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Gynecologic Cancers (JS Ferriss, Section Editor)

Beyond Serous: Treatment Options for Rare Endometrial Cancers

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Opinion statement

Rare endometrial cancers are high-grade, aggressive malignancies which are often diagnosed at an advanced stage, and account for disproportionately more deaths than their more common low-grade counterparts. Standard of care includes a combination of surgery, radiation, and chemotherapy. Surgery consists of complete hysterectomy, and more recent evidence supports replacing a full lymphadenectomy with sentinel node mapping. Paclitaxel and carboplatin remain the mainstays of chemotherapy, while current studies incorporating immunotherapy will inform future practice. Whether and how to incorporate radiation remains controversial, and certain histologic subtypes, such as carcinosarcomas, may benefit from radiation more than others. Owing to their relative rarity, it is difficult to conduct clinical trials in this patient population, which has hindered the development of effective therapies for rare malignancies. Molecular profiling has offered insight into the pathogenesis of rare endometrial cancers, providing actionable targets for personalized therapy.

Introduction

Rare endometrial cancers consist of molecularly heterogeneous, aggressive adenocarcinomas. Histologic subtypes include clear cell (CC), mucinous, squamous, transitional cell, mesonephric, neuroendocrine, and undifferentiated (UEC) adenocarcinomas; carcinosarcomas (UCS), and serous adenocarcinomas (discussed separately). The majority of endometrial cancers are diagnosed at an early stage with survival rates approaching 90%. In the subset of rare

endometrial cancers—which comprise approximately 20% of endometrial cancers—the prognosis is worse, owing to their aggressive behavior and late stage at the time of diagnosis. For example, women with carcinosarcomas have a 5-year survival rate of 33% [1], and at the time of diagnosis, 50% of women with high-grade endometrial cancers have advanced disease [2]. Molecular classification of rare endometrial cancers has proven challenging given their rarity and molecular heterogeneity. The Cancer Genome Atlas Study, which led to classification of endometrial cancers into four molecular subtypes, did not include these rarer histologic types [3], thereby limiting applicability. However, others have investigated the molecular landscape of rare endometrial cancers, with reports of actionable molecular targets, which will be described in the following chapter.

Individual subtypes

Uterine carcinosarcomas

Uterine carcinosarcomas are biphasic tumors, containing both mesenchymal and epithelial elements, often referred to as malignant mixed Mullerian tumors or "MMMTs." While accounting for only 5% of endometrial cancers, they are responsible for 15% of endometrial cancer-related deaths [4]. They disproportionately affect African American women, and recently have become more prevalent, with a 1.7% increase in incidence per year [1]. The cause for this increase remains unknown. Once considered sarcomas, it is now widely accepted that UCS represent carcinomas which arise from a monoclonal precursor and undergo an epithelial to mesenchymal transition to sarcomas [5]. A recent extensive molecular characterization of UCS revealed similarities to high-grade ovarian and uterine serous carcinomas, supporting a hypothesis that UCS may arise from dedifferentiation of uterine serous carcinomas [6]. Individual efforts at molecular profiling of UCS have identified mutations in *TP53*, *PIK3CA*, *FBXW7*, *PTEN*, *KRAS*, *PPP2R1A*, and *ARID1A* [7]. Tumor mutational burden is generally low in UCS, with intact mismatch repair in most cases.

Clear cell carcinomas

Clear cell carcinomas also represent 5% of endometrial cancers, and similar to UCS, behave aggressively with a worse prognosis than usual-type endometrial carcinomas. One multi-institutional review which characterized 99 patients with CC found that at the time of surgery, 52% of patients had extrauterine spread, and only 55% of patients survived 5 years [2]. The origin of clear cell carcinomas remains poorly understood; they typically develop in older women in a background of atrophy. One group identified adjacent atypical glandular changes in 30 patients with CC, suggesting the presence of a putative precursor lesion [8]. On a molecular level, CC harbor similarities to both endometrioid and serous histologies, with alterations reported in *PIK3CA*, *PTEN*, *PIK3R1*, *KRAS*, *ARID1A*, *TP53*, *FBXW7*, *PP2R1A*, *TAF1*, *SPOP* and *ERBB2* [9, 10].

Undifferentiated endometrial cancer

A recent review of the National Cancer Database reported a 1.1% incidence of undifferentiated endometrial cancer [11]. Median age at diagnosis was 65, 58% of patients had early-stage disease, and 5-year survival was 57%. Loss of expression of switch/sucrose nonfermenting (SWI/SNF) proteins has been reported in up to

60% of cases and implied in their pathogenesis [12]. Aberrations in *PIK3CA*, *CTNNB1*, *TP53*, *FBXW7*, *and PPP2R1A* have also been reported [13].

Others

Squamous cell carcinomas of the endometrium are exceedingly rare, and should be distinguished from primary squamous cell carcinomas of the cervix. Mesonephric-like endometrial cancers (MLEC) are similarly rare, and exhibit mesonephric markers such as CD10, GATA3, and TTF1, with absence of ER/PR expression, and wild-type p53 [14]. In a multi-institutional study of 44 patients with MLEC, 58% presented at an advanced stage, 92% experienced recurrence with a predilection for pulmonary metastases, and five-year survival was 72% [14].

While many endometrioid adenocarcinomas may display mucinous features, gastric-type mucinous adenocarcinomas exhibit distinct markers such as CK20, CDX2, and MUC6, absent ER expression, and appear microscopically similar to gastrointestinal malignancies, which must be ruled out. As such, they are considered separate entities. Unlike endometrioid carcinomas with mucinous features which typically behave in an indolent fashion, gastrointestinal type endometrial carcinomas display aggressive behavior [15].

Neuroendocrine carcinomas of the endometrium (NEEC) comprise <1% of endometrial cancers, express neuroendocrine markers such as synaptophysin, chromogranin, and CD56, and are typically subdivided into small and large cell carcinoma. While most neuroendocrine carcinomas arise within the cervix, primary neuroendocrine carcinomas of the endometrium are often admixed with endometrioid carcinomas. A large-scale national database review of 364 women with NEEC found that compared to endometrioid adenocarcinomas, women with NEEC were more often non-white and presented at a later stage of disease [16]. Furthermore, women with NEEC had a lower median survival (17 vs. 144 months), which persisted even when controlling for stage at diagnosis.

Clinical presentation and diagnosis

Although rare endometrial cancers represent a molecularly heterogeneous group of malignancies, most present with typical symptoms, specifically postmenopausal bleeding. While most patients diagnosed with rare types of EC are postmenopausal, irregular bleeding in premenopausal women also warrants attention. Work-up for postmenopausal or irregular bleeding includes transvaginal ultrasound and endometrial biopsy. As non-endometrioid types of adenocarcinomas may arise in a background of atrophy rather than a lush endometrium, continued bleeding in the presence of a normal ultrasound and/or endometrial biopsy merits further investigation with dilation and curettage, ideally with assistance of hysteroscopy to directly visualize any lesions. For example, in one study of women with high-grade endometrial cancers, 35% had a thin endometrium on ultrasound [17]. Uniquely, carcinosarcomas may present with a large polypoid mass emanating from the cervix. Given the high likelihood of extra-uterine disease and advanced stage with rare endometrial cancers, imaging including a CT scan of the chest, abdomen, and pelvis should

be obtained at the time of diagnosis, in order to direct surgical planning and guide further treatment. PET scan offers no particular diagnostic advantage and increases patient cost.

Treatment for rare endometrial cancers

Surgery

Primary surgery remains standard of care for women with newly diagnosed endometrial cancer, regardless of histology. Certain patients with poor functional status, medical comorbidities which preclude surgery, or widespread metastatic disease not amenable to resection may benefit from chemotherapy and/or radiation with delayed surgery pending clinical improvement. Fertility-sparing surgeries are not recommended in patients with rare endometrial cancers, even in stage I disease. As with usual-type endometrial cancers, a minimally invasive approach with laparoscopy and/or robotic assistance remains standard of care in early-stage disease. In 2009, the LAP-2 trial, which randomized over 2500 women with endometrial cancer to laparotomy versus laparotomy, demonstrated similar overall survival in both cohorts, with shortened hospital stays, fewer adverse events, and improved quality of life in the laparoscopic cohort—thus establishing a minimally invasive approach as standard of care [18]. While the majority of women in LAP-2 had low-risk histology, studies have expanded to patients with high-risk subtypes and demonstrated consistent findings of safety and efficacy. A multi-site study involving 383 women with high-grade endometrial cancer undergoing open versus minimally invasive surgery demonstrated similar progression-free survival between groups, with a higher mean lymph node count, shorter hospital stay, and fewer complications in the minimally invasive group [19]. Similarly, a large cohort of patients including those with high-grade endometrial cancer demonstrated equivalent efficacy and safety between laparoscopic and robotic approaches [20]. Comprehensive surgical staging remains paramount in rare endometrial cancers, as failure to do so may result in downstaging and lead to lack of appropriate adjuvant therapy, thereby affecting survival. For example, in one study of women with clear cell carcinomas and disease clinically confined to the uterus, 52% were found to have metastatic disease at the time of staging [2].

In patients with metastatic disease, efforts at maximal debulking should be pursued, as optimal resection results in improved survival. For example, women with stage IIIC to IV clear cell EC who underwent complete cytoreduction had an improved overall survival compared to women with residual disease [2]. Harano et al similarly found that optimal cytoreduction in a cohort of patients with stages III-IV carcinosarcoma improved overall survival, with a mean OS of 38 versus 18 months for patients who underwent optimal cytoreduction to <1 cm of residual disease, versus suboptimal cytoreduction [21]. For patients with advanced disease or bulky adenopathy, an open approach may be more appropriate, to allow for optimal visualization and improve abdominal access. In the context of grossly metastatic disease, sentinel lymph node mapping and systematic lymphadenectomy offer no benefit, as they may increase morbidity without a survival advantage. However, resection of bulky adenopathy may improve survival and should be pursued as part of tumor debulking [22].

For patients with unresectable disease or poor functional status due to disease burden, neoadjuvant chemotherapy followed by interval debulking

surgery is a reasonable approach. One large review of 5844 patients with advanced endometrial cancer compared patients who had undergone up front versus interval surgery after neoadjuvant chemotherapy, and found that neoadjuvant chemotherapy improved rates of optimal cytoreduction, and shortened hospital stay and operative times, although the authors did not report outcomes by histology [23]. A smaller retrospective review of patients who received neoadjuvant chemotherapy reported on patients with CC, UCS, and mixed adenocarcinomas, and found that less than half were able to undergo interval cytoreduction, for the most part due to disease progression [24]. As these rare and high-grade endometrial cancers may not respond to systemic chemotherapy, the decision to administer neoadjuvant chemotherapy must be balanced against the likelihood of response, patient comorbidities, and disease burden. In our practice, we reserve neoadjuvant chemotherapy for patients with unresectable disease or poor functional status.

Approach to lymphadenectomy

Surgical staging for high-grade endometrial cancers has traditionally included hysterectomy, bilateral salpingo-oophorectomy, and systematic lymphadenectomy with evaluation of both pelvic and paraaortic lymph nodes. As sentinel lymph node mapping gained acceptance in low-risk histology, concerns remained about "missing" metastatic nodal disease in high-grade subtypes, with continued debate over therapeutic versus prognostic benefit of lymphadenectomy. Over time, replacing systematic lymphadenectomy with sentinel lymph node mapping in high-grade endometrial cancers with apparent early-stage disease has gained acceptance. Schlappe et al. reported on over 200 patients with serous or clear cell histology who had undergone sentinel node mapping versus comprehensive lymphadenectomy, and did not appreciate an overall survival difference between the groups [25]. A more recent trial examined 126 patients with high-grade endometrial cancer who underwent sentinel node biopsy followed by full lymphadenectomy, and validated the accuracy of sentinel node biopsy, with improvement in detection of node-positive cases [26]. The study included patients with clear cell and undifferentiated adenocarcinomas, as well as carcinosarcomas. A subsequent literature review including 429 patients with high-grade endometrial cancer reported comparable false-negative rates to low-grade endometrial cancer and suggested sentinel node biopsy replace full lymphadenectomy as standard of care for patients with high-grade endometrial cancer [27]. In our practice, we have adopted sentinel lymph node mapping for patients with early stage rare endometrial cancers.

Adjuvant treatment—early-stage disease

Small sample sizes limit definitive conclusions about optimal treatment for early-stage disease, hence recommendations from retrospective studies—or larger trials which included a small number of rare endometrial cancers—guide treatment decisions. Given the propensity for recurrence even in early-stage disease, most guidelines recommend adjuvant chemotherapy, radiation, or a combination of both (Table 1). However, the decision to proceed

Table 1. Treatment of rare EC based on histology, stage, and molecular profiling

Stage	Histology	Treatment
IA-IB	UCS, UDEC, NEEC*, MLEC, CC**	Chemotherapy x 6 cycles + VBT Consider pelvic RT in deep myoinvasion +/- LVSI
II	UCS, UDEC, NEEC*, MLEC, CC	Chemotherapy x 4-6 cycles*** Pelvic RT +/- VBT
III	UCS, UDEC, NEEC*, MLEC, CC	Chemotherapy x 6 cycles +/- pelvic RT****
IV	UCS, UDEC, NEEC*, MLEC, CC	Chemotherapy x 6 cycles Radiation for palliative purposes only
III-IV	Any + MSI-high, MMRd, high TMB	Consider addition of immunotherapy
III-IV	Any + Her-2 positive	Consider addition of trastuzumab

LVSI, lymphovascular space invasion; *pelvic RT*, pelvic radiation; *VBT*, vaginal brachytherapy
*Neuroendocrine endometrial cancer patients recommend cisplatin and etoposide
**VBT can be considered alone in clear cell carcinoma without myoinvasion
***Four cycles can be considered in patients undergoing pelvic RT
****Consider pelvic RT in patients with node-positive disease

with multimodal treatment must be considered in the context of efficacy and toxicity.

Cantrell et al conducted a retrospective review of 111 patients with stage I-II UCS, and found that adjuvant chemotherapy improved progression free but not overall survival [28]. Only 15 patients received combination chemotherapy and radiation, thus limiting any conclusions regarding efficacy of radiation. A SEER review of 1819 women with early stage UCS did demonstrate a 21% reduction in mortality with the addition of radiation, but this was *not* significant in women who had undergone lymphadenectomy, again highlighting the importance of proper staging [29]. Finally, in another multi-institutional retrospective review of 443 women with stage I UCS, chemotherapy decreased the risk of local and distant recurrence, while combination chemoradiation decreased the risk of local recurrence [30]. While adjuvant pelvic radiation in women with UCS decreases the risk of pelvic recurrence, they remain at risk of distant metastasis, thus underscoring the need for systemic treatment.

In undifferentiated endometrial carcinomas, a retrospective review demonstrated a nonsignificant trend towards survival benefit to chemotherapy in stages I-II disease. Five-year OS was 92% for patients treated with chemotherapy versus 73% without ($p = 0.38$) [31]. There was also a trend towards higher rate of vaginal relapse without brachytherapy. The same phenomenon has been observed in women with NEEC, with a decreased trend towards death with adjuvant chemotherapy, and a reduction in risk of recurrence but not death with radiation [16].

In clear cell carcinoma, the role of chemoradiation is less clear. One group demonstrated improvement in recurrence-free survival with the addition of chemotherapy [32]. Bogani et al. suggest using molecular profiling to guide treatment decisions, and even omitting treatment in fully staged patients with stage I disease and POLE mutations [33]. However, they also acknowledge that the majority of CC patients have a poor prognosis and merit further treatment with either vaginal brachytherapy (stage IA with no

invasion), or combination chemotherapy and brachytherapy in patients with myoinvasive disease.

Indeed, many have begun advocating for molecular profiling to steer adjuvant treatment in early-stage disease. In general, POLE mutations—even in high-grade EC—confer more favorable biologic behavior and foregoing adjuvant treatment in cancers expressing POLE may avoid unnecessary treatment-related toxicities [15]. Similarly, microsatellite-high tumors may benefit from the introduction of immunotherapy in the up-front setting, or even in lieu of chemotherapy. While TCGA classification has not yet replaced current guidelines for management, the cadre of clinical trials incorporating these algorithms continues to broaden, and undoubtedly will dictate management rather than absolute histology in the near future. Until that data matures, treatment of early-stage rare EC consists of chemotherapy for 6 cycles with or without vaginal brachytherapy. In patients with deep myoinvasion, cervical involvement, and/or lymphovascular space invasion, pelvic radiation may reduce the risk of pelvic recurrence, but chemotherapy provides the greatest benefit in terms of overall survival.

Adjuvant treatment—advanced disease

In advanced stage disease, rare EC has a poor prognosis, with 5-year survival rates below 50%. Chemotherapy remains standard of care for patients with advanced endometrial cancers, with or without the addition of radiation. In most cases, a regimen of paclitaxel 175 mg/m^2 and carboplatin at an AUC of 6 administered IV every 21 days is employed for 6 cycles. In patients with advanced uterine carcinosarcoma, a randomized controlled trial comparing carboplatin/paclitaxel to ifosfamide/paclitaxel demonstrated improved overall and progression free survival in the carboplatin/paclitaxel group (37 versus 29 months OS, 16 versus 12 months PFS) with an improved toxicity profile, thus leading to acceptance of carboplatin/paclitaxel as standard of care [34]. These agents are also effective for clear cell carcinomas of the endometrium, although the available data is limited to small numbers of patients with CC who were included in larger clinical trials. Similarly, most patients with advanced undifferentiated endometrial cancer receive combination chemotherapy, but trials including UDEC are limited by sample size [12]. An exception to the carboplatin/paclitaxel paradigm, neuroendocrine carcinomas of the endometrium are often treated with a regimen derived from non-small cell lung cancer, consisting of cisplatin and etoposide. Schlechtweg et al conducted a large database review of 364 women with NEEC, and found that while 60% of patients received chemotherapy, overall prognosis was poor and there was no standardization of treatment [16]. In our practice, we administer cisplatin 80 mg/m^2 on day 1, and etoposide 100 mg/m^2 on days 1, 2, 3 IV on an every 21-day cycle. Data in small cell lung cancer demonstrated improved OS with the addition of atezolizumab to cisplatin/etoposide [35], although this has not been specifically studied in NEEC.

In women with distant (stage IVB) disease, radiation provides little benefit other than palliation of symptoms. In the context of lymphatic metastases, or stage III disease, pelvic or extended field radiation may offer local disease control. A phase 2 sandwich trial in patients with UCS did demonstrate benefit but with considerable toxicity [36]. In patients with advanced disease, we

recommend carboplatin and paclitaxel, with incorporation of external beam radiation in the context of node-positive only disease.

Recurrent disease/future directions

In patients with recurrent rare EC, we recommend molecular profiling and/or enrollment in a clinical trial. For patients who have not yet received carboplatin and paclitaxel or have platinum-sensitive disease, carboplatin and paclitaxel are typically revisited, but yield low response rates. Response rates beyond platinum-based treatment are dismal, and again small sample size limits reporting, but in general single-agent chemotherapy remains standard of care. A retrospective review of 101 patients with recurrent endometrial cancer, which included carcinosarcoma and other rare subtypes, who were treated with bevacizumab revealed a 19% clinical benefit rate [37]. It is therefore reasonable to add bevacizumab to chemotherapy in the setting of recurrence. The role of radiation and/or surgery is limited but may prove beneficial for patients with a long disease-free period and oligometastatic disease.

HER-2 overexpression has been observed in several subsets of rare endometrial cancers. In the up-front setting, the addition of trastuzumab to carboplatin and paclitaxel in patients with uterine serous carcinoma improved progression-free and overall survival in patients with HER-2 overexpressing tumors and now represents standard of care for uterine serous carcinomas [38]. Approximately 10% of UCS overexpress HER-2, and preclinical data has suggested activity in HER-2 overexpressing cell lines [7, 39]. An ongoing clinical trial, NCT04513665, is evaluating a HER-2 targeted antibody in HER-2 overexpressing endometrial cancers and includes patients with UCS.

Immunotherapy should be considered in patients with microsatellite instability (MSI-H), mismatch repair deficiency (dMMR), POLE mutations, or a high tumor mutational burden. Keynote-158 enrolled 90 patients with advanced or metastatic MSI-H or dMMR endometrial carcinoma, and found an objective response rate of 46%, with 68% of patients experiencing a duration of response >12 months [40]. POLE mutations similarly confer sensitivity to immunotherapy, with a case report of a durable response in a patient with USC with a POLE mutation treated with pembrolizumab [41].

In clear cell carcinomas, POLE mutations and MMRd occur in 4% and 10% of patients, respectively [33]. Several ongoing trials with novel immunotherapy agents such as atezolizumab, dostarlimab, and nivolumab are evaluating efficacy in endometrial cancer, many of which include CC and UCS, and combine immunotherapy with chemotherapy or another targeted agent. Combination immunotherapy and tyrosine kinase inhibition with pembrolizumab and lenvatinib was evaluated in a trial of patients with metastatic endometrial cancer and yielded a 38% response rate [42]. Unfortunately, the trial did not include other types of rare EC, but one third of patients had serous carcinoma, and given the molecular similarities between UCS and serous carcinomas, ongoing trials are examining the combination's utility in other tumor types. For example, NCT04149275 explores nivolumab and ipilimumab in combination with the tyrosine kinase inhibitor cabozantinib in recurrent gynecologic carcinosarcoma. NCT05147558 is studying the combination of pembrolizumab and Lenvatinib in women with

advanced uterine carcinosarcoma.

The AKT pathway represents a common node for many endometrial cancers, with mutations in *PI3KCA* and PTEN offering a potential role for mTOR and PI3 kinase inhibition. Mesonephric-like carcinomas, uterine carcinosarcomas, and clear cell carcinomas have all been reported to harbor mutations in these pathways. A recent phase 2 study of a PI3K inhibitor in women with endometrial cancer demonstrated an ORR of 16%, with a 28% clinical benefit rate [43]. While the study included patients with UCS, the drug yielded only a modest response and further studies are needed to clarify the role of PI3 kinase and mTOR inhibition in rare endometrial cancers.

Mutations in the chromatin remodeling complex, particularly ARID1A, have been frequently reported in clear cell carcinomas, which represents an attractive target for ATR inhibition. One ongoing study is examining the ATR inhibitor ceralasertib as a single agent and in combination with the PARP inhibitor olaparib in patients with clear cell and other histologies including UCS [44]. ARID1A mutations have also been described in mesonephric-like carcinomas.

Galusertinib is a TGF-β inhibitor which has shown in vivo efficacy in UCS [45], and is currently under investigation in a clinical trial in UCS in combination with paclitaxel and carboplatin (NCT03206177).

Indeed, triaging treatment based on molecular profiling may provide women the most benefit in the future. One group reported on 189 patients with endometrial cancer whose tumors underwent molecular sequencing. This included women with CC, UCS, and mixed tumor types. Of the 68% of women who harbored actionable mutations, 27% were enrolled to a matched clinical trial, and 47% experienced a clinical benefit [46].

Conclusion

Rare endometrial cancers represent a group of aggressive, molecularly heterogeneous malignancies. Standard of care includes a combination of surgery, chemotherapy, and/or radiation in select cases. Even in early-stage disease, the risk of recurrence is high and adjuvant chemotherapy mitigates the risk of distant metastases. In the recurrent and advanced setting, prognosis is poor, and molecular profiling may reveal actionable targets. Given the difficulty studying rare tumors, future basket or umbrella trials will yield more informative results, with triage to treatment based on molecular profiling rather than histology alone. Despite their rarity, high-grade endometrial cancers account for more deaths than their slow-growing low-grade counterparts and thus their inclusion in clinical trials is paramount to improving outcomes for women affected by endometrial cancer.

Compliance with Ethical Standards

Conflict of Interest

Erin Crane declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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