



Contents lists available at ScienceDirect

## Gynecologic Oncology

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)

## Review

## Management of women with clear cell endometrial cancer A Society of Gynecologic Oncology (SGO) review<sup>☆</sup>

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## ARTICLE INFO

## Article history:

Received 8 December 2008

Available online xxx

## Keywords:

Clear cell

Staging

Radiotherapy

Chemotherapy

## ABSTRACT

**Objective.** Clear cell endometrial cancer (CCE) is an uncommon but important disease because of its aggressive behavior. Furthermore, prospective, randomized studies are either too difficult or impossible because of the small number of women affected. This review explores the differences between clear cell and endometrioid endometrial cancer. In addition, it uses available evidence to determine the best approach to management.

**Methods.** Medline was searched between January 1, 1966 and December 31, 2008 for all publications in English where the studied population included women diagnosed with CCE. Qualifying studies must have had at least 30 patients.

**Results.** Clear cell histology is diagnosed in less than 6% of all endometrial cancers and its incidence increases with age. Diagnosis can be made using the same tests that are used in the diagnosis of other types of endometrial cancer.

Clear cell histology is morphologically and genetically different from the more prevalent endometrioid endometrial cancer histology. It shares many similarities with clear cell neoplasms of the ovary and kidney. Comprehensive surgical staging is critical in order to plan appropriate postoperative management. Adjuvant pelvic and/or whole abdominal radiotherapy have not been shown to be clearly beneficial in women diagnosed with clear cell endometrial cancer. Adjuvant chemotherapy with cisplatin, taxol and doxorubicin either in a doublet or triplet combination has demonstrated efficacy.

**Conclusions.** Women diagnosed with CCE require comprehensive surgical staging. Platinum based adjuvant chemotherapy in a doublet or triplet format in combination with paclitaxel and/or doxorubicin should be considered as part of treatment of these women. Careful long term surveillance following treatment is indicated given the higher rate of recurrence compared to endometrioid endometrial cancer.

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<sup>☆</sup> The Society of Gynecologic Oncologists Clinical Practice Committee is providing this evidence-based medicine summary of current clinical science to SGO members to help facilitate treatment planning.

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doi:[10.1016/j.ygyno.2009.02.003](https://doi.org/10.1016/j.ygyno.2009.02.003)

Please cite this article as: Olawaiye AB, Boruta D., Management of women with clear cell endometrial cancer, Gynecol Oncol (2009), doi:[10.1016/j.ygyno.2009.02.003](https://doi.org/10.1016/j.ygyno.2009.02.003)

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## Introduction

### Questions

1. What are the differences between clear cell, papillary serous and endometrioid endometrial cancer?
2. Based on available evidence, what is the best approach to the management of women with clear cell endometrial cancer?

### Choice of topic and rationale

Endometrial cancer remains the most common genital tract malignancy in women in the United States. In 2008, it is estimated that 40,100 new cases will be diagnosed 7470 deaths will result from endometrial cancer. The incidence of endometrial cancer is approximately the same as the incidence of all other female genital tract malignancies combined [1].

By far, the most prevalent histological type is endometrioid endometrial cancer which represents over 50% of all histological types of endometrial cancer [2,3]. This is followed by papillary serous which is diagnosed in 17 to 22% of cases [4–6]. By contrast, endometrial clear cell cancer is rare and only accounts for 1% to 6% of all endometrial cancers [2,3,7–9].

Due to its rarity, it has been difficult to study clear cell endometrial cancer making the development of evidence-based management challenging. Consensus regarding management has been lacking. On this note, the Society for Gynecologic Oncologists (SGO) working through the Clinical Practice Committee (CPC) decided to develop a series of reviews addressing gynecologic malignancies for its members and affiliates. This is the first of these reviews.

## Methods

In 2007, at the 38th Annual Meeting on Women's Cancer, sponsored by the SGO, a subcommittee of the CPC was formed to consider development of clinical reviews for subject areas where consensus was perceived as lacking. The subcommittee determined an initial set of topics and prepared initial drafts of guidelines to be presented to the CPC for review. Final drafts are to be discussed with the SGO Council and other appropriate SGO committees before publication.

### Literature search strategy

Pubmed was used to search the English literature from January 1966 to December 2008. Search terms included endometrium, cancer, clear cell, endometrial adenocarcinoma and endometrial cancer. These terms were used separately and combined in order to capture the available literature comprehensively.

Inclusion criteria were: publication in English, original report, studies with subject numbers  $\geq 30$ , randomized controlled trials,

prospective non-randomized trials and retrospective studies. Preference is given to articles that contain a pure population of clear cell endometrial cancer patients and those with a subsection analysis on this select group of patients.

Exclusion criteria were: non-English publications, reviews, abstracts/proceedings from meetings that have not been formally published in a peer review format and studies with subjects  $< 30$  (one study was included that did not meet this criterion because of its unique information) [10]. Endometrial cancer papers that do not include clear cell patients are also excluded.

## Results

### Etiology

The etiology of clear cell endometrial cancer is not well understood, but appears to be unique from endometrioid histology. One recent study identified putative precursor lesions in 90% of uterine specimens from women with endometrial clear cell cancer. These lesions were typically isolated glands or surface epithelium within an otherwise normal endometrial region that displayed cytoplasmic clarity and/or eosinophilia with varying degrees of nuclear atypia. In the same study, none of the benign or endometrioid cancer uterine specimens evaluated showed these lesions. Uterine papillary serous cancer was not included in this study [11].

Using cDNA microarray technology, Zorn et al. assessed the gene expression pattern of endometrioid, serous and clear cell cancers from the endometrium and ovary. Renal clear cell cancer was included for clear cell analysis. Endometrioid and serous cancers showed expression patterns unique to the organ of origin. Interestingly, clear cell histologic type showed a remarkable similarity of gene expression pattern across the three organ sites i.e. endometrium, ovary, and kidney [10].

Compared to endometrioid, clear cell endometrial cancer may be more common in older women, among tamoxifen-treated breast cancer patients, and women diagnosed with endometrial cancer following pelvic radiation for another condition [12,13].

### Diagnosis

The majority of women with clear cell endometrial cancer are diagnosed after presenting with post menopausal bleeding. Less commonly, clear cell endometrial cancer is diagnosed subsequent to an abnormal Pap smear. Although Pap smear is not a reliable screening method for endometrial cancer, it tends to be abnormal in women with clear cell endometrial carcinoma [14–16].

Diagnosis of clear cell endometrial cancer may be made utilizing the same tests as are used in the diagnosis of other types of endometrial cancer. Endometrial biopsy, including those performed with an endometrial Pipelle in the office, is highly reliable in obtaining a diagnosis with a sensitivity of over 99% [17].

Pelvic ultrasound can aid in diagnosis. However, caution must be exercised when interpreting the results of ultrasound in women with post-menopausal vaginal bleeding. In one study of women diagnosed with high-grade endometrial cancer, including clear cell histology, ultrasound measurement of the endometrial stripe was <5 mm in 35% of cases [18].

### Pathology

Clear cell endometrial cancer has no characteristic gross features. Histologically, it can have any of the following; papillary, tubulocystic or solid patterns. These features can exist alone or in combination. The papillary pattern appears to be the most common [9]. The papillae may be filiform and regular or irregular in size and shape with cores that are hyalinized or sometimes edematous with an open or ring type pattern. The constituent cells can be one or more of 5 types: (1) polygonal with clear, glycogen-rich cytoplasm and eccentric nuclei; (2) hobnail; (3) polygonal with oxyphilic cytoplasm; (4) flattened; and (5) cuboidal. The nuclear features are typically grade 2 or 3. Other common features include intraluminal mucin, focal presence of intracytoplasmic vacuoles containing eosinophilic hyaline mucin droplets and stromal hyalinization and deposition of basement membrane material.

Immunohistochemistry shows a high Ki-67 index, low immunoreactivity for p53 and absence of estrogen receptor (ER) and progesterone receptor (PR). These can further help to distinguish clear cell cancer from endometrioid (usually ER/PR positive) and papillary serous endometrial cancer (high p53 immunoreactivity) [19].

Clear cell histology should comprise more than 50% of a tumor before the tumor can be designated as clear cell carcinoma (by agreement of GOG pathology committee).

### Treatment

Treatment for clear cell endometrial cancer incorporates surgery, chemotherapy, and/or radiotherapy, often in a multimodal combination. However, because of the rarity of this cancer, there are no prospective trials evaluating these treatments in a study population comprised solely of women with clear cell endometrial cancer. Available data from prospective studies is derived from subsection analysis of large studies wherein the majority of study subjects had more common endometrial cancer histologies, namely endometrioid and papillary serous. Data from small, retrospective studies reporting only women with clear cell endometrial cancer are available. While useful, they are limited in their strength of conclusion due to well known limitations of such studies.

### Surgery

Clear cell endometrial cancer is more likely to present with extra-uterine spread compared to lower grade endometrioid histologies [20]. Extra-uterine disease that goes undiscovered due to failure to perform complete surgical staging may lead to inadequate adjuvant treatment resulting in a missed opportunity for improved survival. Alternatively, without knowledge of surgical stage, adjuvant treatment decisions must be made upon uterine pathology alone. Given that women with clear cell endometrial cancer are known to be at high risk of extra-uterine disease, management with aggressive adjuvant therapy may be recommended. In cases wherein disease is truly confined to the uterus, some of the treatment may be overzealous, resulting in unnecessary cost and potential morbidity. Furthermore, evidence from available literature, most of which come from studies on women with the less aggressive but more common endometrioid endometrial cancer support the concept of upfront comprehensive surgical staging. There are many good reasons for surgical staging.

Clinical staging of women with endometrial cancer carries a large margin of error with regard to the true extent of disease [21,22].

Among a broad population of women with apparent clinical stage I disease including all histologies, as many as 25% had disease spread outside the uterus at the time of surgical staging [23,24] and in clinical stage II disease, some authors report more than 50% margin of error in the estimated extent of disease [25,26]. This represents a major problem since the need for adjuvant therapy or lack thereof, is based on the extent of disease. Many prognostic factors have been reported for endometrial cancer among which tumor grade is the only one that can be reliably determined prior to surgical staging.

The importance of comprehensive surgical staging in clear cell endometrial cancer was emphasized in a recent review by Thomas et al. [27]. In this study, 52% of patients presenting with disease clinically confined to the uterus were found to have extra-uterine disease during comprehensive surgical staging. Accurate identification of the presence of extra-uterine disease allows women with clear cell endometrial cancer to consider the potential utility of adjuvant therapy. Alternatively, it may be reasonable to defer or reduce the extent of adjuvant therapy in patients without extra-uterine disease. In the study by Thomas et al., 50% of women with disease truly confined to the uterus were managed without adjuvant therapy and underwent close surveillance only. No hematologic, lymphatic or peritoneal failures were detected in this cohort at a median follow-up of 44 months [27].

Women with extra-uterine disease may also benefit from maximum cytoreductive effort. In the same study by Thomas et al. [27], women with stage IIIC to IV disease who were completely cytoreduced had a superior progression free and overall survival compared with patients with residual disease at the end of surgery. The study by Thomas et al. is the only study that addressed the role of surgery in a homogenous population of clear cell endometrial cancer patients. Saygili et al. [28] found omental metastasis in 6% of patients with apparent stage 1 endometrial cancer. The omental involvement was occult (micrometastasis) in most of these cases. Overall, only 5% of the patients had clear cell histology in this study but among patients with omental metastasis 33% were from the clear cell histology subgroup. None of the patients with papillary serous histology in this study had an omental metastasis. It is important to note however that omental metastasis has been reported in up to 25% of patients diagnosed with papillary serous endometrial cancer in other studies [29].

Based on the available limited evidence, comprehensive surgical staging in medically fit women diagnosed with clear cell endometrial cancer should include; (1) peritoneal cavity evaluation with washing, smears and biopsies of suspicious looking areas of peritoneum (1) total hysterectomy, (2) bilateral salpingo oophorectomy, (3) pelvic and para-aortic lymphadenectomy (4) omentectomy. In the presence of clinically obvious extra-uterine disease, a maximum attempt should be made to resect all visible lesions (maximum cytoreductive effort).

In conclusion, comprehensive surgical staging and optimal cytoreduction of metastatic disease appears to benefit women with clear cell endometrial cancer and should be considered the first step in most treatment programs.

### Radiotherapy

Treatment of endometrial cancer using radiotherapy alone, without surgical removal of the uterus has been reported. A retrospective review of endometrial cancer cases treated in a single large institution with radiotherapy alone was reported by Kupelian et al. [30]. The disease specific survival of patients with clear cell and papillary serous histology in this study was significantly worse than others. In addition, recurrence of disease within the uterus occurred in up to 15% of women with clinical stage I or II disease.

Both pre-surgery and post-surgery radiotherapy have been evaluated in the treatment of women with high risk endometrial cancer including clear cell histology. Most of the reports in the literature regarding pre-surgery radiotherapy are single institution experiences. These studies did not find significant improvement in

outcome with pre-surgery radiotherapy [31,32]. Radiotherapy in the treatment of endometrial cancer is therefore primarily utilized in the post-operative adjuvant setting. Primary radiotherapy may be appropriate, however, in women whose medical status makes them unfit for surgery.

Post-operative whole abdominopelvic radiation (WAPI) for high-risk histology endometrial cancers, including clear cell, was evaluated in two recent retrospective studies [33,34]. These studies reported a disease free survival (DFS) and overall survival (OS) in women with surgical stage I and II clear cell endometrial cancer at 5 years in excess of 80% and 60% respectively. These results compare unfavorably to DFS and OS in women with similar stage endometrioid endometrial cancer treated with post-operative WAPI. DFS and OS were worse for advanced stage clear cell endometrial cancer compared to early stage clear cell histology or advanced endometrioid endometrial cancer. Both studies reported a long term major complication rate of 7 to 12% with the use of post-operative WAPI in these populations.

In another retrospective study of women with all stages of clear cell endometrial cancer treated with post-operative WAPI, age was found to be a significant prognostic factor independent of other prognostic factors such as FIGO stage, grade of tumor and lymphovascular space invasion (LVSI). The five year event free survival (EFS) and OS were significantly better in women older than 63 years of age compared to younger women, 76% vs. 55% and 85% vs. 63% respectively [35]. However, Mundt et al. reported on the outcome of post-operative radiotherapy in patients with stage I to IV clear cell endometrial cancer. Modalities evaluated included vaginal brachytherapy, whole pelvic with extended field radiation (EFRT) and WAPI. He found a reduced failure rate in the women treated with EFRT. Only one patient in the study had received WAPI, and yet the abdominal failure rate was only 13% compared to a distant failure rate of 40%. This is in contrast to papillary serous endometrial cancer which has a propensity for abdominal failure. He concluded that the low rate of abdominal failure does not support the routine use of WAPI in these women and that the predominance of failure in distant sites indicates a need for development of more chemotherapy protocols [36]. This is the only study of adjuvant radiotherapy in women with clear cell endometrial cancer.

All the studies above are small, retrospective, single institution studies with heterogeneity of patients and therapies. The results are informative but not totally generalizable. Table 1 is a summary of available prospective randomized trials of post-operative radiotherapy in endometrial cancer where clear cell histology is included [37–39].

The two reports by Sutton et al. [37] (GOG-94) are from the largest prospective trial ever done in women with papillary serous or clear cell endometrial cancer [32]. In this phase II trial, clear cell histology constituted 38% of the trial subjects. The PFS in women with stage I and II disease treated with post-operative WAPI was 54%. Of note is the fact that over half of the failures occurred in the radiation field. On the other hand, the PFS in stage III and IV high-risk endometrial cancer was only 27%. This is similar to the PFS of 29% reported for stage-matched patients with endometrioid endometrial cancer. Overall survival was not reported.

The PORTEC trial, reported by Creutzberg et al., was a large phase III trial randomizing women with clinical stage 1 endometrial cancer between treatment with surgery alone versus surgery followed by

pelvic radiotherapy [38]. Patients with clear cell histology comprised only 1% of the total study population. None of the study patients was surgically staged. Drawing meaningful conclusions regarding appropriate management of women with clear cell endometrial cancer is severely limited by both of these factors. Regardless, no significant difference in OS was reported.

The most important treatment related toxicities noted in these prospective trials were hematologic and gastrointestinal [37–39]. The rates for grades 3 to 4 hematologic and gastrointestinal toxicities from the two GOG trials were 9–13% and 15–18%, respectively [37,39]. In the PORTEC trial, a complete break down of toxicity rates was not reported, but a significant difference in treatment related late complications was reported between the group that had radiotherapy (25%) and the group that had no further treatment (6%), [ $p < 0.001$ ]. Additionally, most of the late complications from the radiotherapy group involved the gastrointestinal tract [38]. Two treatment related deaths were reported from all three prospective trials combined [37–39].

Although we continue to give [volume-directed] radiation therapy for high-risk endometrial cancer, we have never conducted a phase III investigation of adjuvant chemotherapy plus radiation therapy compared to adjuvant chemotherapy alone. Also, the proper sequencing of radiation therapy and chemotherapy in the postoperative treatment of women with high risk endometrial cancer including clear cell histology has not been defined in a prospective setting.

In conclusion, although currently available studies exploring the use of adjuvant radiotherapy in the management of women with clear cell endometrial cancer have not demonstrated improvements in OS, they have been underpowered to show one. The lack of adequately powered, prospective controlled trials limits the ability of this review to make definitive conclusions regarding any potential role for post-operative radiotherapy in the treatment of women with clear cell endometrial cancer. Improved local control following postoperative radiotherapy in women at increased risk of recurrence is generally acknowledged. At present, treatment may be justified with this benefit in mind after giving consideration to potential morbidity.

#### Chemotherapy

None of the chemotherapy studies that meet our inclusion criteria was done in a homogenous population consisting of clear cell endometrial cancer. A few retrospective studies that examined the role of chemotherapy in high risk (papillary serous and clear cell histology) endometrial cancer are available. In one such study, following surgical staging, patients with stage 1 to IV endometrial cancer were given cisplatin (50 mg/m<sup>2</sup>), doxorubicin (50 mg/m<sup>2</sup>) and cyclophosphamide (500 mg/m<sup>2</sup>) [PAC] intravenously every 4 weeks for six cycles. At a median follow up of 37 months, recurrence free survival (RFS) and median progression free interval were 52% and 26 months for those with extra-uterine disease. For those patients without extra-uterine disease, the corresponding figures were 76% and 36 months respectively. Clear cell histology was not a significant prognostic factor in both univariate and multivariate regression analysis [40].

The Gynecologic Oncology Group (GOG) and other groups have conducted several phase II trials to identify active cytotoxic agents in endometrial cancer including high risk histologic types such as clear cell. Based on these trials, adriamycin, cisplatin and paclitaxel were found to be the most active agents in this disease [41–44].

**Table 1**

Summary of prospective studies of post-operative radiation in endometrial cancer including clear cell histology

Author, year	Surgical staging	Stage	ARMS	RAD	PFS (3 or 5 years)	<i>p</i>	OS (3 or 5 years)	<i>p</i>
Sutton et al., 2006 (GOG-94)	Yes	I and II	Single	WAPI	54%	N/A	N/A	N/A
Creutzberg et al., 2000	No	I	PXRT NFT	PXRT NONE	96% 86%	<0.001	81% 85%	NS
Sutton et al., 2005 (GOG-94)	Yes	III and IV	Single	WAPI	27%	N/A	35%	N/A

PFS=progression free survival, OS=overall survival, *p*=measure of significant, PXRT=pelvic radiotherapy, NFT=no further treatment, WAPI=whole abdomen and pelvic radiotherapy, N/A=not applicable and NS=not significant.

Subsequently, four randomized phase III trials incorporating these agents in various combinations have been carried out. These studies have included stage III, IV or recurrent endometrial cancer, including clear cell histology and are summarized in Table 2 [4–6,45].

In summary, these phase III trials indicate an overall response rate of 25% for single agent doxorubicin (A) [5], 34–49% for the doxorubicin/cisplatin (AC) or doxorubicin/paclitaxel (AP) doublet [4–6,45] and 57% for the doxorubicin, paclitaxel and cisplatin (TAP) triplet. The triplet regimen, TAP had a statistically significant improvement in overall survival when compared to the doublet regimen, AC. However, neurologic toxicity was worse in patients receiving TAP compared to those receiving AC (27% vs. 4% grade 3 neuropathy respectively) [6]. All the combinations have significant hematologic toxicities when compared to single agent therapy.

The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first line GOG chemotherapy trials was examined in a more recent study (GOG-139) [2]. This study is particularly important because it comprises the largest population of clear cell endometrial cancer patients evaluated for chemotherapy response in a prospective setting. All the patients from the 4 trials listed in Table 2 were combined in this study. Women with clear cell endometrial cancer comprised only 3.7% of the total study populations on these trials. Overall response rate was 32% for clear cell compared to 44% for endometrioid and papillary serous endometrial cancers. Final analysis indicated that histologic type was not an independent predictor of response. However clear cell histology was a predictor of progression free survival (PFS) and overall survival (OS). Patients with clear cell had a 24-month OS of 13% and median OS of 7.9 months compared to those with papillary serous and endometrioid tumors who had 24-month and median OS of 17% and 11.1 months and 27% and 12.8 months respectively. The relative hazard ratio (HR) for death in women with clear cell histology was 1.5 ( $p=0.01$ ) [2].

In all of the GOG trials investigating chemotherapy in women with endometrial cancer that have included clear cell histology (Table 2), seven or more cycles of each regimen were given. Therefore, patients with advanced or recurrent clear cell endometrial cancer undergoing platinum based chemotherapy are best given six to eight cycles.

The value of adjuvant chemotherapy in surgically staged clear cell endometrial cancer patients with disease confined to the uterus (stages I and II) has not been thoroughly assessed. It is doubtful that such a study could be accomplished in the prospective setting given the rarity of clear cell histology. Several, small, uncontrolled, retrospective series have suggested a potential benefit with administration of adjuvant platinum based chemotherapy in women with early stage clear cell endometrial cancer [40,46,47].

None of the studies has used less than six cycles of chemotherapy, except in the setting of toxicity. In the excellent review by Thomas et al. [27], it was suggested that adjuvant chemotherapy may not be necessary in thoroughly surgically staged clear cell endometrial cancer patients with disease truly confined to the uterus. A definitive conclusion cannot be made from this single study.

Following the demonstration of cisplatin's efficacy in women diagnosed with advanced or recurrent endometrial cancer (as a single agent and as part of different combinations) discussed above, several researchers continued to explore the utility of other chemotherapy agents in the treatment of these women. Carboplatin has attracted a lot of interest because of its favorable side effect profile compared to cisplatin. Some of the available retrospective studies exploring the utility of carboplatin in women with endometrial cancer do not give a breakdown of the histologic subtype of the study subjects [48], many of the studies where the data regarding histologic subtype was given excluded women with clear cell histology [49–51] and a good number of studies incorporating women with clear cell histology were made up of small sample size (less than 30 patients) [52,53]. However, three studies involving the use of carboplatin in endometrial cancer meet the inclusion criteria of this review [54–56]. Sovak et al. [54] reported on the use of paclitaxel and carboplatin in women with high risk stage III and IV endometrial cancer (including clear cell histology). In this study, the patients all underwent surgical resection. Twenty percent of the patients had adjuvant radiation therapy prior to the administration of carboplatin (AUC of 5–6) and paclitaxel (175 mg/m<sup>2</sup>). Although the response rate was not reported, the progression free survival (PFS), disease specific survival (DSS) and overall survival (OS) were similar between patients with clear cell histology and others [54]. In a follow-up study led by the same author, 139 patients with advanced or recurrent endometrial cancer, 4.7% of whom had clear cell histology were treated with carboplatin and paclitaxel (TC) combination. Sixty three of the patients had measurable disease by RECIST criteria and therefore assessable for response. The overall response rate was 43% with a complete response of 5% and partial response of 38%. In approximately 8% of the study population, treatment was discontinued due to toxicity [55]. The response rate demonstrated in this study is superior to the AP doublet and slightly inferior to the TAP triplet in the GOG phase III trial chaired by Fleming [6]. However, if we look at the frequency of treatment termination owing to toxicity, TC (8%), AP (9%) and TAP (24%), the potential advantage of the TC doublet becomes readily obvious. Finally, a prospective phase II study of carboplatin and liposomal doxorubicin as first-line chemotherapy for patients with advanced or recurrent endometrial cancer (END-1 study) was reported by Pignata et al. In this study of 42 patients (5% with clear cell histology), overall response rate was 59% with a CR of 7% and PR of 52%. Termination of treatment for unacceptable toxicity occurred in 12% of the study subjects [56].

Carboplatin and paclitaxel (TC) combination appears to have efficacy in the treatment of women with clear cell endometrial cancer. Furthermore, TC may be less toxic and therefore better tolerated in these women when compared to the TAP triplet. The important question that remains to be answered is whether TC and TAP have equivalent efficacy in this setting. Answers to this important question and many others regarding these two combinations will hopefully come from the GOG protocol 209, a randomized phase III trial of TAP and G-CSF versus TC in patients with stage III and IV or recurrent endometrial cancer.

**Table 2**

Results of phase III trials of intravenous chemotherapy in endometrial cancer including clear cell histology

Author, year	ARMS (chemotherapy)	OR (%)	<i>p</i>	PFS (m)	<i>p</i>	OS (m)	<i>p</i>
Thigpen et al., 2004 (GOG-107)	A, 60 mg/m <sup>2</sup>	25	0.004	3.8	0.014	9.2	NS
	A, 60 mg/m <sup>2</sup> +C, 50 mg/m <sup>2</sup>	42		5.7		9	
Fleming et al., 2004 (GOG-163)	A, 60 mg/m <sup>2</sup> +C, 50 mg/m <sup>2</sup>	40	NS	7.2	NS	12.6	NS
	A, 50 mg/m <sup>2</sup> +P, 150 mg/m <sup>2</sup> (24-h)+F	43		6		13.6	
Fleming et al., 2004 (GOG-177)	A, 60 mg/m <sup>2</sup> +C, 50 mg/m <sup>2</sup>	34	<0.01	5.3	<0.01	12.3	0.037
	A, 45 mg/m <sup>2</sup> +C, 50 mg/m <sup>2</sup> +P, 160 mg/m <sup>2</sup> +F	57		8.3		15.3	
Gallion et al., 2003 (GOG-139)	A, 60 mg/m <sup>2</sup> +C, 60 mg/m <sup>2</sup> (ST)	46	NS	6.5	NS	5.9	NS
	A, 60 mg/m <sup>2</sup> +C, 60 mg/m <sup>2</sup> (CT)	49		11.2		13.2	

A=Adriamycin, C=Cisplatin, P=Paclitaxel, F=Filgrastim, *p*=measure of significance, OR=Overall response rate, PFS=Progression free survival, OS=Overall survival, m=months, NS=Not significant.

Considering its propensity for early recurrence and aggressive behavior, it seems reasonable to discuss the option of adjuvant platinum based chemotherapy in all women diagnosed with clear cell endometrial cancer, including those with disease confined to the uterus at the time of diagnosis.

### Prognosis

The impact of clear cell histology relative to other “high risk” endometrial cancer histologies is controversial. Two recent studies found no difference in survival between women with stage I and II clear cell endometrial cancer versus similar stage FIGO grade-3 endometrioid endometrial cancer [20,57]. Survival in women with clear cell histology was, however, worse compared to FIGO grades 1 and 2 endometrioid histology [20,57]. Other studies suggest a worse prognosis for clear cell histology when compared to FIGO grade 3 endometrioid endometrial cancer. In one study comparing outcomes in women with endometrial cancer of either papillary serous, clear cell or FIGO grade 3 endometrioid histology. The proportion of patients with FIGO stage III–IV disease at the time of diagnosis was 36 versus 29% and the 5-year disease specific survival was 68 versus 77%, for clear cell versus FIGO grade 3 histology. In addition, clear cell histology accounted for only 3% of the subjects but was responsible for 8% of disease related deaths [58]. In a second study, clear cell histology was more likely to exhibit a high nuclear grade, deep myometrial invasion, lymphovascular space invasion and extra-uterine disease compared to endometrioid endometrial cancer. Clear cell histology was an independent predictor of poor prognosis [59].

### Future trials

The suggestion by some recent studies that clear cell endometrial cancer may have a premalignant lesion deserves more studies. There is a need for adjuvant chemotherapy and radiation trials in women diagnosed with clear cell endometrial cancer.

Since clear cell endometrial cancer may share a genetic similarity to clear cell ovarian and renal cancers, other therapies such as biologics that are being investigated in these other organ sites should be investigated in clear cell endometrial cancer.

### Conflict of interest statement

The authors of this review have no conflict of interests to declare.

### Summary and recommendations

#### Questions

1. What are the differences between clear cell endometrial cancer, papillary serous and endometrioid endometrial cancer?
2. Based on available evidence, what is the best approach to the management of women with clear cell endometrial cancer?

#### Target population

This review is focused on women with primary or recurrent clear cell endometrial adenocarcinoma.

#### Key evidence

- Clear cell histology is diagnosed in less than 6% of all endometrial cancers.
- The incidence of clear cell histology increases with age.
- Diagnosis can be made using the same tests that are used in the diagnosis of other types of endometrial cancer.
- Adequately powered prospective trials addressing questions pertaining to the management of clear cell endometrial cancer are lacking.

- Clear cell histology is morphologically and genetically different from the more prevalent endometrioid endometrial cancer histology. It shares many similarities with clear cell neoplasms of the ovary and kidney.
- Comprehensive surgical staging is critical in order to plan appropriate postoperative management.
- Adjuvant pelvic and/or whole abdominal radiotherapy have not been shown to be clearly beneficial in women diagnosed with clear cell endometrial cancer.
- In stage III or IV clear cell endometrial cancer and in women with recurrent disease, adjuvant chemotherapy with cisplatin, taxol and doxorubicin either in a doublet or triplet combination has demonstrated efficacy. The triplet combination is more toxic

### Recommendations

- Comprehensive surgical staging including simple hysterectomy, bilateral salpingo-oophorectomy, pelvic, para-aortic lymphadenectomy, omentectomy and cytologic evaluation of the abdominal/pelvic peritoneum should be performed in all medically fit women diagnosed with clear cell endometrial cancer to allow for planning of appropriate adjuvant treatment and surveillance.
- Platinum based adjuvant chemotherapy in a doublet or triplet format in combination with paclitaxel and/or doxorubicin should be considered in women presenting with extra-uterine disease. Similar regimens can be utilized in women with recurrent disease.
- Given the relatively high incidence of distant recurrence of disease, use of adjuvant treatment with platinum based chemotherapy may be reasonable in women diagnosed with stage I and II clear cell endometrial cancer after appropriate counseling.
- Careful long term surveillance following treatment is indicated given the higher rate of recurrence compared to endometrioid endo-metrial cancer.

### Acknowledgments

Members of the Clinical Practice Committee:

Dr Karl Podratz,  
Dr Richard Barakat,  
Dr Steven Waggoner,  
Mary Eiken (SGO administration) and  
Jennifer Bethke (SGO administration).

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