Chapter 21
Other Uterine Sarcomas

Beyond leiomyosarcoma, uterine sarcomas and tumors that contain "sarcoma" in the name (i.e., carcinosarcoma) are well-recognized biological entities. The non-leiomyosarcoma tumors, (low grade) endometrial stromal sarcoma, high grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, and mixed Müllerian tumors (including carcinosarcoma) are all very different from one another biologically. A new classification of these tumors was undertaken in the 2014 WHO fascicle on gynecological tumors [1, 2]. They are often omitted in discussions of soft tissue pathology as different groups of pathologists generally review such cases in expert centers than those who review soft tissue or bone tumors. Age distribution for adult uterine endometrial stromal tumors is shown in Fig. 21.1.

21.1 Low Grade Endometrial Stromal Sarcoma

Low grade endometrial stromal sarcoma (LGESS) resembles proliferating endometrial stroma, but a distinct malignancy compared to its benign relative, endometrial stromal nodule (ESN). LGESS is relatively indolent, but can be associated with locoregional (Fig. 21.2) as well as lung metastatic disease (Fig. 21.3) over the course of many years (not uncommonly a decade or more) in as many as a third of patients [3, 4]. It is the one sarcoma in which hormonal therapy reproducibly controls disease in a manner not dissimilar from estrogen receptor positive (ER+) breast adenocarcinoma. LGESS is usually both ER+ and progesterone receptor positive (PR+).

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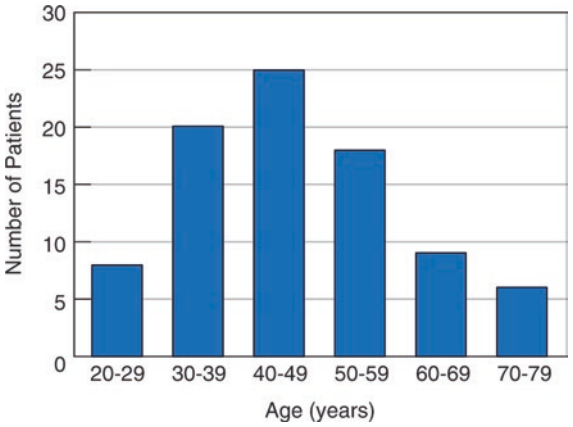

Fig. 21.1 Age distribution of adult patients with uterine endometrial sarcomas, all grades. MSKCC 7/1/1982–6/30/2010 $n = 86$

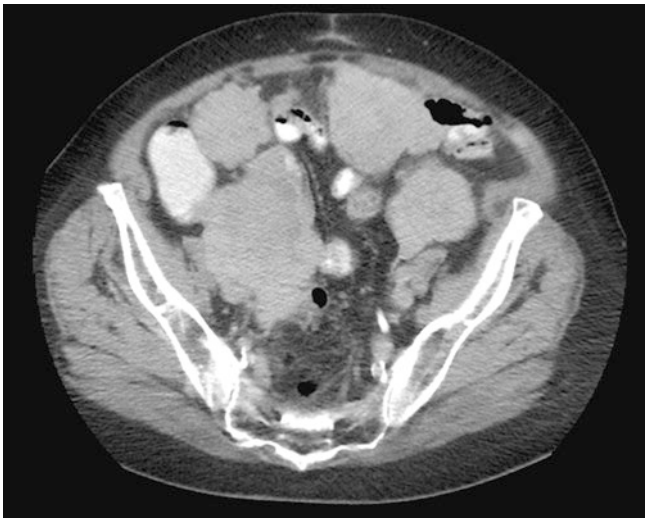

Fig. 21.2 Intravenous and oral contrast-enhanced CT image of a 71-year-old woman with metastatic endometrial stromal sarcoma

21.1.1 Diagnosis

Like many endometrial stromal nodules, LGESS usually contains a translocation t(7;17)(p15;q21) involving *JAZF1* at 7p15 and *SUZI2* at 17q21 as the most common change, although t(6;7) and t(6;10) and others have been described, more since the era of tumor RNA sequencing arrived [5–9]. What has been called in the past high grade endometrial stromal sarcoma may represent a separate entity, and distinct from what is now termed undifferentiated endometrial sarcoma, and thus is a diagnosis in transition, based on the genomics of these tumors (see below). These findings were incorporated into the WHO tumor fascicle on gynecological tumors from 2014 [10].

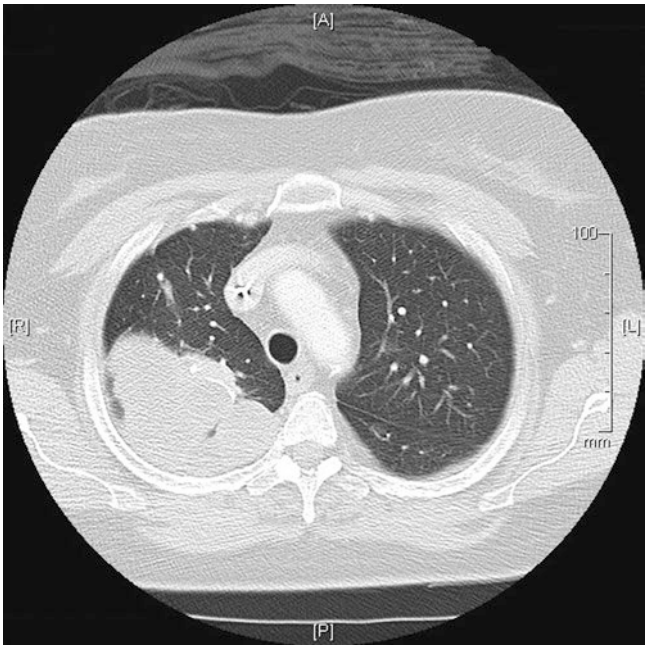

Fig. 21.3 Intravenous contrast-enhanced CT image of metastatic disease in a patient with undifferentiated endometrial sarcoma

21.1.2 Treatment

Primary treatment is hysterectomy. Small studies and analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database have examined if lymphadenectomy improved survival, since nodes are positive in 5–10 % of patients with ESS. No survival advantage was noted, so it is difficult to routinely recommend the more extensive operation [11–14]. Radiation did not appear to affect clinical outcome and is generally not administered for patients with adequate primary surgery [11].

There are no randomized data to suggest the utility of hormonal therapy in the adjuvant setting for ESS [15–17], oophorectomy or GnRH agonists have activity as other means to affect estrogen levels in ESS, and patients who undergo total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) as primary therapy may contaminate any benefit seen from adjuvant therapy.

For metastatic disease, progestins and antiestrogens are effective and usually relatively less toxic systemic therapy than chemotherapy, which also has activity [18–20]. It is also worth noting that given the slow evolution of disease in most patients it is worthwhile considering surgery in the metastatic disease in selected patients (Table 21.1).

Table 21.1 Treatment recommendations for low grade endometrial stromal sarcoma

Clinical scenario		Comments
Adjuvant systemic therapy		None; no clear benefit of adjuvant systemic therapy given long evolution of disease and effects of oophorectomy or other surgical procedures; for large bulky tumors, neoadjuvant hormonal therapy can be contemplated
Metastatic disease	First line	Progestins, e.g., medroxyprogesterone, megestrol; oophorectomy or GnRH agonists in selected patients
	Second line	Antiestrogens, e.g., aromatase inhibitors
	Third line	Anthracyclines + olaratumab; ifosfamide; clinical trial. In particular, given hormone sensitivity, CDK4 inhibitors may be useful, in analogy to hormone receptor positive breast cancer. Immune checkpoint inhibitors are untested as of 2016

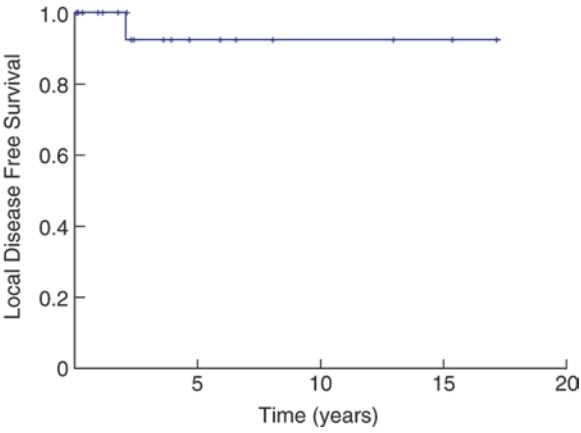

Fig. 21.4 Local disease-free survival for adult patients with primary uterine endometrial stromal sarcoma, all grades. MSKCC 7/1/1982–6/30/2010 $n = 29$

21.1.3 Outcome

Outcome for local recurrence and disease-specific survival for primary endometrial stromal tumors are shown in Figs. 21.4 and 21.5.

21.2 High Grade Endometrial Stromal Sarcoma

High grade endometrial stromal sarcoma (HGESS) is now accepted as a separate entity from low grade endometrial stromal sarcoma, and is further differentiated from undifferentiated uterine sarcoma (UUS), largely based on mitotic rate (greater than LGESS) and cytomorphology, but now also by their genomic profile. HGESS is usually estrogen receptor negative (ER−) and progesterone receptor negative (PR−), which differentiates HGESS from LGESS (Fig. 21.6). Furthermore, HGESS

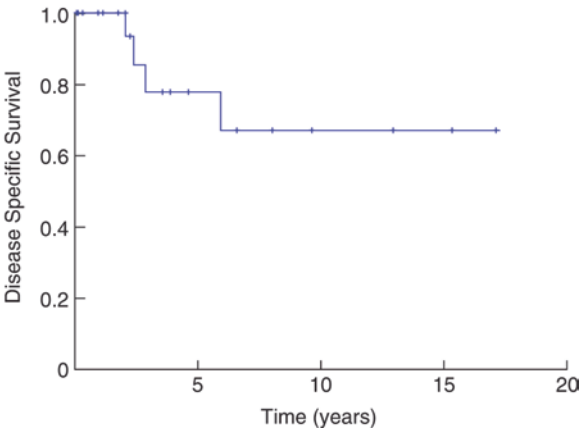

Fig. 21.5 Disease-specific survival for adult patients with primary uterine endometrial stromal sarcoma, all grades. MSKCC 7/1/1982–6/30/2010 $n = 29$

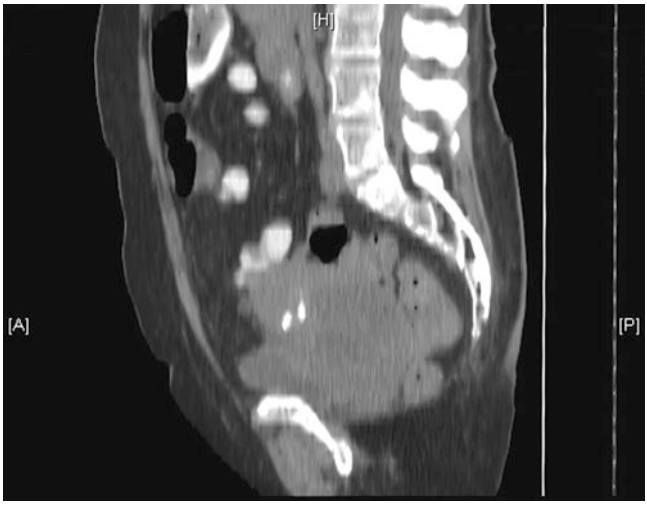

Fig. 21.6 CT image of a patient with a primary undifferentiated endometrial sarcoma, with extensive local extension

does not appear to contain the translocations typically observed in LGESS [21]. A collaborative effort has identified group of translocations involving *YWHAE*, which hopefully will impact therapy for this aggressive sarcoma [22]. The t(10;17)(q22;p13) translocation, resulting in *YWHAE-NUTM2A/B* fusions, was associated with a high grade round cell morphology and aggressive clinical behavior compared to JAZF1-positive LGESS [23]. However, in a subset of these high grade lesions in addition to the undifferentiated round cell areas, there was a cytologically bland and mitotically weakly active spindle cell component, which was diffusely positive for ER, PR, and CD10, in contrast to the round cell areas, which were negative. This latter finding suggests the possibility of a histologic progression from an HGESS to

Table 21.2 Treatment suggestions for high grade endometrial stromal sarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		Not recommended, since the response rate in the metastatic setting is low despite the tumor's aggressive nature
Metastatic disease	First line	Minor responses have been observed with ifosfamide-based therapy; doxorubicin + olaratumab is untested as of 2016, though doxorubicin has little activity as a single agent
	Second line	Clinical trials are most appropriate; IGF1R inhibitors could have minor activity, as may drugs impacting epigenetics of the tumor subtype. There are not enough data with any specific chemotherapy to be sanguine about any specific systemic therapeutic. Immune checkpoint inhibitors are untested as of 2016

a UUS, which is borne out by the idea that UUS have highly aneuploid karyotypes. Of note, the same *YWHAE-NUTM2A/B* translocation was reported in the clear cell sarcoma of kidney [24].

In our experience, ifosfamide has at best modest activity in this disease, but the response rate is low, making it difficult to recommend adjuvant chemotherapy for women with this diagnosis [20] (Table 21.2). We observed relatively long-lasting stable disease in one patient treated with an IGF1 receptor inhibitor, a finding we hope will be explored further, since YWHAE, a 14-3-3 protein, can interact with IGF1R-associated protein IRS1.

21.2.1 Outcome

An analysis utilizing the prior 2003 WHO classification of three endometrial stromal sarcoma (ESS) subtypes, including noninvasive, invasive low grade, and invasive undifferentiated [25], indicated 5- and 10-year recurrence-free survival for 91 invasive ESS was 82 and 75 %. Necrosis was an important prognostic predictor for overall survival, with 10-year survival of 89 % in the absence of necrosis and 49 % in those with prominent necrosis. By defining ESS low grade as mild atypia with no necrosis, and undifferentiated as moderate/severe atypia present or necrosis present, disease-specific survivals were 98 vs. 48 %. Updated data for the new stratification of uterine sarcomas are being collected.

21.3 Undifferentiated Uterine Sarcoma (UUS)

Undifferentiated uterine sarcoma (UUS) is a diagnosis evolving from the increasing genomic analysis of uterine sarcomas. It is clear that UUS have a distinct cytomorphology, and are the most aneuploid of these tumors, with copy number changes found on all chromosomes, with the greatest number of changes found on

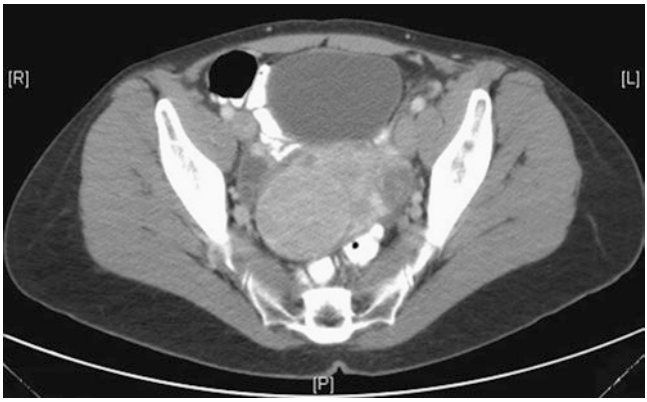

Fig. 21.7 Intravenous contrast-enhanced CT scan of a patient with a 6 cm PEComa of the uterus

chromosomes 1q, 2q, 13 and gains of 1q and 17p [26]. Primary treatment is the same for other uterine sarcomas, but the risk of metastatic disease is higher than other uterine sarcomas. However, this subset of a rare tumor can respond to systemic therapy, with responses documented to both doxorubicin-based therapy and gemcitabine-docetaxel [27]. The existence of these entities confirms that sarcomas are different from carcinomas of the gynecological tract and that agents other than carboplatin and paclitaxel have to be employed for these unusual tumors.

21.4 PEComas

Perivascular epithelioid cell tumors (PEComas) are a relatively newly coined diagnostic category of tumors having hybrid smooth muscle and melanocytic differentiation. The uterus is among the most common sites of origin of this rare tumor (Fig. 21.7). Uterine PEComas, similar to other anatomic sites, have either mutations in *TSC2* or translocations involving *TFE3* [28]. In contrast with other sites, a small subset of uterine PEComas harbor *RAD51B* fusions, which may occur in association with *TSC2* mutations [28].

21.5 Uterine Carcinosarcomas and Other Malignant Mixed Müllerian Tumors

Though carcinosarcomas appear to represent divergent differentiation of what is at heart a uterine carcinoma, they are encountered frequently enough in a sarcoma practice to be mentioned here. The age distribution for adult carcinosarcoma is shown in Fig. 21.8. Mixed Müllerian tumors have elements of both stroma and

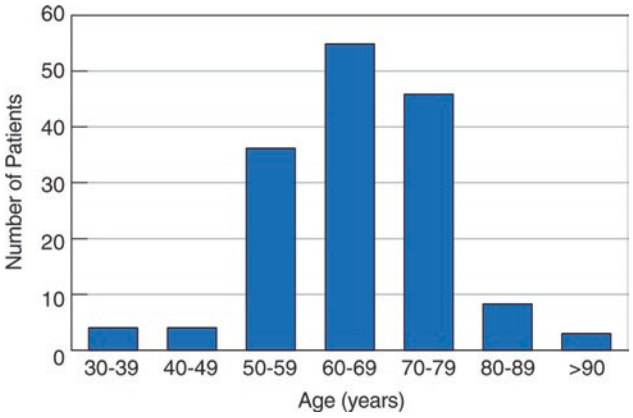

Fig. 21.8 Age distribution of adult patients with uterine carcinosarcoma (malignant mixed Müllerian tumors). MSKCC 7/1/1982–6/30/2010 $n = 156$

epithelium, and include adenofibroma, adenosarcoma, carcinofibroma, and carcinosarcoma. While adenofibroma is benign, the other tumors are malignancies. Carcinosarcoma, which presents in postmenopausal women as uterine bleeding, may represent a uterine carcinoma with divergent differentiation towards a sarcoma lineage. CA125 is often elevated in patients with carcinosarcoma and may serve as a tumor marker. Carcinosarcoma is more aggressive overall compared to uterine carcinomas, with frequent metastasis to both peritoneum and lung, and thus appears to be clinically distinct from uterine carcinoma.

No recurrent genetic event has been observed in carcinosarcoma, and the tumors are generally aneuploid. Gene expression analysis of uterine carcinomas showed greater kinship with uterine sarcomas than uterine carcinoma, despite the higher potential for metastasis as the carcinomatous part of the carcinosarcoma over time. In one study of carcinosarcomas vs. uterine sarcoma vs. endometrial carcinomas, chromosome 19q13.1 appeared amplified in carcinosarcomas, which include the *TGFB1* locus, a gene involved in so-called "epithelial mesenchymal transition" (EMT) observed in some carcinomas. Essentially by definition, carcinosarcoma is a cancer demonstrating EMT, or at least a dual phenotype not observed in most carcinomas [29].

Primary therapy for carcinosarcoma is TAH-BSO, and proper gynecological staging with lymphadenectomy, omentectomy, and testing of peritoneal cytology. Both local–regional relapse and metastatic spread of carcinosarcoma are common, which has raised the question of the utility of abdominal radiation and systemic chemotherapy in the adjuvant setting. A randomized study of adjuvant radiation for early stage uterine sarcomas and carcinosarcomas showed better local control but no improvement in overall survival. Conversely, a retrospective analysis of a large number of patients treated with radiation suggested possible clinical benefit from adjuvant irradiation [30, 31].

Table 21.3 Treatment suggestions for undifferentiated uterine sarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		Not recommended, since the response rate in the metastatic setting is low. Given the activity of systemic therapy in metastatic disease and high risk of high mortality rate from this sarcoma subtype, adjuvant therapy as used for metastatic disease cannot be faulted
Metastatic disease	First line	Doxorubicin + olaratumab, given futility of other chemotherapy options in the past; ifosfamide can also be contemlated
	Second line	Gemcitabine + docetaxel, ifosfamide or trabectedin where available. Clinical trials; immune checkpoint inhibitors are untested as of 2016

A phase III GOG study showed that adjusting for stage and age, the recurrence rate was 21 % lower for patients who received ifosfamide-cisplatin adjuvant therapy over whole abdominal radiation for stage I–IV carcinosarcoma, although the crude data showed no significant difference in the recurrence rate [32]. While thus a reasonable standard of care in the adjuvant setting, cisplatin-ifosfamide is obviously a toxic regimen, and careful patient selection for such treatment is necessary.

Other agents active in carcinosarcoma include carboplatin and taxanes. For example, carboplatin and paclitaxel were tested in stage III and IV disease (in 46 evaluable patients), with a RECIST CR rate of 13 % and PR rate 41 %, for an overall response rate of 54 %. The GOG conducted a randomized trial comparing paclitaxel plus carboplatin to paclitaxel plus ifosfamide. The results from this trial will help answer the question of whether ifosfamide is needed in carcinosarcoma. For patients with stage I–II disease, a combination of multiagent chemotherapy and intravaginal brachytherapy has been shown to be feasible [33].

For metastatic disease, agents not used in the adjuvant setting can be considered. Cisplatin, ifosfamide, carboplatin, and paclitaxel all appear to have some activity. Topotecan has modest activity in metastatic disease [34], as may doxorubicin or gemcitabine as a single agent. The combination of gemcitabine and docetaxel [35] has minor activity. Imatinib, sorafenib, pazopanib, and thalidomide are all largely inactive against carcinosarcoma from phase II studies. Immune checkpoint inhibitors are untested in this diagnosis as of 2016; the National Cancer Institute is including carcinosarcomas in the list of rare cancers they will treat with nivolumab and ipilimumab in a coming study (Table 21.3).

21.6 Outcome

Outcome for primary adult carcinosarcoma by local and disease-specific survival are shown in Figs. 21.9 and 21.10. Outcome, as with other uterine malignancy, is highly stage dependent, with curative surgery with or without adjuvant therapy, and

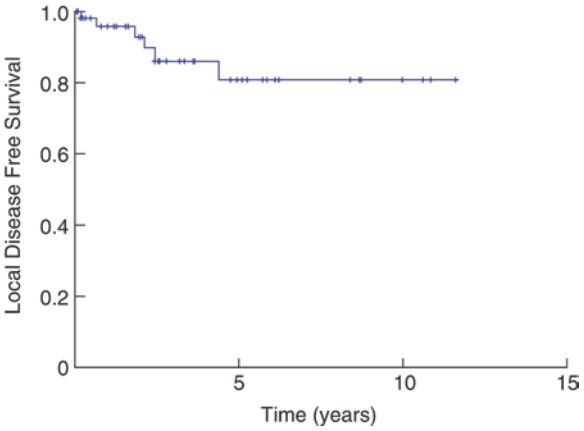

Fig. 21.9 Local disease-free survival for adult patients with primary uterine carcinosarcoma (mixed malignant Müllerian tumor). MSKCC 7/1/1982–6/30/2010 $n=56$

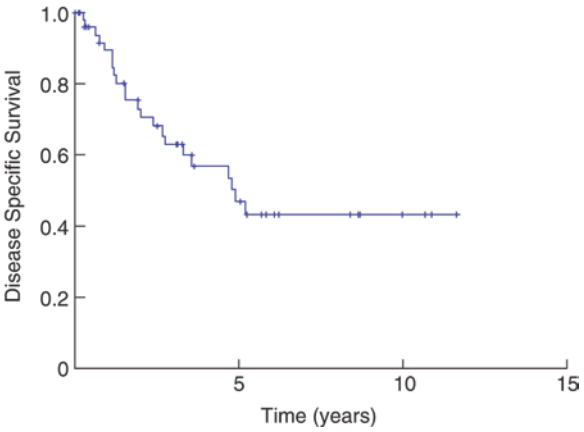

Fig. 21.10 Disease-specific survival for adult patients with primary uterine carcinosarcoma (mixed malignant Müllerian tumor). MSKCC 7/1/1982–6/30/2010 $n=56$

poor long-term prognosis in advanced or metastatic disease. For the uncommon patient with uterine carcinosarcoma arising in the setting of hereditary nonpolyposis colorectal cancer, in which DNA mismatch repair defects occur, immunotherapy is a consideration given impressive responses of colorectal cancer to immune checkpoint inhibitors in this setting (Table 21.4).

Table 21.4 Treatment recommendations for uterine carcinosarcomas and other malignant mixed Müllerian tumors

Clinical scenario		Comments
Primary therapy		For completely resected disease, cisplatin-ifosfamide is superior to whole abdominal radiation therapy, but risk is still high for relapse; carboplatin-paclitaxel is used by many clinicians instead of the more toxic doublet
Metastatic disease	First line	Topotecan, platinum agents, taxanes, combinations
	Second line	Clinical trials, gemcitabine or combinations. Pazopanib has negligible activity. Immune checkpoint inhibitors are untested as of 2016, but are appealing given mismatch repair defects seen in some uterine carcinomas

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