Abdominal Radiology (2019) 44:2874–2885
https://doi.org/10.1007/s00261-019-02038-8

REVIEW

Uterine carcinosarcoma: a primer for radiologists

Pavitra Ravishankar[1] · Daniel A. Smith[1] · Stefanie Avril[2] · Elias Kikano[1] · Nikhil H. Ramaiya[1]

Published online: 27 April 2019

Abstract

Objective To provide a modern overview for radiologists of the unique radiological, pathological, and clinical features of uterine carcinosarcoma (UCS).

Results UCS is a unique gynecological malignancy that continues to present diagnostic and therapeutic challenges to the field of oncology. The classification and clinical understanding of this malignancy have evolved in recent years, yielding a modern conceptualization of a neoplastic entity that has been well studied but incompletely understood. As UCS causes a significant proportion of deaths secondary to uterine cancer, developing a familiarity with the imaging and clinical features of this entity is critical. In addition to summarizing the modern understanding of this tumor variant, an overview of the common imaging features of UCS will be presented. The role of radiological staging, imaging findings on presentation and follow-up imaging, and modern treatment paradigms will be discussed. Lastly, the current treatment paradigms and surveillance recommendations for UCS will be summarized.

Conclusion Knowledge of the modern understanding of uterine carcinosarcoma, including its relevant imaging and clinical features, is critical for radiologists.

Keywords Carcinosarcoma · Uterine neoplasms · Endometrial cancer · Radiologists · Diagnostic imaging · Neoplasm staging

Introduction

Uterine carcinosarcoma (UCS), also known as malignant mixed Müllerian tumor, is a rare mixed epithelial and mesenchymal tumor of the female reproductive tract composed of both high-grade sarcomatous and carcinomatous elements [1–3]. Molecular studies indicate a monoclonal origin for most UCS and favor their epithelial derivation, likely representing carcinomas from which a sarcomatous component has evolved [4–6]. With an annual incidence of 2 in 100,000, UCS represents the rarest subtype of endometrial carcinoma as well as the most aggressive. Despite the fact that less than 5% of all uterine malignancies are UCS, this diagnosis is responsible for over 15% of all deaths related to uterine cancer [7]. UCS tends to be particularly aggressive in behavior and often metastasizes to the lymph nodes and lung, in addition to various other potential locations of metastasis (Fig. 1) [3]. Outcomes for patients diagnosed with UCS tend to be relatively poor, with approximately 30–40% of all women presenting with extra-uterine disease at the time of diagnosis. Over half of all patients with UCS will develop recurrent disease despite surgery and adjuvant therapy, with limited salvage treatment options available [1]. Treatments traditionally utilized in the management of high-grade endometrial carcinoma such as platinum-based chemotherapy have shown some benefit in recurrence-free survival but no definitive improvement in overall survival.

✉ Daniel A. Smith
Daniel.Smith3@uhhospitals.org

Pavitra Ravishankar
pxr207@case.edu

Stefanie Avril
Stefanie.Avril@UHhospitals.org

Elias Kikano
Elias.Kikano@UHhospitals.org

Nikhil H. Ramaiya
Nikhil.Ramaiya@UHhospitals.org

1 University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH 44106, USA

2 Department of Pathology, Case Western Reserve University School of Medicine, University Hospitals Cleveland Medical Center and Case Comprehensive Cancer Center, 10900 Euclid Ave, Cleveland, OH 44106, USA

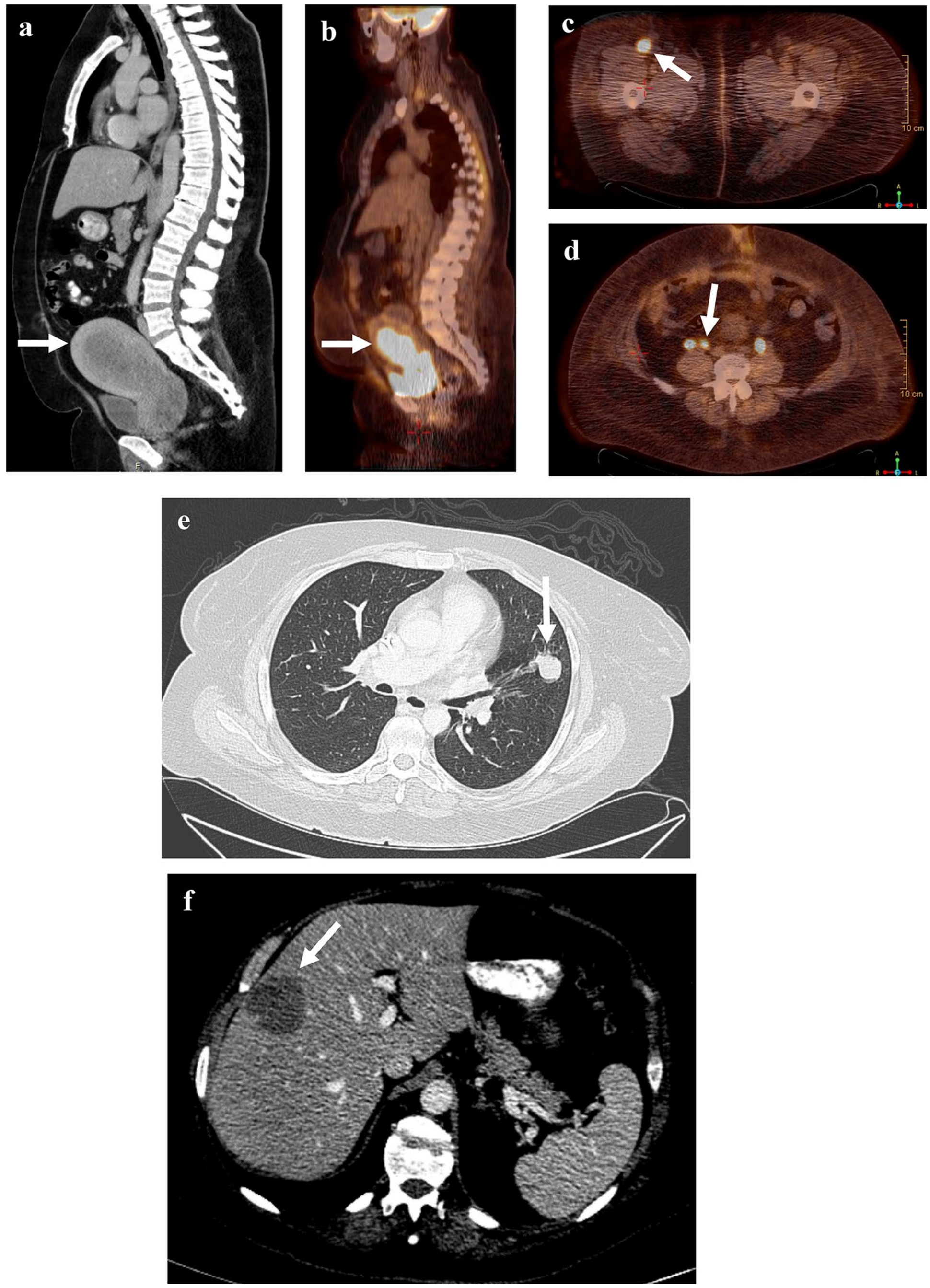

Fig. 1 44-year-old woman presenting with heavy vaginal bleeding and severe anemia; diagnosed with stage III carcinosarcoma of the uterus. **a** Sagittal contrast-enhanced CT image demonstrates an enlarged and heterogeneously enhancing uterus (white arrow). **b** Sagittal PET/CT image shows an enlarged uterus with intensely high hypermetabolic activity (maximum SUV of 24) involving the uterus, cervix, and vaginal region (white arrow). **c**, **d** Axial images of the same PET/CT study demonstrate an intensely FDG-avid right inguinal lymph node (white arrow c, maximum SUV of 21) and a hypermetabolic right paracaval lymph node (white arrow in d, maximum SUV of 7.4), suggestive of lymph node metastases. **e**, **f** Axial contrast-enhanced CT images obtained 7 months later after pelvic external beam radiation and six cycles of carboplatin/paclitaxel demonstrate a new 2 cm metastatic pulmonary nodule in the left upper lobe (white arrow in e) and a 4 cm metastatic lesion in hepatic segment 8 (white arrow in f)

Recent molecular studies hold some promise and may provide a path to counter the poor prognosis of UCS with targeted treatments [4].

Characterized by a unique and continuously evolving classification over the years, UCS is a neoplasm that remains well-studied but incompletely understood. In this review, we provide a comprehensive discussion of the staging, diagnostic workup, and treatment of UCS, with an emphasis on the role of imaging in UCS management. This review will thus function as a radiologist's guide to the critical imaging, pathological, and clinical features of this unique gynecological malignancy. In addition to describing the historical and modern classification of UCS, an emphasis will be placed on the radiological presentation of UCS on initial and follow-up imaging. An array of cases will be presented to highlight the distinctive imaging features of UCS. Methods of staging via imaging will also be described, as well as a discussion of the modern treatment paradigms of this unique malignancy.

Overview of UCS: pathological classification and clinical features

UCS almost exclusively occurs in post-menopausal women during the 6th and 7th decades of life, with a higher incidence in African American women [1, 7]. Similar to endometrial carcinoma, exposure to prior pelvic radiation, exogenous estrogen, tamoxifen therapy, nulliparity, and obesity are considered risk factors for the development of UCS [8, 9]. UCS most commonly arises from the uterus but, in rare cases, may originate from the fallopian tube, cervix, or peritoneum [2]. A recent comprehensive molecular characterization of 57 patients with UCS demonstrated that UCS share molecular features and genomic alterations with other high-grade endometrial carcinomas, in particular high-grade serous carcinomas [4]. *TP53* mutations were identified in 91% of tumors. Additionally, about half of UCS demonstrate mutations in PI3 K pathway genes, most commonly *PIK3CA* (35%), which hold potential as sites for targeted therapies [4].

There are two prevalent hypotheses for the tumorigenesis of carcinosarcoma, including "multiclonal" and "monoclonal" models. Traditionally, as per the multiclonal hypothesis, UCS was considered to be a subset of uterine sarcomas and believed to possess two distinct cellular origins [1, 4, 10]. However, advances in the understanding of underlying molecular alterations and tumor behavior, including the lack of hematogenous spread, have shifted support towards the monoclonal hypothesis [4]. Multiple genetic studies of DNA mutation patterns have found distinct similarities between the carcinomatous and sarcomatous components of resected specimens. Whole-exome sequencing of carcinosarcomas has suggested that these components are derived from a common precursor with classical carcinoma-associated mutations. Mutations that have been found to be frequently present in carcinosarcomas include carcinoma-associated mutations in *TP53*, *PIK3CA*, *PTEN, KRAS, PPP2R1A*, *CHD4*, and. *BCOR*. Alterations in the expression of histones H2A/H2B have also been linked to the development of carcinosarcoma [11].

UCS was reclassified as a high-risk endometrial carcinoma variant in 2009, prompting adjustment in the current trajectory of medical practice to reflect this decision. UCS is postulated to arise from a single-malignant epithelial clone that proceeds to undergo epithelial–mesenchymal transition or trans-differentiation to form the sarcomatous element of UCS tumors [4, 5, 11, 12]. Histologically, UCS is a biphasic tumor characterized by the presence of distinct carcinomatous and sarcomatous components which are usually, at least focally, intimately admixed (Fig. 2). The carcinomatous component most commonly comprises of high-grade serous, endometrioid or nonspecific adenocarcinoma. The sarcomatous component is usually high-grade and can be either homologous, resembling undifferentiated uterine sarcoma, or heterologous. Heterologous sarcomatous elements, including rhabdomyosarcoma, chondrosarcoma, and osteosarcoma, are present in about 50% of cases and have been inconsistently associated with a worse prognosis. Histologic diagnosis mainly relies on thorough morphologic evaluation and comprehensive sampling to detect both the carcinomatous and sarcomatous components, since one or the other may predominate.

Currently, it is not possible to distinguish UCS from endometrial carcinoma by clinical features alone. Patients often present with a classic symptomatic triad of abnormal uterine bleeding, pain, and a rapidly enlarging uterus [13]. UCS classically presents as a sizable polypoid mass that may protrude through the cervix and, in rare cases, trigger inversion of the uterus UCS frequently displays lymphatic spread, a common finding in advanced stages of both uterine carcinomas and uterine sarcomas [13, 14]. Though UCS is considered to behave like type II high-grade endometrial carcinomas, it demonstrates higher rates of lymphatic spread, peritoneal seeding, and pulmonary metastasis [15, 16]. Over 10% of patients will present with metastatic disease, and up to 15% will have involvement of the cervix, visible through endocervical curettage or cervical biopsy [17]. Extrauterine nodal spread is common at time of presentation, and many cases are upstaged during surgery due to lymph node metastasis [14]. The differential diagnosis of UCS includes other high-grade endometrial carcinomas, including endometrioid, serous, clear cell, and dedifferentiated carcinomas, and mesenchymal uterine malignancies such as adenosarcoma, leiomyosarcoma, and undifferentiated uterine sarcoma [13].

Staging and workup: the role of imaging and surgical staging

Stage of disease at the time of diagnosis is consistently the most important predictive factor of survival of UCS. 5-year survival rates for early stage (FIGO stage I/II) have been reported with ranges up to 47%, dropping as low as 10% with further progression of disease [1, 2, 16]. Following recent reclassifications, UCS is surgically staged in accordance with the 2017 International Federation of Gynecology and Obstetrics (FIGO) Tumor, Node, Metastasis (TNM) classification system. In concordance with our shifted understanding of the origins of UCS, this is the same system as for endometrial carcinoma. According to the National Comprehensive Cancer Network (NCCN), initial work-up of UCS should begin with endometrial and cervical biopsy and histological examination. If a high-risk uterine malignancy is suspected, additional workup to evaluate for extrauterine

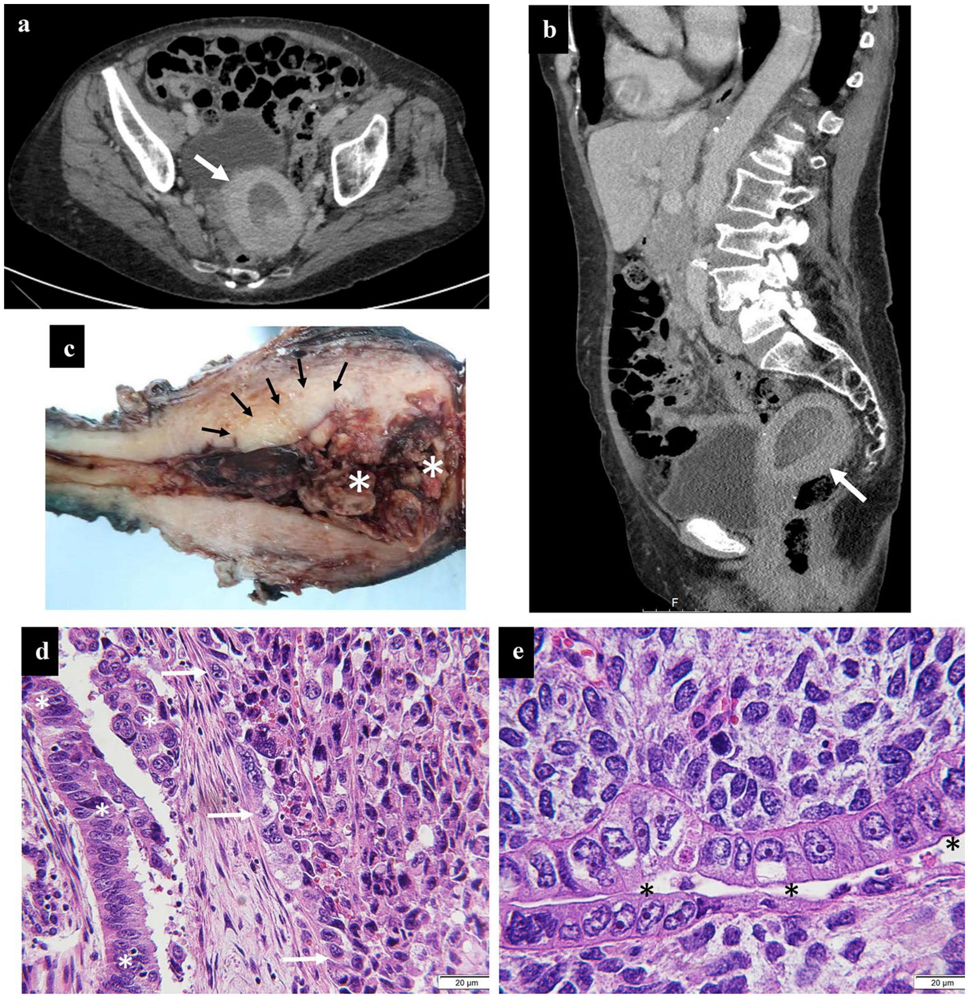

Fig. 2 64-year-old female diagnosed with uterine carcinosarcoma. **a**, **b** Initial contrast-enhanced axial and sagittal of the abdomen/pelvis at the time of diagnosis demonstrates marked thickening of the endometrial canal (arrows) measuring up to 3.1 cm. The patient subsequently underwent total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic sentinel lymph node dissection. **c** Macroscopic image status post resection shows a polypoid, exophytic, partially hemorrhagic and necrotic tumor mass within the uterine cavity (stars) with invasion into the inner half of the myometrium (arrows). **d** Photomicrograph (H&E ×100 magnification) showing the characteristic biphasic tumor growth pattern comprising of a high-grade carcinomatous (left side of image, stars) and high-grade sarcomatous tumor component (right side of image, arrows). **e** High-power magnification (H&E x400 magnification) showing a malignant gland with high-grade serous phenotype (carcinomatous component) in the lower center of the image (stars), surrounded by the high-grade sarcomatous component (top and bottom of image)

disease in the form of chest/abdominal/pelvic CT is recommended, along with CA-125 screening. MRI and PET/CT is recommended in the evaluation of suspected extrauterine disease.

The standard comprehensive staging procedure consists of total hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, peritoneal/serosal/omental evaluation, and pelvic and para-aortic lymphadenectomy. Maximal tumor debulking is strongly recommended for gross disease. Adjuvant chemotherapy, either with or without the addition of external beam radiation therapy or vaginal brachytherapy, is the preferred method of treatment for any stage of disease [18]. Staging is done primarily on a surgical and histologic basis, although studies have shown imaging to be capable of accurately delineating the extent of local and extra-uterine disease. Around 20% of Stage I/II tumors are upstaged at surgery due to the presence of lymph node metastases. Overall, pelvic or para-aortic lymph node metastases are detected in 35% of patients at presentation [19]. The presence of vaginal or parametrial involvement, invasion of the adnexa, or invasion of the uterine serosa also upstages a tumor to stage III [7]. Lymphadenectomy is the primary method used to assess nodal disease and is an integral part of standard comprehensive staging, conferring survival benefit even in early stages of UCS [8]. A positive lymphadenectomy upstages UCS tumors of any size to stage IIIC, which is defined as the presence of positive pelvic lymph nodes (IIIC1) or positive para-aortic lymph nodes (IIIC2) (Fig. 1) [20].

Though not formally included in FIGO staging, imaging is used at many institutions as an integral part of the pre and post-surgical evaluation of UCS [20]. MRI and PET/CT show potential to be used to determine the preoperative presence of lymph node metastasis [21, 22]. Additionally, imaging modalities have shown significant utility in planning adjuvant therapies. However, the validity of these findings is difficult to determine due to the low incidence of UCS and deficit of the available data.

For radiologists interpreting initial imaging studies for UCS, it is critical to have an understanding of staging criteria. Stage I tumors are defined as being confined to the corpus uteri. Stage IA tumors display less than half myometrial invasion while, stage IB tumors demonstrate invasion to half or more than half of the myometrium. Stage II tumors invade the cervical stroma but do not extend beyond the uterus [23]. Sonography is often the first-line imaging study in cases of suspected uterine malignancies, though typically as an initial assessment modality rather than for staging. Stage I and II tumors classically present on ultrasound as hyperechoic masses relative to the endometrium and may show expansion of the endometrial canal. Abnormal thickening and heterogeneous appearance of the endometrial lining are common findings on pelvic ultrasound (Fig. 3). However, these findings are not pathognomonic for UCS, and findings on ultrasound cannot be used to distinguish between UCS and other endometrial carcinomas [24].

On cross-sectional imaging, stage I and II UCS appears as heterogenous masses and typically have a greater craniocaudal width than other endometrial carcinomas (Fig. 4) [13]. These tumors typically present as ill-defined hypodense masses on CT, and dilation of the endometrial cavity is detectable in the majority of cases. A study with 14 UCS patients by Tao et al. described concomitant dilation in 12 patients when imaged by CT [24].

Due to the excellent contrast of normal-zonal uterine anatomy, malignancies of the uterus are best identified with MRI, with particular utility of T2-weighted imaging. Endometrial carcinoma is usually isointense relative to normal endometrium on T1-weighted images and hypointense to the endometrium on T2-weighted images (T2WI) [20]. Early and persisting enhancement can be seen within areas of sarcomatous differentiation, a feature that distinguishes UCS from endometrial adenocarcinoma. A study by Kamishima et al. with 52 patients demonstrated that inhomogeneity on T2WI, higher predominant signal intensity on T2WI compared to muscle, and the presence of hyperintense areas on T1WI compared to myometrium were significant predictors of carcinosarcoma on unenhanced MRI [25]. Upon administration of gadolinium contrast, UCS tumors demonstrate slower enhancement relative to the surrounding myometrium on T1WI. UCS tumors demonstrate high-signal intensity on diffusion-weighted images, similar to other endometrial tumors, and low-signal intensity on ADC maps [17, 20].

Specific imaging-based measurements on MRI may also aid in diagnosing UCS. For example, one analysis of MRI characteristics in UCS found that a 0.63 ratio of anteroposterior uterine dimension to endometrial thickness was the optimal cutoff for distinguishing UCS from endometrial adenocarcinoma [26]. This same study also found significant differences in absolute anteroposterior and longitudinal uterine measurements between UCS and endometrial adenocarcinoma. Other quantitative features on MRI may also be useful from a prognostic standpoint. For example, one analysis of MRI features of pathologic necrosis found that the presence of greater than 10% unenhanced region on MRI is a predictor of poor prognosis for UCS [10].

Due to the morbidity associated with lymphadenectomy, multiple studies have examined alternatives to total surgical removal with a focus on FDG PET/CT and sentinel lymph node mapping (SLNM). While the role of SLNM in endometrial carcinoma has not been explored in depth, a significant amount of literature can be pooled, testifying to the benefit of minimally invasive nodal disease detection. In a retrospective study of 136 UCS patients who underwent either SLNM or pelvic lymphadenectomy, Schiavone et al. found that patients in both categories experienced similar patterns of multifocal distant recurrence (70% to 74%), suggesting that progression free survival might be maintained with minimally invasive SLNM rather than lymphadenectomy. However, this study was limited by short follow-up times, and further studies with longer follow-up are required to validate these early results [3].

UCS tumors are typically positive on FDG PET/CT, demonstrating increased FDG uptake. FDG PET/CT is well known to be highly sensitive to the detection of regional node metastasis in many conditions and has been used for endometrial carcinoma staging. In a study that included 57 patients with biopsy-proven UCS, Lee et al. showed FDG CET/PET to be more sensitive (68% vs 50%) but less specific (88% vs 93%) than MRI at predicting lymph node metastasis. However, the investigators concluded that the potential of missing micro-metastatic disease due to the lower sensitivity was too great a risk and that lymphadenectomy should remain the default modality for nodal assessment [22]. Despite these limitations, FDG PET/CT may be useful for initial staging in patients who present with locally advanced or metastatic disease.

PET/MRI is also emerging as a promising modality for the evaluation of endometrial cancer with potential applications for the evaluation of UCS (Fig. 3). Although PET/CT is a superior method for detecting metastatic spread elsewhere in the body, MRI is capable of better delineating pelvic anatomy and evaluating extent of local disease for

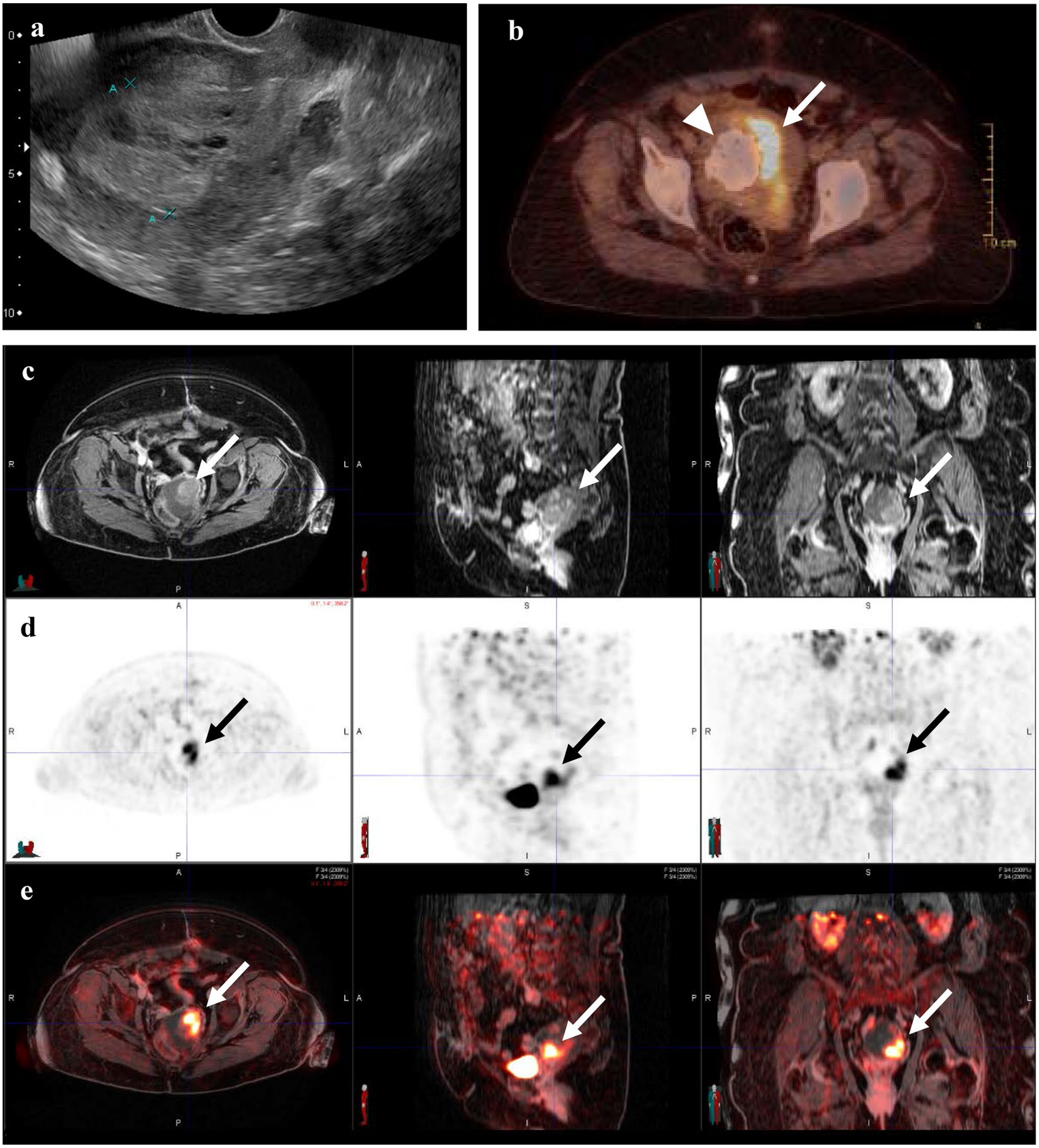

Fig. 3 72-year-old woman presenting with post-menopausal bleeding; diagnosed with stage IA carcinosarcoma of the uterus. **a** Transvaginal ultrasound demonstrates an abnormally thickened and heterogenous endometrial lining (blue markers). **b** Axial PET/CT image of the pelvis shows hypermetabolic activity (maximum SUV of 4.2) in the endometrial canal at time of diagnosis (white arrow); an adjacent fibroid is also seen (arrowhead). The patient subsequently underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, external beam radiation to the upper vagina, CyberKnife radiosurgery, and multiple cycles of carboplatin/paclitaxel and doxorubicin. **c**, **d**, **e** Post-contrast T1W (**c**), PET (**d**), and T1W PET/MR fusion images obtained 12 months later demonstrate local recurrence with identification of a FDG-avid mass (maximum SUV of 4.8) in the cul-de-sac within the surgical bed (arrows), tethered to the vaginal cuff. This mass demonstrates mixed solid and cystic components and was found to abut the bladder wall and rectum

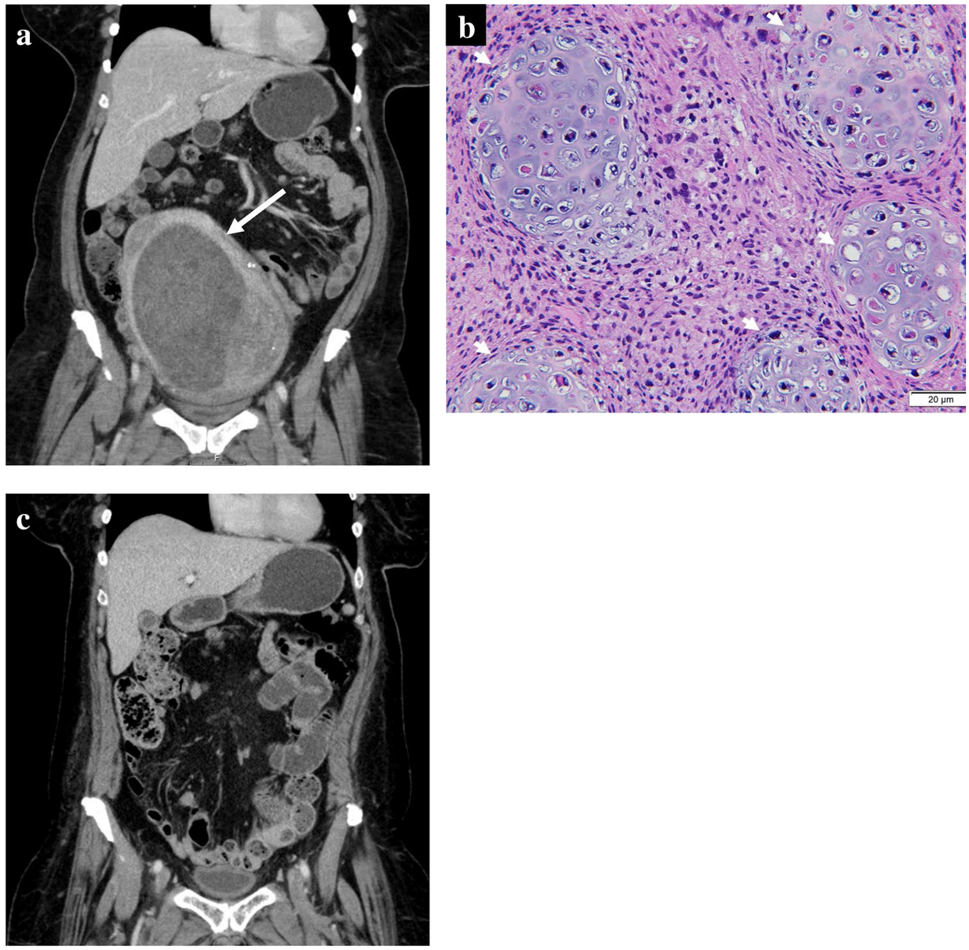

Fig. 4 62-year-old woman presenting with post-menopausal bleeding, hematuria, abdominal discomfort; diagnosed with stage IIIC1 carcinosarcoma of the uterus. **a** Coronal contrast-enhanced CT image of the pelvis demonstrates a large heterogenous mass measuring 11 × 14 × 20 cm which replaces the uterus and fills the endometrial canal (white arrow). **b** The sarcomatous tumor component of this case comprised heterologous chondrosarcomatous elements. Arrowheads indicate islands of malignant cartilage within the homologous high-grade sarcomatous tumor component. **c** Coronal contrast-enhanced CT image of the pelvis demonstrates no evidence of disease recurrence 3 years following radical hysterectomy & bilateral salpingo-oophorectomy and treatment with nine cycles of carboplatin/paclitaxel and pelvic radiotherapy

endometrial cancers [27]. A recent study by Kitajima et al. demonstrated that PET/MRI detected approximately 97% of primary endometrial tumors, compared to 93% for PET/CT [28]. This same study found that PET/MRI has superior accuracy for evaluation of primary tumor extent (T stage) relative to PET/CT and similar accuracy for the detection of pelvic nodal metastases.

Stage IV disease is defined as the presence of distant metastasis, including intraabdominal metastases and/or inguinal lymph nodes, or invasion of the bladder and bowel mucosa [23]. Metastasis has been described in virtually every organ, typically seen as metabolically active lesions on FDG PET/CT [7]. Distant metastasis of UCS most frequently affects the lungs (49% of UCS cases), followed by the peritoneum (44%) [19]. Hepatic and osseous metastatic disease occur with estimated incidence of 15% and 17%, respectively [29]. Although less common, metastases to the central nervous system can also be seen in approximately 8% of patients with metastatic UCS, which portends a poor prognosis (Fig. 5). While MRI is the primary method of imaging the uterus in carcinosarcoma, CT is typically preferred for staging, follow-up, and evaluation of distant metastases [30].

Treatment and management

Treatment of UCS typically follows a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. Knowledge of these treatment strategies is critical for radiologists tasked with interpreting follow-up imaging in UCS patients. Surgery remains uncontested as the cornerstone of UCS treatment, as the ideal standard of care for surgical candidates is radical removal of the reproductive tract [18]. Although there is a lack of consensus regarding treatment, UCS patients who are surgical candidates typically undergo total hysterectomy and bilateral salpingo-oophorectomy with surgical staging. Local recurrence is generally managed with radiotherapy or systemic chemotherapy. Both treatment options are typically pursued as an adjuvant course, although specific treatment regimens greatly differ between physicians [1, 18]. For patients with a single-metastatic CNS lesion, treatment with surgical removal of the tumor or stereotactic radiosurgery, followed by adjuvant whole brain radiotherapy, is the standard treatment [31]. In contrast, patients with multiple CNS metastases typically pursue palliative treatment with steroids and whole-brain radiation. As with other stages of UCS, combination

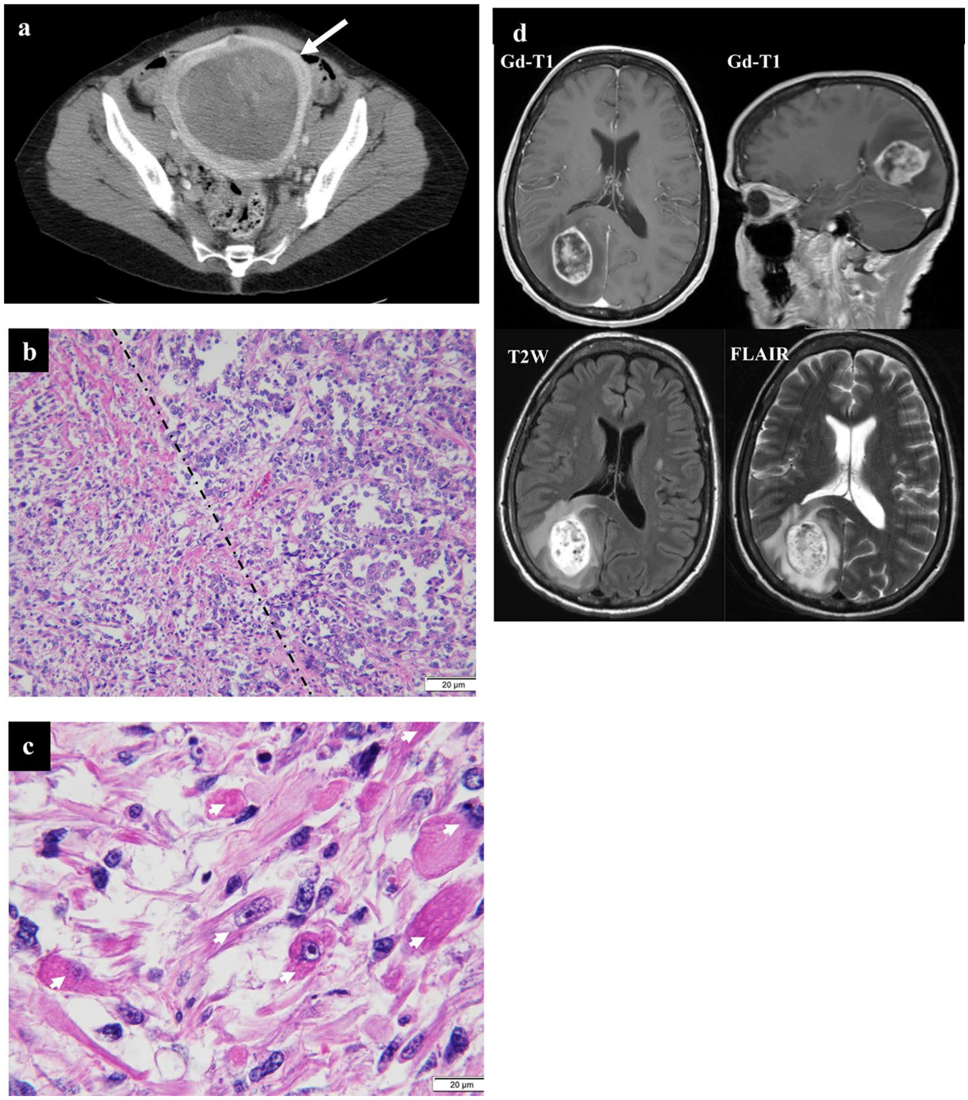

Fig. 5 57-year-old woman presenting with post-menopausal bleeding; diagnosed with stage IIIC1 carcinosarcoma of the uterus. **a** Axial contrast-enhanced CT image of the pelvis reveals a large 12 cm mass (white arrow) extending from the anterior surface of the uterus with central heterogeneous appearance consistent with central necrosis. Pathology confirmed the diagnosis of carcinosarcoma. **b** Microscopic examination (H&E ×100 magnification) revealed a combination of carcinomatous/glandular (upper right) and sarcomatous (lower left) tumor components, diagnostic of carcinosarcoma. **c** H&E ×400 magnification images show the sarcomatous component of this case with focal rhabdomyosarcomatous differentiation indicated by atypical spindle cells and abundant eosinophilic cytoplasm and cross-striations (stars). **d** Gadolinium contrast-enhanced brain MRI obtained after the patient presented with visual changes 7 months following total abdominal hysterectomy, bilateral salpingo-oophorectomy, and 5 cycles of carboplatin/paclitaxel with vaginal cuff brachytherapy. Post-contrast T1 axial and sagittal, T2 axial, and FLAIR axial images demonstrate a solitary 4 cm enhancing lesion in the right parieto-occipital region with heterogeneous intrinsic FLAIR signal and patchy foci of heterogeneous enhancement. There is considerable perilesional FLAIR hyperintensity with associated mass effect concerning for vasogenic edema. A right parieto-occipital craniotomy with resection of the mass was performed; pathology confirmed metastatic endometrial carcinosarcoma

chemotherapy regimens are also indicated for most of these patients seeking to pursue treatment. Recurrence rates can be as high as 60% and are typically linked to initial staging of the disease [1].

There exists a great deal of debate in the literature surrounding which adjuvant therapy regimen is most effective. While it is agreed that adjuvant therapy conveys a significant progression-free survival (PFS) advantage, most studies have been unable to demonstrate improved overall survival (OS), and the relative benefit of radiotherapy or chemotherapy vs combined therapy is still uncertain. One study involving 111 UCS patients found that while administration of adjuvant therapy was associated with a significant progression-free survival (PFS), there was no significant differences between specific adjuvant therapies (radiotherapy, chemotherapy, or combined therapy) [32]. Moreover, within chemotherapy regimens, debate continues as to the most efficient combination of systemic chemotherapy agents. Due to the rarity of UCS and subsequent difficulty of conducting randomized controlled trials, few studies have been able to conclusively establish a single-treatment regimen as superior. Despite this, advances in the understanding of UCS tumorigenesis from endometrial carcinoma and the findings of molecular profiling studies provide directions for future research into UCS treatment.

Radiotherapy

While multiple studies have found the use of radiotherapy to be associated with increased PFS and improved locoregional control, no study to date in the literature has been able to establish an overall survival advantage for radiotherapy [32, 33]. In a study that included 235 patients that underwent radiotherapy, along with brachytherapy and/or pelvic radiotherapy, investigators found that RT and non-RT groups had similar outcomes as defined by PFS [33]. Although no significant associations have been found, a phase II prospective trial by the Gynecologic Oncology Group (GOG) with 232 UCS patients did see slightly better overall and progression-free survival in patients who underwent chemotherapy over radiotherapy. These associations were not statistically significant but could hold clinical significance regarding the future use of radiotherapy in UCS management. However, the focus of UCS adjuvant therapy appears to be shifting towards new chemotherapy or combined therapy modalities, given their greater success in treating these aggressive malignancies.

Chemotherapy

While surgery remains the mainstay of UCS treatment, adjuvant chemotherapy has shown superiority to radiotherapy in randomized controlled trials. However, given the relative rarity of UCS, there exists limited data as to the effectiveness of individual chemotherapy regimens [34, 35]. Given the low incidence of UCS, prospective trials of chemotherapeutic treatments have been difficult to conduct, and the preferred first-line chemotherapy for UCS tumors remains unknown. Due to the high rates of recurrence in these tumors, UCS was historically treated with the first-line therapy of uterine sarcomas: ifosfamide/paclitaxel. Multiple phase III trials have underscored the benefit of combination ifosfamide therapy compared to ifosfamide monotherapy [36, 37].

Phase II studies investigating the efficacy of paclitaxel/carboplatin regimens in managing UCS have demonstrated reduced toxicity and moderate tumor reduction with this approach as compared to traditional ifosfamide-containing regimens [38–40]. A retrospective study examining the role of taxane-platinum combination therapy, a traditional treatment for endometrial carcinoma, in first-line salvage chemotherapy compared outcomes of multi-agent therapies in 148 UCS patients with recurrent disease. The investigators, Matsuo et al., found that patients who underwent taxane-platinum doublet treatment as compared to other multi-agent approaches experienced a 2-year increase in survival after recurrence [41]. These results form the basis of a prospective phase III randomized controlled trial conducted by the GOG examining the relative effectiveness of paclitaxel/carboplatin over ifosfamide/paclitaxel therapies [1, 41]. Given the prognostic benefits of paclitaxel/carboplatin regimens as demonstrated in retrospective studies like those by Bracknell et al. and their more favorable toxicity profile compared to ifosfamide regimens, clinicians have continued to treat UCS patients with adjuvant paclitaxel/carboplatin treatment as the commonly preferred therapy.

For patients with advanced stage or recurrent disease, chemotherapy is recommended. Despite this, tumors are frequently resistant to treatment, and alternatives to ifosfamide or paclitaxel approaches are scarce [7]. Recent molecular studies of UCS have identified common alterations in the PI3 K/AKT/MTOR pathway, holding promise for future targeted therapies such as PI3 K inhibition or anti-*HER2* treatment, although much work is still required before targeted therapies can be developed [4, 42, 43].

Potential multi-modality therapies are still being examined to date, such as therapies involving chemotherapy regimen sandwiched between two rounds of radiotherapy [44]. One study with 15 UCS patients found that administration of a carboplatin–paclitaxel regimen for four weeks followed by brachytherapy-whole pelvic radiotherapy was associated with an increase in 3-year overall survival when compared to chemotherapy alone [45]. Another such study with 121 UCS patients did not find any significant benefit to combined modality therapy [46]. More prospective studies comparing the effectiveness of combined modality therapy to specific chemotherapy and radiotherapy regimens are needed to conclusively determine the effectiveness of this treatment plan.

Follow-up and prognosis

Once the initial diagnosis of UCS is made, patients will require close follow-up, regardless of disease state, given the high potential for local recurrence and distant metastasis. Recurrence risk is increased with larger tumor size, increased tumor stage upon presentation, presence of lymphovascular invasion, and increased myometrial invasion [9, 14]. Surveillance commonly constitutes a physical exam and vaginal cytology every 3 months for 2 years followed by every 6 months for 5 years. While the optimal role of imaging follow-up has not been clearly defined, NCCN guidelines recommend basing imaging on symptomology and clinical concern for recurrent or metastatic disease. For patients with treated FIGO stage III/IV UCS, an optional full-body or pelvic CT is recommended every 6 months for 3 years followed by 6–12 months intervals for 2 years. Radiological follow-up is critical for these patients, as UCS recurs in approximately 50% of all patients (Fig. 6) [1, 7]. If there is clinical concern for recurrence or metastasis, abdominal/pelvic or chest CT is recommended. Whole-body PET/CT should be considered in select patients who are good candidates for locoregional therapy or surgery [18].

Local recurrence of UCS is commonly managed with systemic chemotherapy, both single agent and combination regimens [2, 7]. Metastatic recurrences may demand the use of multi-modal therapies, though no clear treatment algorithm

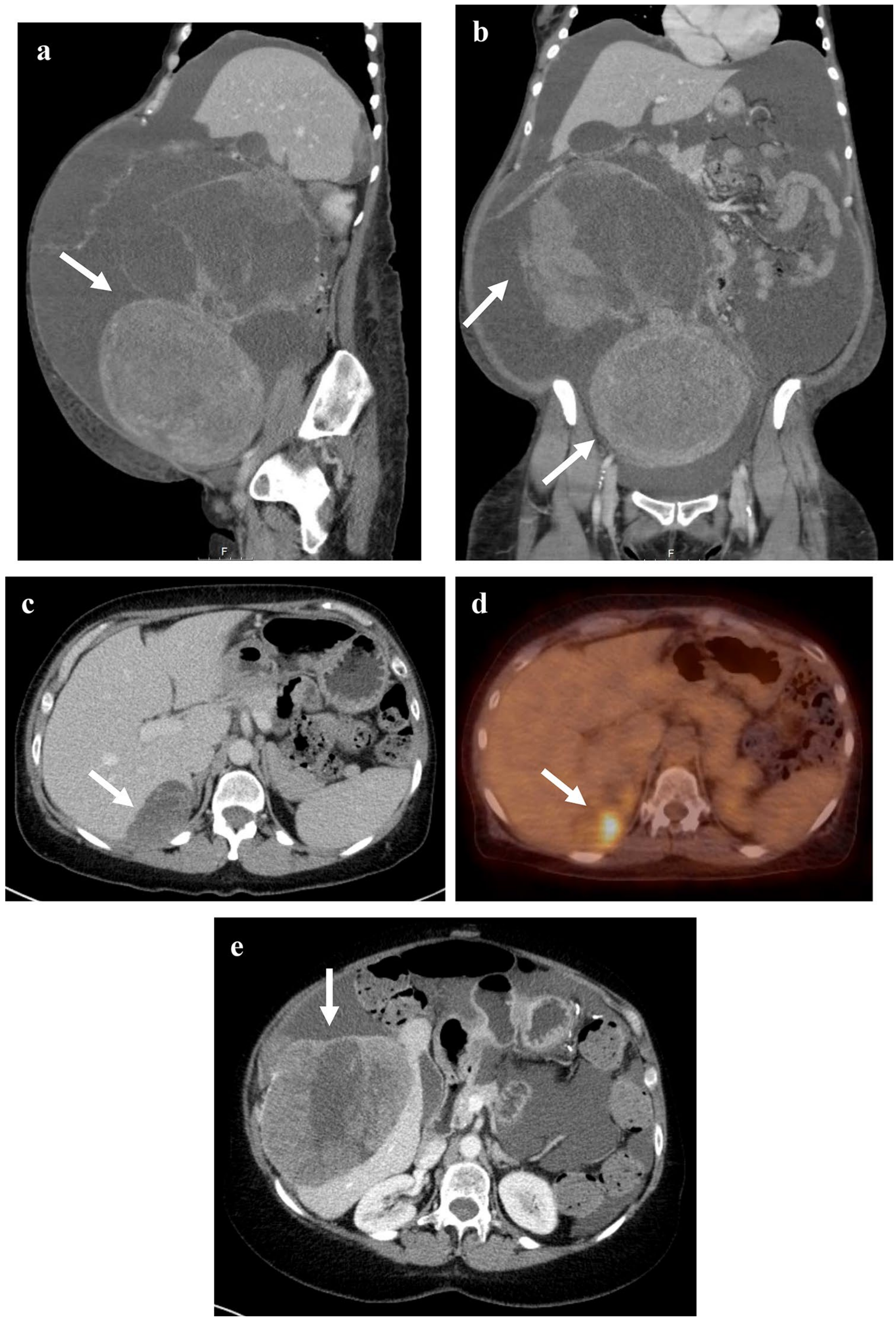

Fig. 6 63-year-old woman presenting with abdominal fullness; diagnosed with stage IIIC carcinosarcoma of the uterus. **a**, **b** Sagittal (**a**) and coronal (**b**) contrast-enhanced CT images of the abdomen & pelvis demonstrate multilobulated exophytic bulky heterogeneous masses (white arrows) contiguous with the uterus. Both lesions demonstrate variable enhancement with internal septations containing solid and fluid elements. Pathology following abdominal hysterectomy, bilateral salpingo-oophorectomy, and tumor debulking confirmed carcinosarcoma involving the fallopian tubes and ovary with metastatic disease to the right diaphragm and omentum. **c** Axial **c**contrast-enhanced CT image of the abdomen obtained following surgery and 3 cycles of carboplatin/paclitaxel reveals a 5 cm heterogeneously enhancing soft tissue mass arising from the peritoneum in Morison's pouch adjacent to hepatic segment 6. **d** Axial PET/CT image of the abdomen confirms hypermetabolic activity in the previously identified posterior peritoneal soft tissue mass abutting the liver (arrow), compatible with metastatic disease. **e** Axial contrast-enhanced CT image of the abdomen obtained 1 year following partial hepatectomy of segments 6/7 and peritoneal tumor resection shows a new metastatic peripheral mass along the right hepatic surface with enhancing components and central necrosis

currently exists. Poor prognostic factors associated with UCS include increased CA-125 levels, heterologous sarcoma component, presence of a rhabdomyosarcoma component, and extrauterine disease [8, 9, 47, 48]. Multimodal therapy and lymphadenectomy are both positive predictors of survival [8]. A SEER retrospective analysis assessing the overall survival of patients diagnosed with UCS examined 1855 patients and found a significant increase in the 5-year overall survival (49%) and median survival (54 months) for those who underwent pelvic lymphadenectomy following diagnosis versus those who did not [14].

Conclusion

Uterine carcinosarcoma is a unique gynecological malignancy that is characterized by distinct pathological characteristics, imaging presentations, and recurrence patterns. This highly aggressive neoplasm has traditionally been associated with poor survival, with high propensity for recurrence and metastatic spread to various sites. Different imaging modalities such as PET/CT play crucial roles in the initial staging and follow-up of UCS. Knowledge of the modern multidisciplinary treatment paradigms of UCS is critical for radiologists who interpret imaging from UCS patients. As our knowledge of this complex malignancy continues to evolve, it is becoming increasingly important for radiologists to develop a thorough understanding of the radiological, pathological, and clinical features of UCS.

Funding Stefanie Avril, MD is supported by the Clinical and Translational Science Collaborative of Cleveland, (CTSCA/KL2 TR0002547). The remaining authors have no disclosures.

References

1. Cantrell LA, Blank S V, Duska LR. Uterine carcinosarcoma: A review of the literature. Gynecol Oncol [Internet]. 2015 Jun 1;137(3):581–8. Available from: https://doi.org/10.1016/j.ygyno.2015.03.041
2. Singh R. Review literature on uterine carcinosarcoma. J Cancer Res Ther. 2014;10(3):461–8.
3. Schiavone MB, Zivanovic O, Zhou Q, Leitao MMJ, Levine DA, Soslow RA, et al. Survival of Patients with Uterine Carcinosarcoma Undergoing Sentinel Lymph Node Mapping. Ann Surg Oncol. 2016 Jan;23(1):196–202.
4. Cherniack AD, Shen H, Walter V, Stewart C, Murray BA, Bowlby R, et al. Integrated Molecular Characterization of Uterine Carcinosarcoma. Cancer Cell. 2017 Mar;31(3):411–23.
5. Ashley CW, Da Cruz Paula A, Kumar R, Mandelker D, Pei X, Riaz N, et al. Analysis of mutational signatures in primary and metastatic endometrial cancer reveals distinct patterns of DNA repair defects and shifts during tumor progression. Gynecol Oncol. 2018;(xxxx):1–9.
6. McConechy MK, Hoang LN, Chui MH, Senz J, Yang W, Rozenberg N, et al. In-depth molecular profiling of the biphasic components of uterine carcinosarcomas. J Pathol Clin Res. 2015 Jul;1(3):173–85.
7. Arend R, Doneza JA, Wright JD. Uterine carcinosarcoma. Curr Opin Oncol. 2011 Sep;23(5):531–6.
8. Harano K, Hirakawa A, Yunokawa M, Nakamura T, Satoh T, Nishikawa T, et al. Prognostic factors in patients with uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese Gynecologic Oncology Group. Int J Clin Oncol. 2016;21(1):168–76.
9. Kurnit KC, Previs RA, Soliman PT, Westin SN, Klopp AH, Fellman BM, et al. Prognostic factors impacting survival in early stage uterine carcinosarcoma. Gynecol Oncol. 2018;152(1).
10. Inoue A, Yamaguchi K, Kurata Y, Murakami R, Abiko K, Hamanishi J, et al. Unenhanced region on magnetic resonance imaging represents tumor progression in uterine carcinosarcoma. J Gynecol Oncol. 2017;28(5):1–10.
11. Zhao S, Bellone S, Lopez S, Thakral D, Schwab C, English DP, et al. Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition. Proc Natl Acad Sci U S A. 2016 Oct;113(43):12238–43.
12. Dickson EL, Vogel RI, Gehrig PA, Pierce S, Havrilesky L, Secord AA, et al. A multi-institutional study of outcomes in stage I-III uterine carcinosarcoma. Gynecol Oncol. 2015 Nov;139(2):275–82.
13. Tirumani SH, Ojili V, Shanbhogue AKP, Fasih N, Ryan JG, Reinhold C. Current concepts in the imaging of uterine sarcoma. Abdom Imaging. 2013;38(2):397–411.
14. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: A SEER analysis. Gynecol Oncol. 2008;111(1):82–8.
15. Kanthan R, Senger J-L. Uterine Carcinosarcomas (Malignant Mixed Müllerian Tumours): A Review with Special Emphasis on the Controversies in Management. Obstet Gynecol Int. 2011;2011:1–13.
16. Pradhan TS, Stevens EE, Ablavsky M, Salame G, Lee YC, Abulafia O. FIGO staging for carcinosarcoma: Can the revised staging system predict overall survival? Gynecol Oncol. 2011;123(2):221–4.
17. Takahashi M, Kozawa E, Tanisaka M, Hasegawa K, Yasuda M, Sakai F. Utility of histogram analysis of apparent diffusion coefficient maps obtained using 3.0T MRI for distinguishing uterine carcinosarcoma from endometrial carcinoma. J Magn Reson Imaging. 2016;43(6):1301–7.
18. Koh W-J, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018 Feb;16(2):170–99.
19. Ho K-C, Lai C-H, Wu T-I, Ng K-K, Yen T-C, Lin G, et al. 18F-fluorodeoxyglucose positron emission tomography in uterine carcinosarcoma. Eur J Nucl Med Mol Imaging. 2008 Mar;35(3):484–92.
20. Freeman SJ, Aly AM, Kataoka MY, Addley HC, Reinhold C, Sala E. The Revised FIGO Staging System for Uterine Malignancies: Implications for MR Imaging. RadioGraphics. 2012;32(6):1805–27.
21. Akin EA, Kuhl ES, Zeman RK. The role of FDG-PET/CT in gynecologic imaging: an updated guide to interpretation and challenges. Abdom Radiol. 2018;43(9):2474–86.
22. Lee HJ, Park JY, Lee JJ, Kim MH, Kim DY, Suh DS, et al. Comparison of MRI and18F-FDG PET/CT in the preoperative evaluation of uterine carcinosarcoma. Gynecol Oncol. 2016;140(3):409–14.
23. Lewin SN. Revised FIGO staging system for endometrial cancer. Clin Obstet Gynecol. 2011 Jun;54(2):215–8.

24. Teo SY, Babagbemi KT, Peters HE, Mortele KJ. Primary malignant mixed mullerian tumor of the uterus: findings on sonography, CT, and gadolinium-enhanced MRI. AJR Am J Roentgenol. 2008 Jul;191(1):278–83.
25. Kamishima Y, Takeuchi M, Kawai T, Kawaguchi T, Yamaguchi K, Takahashi N, et al. A predictive diagnostic model using multiparametric MRI for differentiating uterine carcinosarcoma from carcinoma of the uterine corpus. Jpn J Radiol. 2017;35(8):472–83.
26. Genever A V, Abdi S. Can MRI predict the diagnosis of endometrial carcinosarcoma? Clin Radiol [Internet]. 2011 Jul 1;66(7):621–4. Available from: https://doi.org/10.1016/j.crad.2011.02.008
27. Shih I-L, Shih TT-F. PET/MR hybrid imaging of cervical and endometrial cancer. J Cancer Res Pract [Internet]. 2018;5(3):91–8. Available from: http://www.sciencedirect.com/science/article/pii/S2311300617301118
28. Kitajima K, Suenaga Y, Ueno Y, Kanda T, Maeda T, Takahashi S, et al. Value of fusion of PET and MRI for staging of endometrial cancer: Comparison with 18F-FDG contrast-enhanced PET/CT and dynamic contrast-enhanced pelvic MRI. Eur J Radiol [Internet]. 2013 Oct 1;82(10):1672–6. Available from: https://doi.org/10.1016/j.ejrad.2013.05.005
29. Zwahlen DR, Schick U, Bolukbasi Y, Thariat J, Abdah-Bortnyak R, Kuten A, et al. Outcome and Predictive Factors in Uterine Carcinosarcoma Using Postoperative Radiotherapy: A Rare Cancer Network Study. Rare Tumors [Internet]. 2016 Jun 29;8(2):6052. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27441069
30. Shah SH, Jagannathan JP, Krajewski K, O'Regan KN, George S, Ramaiya NH. Uterine sarcomas: Then and now. Am J Roentgenol. 2012;199(1):213–23.
31. Healy V, O'Halloran P, O'Brien S, Beausang A, Caird J. CNS metastasis secondary to malignant-mixed Müllerian tumor: case report and review of therapeutics. CNS Oncol. 2017/10/09. 2017 Oct;6(4):315–23.
32. Cantrell LA, Havrilesky L, Moore DT, O'Malley D, Liotta M, Secord AA, et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. Gynecol Oncol. 2012;127(1):22–6.
33. Cha J, Kim YS, Park W, Kim HJ, Kim JY, Kim JH, et al. Clinical significance of radiotherapy in patients with primary uterine carcinosarcoma: A multicenter retrospective study (KROG 13-08). J Gynecol Oncol. 2016;27(6):1–12.
34. Kumar Dandamudi R, Aslam S, Walji N, El-Modir A, Fernando I. Chemotherapy for uterine carcinosarcoma with carboplatin, ifosfamide and mesna. Anticancer Res. 2015;35(9):4841–8.
35. Brackmann M, Stasenko M, Uppal S, Erba J, Reynolds RK, McLean K. Comparison of first-line chemotherapy regimens for ovarian carcinosarcoma: A single institution case series and review of the literature. BMC Cancer. 2018;18(1):1–7.
36. Homesley HD, Filiaci V, Gibbons SK, Long HJ, Cella D, Spirtos NM, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol. 2009 Mar;112(3):543–52.
37. Sutton G, Brunetto VL, Kilgore L, Soper JT, McGehee R, Olt G, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study. Gynecol Oncol. 2000 Nov;79(2):147–53.
38. Lacour RA, Euscher E, Atkinson EN, Sun CC, Ramirez PT, Coleman RL, et al. A phase II trial of paclitaxel and carboplatin in women with advanced or recurrent uterine carcinosarcoma. Int J Gynecol Cancer. 2011 Apr;21(3):517–22.
39. Lorusso D, Martinelli F, Mancini M, Sarno I, Ditto A, Raspagliesi F. Carboplatin-Paclitaxel versus Cisplatin-Ifosfamide in the treatment of uterine carcinosarcoma: a retrospective cohort study. Int J Gynecol Cancer. 2014 Sep;24(7):1256–61.
40. Powell MA, Filiaci VL, Rose PG, Mannel RS, Hanjani P, Degeest K, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin Oncol. 2010 Jun;28(16):2727–31.
41. Matsuo K, Ross MS, Yunokawa M, Johnson MS, Machida H, Omatsu K, et al. Salvage chemotherapy with taxane and platinum for women with recurrent uterine carcinosarcoma. Gynecol Oncol. 2017;147(3):565–71.
42. Vitale SG, Laganà AS, Capriglione S, Angioli R, La Rosa VL, Lopez S, et al. Target therapies for uterine carcinosarcomas: Current evidence and future perspectives. Int J Mol Sci. 2017;18(5):1–16.
43. Makker V, Recio FO, Ma L, Matulonis UA, Lauchle JO, Parmar H, et al. A multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study). Cancer. 2016 Nov;122(22):3519–28.
44. Einstein MH, Klobocista M, Hou JY, Lee S, Mutyala S, Mehta K, et al. Phase II trial of adjuvant pelvic radiation "sandwiched" between ifosfamide or ifosfamide plus cisplatin in women with uterine carcinosarcoma. Gynecol Oncol. 2012 Jan;124(1):26–30.
45. Sozen H, Çiftçi R, Vatansever D, Topuz S, Iyibozkurt AC, Bozbey HU, et al. Combination of adjuvant chemotherapy and radiotherapy is associated with improved survival at early stage type II endometrial cancer and carcinosarcoma. Aust New Zeal J Obstet Gynaecol. 2016;56(2):199–206.
46. GGonzalez Bosquet J, Terstriep SA, Cliby WA, Brown-Jones M, Kaur JS, Podratz KC, et al. The impact of multi-modal therapy on survival for uterine carcinosarcomas. Gynecol Oncol. 2010;116(3):419–23.
47. Yamada SD, Burger RA, Brewster WR, Anton D, Kohler MF, Monk BJ. Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus. Cancer. 2000 Jun;88(12):2782–6.
48. Matsuo K, Ross MS, Yunokawa M, Johnson MS, Machida H, Omatsu K, et al. Clinical utility of CA-125 in the management of uterine carcinosarcoma. Vol. 29, Journal of Gynecologic Oncology. Korea (South); 2018. p. e88.