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ULTRASOUND
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Uterine Carcinosarcomas

T.L. Sagebiel, MD, P.R. Bhosale, MD, M. Patnana, MD, S.C. Faria, MD, and C.E. Devine, MD

Uterine carcinosarcoma (UCS) is a rare and aggressive variant of endometrial cancer, distinguished by its containment of both epithelial and sarcomatous elements. This article reviews the epidemiology, pathologic classification and staging of UCS, along with the typical findings seen on different imaging modalities. Prognosis and therapies will also be discussed.
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Introduction

Carcinosarcomas, also known as malignant mixed Müllerian tumors (MMMTs), can develop anywhere in the lower female genital tract, but most commonly arise in the uterus. Uterine carcinosarcomas (UCS) are characterized by the presence of both carcinomatous (epithelial) and sarcomatous (connective tissue) elements. Previously included with uterine sarcomas, UCS is currently considered a variant of endometrial adenocarcinoma due to their similar epidemiology, risk factors, and clinical behavior.

The imaging and clinical findings of UCS are not pathognomonic and their differential diagnosis includes endometrial cancer, endometrial stromal sarcoma, and leiomyosarcoma.

UCS is rare and aggressive, with no significant improvement in patient median survival since the tumor was first described in 1940.

Epidemiology and Risk Factors

UCS is rare, accounting for less than 5% of uterine cancers, but causes greater than 16% of uterine cancer-related deaths. In the United States their incidence is 1-4 per 100,000 women.[1] UCS is more common in black women and the median age at diagnosis is between 62 and 67 years old.[2-4]

Risk factors for developing UCS are the same as endometrial cancer and include advanced age, obesity, nulliparity, exogenous estrogen use, pelvic radiation, and tamoxifen.[5-16]

The University of Texas MD Anderson Cancer Center, Diagnostic Radiology, T. Boone Pickens Academic Tower (FCT15.5023), Houston, TX.

Address reprint requests to Tara Sagebiel, The University of Texas MD Anderson Cancer Center, Diagnostic Radiology, T. Boone Pickens Academic Tower (FCT15.5023), 1515 Holcombe Blvd, Houston, TX 77030.

E-mail: tsagebiel@mdanderson.org

The relative risk of developing UCS after tamoxifen use is actually higher than risk of developing endometrial carcinoma (4.62-fold vs 2.07-fold risk increase). UCS is reported to occur at a median of 9 years after tamoxifen therapy.[13,17]

Pathology

UCS was previously considered a sarcoma subtype and classified with MMMTs of the female genital tract. UCS has a different histology than other uterine sarcomas, containing an epithelial component in addition to the shared stromal component. Their biologic behavior is also different than the other uterine sarcomas.[18,19] The revised 2009 International Federation of Gynecology and Obstetrics (FIGO) classification groups UCS with endometrial carcinomas, due to their similar risk factors and clinical behavior.[5,8,20,21]

Most current evidence supports the "metaplastic monoclonal or conversion theory", where UCS develops from the metaplastic transformation of a single neoplastic cell type.[8,22] UCS is thought to be caused by an epithelial-mesenchymal transition (EMT), which allows a polarized epithelial cell to assume a mesenchymal cell phenotype, giving it the ability to migrate away from the epithelial layer it originated.[23] The EMT theory is supported by the fact that the histological components of most carcinosarcomas share similar chromosomal abnormalities.[24,25]

In most cases, there is a single epithelial component, usually a poorly differentiated serous carcinoma. However, endometrioid, clear cell, mucinous, squamous, and undifferentiated histologies can also occur. A sole epithelial component of squamous cell carcinoma is rare. Occasionally the epithelial component contains 2 or 3 different histologies.[26]

The majority of UCS also only contains a single sarcomatous component, with high-grade stromal sarcoma being the most common. Around one-third of cases contain 2 or more sarcomatous components. In addition to stromal sarcoma

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Table 1 Primary Tumor

T Category	FIGO Stage	T Criteria
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the corpus uteri, including endocervical glandular involvement
T1a	IA	Tumor limited to the endometrium or invading less than half the myometrium
T1b	IB	Tumor invading one half or more of the myometrium
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does not include endocervical glandular involvement
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	IIIA	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes (N)		
N Category	FIGO stage	N criteria
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(*i+*)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N1mi	IIIC1	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes
N1a	IIIC1	Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2mi	IIIC2	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2a	IIIC2	Regional lymph node metastasis (greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes
Distant metastasis (M)		
M category	FIGO stage	M criteria
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intra-peritoneal disease, lung, liver, or bone). (It excludes metastasis to pelvic or para-aortic lymph nodes, vagina, uterine serosa, or adnexa)
Stage groups		
I	T1, N0, M0	
IA	T1a, N0, M0	
IB	T1b, N0, M0	
II	T2, N0, M0	
III	T3, N0, M0	
IIIA	T3a, N0, M0	
IIIB	T3b, N0, M0	
IIIC1	T1-T3, N1/N1mi/N1a, M0	
IIIC2	T1-T3, N2/N2mi/N2a, M0	
IVA	T4, Any N, M0	
IVB	Any T, Any N, M1	

FIGO, International Federation of Gynecology and Obstetrics.

these components may include rhabdomyosarcoma, chondrosarcoma, osteosarcoma, and liposarcoma.[26]

While the uterine tumor contains both elements, both local and distant metastases usually contain only the epithelial component, suggesting the epithelial component is more aggressive than the sarcomatous component.[27-30]

The epithelial components of UCS stain positive for anti-cytokeratin antibodies and epithelial membrane antigen

(EMA), while the mesenchymal elements are positive for vimentin.[31]

Clinical Presentation

UCS typically presents as a bulky, polypoid uterine cavity mass in a postmenopausal woman. Vaginal bleeding is the most common presenting symptom.[32-34] Additional initial symptoms include pelvic pain and abdominal distention from uterine enlargement. Sixty percent of patients will present with extrauterine disease and over 10% will present with distant metastases.[35,36]

Diagnostic Workup

UCS requires a histologic diagnosis, usually obtained by endometrial biopsy, since it cannot be reliably distinguished from endometrial cancer or uterine sarcoma based on imaging or clinical factors.

Laboratory Findings

Cancer antigen 125 (CA-125) can be elevated in UCS and correlates with the amount of tumor burden.[37] CA-125 can also be used to monitor for tumor recurrence.

Staging

Clinicopathological staging of UCS is done surgically according to the 2017 FIGO/Tumor, Node, Metastasis (TNM) classification system and is the same as endometrial cancer (Table 1). Almost 60% of patients initially present with metastatic disease, with the lungs, peritoneum, and pelvic and para-aortic lymph nodes as the most common sites.[38] The presence of lymphovascular space invasion (LVSI) and myometrial invasion greater than 50% are associated with a greater risk of lymph node metastases, as in endometrial cancer.[39] Cervical involvement is present in around 15% of patients.[34]

Imaging

The imaging appearance of UCS is not pathognomonic. Bharwani et al reviewed the MRI appearance of 51 pathologically confirmed uterine carcinosarcomas and found that in 88% of cases, the imaging findings were indistinguishable from those of endometrial adenocarcinoma.[40] They did find that UCS had significantly more cervical invasion and lymphadenopathy compared to endometrial cancer.[40] They also found that UCS enhanced equal to or greater than that of the myometrium, unlike endometrial cancer which tends to be hypoenhancing (Fig. 1).[40] Other imaging findings that suggest UCS are a large mass with extra-uterine extension, areas of internal hemorrhage and necrosis and dilation of the endometrial canal (Fig. 2).[20,25] Genever et al have proposed

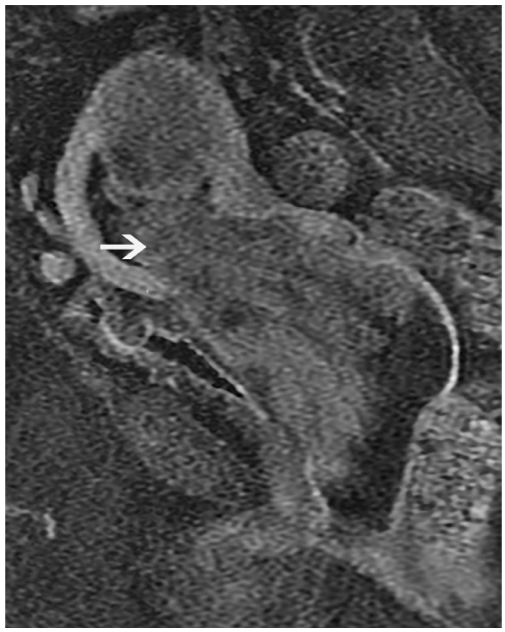

Fig. 1 Sagittal, postcontrast, T1-weighted MRI image shows the UCS (white arrow) as a large intracavitary mass with similar enhancement to the myometrium. UCS, uterine carcinosarcoma.

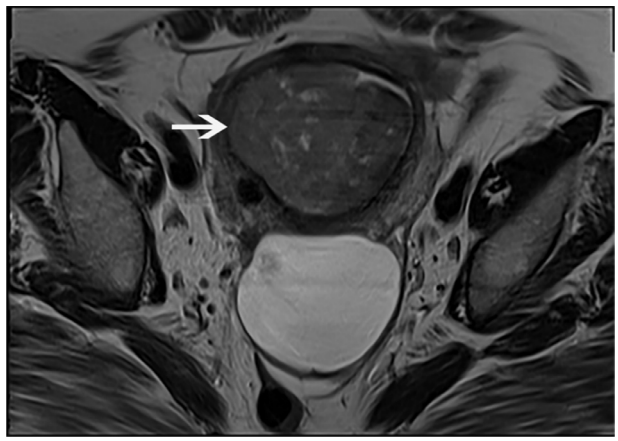

Fig. 2 Axial, T2-weighted MRI image shows the UCS (white arrow) as a heterogeneous mass with internal areas of cystic necrosis expanding the endometrial cavity. UCS, uterine carcinosarcoma.

that an anteroposterior tumor ratio >0.63 can be used to differentiate UCS from endometrial cancer.[23]

On ultrasound, UCS typically appears as an intracavitary mass that is hyperechoic to the myometrium (Fig. 3).[23,25,26] On CT, they have heteregenous enhancement and are hypoenhancing (Fig. 4).[15,25] On MRI, UCS is typically isointense to myometrium and endometrium on T1-weighted images and hyperintense to the myometrium and either hypointense or isointense to the endometrium on T2-weighted images (Fig. 5).[40] On dynamic contrast MR imaging, UCS typically enhances avidly, with both early and persistent enhancement.[41]

Imaging is not currently part of the staging process for UCS, however, imaging can provide useful information for surgical planning. Imaging can be used to detect metastatic disease, which obviates the need for complete surgical staging. CT, MRI and PET-CT can all be used for metastatic

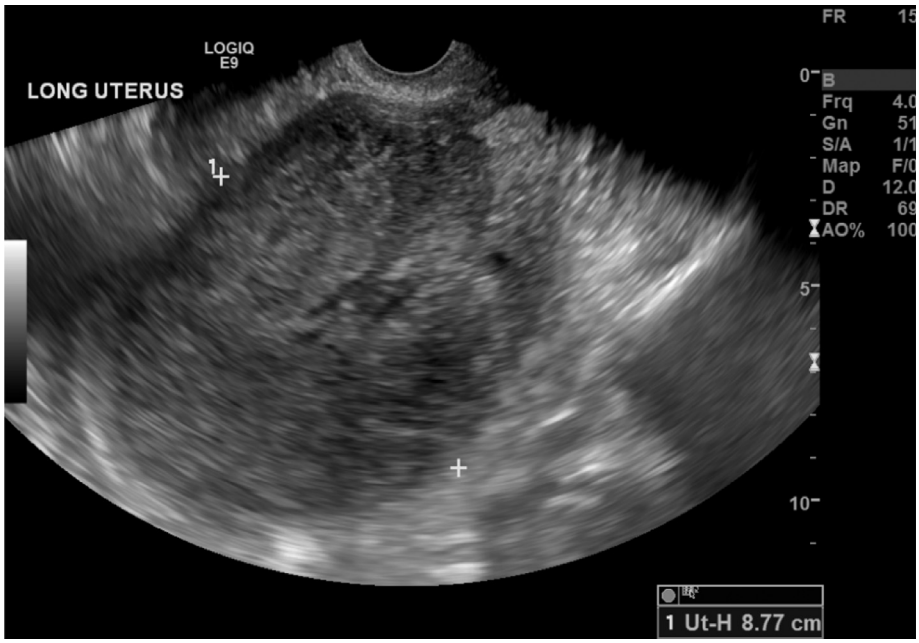

Fig. 3 Sagittal ultrasound image shows UCS as heterogeneous mass distending the endometrial cavity. UCS, uterine carcinosarcoma.

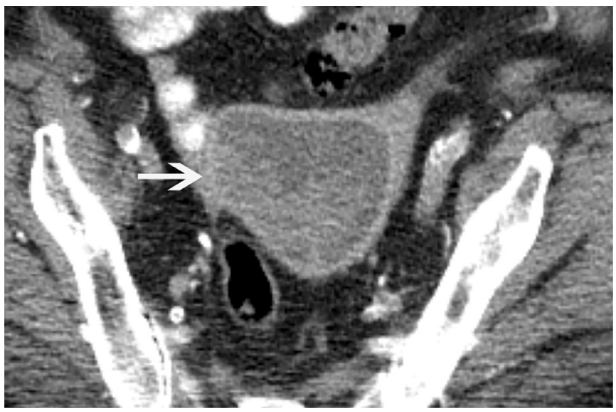

Fig. 4 Axial, contrast-enhanced CT image shows UCS (white arrow) as a heterogeneously enhancing mass that expands the endometrial cavity. UCS, uterine carcinosarcoma.

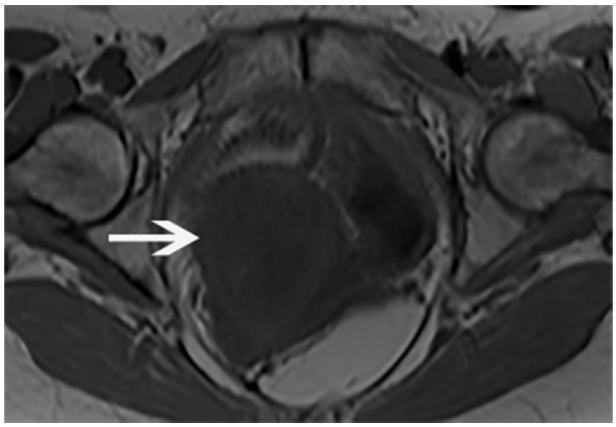

Fig. 5 Axial T1-weighted MRI image shows UCS (white arrow) has similar signal intensity to the myometrium. UCS, uterine carcinosarcoma.

evaluation (Fig. 6). Lee et al compared (18)F-FDG PET/CT with MRI and found the sensitivity of PET-CT to detect paraaortic lymph nodes was 77.8% vs 51.9% for MRI and the sensitivity for the detection of pelvic lymph nodes was 61.1% for PET-CT vs 50% for MRI.[42] PET-CT had 100% sensitivity for detecting non-nodal extrauterine metastatic disease.[42] MRI can be used to detect cervical invasion, which would determine if a radical hysterectomy needs to be performed. MRI can also provide prognostic information by determining the depth of myometrial invasion.[43]

Treatment

Treatment is based on the disease stage. The primary initial treatment of UCS without metastases or metastatic disease limited to the abdomen is surgical resection. This includes

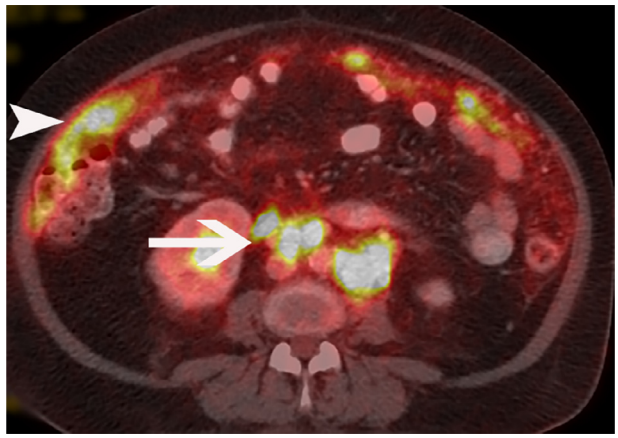

Fig. 6 Axial fused PET-CT image shows avid FDG uptake in the metastatic retroperitoneal adenopathy (white arrow) and peritoneal metastases (white arrowhead).

total hysterectomy, bilateral salpingo-oophorectomies, omentectomy, and peritoneal washings for cytology. Patients with cervical stromal invasion should have a radical hysterectomy instead of a total hysterectomy.[22]

Pelvic and para-aortic lymphadenectomy is recommended in all patients with UCS undergoing surgery, since the results not only impact staging, but may improve overall survival (OS).[39,44]

Survival outcomes and risk of recurrence are similar between minimally invasive vs open surgery for stage I and II disease.[45]

Surgical staging has limited value in patients with extra-abdominal metastatic disease and palliative therapy is recommended for these patients.

Adjuvant Therapy

Adjuvant therapy is independently associated with OS and is indicated in stages IB-IV of UCS.[46] Current adjuvant therapy recommendations are based on the Cochrane database review findings, which included 3 randomized controlled trials comprised of 579 patients that evaluated radiotherapy and/or systemic chemotherapy in the management of stage III-IV persistent or recurrent UCS. Two of the trials found that women with stage III-IV persistent or recurrent disease treated with combination chemotherapy had a significantly lower risk of disease progression and death than those who were only treated with ifosfamide. One of the trials found no significant statistical difference in the risk of disease progression and death in women treated with whole abdominal irradiation and chemotherapy. The Cochrane review concluded that radiotherapy to the abdomen is not associated with improved survival and that adjuvant combination chemotherapy with ifosfamide and paclitaxel should be considered as the primary treatment of advanced stage metastatic and recurrent UCS.[47,48] Due to the toxicities associated with ifosfamide, carboplatin are often used instead.

There is insufficient data to determine if adjuvant therapy improves the prognosis of stage 1A patients. These patients can be observed or offered adjuvant chemotherapy.[49-51]

Prognosis

UCS has a worse prognosis compared to high-risk uterine endometrial carcinoma.[52-54] The surgical stage is the most important prognostic factor for patients with UCS.[44] According to a study by Gonzalez Bosquet et al, the 5-year disease-specific survival rates were 59% for stage I/II disease, 22% for stage III disease and 9% for stage IV disease, regardless of therapy.[30] Other factors associated with a worse prognosis include the depth of myometrial invasion, LVSI, lymph node metastases and peritoneal seeding.[55]

The effect on prognosis of a heterologous sarcomatous component is controversial. One study found that the presence of heterologous sarcomatous components is a strong negative prognostic factor in patients with surgical stage I UCS, with a 3-year OS rate of 45% in women with heterologous vs 93% with homologous components.[56] Other studies did not find the presence of heterologous components to have any prognostic significance.[57,58]

Lymphadenectomy improves prognosis. A retrospective analysis of SEER data showed lymphadenectomy improved median OS in patients with stage I-III UCS from 23 to 29 months and 5-year OS from 33.4 to 35.8%.[44] Cytoreductive surgery to no gross residual disease is associated with a significantly better OS in patients with stage III and IV disease.[46,59]

Follow Up

Post-treatment surveillance for UCS is the same as endometrial adenocarcinoma. The United States National Comprehensive Cancer Network (NCCN) and the Society for Gynecologic Oncologists (SGO) recommend physical examination and review of symptoms every 3 to 6 months for 2 years, then every 6 months or annually.[22,60] If CA-125 was positive prior to therapy, it should be monitored during follow-up. Imaging with CT, MRI, or PET-CT is recommended for patients who develop symptoms or have an abnormal physical examination that suggests recurrence.[60]

Conclusion

UCS is a rare and aggressive tumor that can be indistinguishable from endometrial cancer on imaging and clinical presentation. Despite advances in therapy, survival remains poor. Imaging plays an important role in the initial surgical planning, measuring response to therapy and detecting recurrent disease.

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