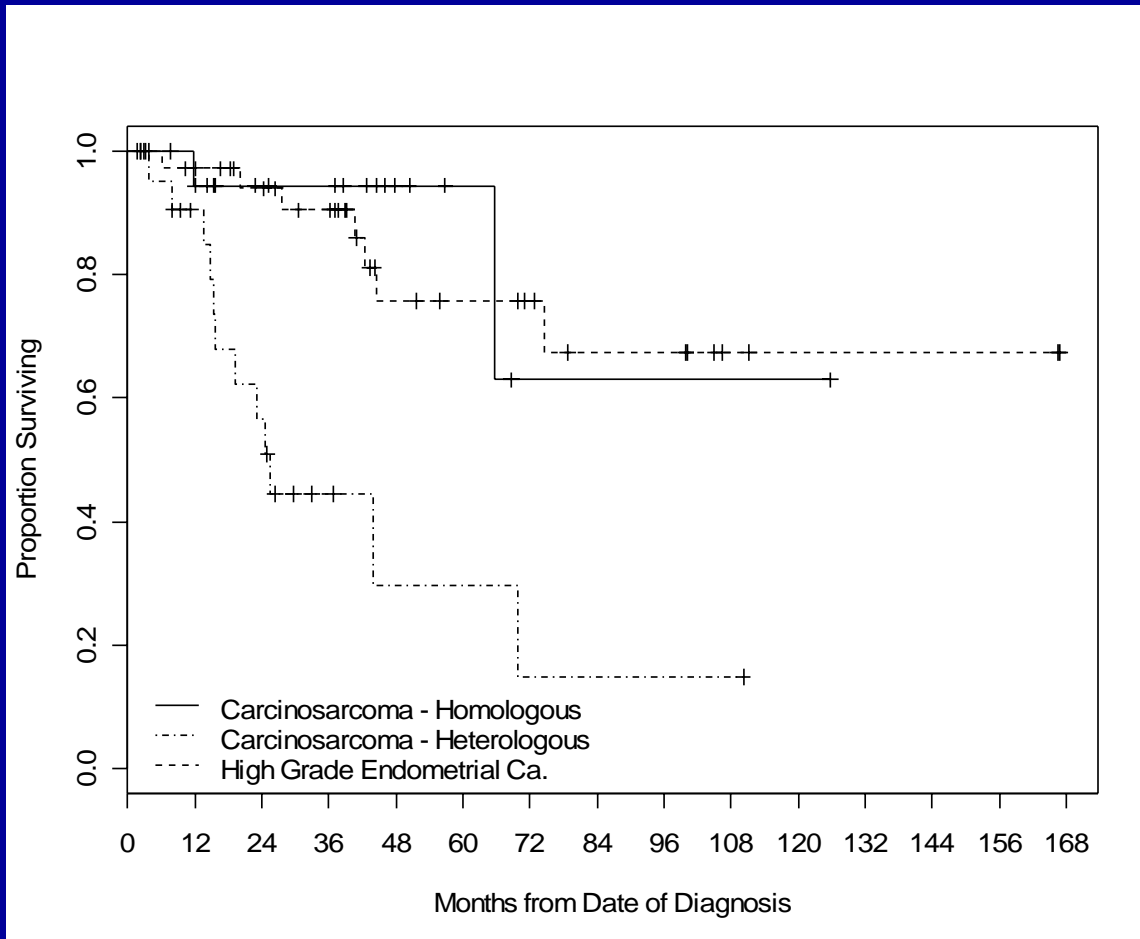
- 47 surgically staged patients
- Pathologic features of possible prognostic significance
 - Tumor size
 - Myometrial and lymphovascular invasion
 - Grade, type and prevalence of epithelial and mesenchymal components
 - Heterologous vs homologous

Carcinosarcoma vs high-grade endometrial adenocarcinoma



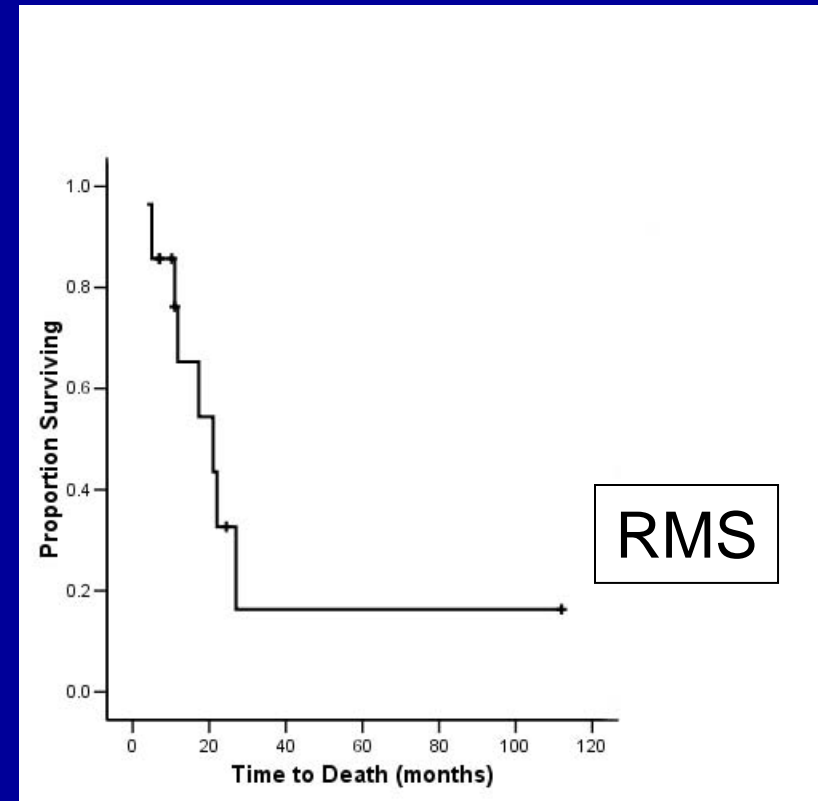
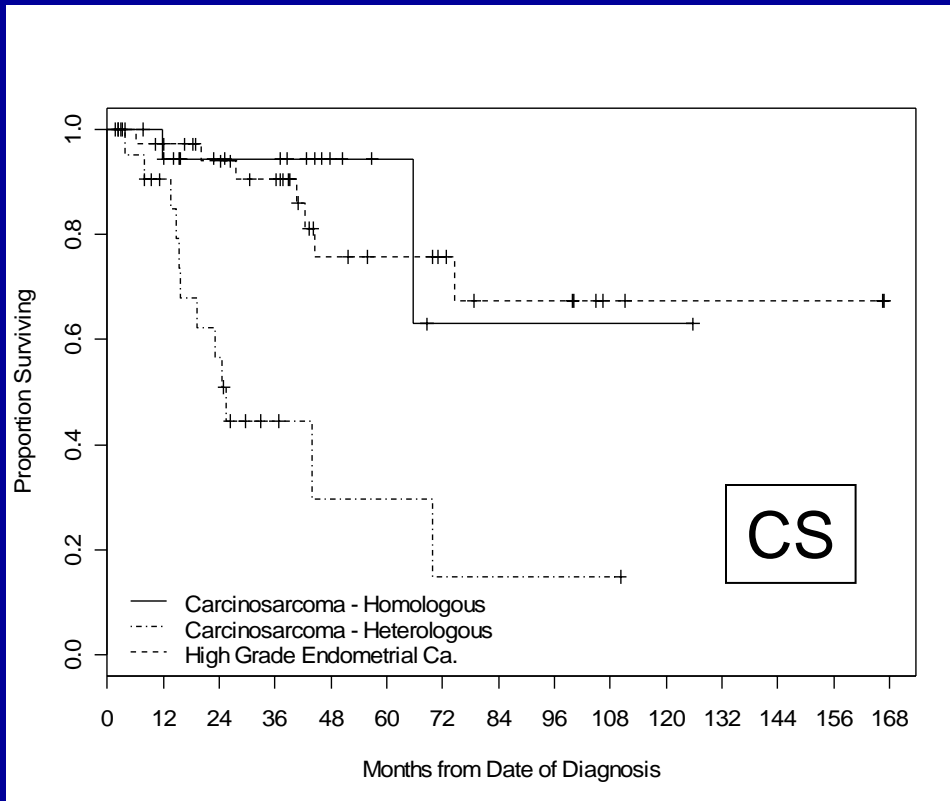
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Carcinosarcoma vs high-grade endometrial adenocarcinoma



Ferguson SE, et al. *Am J Surg Pathol* 2007 Nov;31(11):1653-61.

Heterologous CS vs Rhabdomyosarcoma



Ferguson SE, et al. *Am J Surg Pathol* 2007 Nov;31(11):1653-61

Ferguson SE, et al. *Am J Surg Pathol* 2007 Mar;31(3):382-9

Carcinosarcoma (CS)

- FIGO stage I CS with heterologous elements are highly aggressive (as aggressive as pure rhabdomyosarcoma)
- FIGO stage I CS without heterologous elements are no more aggressive than high grade endometrial carcinomas

Carcinosarcoma (CS)

- FIGO stage I CS with heterologous elements are highly aggressive (as aggressive as pure rhabdomyosarcoma)
 - Sarcoma-like?
- FIGO stage I CS without heterologous elements are no more aggressive than high grade endometrial carcinomas
 - Carcinoma-like?

Differential diagnosis

- Adenosarcoma
- Endometrioid carcinoma with spindle cell elements
- “Dedifferentiated endometrial carcinoma”
- Combined adenocarcinoma and neuroendocrine carcinoma
- Collision tumors

De-differentiated endometrial carcinoma

- Well- or moderately-differentiated endometrioid carcinoma juxtaposed with an undifferentiated carcinoma
- Endometrium>>ovary
 - Synchronous or metachronous
- Prognosis: 20/21 patients DOD or AWD

Silva EG, et al. Int J Gynecol Pathol 2006;25:52-8

Undifferentiated component

- Morphology:
 - Small, round cells; not overtly pleomorphic
 - Solid sheets; no glands, no squamous
 - Myxoid stroma and rhabdoid cells
- Immunohistochemistry:
 - Relative loss of pan-keratin and ER/PR
 - EMA, CK18 retained in minority of cells
 - Minor neuroendocrine marker expression allowed

Silva EG, et al. Int J Gynecol Pathol 2006;25:52-8

Algorithm study: secondary observations

- DNA MMR loss correlated with:
 - Personal and family history of relevant cancers
 - Lower uterine segment tumors
 - Synchronous tumors (ovarian clear cell; endometriosis-associated; colorectal)
 - De-differentiated carcinoma (5/27)
 - MLH1/PMS2 (3); MSH2/6 (2)

Biphasic tumor overview

	Mechanism	Spread	Outcome
Low grade CA* → Undiff	?cell adhesion	Like carcinoma	Dismal
LG CA → LG spindle cell	?	Like LG carcinoma	Favorable
HG CA → HG spindle cell (homologous)	EMT	Like HG carcinoma	Guarded
HG CA → HG spindle cell (heterologous)	EMT	Like HG carcinoma ? sarcoma	Highly unfavorable

*DNA mismatch repair abnormalities/MSI-H

Summary

- Homologous CS—like high grade carcinoma
- Heterologous CS—like rhabdomyosarcoma
- EC with spindle cells—like FIGO grade 1 or 2 carcinoma
- Dedifferentiated EC—like high grade carcinoma, but worse