Gynecologic Oncology 115 (2009) 142–153

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

# Management of women with uterine papillary serous cancer: A Society of Gynecologic Oncology (SGO) review ☆

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ARTICLE INFO

*Article history:*
Received 7 May 2009
Available online 9 July 2009

*Keywords:*
Uterine papillary serous carcinoma
Endometrial cancer
Staging
Radiotherapy
Chemotherapy

ABSTRACT

*Objective.* Uterine papillary serous carcinoma (UPSC) is a clinically and pathologically distinct subtype of endometrial cancer. Although less common than its endometrioid carcinoma (EEC) counterpart, UPSC accounts for a disproportionate number of endometrial cancer related deaths. To date, limited prospective trials exist from which evidence-based management can be developed. This review summarizes the available literature concerning UPSC in an effort to provide the clinician with information pertinent to its management.

*Methods.* MEDLINE was searched for all research articles published in English between January 1, 1966 and May 1, 2009 in which the studied population included women diagnosed with UPSC. Although preference was given to prospective studies, studies were not limited by design or by numbers of subjects given the paucity of available reports.

*Results.* UPSC is morphologically and genetically different from EEC. Women often present with postmenopausal vaginal bleeding, but may also present with abnormal cervical cytology, ascites, or a pelvic mass. In some cases, the diagnosis may be made with endometrial biopsy, while in other cases it is not made until the time of definitive surgery. Metastatic disease is common and best identified via comprehensive surgical staging. Local and distant recurrences occur frequently, with extra-pelvic relapses reported most commonly. Optimal cytoreduction and adjuvant platinum/taxane-based chemotherapy appear to improve survival, while adjuvant radiotherapy may contribute to loco-regional disease control.

*Conclusions.* Women diagnosed with UPSC should undergo comprehensive surgical staging and an attempt at optimal cytoreduction. Platinum/taxane-based adjuvant chemotherapy should be considered in the treatment of both early- and advanced-stage patients. Careful long-term surveillance is indicated as many of these women will recur. Prospective clinical trials of women with UPSC are necessary in order to delineate the optimal therapy for women with newly diagnosed and recurrent disease.



**Contents**



☆ 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.2009.06.011

## Introduction

*Questions*

1. What distinguishes uterine papillary serous carcinoma (UPSC) from endometrioid (EEC) and other endometrial histologic subtypes?
2. Based on available evidence, what is the best approach to the management of women with UPSC?

*Choice of topic and rationale*

Endometrial cancer remains the most common gynecologic malignancy in women in the United States. In 2008, an estimated 40,100 new cases of endometrial cancer will be diagnosed and 7470 deaths will occur. The incidence of endometrial cancer is approximately the same as the incidence of all other female genital tract malignances combined [1]. While the incidence and mortality rates from several other cancers have plateaued or decreased in the last decade, rates for endometrial cancer continue to rise [1]. Although the reasons for this are likely multifactorial, findings from a recent SEER database study of more than 45,000 women with endometrial cancer suggest that the increase in mortality may be related to an increased rate of advanced-stage cancers and high-risk histologies including UPSC [2].

Although UPSC represents approximately 10% of all endometrial cancer diagnoses, it accounts for up to 39% of endometrial cancer related deaths [2–4]. This disproportion makes clear the need for improved management. Unfortunately, prospective randomized study of UPSC has been hampered by its relative rarity. Evidence-based management is thus difficult to develop and expert consensus has been slow to evolve.

On this note, the Society for Gynecologic Oncologists (SGO) working through the Clinical Practice Committee (CPC) initiated development of a series of reviews addressing the less common gynecologic malignancies for its members and affiliates. The current report pertains to UPSC.

## Methods

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

*Literature search strategy*

A MEDLINE search of English literature published between January 1966 and June 2009 was performed. All publications with the keywords “uterine neoplasm” or “endometrial neoplasm” were combined and then searched for the keyword “serous” in order to develop a comprehensive list of literature related to UPSC. Additional publications were identified by survey of reference lists within identified publications.

While developing this review, especially the portion devoted to management, the merit of creating inclusion and exclusion criteria based upon subject numbers within each study was considered. Ultimately, the lack of data in the form of large trials was felt to prohibit exclusion of publications reporting small pools of UPSC patients. Thus, all peer reviewed original report publications containing the appropriate subjects were considered. In the studies that include different histologic types of endometrial cancer, we extracted subsection analysis specific to the papillary serous subtype whenever such were available. However, as many of the grade 3 endometrial cancers are of mixed histologies, we included those in which the papillary serous component was driving the clinical behavior of the tumor.

## Results

*Epidemiology*

Lauchlan and Hendrickson et al. first established UPSC as a distinct subtype of endometrial cancer describing it as histologically similar to serous epithelial ovarian carcinoma [5,6]. Shortly thereafter Bokhman proposed the existence of two categories of endometrial carcinoma characterized by distinct microscopic appearance, epidemiology, and clinical behavior (Table 1) [7]. Type I carcinomas display endometrioid histology and typically arise in relatively younger women with obesity, hyperlipidemia, and signs of hyperestrogenism (endogenous or exogenous). Type II carcinomas include poorly differentiated endometrioid, clear cell, and serous histologies, often arise in thinner, older women, and demonstrate no hormonal risk factors. Although obesity is classically considered a risk factor for Type I carcinomas, recent studies suggest that obesity is a risk factor for the development

**Table 1**
Contrasting features of endometrioid versus papillary serous endometrial carcinoma.

| Feature | EEC | UPSC |
|---|---|---|
| Demographics | Younger age | Older age |
| | Obesity | Thin |
| Risk factors | Hyperestrogenism | Breast cancer[a] |
| | Obesity | *BRCA* gene mutation[a] |
| | Hyperlipidemia | Tamoxifen therapy[a] |
| Pattern of recurrence | Local | Distant |
| Precursor lesion | Atypical hyperplasia | Endometrial glandular dysplasia |
| Histologic grade | Low, intermediate, or high | High |
| Molecular changes | PTEN inactivation | p53 mutation |
| | Defective DNA mismatch repair (MSI) | HER-2/*neu* gene amplification |
| Stage at presentation (%) | I (73) | I (54) |
| | II (11) | II (8) |
| | III (13) | III (22) |
| | IV (3) | IV (16) |
| Survival by stage (%) | I (85–90) | I (50–80) |
| | II (70) | II (50) |
| | III (40–50) | III (20) |
| | IV (15–20) | IV (5–10) |

Data from [10–39]. EEC = endometrioid endometrial carcinoma, UPSC = uterine papillary serous carcinoma, PTEN = phosphatase and tensin homolog tumor-suppressor gene, MSI = microsatellite instability.
[a] Conflicting, but suggestive evidence (see text).

of all endometrial carcinomas [8,9]. Increasing age correlates with higher incidence of Type II carcinomas including UPSC. In a study by Lachance et al., 22% of endometrial cancers diagnosed in women over 75 years old were UPSC as compared to only 3% in women younger than 45 years old [10].

Type I endometrial carcinomas are commonly diagnosed at an early stage and have a favorable prognosis, often with surgical treatment alone. Recurrent disease is usually local (pelvis being the most common site) and frequently curable with tumor-directed radiotherapy. Alternatively, Type II endometrial carcinomas are more likely to present with metastatic disease at diagnosis and carry a poorer prognosis [15]. Creasman et al., examining FIGO Annual Report data, noted stage II–IV disease at presentation in 46% of women with UPSC compared to 21% of women with EEC [40]. While 5-year survival in women with stage I EEC approximates 80–90%, only 50–80% of women with stage I UPSC fare as well [4,39–41]. Furthermore, recurrent disease commonly occurs at distant sites, limiting the ability of radiotherapy, as a single modality, to be delivered with curative intent.

Although it is clear that UPSC confers a worse prognosis than most EEC, conflicting studies have been published regarding its prognosis compared to FIGO grade 3 EEC (G3EC) [3,42–44]. The report by Creasman et al. using FIGO Annual Report data, that included 148 women with stage I UPSC and 325 women with stage I G3EC, found equivalent 5-year survival (72 vs. 76%) [40]. Using the Surveillance Epidemiology and End Results (SEER) database, Hamilton et al. noted a significant difference in 5-year disease-specific survival between 1473 women with UPSC and 2316 women with G3EC, both in stage I/II (74 vs. 86%, $p<0.0001$) and stage III/IV groups (33 vs. 54%, $p<0.0001$) [4]. Endometrial malignancies containing UPSC frequently contain a mixture of histologic types of high-grade carcinoma, including EEC and clear cell. The Gynecologic Oncology Group (GOG) Pathology Committee mandates that UPSC should comprise more than 50% of a mixed component tumor before being designated as UPSC for study protocol purposes. However, results from one retrospective study suggest that the presence of UPSC as even a minor component of a uterine tumor (<10%) confers worse prognosis, even when compared with pure G3EC [43].

UPSC comprises a higher percentage of endometrial cancer diagnosed in African American women and may contribute to the racial disparity in survival of endometrial cancer [11–15]. In their analysis of women with advanced-stage or recurrent endometrial carcinoma treated on 1 of 4 different GOG chemotherapy trials, Maxwell et al. found the incidence of UPSC to be 16% versus 39% in white and black women, respectively [13]. Survival in African American women was significantly worse despite delivery of similar surgical and chemotherapeutic treatment. This disparity, however, was demonstrated regardless of histologic type, suggesting that additional undefined factors contribute to the inferior survival seen in African American women with endometrial cancer.

An association between UPSC and breast cancer has been suggested in a number of retrospective studies [32,37,38]. Gehrig et al., in a study of 54 women, noted that women with breast cancer who later developed endometrial cancer were 2.6 times more likely to develop UPSC as compared to EEC (OR 2.6; 95% CI 1.29–5.23) [32]. Similarly, Geisler et al., in a study of 592 women with endometrial carcinoma, noted development of synchronous or subsequent breast cancers in 25% of patients with UPSC compared to only 3.2% with EEC ($p<0.001$) [38]. Utilizing the SEER database, Chan et al. identified 52,109 women diagnosed with corpus cancer including 1922 with a history of breast cancer [37]. The incidence of UPSC was 9.4% in women with a history of breast cancer compared to 6.3% in women without ($p<0.001$).

Although tamoxifen use may contribute to the apparent association between UPSC and breast cancer, the evidence is conflicting [29–36]. The largest relevant study, a report of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1), found no association between tamoxifen use and UPSC. In this trial, 6681 women were treated with tamoxifen for 5 years in an effort to reduce their incidence of breast cancer. Although an increase in the risk of endometrial cancer was observed (RR = 3.28, 95% CI = 1.87 to 6.03), none was UPSC [31].

A link between UPSC and hereditary breast-ovarian cancer syndromes has been postulated [24–28]. If it exists, such a link would impact clinical decision-making related to prophylactic risk-reducing surgery, most likely prompting performance of hysterectomy [28]. Lavie et al. described a series of 20 Ashkenazi Jewish women with UPSC [26]. Four were found to be germline carriers of *BRCA1* gene mutations, 7 had a personal history of breast cancer, and 12 had at least one first-degree relative with either breast, ovarian, or colon cancer. In another series documenting 56 women with UPSC, no *BRCA1* or *BRCA2* gene mutations were identified [24]. Despite this, 11% of the women with UPSC had a personal history of breast cancer and 29% had first-degree relatives with breast cancer. The authors concluded that the observed association between UPSC and breast cancer may be due to the presence of mutations in other, as yet undescribed, cancer predisposing genes.

### *Molecular biology and pathogenesis*

The molecular genetic profiles of UPSC and EEC are a topic of ongoing research. Characterization of these profiles may help to explain differences in their behavior. More importantly, potential specific therapeutic targets may be identified. EEC frequently displays inactivation of the PTEN tumor-suppressor gene, defects in DNA mismatch repair leading to microsatellite instability, and mutations in β-catenin and K-*ras* among others [21]. Alternatively, UPSC is characterized by frequent *p53* gene mutations and HER-2/*neu* gene amplification [22, 23]. Several small studies have demonstrated that human epidermal growth factor receptor 2 (HER2, also known as c-*erb*B2 or HER2/*neu*) is frequently over-expressed in UPSC tumors (16–62%) and may contribute to transformation and tumorigenesis [45–47]. Some studies have associated HER-2/*neu* over-expression with advanced-stage disease, poorer progression-free and overall survival outcomes, making Her-2/*neu* a possible candidate marker of worse overall prognosis in USPC [48,49]. However, these genetic alterations, which may confer a worse prognosis, could potentially be taken advantage of with some of the newer targeted molecular agents being developed. cDNA microarray analysis of endometrial carcinomas

of different histologic types have established different gene expression profiles when UPSC is compared with EEC and clear cell endometrial cancer [50,51].

Although EEC is commonly preceded by hormonally induced atypical endometrial hyperplasia, UPSC may arise within atrophic endometrium [16]. Sherman et al. were the first to propose endometrial intraepithelial carcinoma (EIC) as the precursor lesion of UPSC [17]. EIC is characterized by cytologically malignant appearing cells present in surface endometrium, closely resembling cells of invasive serous carcinoma. A study by Ambros et al. provided further evidence for such a relationship, establishing the presence of EIC in 98% of uteri with UPSC compared with only 6% of uteri with EEC [16]. Additional clinical publications however documented the presence of extrauterine UPSC in numerous women with EIC [41,52–57]. This strongly suggests that EIC represents an early form of UPSC as opposed to a precancerous lesion [58]. More recently Zheng et al. have identified endometrial glandular dysplasia and proposed that it is the precursor lesion of UPSC [18–20]. Consensus opinion on clinical management of this new entity has not been developed [18], but its presence on endometrial biopsy or within a hysterectomy specimen should prompt consideration of the possibility of concomitant or subsequent UPSC.

*Diagnosis*

The most common symptom arising in women diagnosed with UPSC is postmenopausal vaginal bleeding. Endometrial biopsy, including those performed with an endometrial Pipelle in the office, is highly sensitive for detection of high-grade endometrial carcinomas. Huang et al. found Pipelle biopsy to be over 99% sensitive in this setting [59]. However, it was less accurate at predicting UPSC specifically among other high-grade endometrial carcinomas. Of 67 women with a final post-operative diagnosis of UPSC, 17 were initially diagnosed with EEC on Pipelle biopsy. In part, false negative Pipelle results may occur because UPSC are often found mixed with other high-grade carcinomas including EEC and clear cell. False positive results for UPSC were less common. Of 234 women with a final diagnosis of EEC, only 2 were thought to have had UPSC based on Pipelle biopsy. As will become evident when management is addressed, accurate pre-operative identification of UPSC is desirable given that initial treatment recommendations differ compared to those for EEC.

Pelvic ultrasound may aid in the evaluation of postmenopausal vaginal bleeding, but caution must be exercised when interpreting a thin endometrial stripe in women with persistent symptoms or other ultrasonographic abnormalities. Wang et al. published a series of 52 women with Type II endometrial carcinomas including 24 with UPSC [60]. Ultrasound measurement of the endometrial stripe was $\leq$5 mm in 35% and <4 mm in 17% of cases. This differs from the data for EEC, which show that of women with endometrial stripe thickness <5 mm, there were no endometrial cancers [61].

*Management*

Formulating an evidenced-based treatment algorithm for the management of UPSC is hampered by the paucity of prospective controlled trial data. As UPSC is relatively rare, extremely few prospective trials have been performed and as yet, specific standards of care are evolving. Most of the currently available data are in the form of small, retrospective single and multi-institutional studies. The strength of their conclusions is limited due to well-known limitations of such studies. Nonetheless, because of its aggressive behavior and pattern of recurrence, treatment of UPSC is increasingly multimodal, incorporating surgery, chemotherapy, and radiotherapy (see Fig. 1).

*Surgery*

The initial management for the majority of women with UPSC is surgical exploration and comprehensive staging. A small number of reports describe successful administration of neoadjuvant chemotherapy to select women considered poor candidates for upfront surgery [62–65]. In most women, however, comprehensive surgical staging is believed to be beneficial. In addition to providing prognostic information, accurate identification of metastatic UPSC, or documentation of the lack thereof, allows for adjuvant therapy and surveillance to be appropriately tailored. Lymphadenectomy specifically may also provide a therapeutic benefit in women with high-grade endometrial cancer, including UPSC [66]. Although a recently completed prospective randomized controlled trial did not find a survival benefit from pelvic lymphadenectomy in women with endometrial carcinoma, only

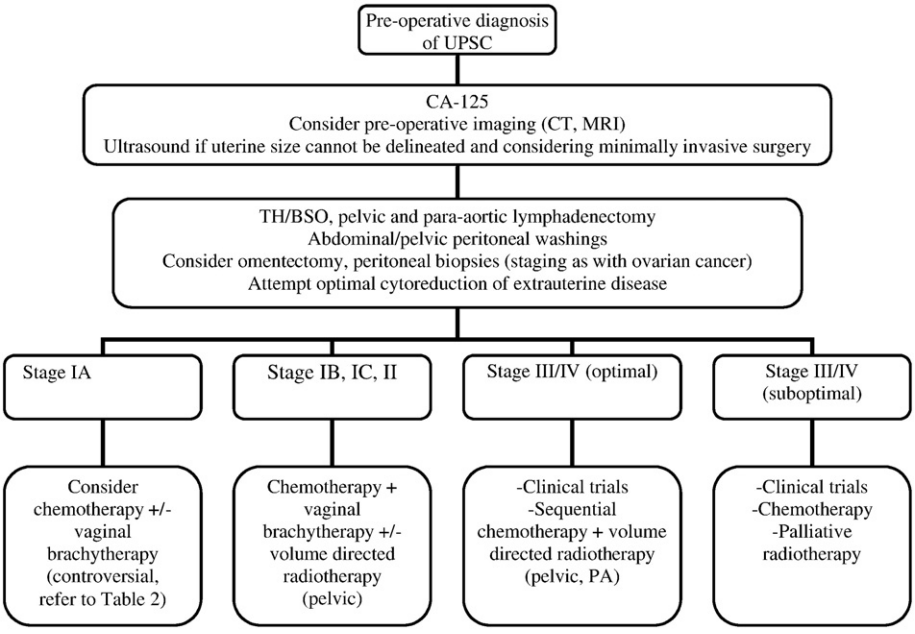


**Fig. 1.** UPSC management algorithm.

4% of the study population had UPSC, and subset analysis was not performed [67]. However, in this trial, treatment versus observation was randomized independent of pathologic staging, which may also contribute to the study findings.

With UPSC, performance of surgical staging selectively, based upon uterine features such as myometrial invasion or lymphovascular-space invasion, is not reliable in its ability to assess for metastatic disease. Numerous investigators utilizing comprehensive staging have documented metastatic UPSC despite the absence of these features [41,52–55,68–70]. In a series of 52 surgically staged women with UPSC, Goff et al. noted similar incidence of lymph node and intraperitoneal metastases in women with either no myometrial invasion or deep invasion (36 vs. 40% and 43 vs. 35%, respectively) [54]. Multiple groups have described series of women with surgically staged UPSC lacking myometrial invasion but with high rates of coincident extrauterine disease (ranging from 37 to 63%) [41,53,69]. Hui et al. noted extrauterine disease in 38% of comprehensively staged women whose uterine disease was solely present within a polyp [69]. The prognostic significance of thorough surgical staging was emphasized by their finding of 94% overall survival in women with tumor limited to their uteri (22 women with 2–73 months of follow-up). Turner et al. noted a significant 5-year survival difference in a group of 38 women with "stage I" UPSC depending on whether complete surgical staging had been performed or not (100% vs. 61%, respectively) [71]. In a study of 206 women with surgical stage I–II UPSC, Fader et al. demonstrated that recurrence and progression-free survival were not associated with increasing percentage of UPSC in the histologic specimen, lymphovascular-space invasion (LVSI), or tumor size [72]. Patients with UPSC in their uterine specimens were at a significant risk for recurrence (21% overall) and poor survival outcomes regardless of the percentage of total tumor comprised of UPSC. Thus, the traditional uterine features used to predict prognosis in patients with early-stage EEC cannot substitute for thorough surgical staging in women with UPSC, including those with only a small fraction of their total tumor comprised of UPSC histology.

International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial carcinoma mandates removal of the uterus, fallopian tubes, and ovaries, along with obtaining abdominopelvic washings for cytology and performance of bilateral pelvic and para-aortic lymphadenectomy. Because of the tendency for UPSC to spread to peritoneal surfaces, as is the case with ovarian serous carcinoma, omentectomy and peritoneal biopsies have been advocated [70,73]. However, in a series of 52 women with UPSC who underwent omentectomy as part of their initial surgery, Gehrig et al. noted 18 patients with omental disease, 16 of whom in which it was grossly evident [74]. Although the omental disease was microscopic in the remaining two women, both had gross metastatic disease elsewhere. The authors concluded that routine inclusion of omentectomy in staging for UPSC may not be necessary.

Unfortunately, a large percentage of women with UPSC present with extrauterine disease at diagnosis. Multiple studies have documented an inverse correlation between survival and the volume of residual disease remaining after cytoreductive surgery in the setting of serous ovarian carcinoma [75,76]. A number of retrospective studies suggest that cytoreductive surgery confers a survival benefit in women with metastatic UPSC as well [77–83]. In a report of 70 women with stage IIIC or IV UPSC by Thomas et al., optimal cytoreduction (defined as no gross residual disease >1 cm in diameter) was achieved in 60%, with no visible residual disease achieved in 37% [83]. A significant difference in median time to recurrence (9 months vs. 6 months, $p=0.04$) and median survival (20 months vs. 12 months, $p=0.02$) was observed between optimally and suboptimally cytoreduced patients. Regression analysis identified the absence of visible residual disease (hazard ratio (HR) = 0.30, $p<0.001$) and the administration of adjuvant chemotherapy (HR = 0.56, $p=0.07$) as independent predictors of overall survival.

*Adjuvant therapy*

*Risk and pattern of recurrence of UPSC*

Surgical staging studies performed by the GOG have defined the spread pattern of EEC [84]. Pathologic findings associated with increased risk of nodal metastasis, as well as disease recurrence, include tumor grade, depth of myometrial invasion, positive peritoneal cytology, tumor within the isthmus-cervix, adnexal involvement, and LVSI [85]. Women with EEC are commonly stratified based upon these features into groups at low, intermediate, and high-risk for recurrence of disease. In contrast, the majority of women with UPSC have a high risk of relapse, even when these other "high-risk" pathologic features are absent [54,86].

While recurrence in most women with early-stage EEC occurs in the vagina or pelvis, the majority of UPSC patients relapse outside of the pelvis, often in multiple sites [87]. Because the pattern and frequency of recurrence differ between women with EEC and UPSC, the evolution of adjuvant therapy prescriptions for each has been distinct. In the case of EEC, adjuvant therapy is increasingly focused locally or even deferred depending on risk factors. For UPSC, adjuvant therapy is being more widely applied, targeting increasingly larger regions and often systemic.

*Early-stage disease*

*Radiotherapy*

Given the excellent prognosis of early-stage, low-grade EEC, adjuvant therapy is considered unnecessary in most cases. Alternatively, stage I UPSC has a poor prognosis with a high rate of recurrence, primarily extra-pelvic in nature. The development of effective adjuvant therapies should be considered a priority in this subgroup of women. Historically, radiotherapy has been the mainstay of adjuvant treatment for endometrial carcinoma. Because of the tendency for UPSC to recur within the peritoneal cavity, most investigation of radiotherapy for early-stage adjuvant treatment has focused on whole abdominal radiotherapy incorporating a pelvic boost (WAPI) [88–92]. Kwon et al. reported on 23 women with stage I UPSC (only one surgically staged) treated with WAPI, none of whom received chemotherapy [88]. Five-year survival was 78.3%, but all recurrences were within the radiated field. An additional retrospective report by Lim et al. described 43 women with clinical stage I UPSC treated with an adjuvant WAPI protocol [89]. Of 10 patients that recurred, 7 did so within the field of radiation.

A retrospective study by Huh et al. reporting a group of 60 women with stage I UPSC is unique in that all were comprehensively surgically staged [93]. Post-operative management consisted of observation alone in 40 women (66%), adjuvant radiotherapy in 12 women (20%), adjuvant chemotherapy in 7 women (12%), and a combination of radiation and chemotherapy in 1 woman (2%). The radiation delivered was WAPI in 3, whole pelvic and brachytherapy in 5, and vaginal brachytherapy alone in 4 women. The risk of recurrence and overall survival were equivalent between those that received either no adjuvant therapy or radiation therapy alone (17 vs. 16%, and 66 and 59%, respectively) prompting the authors to question the benefit of radiotherapy in women with surgically staged UPSC confined to the uterus.

The GOG completed the only prospective study of adjuvant radiotherapy in women with early-stage UPSC [92]. Twenty-one women were treated with WAPI consisting of 3000 cGy at 150 cGy/day to the abdomen and a pelvic boost of 1980 cGy at 180 cGy/day. Eight of 19 evaluable patients died of recurrent UPSC, 5 of whom had recurrent disease within the radiation field. The authors concluded that other adjuvant approaches, namely chemotherapy, perhaps in combination with radiotherapy, should be evaluated in this population.

Based on the propensity for peritoneal recurrence in women with UPSC, Fakiris et al. performed a unique study to evaluate the potential

role of adjuvant treatment with intraperitoneal radioactive phosphorus (32P) [94]. Seventeen of the 21 patients were stage I–IIB, and all had undergone comprehensive surgical staging including maximal cytoreduction with no residual disease >3 mm. Recurrences included two intraperitoneal and two vaginal. The vaginal recurrences prompted addition of vaginal brachytherapy to the regimen, after which no additional vaginal recurrences were noted.

*Chemotherapy*

The high frequency of distant recurrence in stage I UPSC, along with treatment failures within the radiation fields, has led to increasing use of adjuvant chemotherapy and reports of its success. For example, in the above noted study by Huh et al., none of 8 women whose adjuvant treatment included chemotherapy experienced recurrence [93]. Dietrich et al. reported their use of platinum-based adjuvant chemotherapy in 29 women with stage I UPSC [95]. Treatment consisted of carboplatin (AUC 6) and paclitaxel (135–175 mg/m2) in 21 women. All were alive without evidence of disease 10–138 months after treatment. One vaginal recurrence after 3 cycles of adjuvant chemotherapy was successfully treated with chemo-radiation.

In the largest retrospective series in the literature on women with surgical stage I UPSC ($n=141$), Fader et al. demonstrated that while early-stage patients have a significant risk for extra-pelvic recurrence, recurrence and survival outcomes were significantly improved in patients who received platinum/taxane chemotherapy ± radiotherapy compared to women who received no adjuvant therapy or radiotherapy alone [87]. Women treated with platinum/taxane-based chemotherapy had a significantly lower recurrence rate (11.2%) when compared to patients who did not receive chemotherapy (26.9%; $p=.021$). This effect was most pronounced in women with stage IB/IC UPSC. On multiple logistic regression, only chemotherapy and substage impacted recurrence. Progression-free and cause-specific survival for women treated with chemotherapy was more favorable than for women who did not receive chemotherapy ($p=0.024$ and 0.081, respectively). Again, this difference was most pronounced in stage IB/IC UPSC ($p=0.003$). The overall recurrence rate in this study (17%), along with the finding that most recurrences were not salvageable (91.7%), suggests the need for improved systemic therapy in the treatment of early-stage UPSC as well as improved second-line agents.

Unfortunately, there have been no randomized trials exploring the potential utility of adjuvant chemotherapy in treatment of early-stage UPSC. It is also unclear whether adjuvant chemotherapy may be useful for all women with stage I UPSC or only some. While five-year survival in a single institution series of 27 women with surgical stage I UPSC was reported to be 62.9% overall, the prognosis of women confirmed to have stage IA disease appeared to be relatively favorable [41]. Five-year survival was 81.5, 58.6, and 34.3% in stages IA, IB, and IC, respectively. A retrospective, multi-institution study including 83 women with stage I UPSC concluded that observation could be considered in patients with stage IA disease [96]. Although UPSC recurred in 3 of 32 women (9%) with stage IA disease, only 1 of 22 stage IA women (5%) who underwent observation alone experienced recurrence. Recurrence in stage IB/IC disease occurred in 15 of 51 (29%) of women. Similarly, Thomas et al. proposed that women with comprehensively surgically staged IA UPSC should undergo observation, while adjuvant chemotherapy and vaginal brachytherapy be considered for those with stage IB and IC disease [97]. No recurrences were detected among the 15 women with stage IA UPSC, regardless of post-operative management but distant recurrence was noted in 3 of 13 women (23%) with stage IB and IC UPSC who did not receive any adjuvant chemotherapy. Alternatively, in the series by Fader et al. which included 55 women with surgical stage IA UPSC, three of 21 women (14.3%) who did not receive adjuvant therapy (radiotherapy alone or chemotherapy ± radiotherapy) recurred within 2 years [87]. Two of these women died of disease following extra-pelvic recurrence.

Studies by Kelly et al. and Hui et al. attempted to further stratify consideration of observation of women with surgical stage IA UPSC to those without residual disease in the uterine specimen or with disease confined to a polyp, respectively [69,98]. In these series, no recurrences were noted in 12 patients with stage IA disease without residual UPSC or in 22 patients with disease confined to a polyp who were observed post-surgery. In their series of 74 stage I UPSC patients, Kelly et al. also noted a 43% recurrence rate in stage IA patients with residual uterine disease who were observed after surgery. The authors proposed that concomitant platinum-based chemotherapy and vaginal cuff radiation be offered to all women with stage I UPSC except for women with stage IA disease with no residual cancer present in the hysterectomy specimen [98]. Based on the considerable relapse rates noted in some series of stage IA patients with residual uterine disease, consideration of adjuvant treatment, particularly platinum/taxane-based chemotherapy ± radiotherapy, seems justifiable for this subgroup. Patients with disease confined to a polyp or without residual uterine disease should be counseled that the risk of recurrence is quite low but not negligible, and that relapses may be aggressive and not curable.

Whether the addition of radiotherapy to a platinum or platinum/taxane-based regimen improves clinical outcomes for UPSC patients remains unclear. Of 95 patients treated with a platinum/taxane regimen in a multi-institution series of surgical stage I patients, 59 received chemotherapy alone and 36 chemotherapy and radiotherapy [87]. There was no reduction of recurrence observed with the addition of radiotherapy. However, this study was not powered to observe this difference. Kelly et al. advocated a regimen of platinum chemotherapy and vaginal brachytherapy for treatment of stage I UPSC patients, as none of 43 women who received radiation to the vaginal cuff recurred locally as compared to 6/31 (19%) women who did not. Fields et al. treated 18 women with UPSC confined to the uterus with pelvic radiation "sandwiched" between six cycles of platinum/paclitaxel chemotherapy [99]. Another series of 22 women with surgical stage I UPSC treated with adjuvant vaginal brachytherapy alone demonstrated 100% local disease control, although 2 women (9.1%) recurred distally [100]. These studies provide further support for the inclusion of vaginal brachytherapy or pelvic radiotherapy as part of a multimodal program of adjuvant therapy in stage I UPSC. However, prospective studies are required to refine our understanding of the optimal adjuvant regimen and the relative benefit of radiotherapy in stage I UPSC patients. The GOG has proposed a study to evaluate this issue, but it has not yet opened to patient accrual. Table 2 summarizes the outcomes of women with surgically staged stage I UPSC according to the type of adjuvant therapy administered and substage.

Stage II endometrial carcinoma is frequently grouped with "early-stage" disease. A recent retrospective, multi-institution study described a population of surgically staged women with stage II UPSC [105]. Fifty-five women were treated with either observation alone (10), radiotherapy alone (26), chemotherapy alone (7) or a combination of radiation and chemotherapy (12). Treatment with radiation consisted of vaginal brachytherapy, whole pelvic radiotherapy, or WAPI. Chemotherapy consisted of at least three cycles of a platinum/taxane-based regimen. Following a median follow-up of 33 months (range, 10–119), 20 women (36%) had recurred. Most of the recurrences were detected within two years (85%) and were observed outside the pelvis (70%). Adjuvant therapy, however, appeared to reduce the risk of recurrence, with an 11% rate in women treated with chemotherapy ± radiotherapy as compared to 50% in both those treated with radiation alone or simply observed ($p=0.013$). None of the women treated with multimodality therapy experienced a recurrence. Women treated with adjuvant chemotherapy experienced a significant improvement in 5-year progression-free survival (86 vs. 41%, $p=0.10$), although the difference in overall survival (88 vs. 64%) was not statistically significant.

**Table 2**
Recurrence in women with surgical stage I UPSC according to substage and adjuvant therapy.

| Final stage | Overall RR *N* responders/*N* total (%) | Observation only RR *N* responders/*N* total (%) | Adjuvant XRT RR *N* responders/*N* total (%) | Adjuvant CT ± XRT RR *N* responders/*N* total (%) |
|---|---|---|---|---|
| IA | 24/177 (13.6) | 14/115 (12.2) | 10/40 (25) | 3/56 (5.4) |
| No residual disease | 0/13 (0) | 0/10 (0) | 0/1 (0) | 0/2 (0) |
| Polyp only disease | 1/19 (5.3) | 1/9 (11.1) | 0/3 (0) | 0/7 (0) |
| Polyp only or no residual | 1/31 (3.2) | 1/19 (5.3) | 0/4 (0) | 0/9 (0) |
| Other IA | 11/67 (16.4) | 2/27 (14.8) | 4/12 (33.3) | 2/28 (7.1) |
| IB | 10/64 (15.6) | 7/25 (28) | 3/26 (11.5) | 5/66 (7.6) |
| IC | 9/30 (30) | 3/6 (50) | 5/16 (31.3) | 4/24 (16.7) |
| IB and IC combined | 59/212 (27.8) | 25/67 (37.3) | 26/71 (36.6) | 12/107 (11.2) |
| All stage I combined | 78/389 (20) | 41/190 (21.6) | 23/106 (21.7) | 18/165 (10.9) |

Data from [41,52,87,93,96–98,100–104]. UPSC = uterine papillary serous carcinoma, RR = recurrence rate, XRT = radiotherapy, CT = chemotherapy.

*Advanced-stage and recurrent disease*

*Radiotherapy*

Historically, radiotherapy has been used extensively in the management of advanced-stage endometrial carcinoma, including UPSC. Prior to incorporation of surgical staging, radiotherapy was often delivered prior to surgery. Most reports regarding pre-surgery radiotherapy are single institution experiences and are limited by the inadequacies inherent to clinical staging [106]. Post-operative adjuvant radiotherapy for advanced-stage endometrial carcinoma, ranging from tumor volume directed prescriptions to WAPI has been reported by numerous groups. A retrospective report by Smith et al. described administration of WAPI in 18 women with optimally cytoreduced (criterion not defined) stage III/IV UPSC, an unclear number of whom had tumors with a clear cell component [107]. Three-year disease-free and overall survival was 32 and 61%, respectively. Grice et al. identified 17 women with UPSC treated either with WAPI or whole pelvic irradiation with an extended para-aortic field [102]. Of 8 women with stage IIIC disease, two refused adjuvant therapy and six were treated with curative intent. Four of these were alive without disease at 52.5 months, while two others died, one following a vaginal recurrence and the other due to complications of small bowel obstruction with no evidence of recurrent disease. Eight of 9 women with stage IVB disease died despite treatment with a median time to death of 13 months. Kwon et al. reported on 30 women with either stage III or IV UPSC treated with WAPI [88]. Five-year disease-free survival and overall survival was 43 and 45%, respectively. Twenty-two of 25 recurrences occurred within the field of radiation.

Martinez et al. reported a nonrandomized prospective trial of WAPI that included 24 women with optimally cytoreduced (<2 cm) stage III UPSC or clear cell histology [90]. Five-year cause-specific survival was 62% and the incidence of chronic grade 3–4 gastrointestinal toxicity was 14%. An additional prospective study of adjuvant WAPI in optimally cytoreduced (<2 cm) stage III/IV UPSC was conducted by the GOG [108]. Of 20 patients treated, 8 died of disease between 9.6 and 35.2 months following diagnosis. Five women died of other causes, including one from complications of protocol treatment. Over half of the treatment failures occurred within the radiation field.

*Chemotherapy*

Hendrickson et al., in their initial description of UPSC and its aggressive behavior concluded that "it would seem reasonable to try cytotoxic agents such as adriamycin, cytoxan, and cisplatinum which are know to be of some efficacy in treating serous carcinomas of the ovary" [6]. Beginning in 1985, investigators at M.D. Anderson Cancer Center prospectively treated 20 women with UPSC using cisplatin, doxorubicin, and cyclophosphamide (PAC)[109]. The population included 9 women with advanced-stage primary disease, 5 with recurrence, and 6 who received PAC as adjuvant therapy. Only 2 clinical complete responses in women with measurable disease were observed and 5-year survival was 23% [109]. Price et al. similarly evaluated the use of PAC in a heterogeneous group of women with UPSC [110]. Response rate in 11 women with recurrent disease was 27%, but of short duration with a median survival of only 7 months. Of 13 women with stage II–IV disease treated in adjuvant fashion, survival was 42% after 24–41 months of follow-up.

The GOG has completed a series of five phase III randomized prospective trials of chemotherapy for advanced-stage or recurrent endometrial carcinoma [111–115]. The current "gold standard" treatment of advanced-stage or recurrent endometrial carcinoma is based upon the results of these trials. In the most recently completed GOG studies [115], the addition of paclitaxel to cisplatin and doxorubicin (TAP) following surgery (cytoreduction to less than 2 cm maximal residual disease) and radiation (tumor volume directed) was not associated with significant improvement in recurrence-free survival but was associated with greater toxicity in women with advanced-stage endometrial cancer. Approximately 13% of the women on either arm of this trial had UPSC. On multiple variable proportional hazards regression modeling, UPSC was associated with a risk of recurrence that was 4.43 times that of a grade 1 EEC lesion (95% C.I. 2.45–8.02). Subgroup analysis revealed that TAP was associated with a 50% reduction in the risk of recurrence or death among patients with gross residual disease. In addition to TAP potentially improving RFS in women with gross residual disease, there was a trend towards improved outcomes in women with UPSC, though this did not reach statistical significance (HR 0.727). This analysis is further supported by results from an earlier GOG trial of women with measurable, advanced-stage or recurrent endometrial carcinoma [111] wherein TAP significantly improved response rate (57 vs. 34%), progression-free survival (8.3 vs. 5.3 months), and overall survival (15.3 vs. 12.3 months) compared with doxorubicin and cisplatin alone (AP). The authors concluded that although TAP was superior therapy, caution should be used given its high rate of neurotoxicity.

Each of the phase III GOG trials thus far has included a heterogeneous mix of endometrial carcinoma histologies, including UPSC. Women with UPSC comprised 13.2% of the study population in the most recently completed study and 18% within the prior four studies [115,116]. As previously stated, in the most recent GOG trial, a multiple variable proportional hazards regression model determined that histology and grade were statistically significantly associated with recurrence-free survival, with women with UPSC having the worst outcomes [115]. McMeekin et al. analyzed combined data from the four earlier GOG trials [111–114] and concluded that response rate was not associated with histology [116]. These conflicting results add to the ongoing controversy regarding whether women with UPSC and other relatively rare endometrial carcinoma histologies should be included in prospective trials evaluating endometrioid adenocarcinoma or whether individual trials should be developed for the "atypical" histologies as is currently done for uterine carcinosarcoma.

As agents useful in the management of ovarian serous carcinoma have evolved, the utility of chemotherapy in treatment of UPSC has been explored. Zanotti et al. first described administration of paclitaxel with or without either carboplatin or cisplatin in women with UPSC [117]. Objective response was seen in 7 of 11 (64%) of

women treated for recurrent disease and in 8 of 9 (89%) of women treated for residual disease following initial surgery. Eight of 15 women (53%) with stage III and IV UPSC were alive with 10–62 months of follow-up. Overall response rate to paclitaxel alone was 77% in a study by Ramondetta et al. involving 20 women with advanced-stage or recurrent UPSC [118]. A phase II prospective study by Hoskins et al. evaluated carboplatin plus paclitaxel in primary advanced-stage or recurrent endometrial cancer [119]. Sixty-three women were treated, including 18 with advanced-stage UPSC and four with recurrent UPSC. Response in assessable patients was 60% and 50%, respectively. Three-year overall survival in the women with advanced-stage disease was 39%. Additional investigators have published retrospective data that are similarly encouraging regarding the potential utility of carboplatin and paclitaxel [120–122]. These promising results, along with concerns regarding the toxicity of TAP, serve as the backdrop for the currently enrolling GOG phase III trial. In GOG protocol 209, TAP is being compared to intravenous carboplatin and paclitaxel in women with advanced-stage or recurrent endometrial cancer. To date this trial has enrolled 1381 women with a goal accrual of 1350, and thus should be nearing completion.

Administration of intraperitoneal chemotherapy has also been reported for UPSC [123]. Chambers et al. gave intraperitoneal cisplatin along with intravenous doxorubicin and cyclophosphamide to 13 women with stages IA–IVB UPSC. The authors noted that the 3-year overall survival of 24.1% was similar to that of women at their institution treated with intravenous cyclophosphamide, doxorubicin, and cisplatin.

*Chemotherapy vs. radiotherapy*

A number of retrospective series have compared outcomes in women with UPSC treated with adjuvant chemotherapy versus radiotherapy [124–128]. The results have been conflicting and the retrospective nature of the studies limit the power of their conclusions.

GOG protocol 122, a randomized trial comparing WAPI to intravenous AP chemotherapy, enrolled women with stage III or IV endometrial carcinoma with a maximum of 2 cm of post-operative residual disease [129]. Of 396 assessable patients, 202 were randomly assigned to WAPI and 194 to AP. WAPI consisted of 30 Gy in 20 daily fractions to the abdomen, followed by a boost dose of 15 Gy in 8 fractions to the pelvis ± an extended field including the pelvic and para-aortic lymph node region depending on lymph node status. AP consisted of doxorubicin 60 mg/m2 and cisplatin 50 mg/m2 every 3 weeks for seven cycles, followed by one cycle of cisplatin. The hazard ratio for progression adjusted for stage was 0.71 favoring AP (95% CI, 0.55 to 0.91; $p<0.01$). Thus, at 60 months, 50% of women receiving AP were predicted to be alive and disease-free when adjusting for stage compared with 38% of women receiving WAPI. The hazard ratio for death adjusted for stage was 0.68, also favoring AP (95% CI, 0.52 to 0.89; $p<0.01$). Thus, at 60 months and adjusting for stage, 55% of women receiving AP were predicted to be alive compared with 42% of women receiving WAPI. Although over 20% of women in each arm of the study had UPSC, statistically valid subset analyses could not be performed. Regardless, given the results of GOG 122, along with the numerous reports describing disappointing outcomes in women with UPSC treated with WAPI, systemic chemotherapy has become the primary adjuvant therapy in the management of UPSC.

There has not been a phase III investigation of adjuvant chemotherapy plus radiation therapy compared to adjuvant chemotherapy alone. Whether a combination of the two modalities may lead to even better results is unknown. Numerous investigators have reported the feasibility of administering platinum-based chemotherapy regimens in combination with radiation, either sequentially [124,126,130,131] or in "sandwich" fashion [99,132]. A multi-institutional retrospective trial described 109 women with advanced endometrial cancer who received adjuvant therapy in one of the following sequences: chemotherapy followed by radiotherapy, radiotherapy followed by chemotherapy, or radiotherapy "sandwiched" between chemotherapy [133]. The women treated with a "sandwich" regimen had improved 3-year progression-free and overall survival (69 and 88%, respectively) as compared to those receiving radiation then chemotherapy (47 and 54%) or chemotherapy then radiation (52 and 57%). The *p* values for comparison of progression-free and overall survival between the women receiving a "sandwich" regimen versus other therapy sequences were 0.011 and 0.025, respectively. When adjusting for appropriate factors such as stage, age, grade, race, therapy, histology and debulking status, the findings were similar in favor of treatment with a "sandwich" regimen. Because women with UPSC comprised only 15% of the study population subset analyses were not performed. GOG 209 currently allows for women to receive adjuvant radiation as long as it is completed prior to enrollment and administration of chemotherapy. Additional clinical trials exploring the potential benefit of multimodality therapy are necessary. Furthermore, the optimum sequence of multimodal therapy needs to be identified.

*Tumor markers and surveillance*

The histologic similarities between UPSC and ovarian cancer and the propensity for intraabdominal disease have led investigators to explore the potential role of CA-125 to evaluate disease status in women with UPSC. Unfortunately, there have been conflicting results as to its utility. The Cleveland Clinic evaluated CA-125 in 21 women with UPSC and found that in 73% of the women, a rising CA-125 level closely corresponded to or preceded clinical relapse [134]. Another study of 220 serum specimens in 15 women with UPSC found that CA-125 may reflect advanced disease, but may not predict recurrence in the absence of other clinical findings [135].

Investigators have also explored the role that pre-operative CA-125 may play in predicting clinical outcome. Niloff et al. reported that CA-125 levels were elevated in 78% of women with stage IV or recurrent disease [136]. Others have also reported an association between pre-operative CA-125 and advanced extrauterine disease at the time of surgery [137–139]. However, pre-operative CA-125 levels were not predictive of optimal or suboptimal cytoreduction in one study of advanced UPSC [82]. In the largest trial to date of women with UPSC and pre-operative CA-125, Olawaiye et al., found that pre-operative CA-125 correlated with stage of disease at the time of surgery and was predictive of death [140]. When adjusting for covariates, women with a CA-125 $\geq$ 35 had a 3.7 times greater risk of cancer related death as compared to those with a normal pre-operative CA-125.

While CA-125 may be useful, unlike in a significant percentage of women with ovarian cancer, CA-125 alone cannot be used as a surrogate marker for disease status. Therefore, investigators are searching for other markers that can be used either alone or in combination with CA-125. Some of the more novel potential serum markers include HE4, a soluble mesothelin-related peptide [141]; prolactin [142]; and YKL-40, a secreted glycoprotein [143]. However, none of these has been adequately evaluated in women with UPSC.

*Future research*

The development of novel therapeutic agents with targets specific to UPSC is a promising area of research. As discussed earlier in this paper, UPSC is characterized by frequent HER-2/*neu* gene amplification [23]. Several small studies have demonstrated that human epidermal growth factor receptor 2 (HER2) is frequently over-expressed in UPSC tumors [45–47]. These results raise the possibility of therapeutic strategies that target HER2, such as using the antiHER2 monoclonal antibody trastuzumab (Herceptin®). Results from two large randomized clinical trials for patients with HER-2 positive invasive breast cancer show that those patients who received trastuzumab in combination with chemotherapy had a significant

decrease in risk for breast cancer recurrence compared with patients who received the same chemotherapy without trastuzumab [144,145]. To date, trastuzumab therapy and the immunologic basis for its putative activity have not been studied in UPSC.

The optimal approach to studying UPSC has yet to be defined. Given its rarity, UPSC is usually "lumped" with other endometrial cancer subtypes in large, randomized studies, such as those discussed earlier. The percentage of women with UPSC enrolled in these trials is usually low (<20% of all participants), leading to underpowered, and perhaps incorrect, conclusions being drawn regarding the efficacy of specific therapy in this subgroup. Given its more aggressive tumor biology, lethality, and clinicopathologic distinction from EEC, it may be necessary to study UPSC independently. This may be facilitated through an international rare cancer cooperative network. At the very least, it may be necessary to study women with UPSC only alongside women with other "high-risk" histologic subtypes of endometrial carcinoma.

The authors of this paper are certainly not the first to recognize the need for prospective clinical trials of women with UPSC [146,147]. The development of thorough evidence-based guidelines for the management of UPSC awaits their completion. For now, accurate pathologic diagnosis, comprehensive surgical staging, optimal cytoreduction, and a low threshold for initiation of adjuvant chemotherapy, preferably platinum/taxane-based or as part of a clinical trial, must be our guiding principles.

## Summary and recommendations

*Questions*

1. What distinguishes uterine papillary serous carcinoma (UPSC) from endometrioid (EEC) and other endometrial histologic subtypes?
2. Based on available evidence, what is the best approach to the management of women with UPSC?

*Target population*

This review is focused on women with primary or recurrent UPSC.

*Key evidence*

- Although UPSC comprises <10% of all endometrial carcinoma cases, it accounts for a disproportionately high number of endometrial cancer related deaths and affects African American women more frequently than non-Hispanic whites.
- UPSC differs from the other types of endometrial cancer on both molecular and clinicopathologic bases.
- UPSC may present with symptomatic postmenopausal vaginal bleeding and rarely is also detected by Pap smear. It can be diagnosed using office endometrial biopsy.
- Extrauterine disease is common and can be identified with comprehensive surgical staging.
- Optimal cytoreduction of metastatic UPSC appears to confer a survival benefit.
- Randomized prospective trials addressing questions pertaining to the management of UPSC are lacking.
- The incidence of both local and distant recurrence is high among women with stage I UPSC compared to most women with EEC.
- Adjuvant platinum/taxane-based chemotherapy with or without radiotherapy appears to improve progression-free and overall survival outcomes in early-stage UPSC patients.
- Advanced-stage disease is best managed with cytoreductive surgery whenever feasible followed by platinum/taxane-based chemotherapy with or without tumor volume directed radiotherapy.
- Advanced-stage and recurrent disease are best managed with cytoreductive surgery whenever feasible followed by platinum-based chemotherapy with or without tumor-directed radiotherapy. As with early-stage disease, there is a need for prospective clinical trials in this patient population. Traditional therapies are not associated with long-term survival in women with recurrent disease making clear the need for development of novel therapeutic agents.

*Recommendations*

- Comprehensive surgical staging should be performed when feasible in all women diagnosed with UPSC. In addition to simple hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and washings for cytology, performance of omentectomy and peritoneal biopsies should be considered given the propensity for UPSC to metastasize within the peritoneal cavity.
- Adjuvant therapy, including platinum-based chemotherapy and vaginal brachytherapy, should be considered in women with stage I UPSC.
- The relatively favorable prognosis of women with stage IA UPSC with no residual uterine disease after comprehensive surgical staging may justify close observation alone. However, adjuvant chemotherapy and vaginal brachytherapy should be considered in other stage IA patients.
- Women with advanced-stage UPSC are best treated with optimal cytoreduction of metastatic disease followed by adjuvant platinum-based chemotherapy (carboplatin and paclitaxel or cisplatin and adriamycin).
- Careful long-term surveillance following treatment is indicated given the higher rate of recurrence in UPSC patients compared to those with EEC.

**Conflict of interest statement**

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

## Acknowledgments

Members of the Clinical Practice Committee, Mary Eiken (SGO administration) and Jennifer Bethke (SGO administration).

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