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Review Article

Novel Embattled Therapies in Uterine Papillary Serous Carcinoma-A Window of Opportunity

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ABSTRACT

Uterine Papillary serous carcinoma (UPSC) is closely associated with advanced age in patients. The p53 signature (p53S) is considered the earliest indication for the presence of carcinogenesis of UPSC. Based on our previous studies, the presence of p53Ss have almost always been found in elderly women and are suspected of being responsible for the imbalance between the proliferation and apoptosis of endometrial epithelial cells with advanced age. Uterine Papillary serous carcinoma (UPSC) is a highly aggressive variant of endometrial cancer. Although it only represents less than 10% of all cases, it accounts for a disproportionate number of deaths from endometrial cancer. Comprehensive surgical staging followed by carboplatin and paclitaxel chemotherapy represents the mainstay of UPSC therapy. Vaginal cuff brachytherapy is also of potential benefit in UPSC. Recent whole-exome sequencing studies have demonstrated gain of function of the HER2/NEU gene, as well as driver mutations in the PIK3CA/AKT/mTOR and cyclin E/FBXW7 oncogenic pathways in a large number of UPSCs. These results emphasize the relevance of these novel therapeutic targets for biologic therapy of chemotherapy resistant recurrent UPSC.

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INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the developed world. Serous-type uterine cancers are not a recognized feature of any currently defined hereditary cancer syndromes. Several studies have suggested an association between serous uterine cancer and breast cancer. Most studies assessing the link between breast cancer and UPSC, however, have been focused on the proband and there have been no large-scale, in-depth family studies published to date. Although uterine cancer has been implicated in the hereditary breast and ovarian syndrome, an association between serous endometrial cancer and hereditary breast/ovarian syndrome has not been established. Endometrial cancers are typically designed as type I and type II tumors¹. Type I endometrial cancer accounts for 80% of cases and is associated with endometrioid histology, younger age of onset, retention of estrogen receptor and progesterone receptor status, and a history of unopposed estrogen, and deletions in KRAS, PTEN, or mismatch repair mechanisms. Type II endometrial cancers are associated with serous, clear-cell or grade 3 endometrioid histology, loss of estrogen/progesterone receptor, black race, absence of unopposed estrogen, presentation at later stage, reduced E-cadherin expression, aneuploidy, mutations in P53, and HER2/NEU overexpression. Type II endometrial cancers are typically more aggressive than type I cancers and have a poorer prognosis. Of note, 52–70% of type II cancers exhibit extrauterine spread at the time of surgery, compared with 4.6% of low-grade tumors².

UPSC is a clinically aggressive disease that has an early predilection for deep myometrial invasion, lymph-vascular space invasion, and intra-abdominal, as well as distant, spread. It was associated with a 50% relapse rate and had a 5-year survival of 18–27%. In another study, it was found to be responsible for 39% of EC related deaths, despite comprising only 10% of EC cases. Surgical staging remains the mainstay of treatment of UPSC, as the majority of patients with disease clinically confined to the uterus will be upstaged (57–70%). A Gynecologic Oncology Group trial (GOG 94) reported a 35% 5-year disease-free survival when 31 women with stage I and II UPSC received adjuvant postoperative whole-abdomen radiation therapy. Others have not found radiation therapy to be effective. Platinum-based chemotherapy is an

established therapy in advanced-stage UPSC. Conflicting data exist regarding early-stage disease³. Data from a Yale series suggest that the combination of carboplatin, paclitaxel and vaginal apex radiation should be routinely used in stage I UPSC. Only one out of 29 stage IA–IC patients (3.4%) who received platinum-based chemotherapy recurred, whereas 20 out of 32 (62.5%) who did not receive this chemotherapy recurred. Recently, a study of 25 stage I–II UPSC patients treated at the Memorial Sloan–Kettering Cancer Center (NY, USA) with the combination of carboplatin and paclitaxel and vaginal brachytherapy found comparable results. The overall survival of women with UPSC, however, remains approximately 30%. The survival of women with stage I–II UPSC is 35–50% and for stage III–IV UPSC is 0–15%. These figures illustrate the dire need for a deeper understanding of the molecular pathways active in UPSC, as well as the necessity to develop novel and more effective therapeutic modalities against recurrent chemotherapy-resistant disease. In addition to differences in histology, the etiology and survival related to these two subtypes are vastly different. Type I tumors are the prototypical estrogen-dependent tumors; risk factors that increase women's exposure to circulating levels of estrogen are associated with increased risk of Type I EC. Similarly, factors that decrease progesterone are associated with increased risk of Type I EC. Traditionally cited risk factors for Type I EC are obesity, estrogen replacement therapy (ERT), nulliparity, and medical conditions that result in high estrogen levels, such as estrogen-secreting ovarian tumors and polycystic ovarian syndrome. In addition, Type I tumors are more common than Type II tumors in pre- and perimenopausal women⁴.

The concept of an intraepithelial, non-invasive, and possibly precancerous phase of ESC has been recognized for nearly two decades. This lesion has variably been designated as “endometrial intraepithelial carcinoma” (EIC), “serous EIC”, “uterine surface carcinoma”, “endometrial carcinoma in situ” and “minimal serous carcinoma”. This lesion is characterized by the colonization and replacement of benign surface endometrium and glands by cells that are cytologically identical to serous carcinoma, is frequently multifocal, is seen in association with up to 89% of ESC cases, and was postulated to represent the precursor lesion to ESC

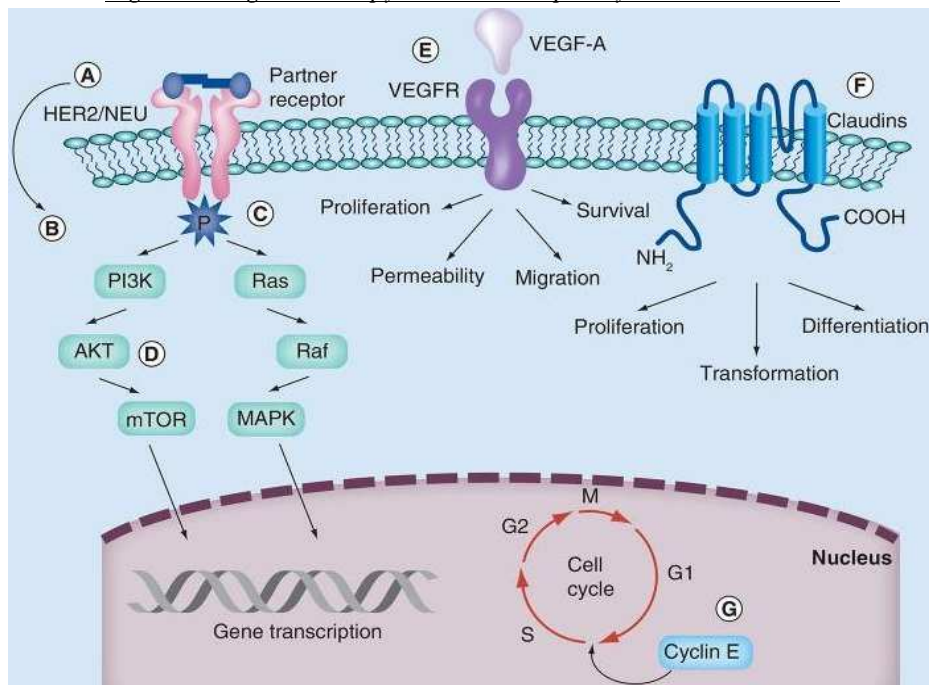
for many years. It has also long been recognized, however, that a significant subset (up to two-thirds) of patients with pure serous EIC (and no ESC as conventionally defined) may have extrauterine disease of the same morphology, immunophenotype, and molecular features. The specific biologic properties of carcinomas with the serous phenotype (possibly related to alterations in cell adhesion molecules) confers upon them the ability to disseminate even in the absence of a morphologically apparent invasive growth. Therefore, as a practical matter, although serous EIC may represent a non-invasive appearing growth pattern of ESC, it has the same clinical implications as the latter, and cannot be considered a precancerous lesion for the purposes of prevention. This recognition is reflected in the patient management recommendations for serous EIC, which largely mirror those for early stage conventional ESC, and include total hysterectomy, bilateral salpingo-oophorectomy, pelvic and periaortic lymph node dissections, multiple peritoneal biopsies and omentectomy, with the need for adjuvant chemotherapy being dependent on the resultant findings. Women diagnosed with UPSC

should undergo comprehensive surgical staging and an attempt at optimal cytoreduction⁵. 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.

MOLECULAR PATHOGENESIS

Type I and type II endometrial cancer differ in their molecular pathogenesis. Type I disease often expresses mutations in KRAS, PTEN and other mismatch repair mechanisms. Type II disease, and UPSC specifically, exhibits aneuploidy and the overexpression of HER2/NEU, as well as cyclin E and claudin-3 and -4. They also have been shown to express mutations in TP53 and other proteins. These mechanisms alter the cell cycle via defects in DNA damage repair, chromatin remodeling, cell cycle and cell proliferation. They also provide potential targets for therapy (Figure 1).

Figure 1 Targeted therapy in Uterine Papillary serous carcinoma.



(A) HER2 antibodies and anti-HER2 vaccines, (B) antibody–drug conjugate, (C) tyrosine kinase inhibitors, (D) PI3K/AKT/mTOR pathway inhibitors, (E) monoclonal antibodies and small-molecule inhibitors, (F) Clostridium perfringens toxin-based therapeutic approaches and (G) CDK inhibitors and curcumin. VEGFR: VEGF receptor.

Because of poor results with surgery alone, both radiation therapy and chemotherapy have been added postoperatively in an effort to improve outcomes. However, the benefit of these modalities, as well as the optimal treatment for each disease stage remains unclear. Recurrence rates in women diagnosed with advanced-stage disease are much higher than for early-stage disease, with rates of 50–90% reported in published studies. These recurrences are often extra pelvic and largely unsalvageable and highlight the need for novel and effective systemic therapy in the treatment of this disease.

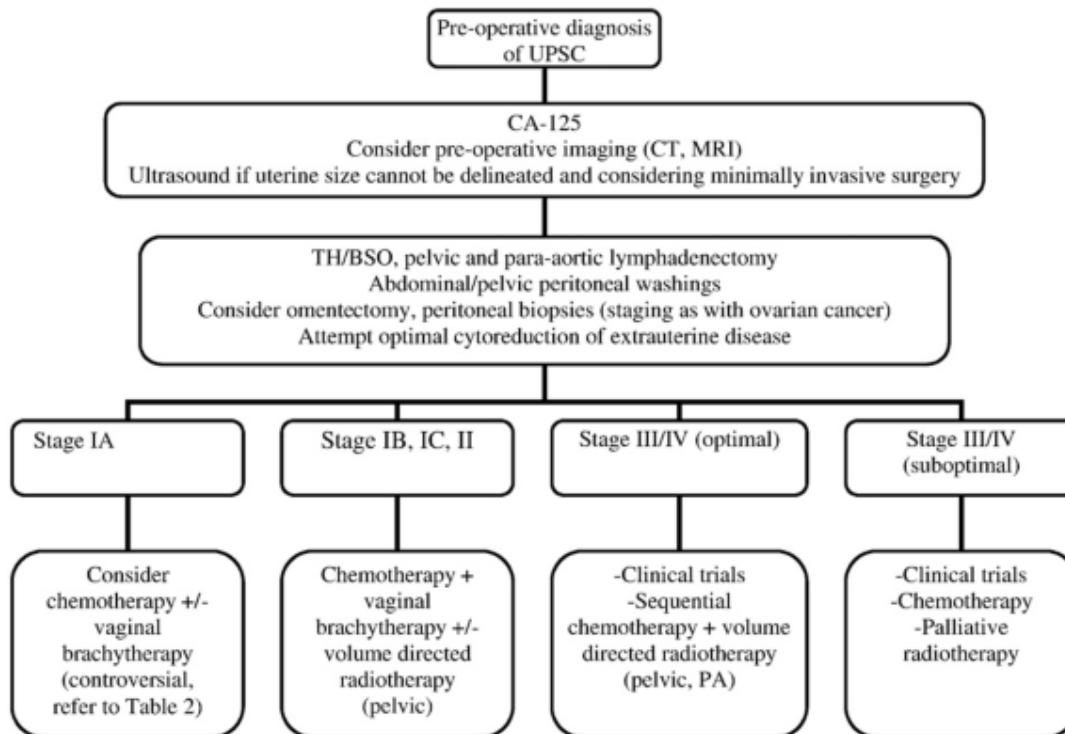
Targeted therapy may represent a reasonable and innovative approach for the treatment of UPSC refractory to standard treatment modalities⁶. Consistent with this view, the HER2/neu, which is targeted by the anti-HER2 monoclonal antibody trastuzumab (i.e., Herceptin), may represent the first of a series of novel diagnostic and therapeutic markers, including but not limited to, EpCAM, kallikrein-6 and -10, TROP-2, claudin-3 and -4,

SAA, α V-integrins, IL-6 and hI-con1, endowed with significant therapeutic potential in UPSC patients harboring advanced and/or recurrent disease.

Chemotherapy and Radiotherapy

Owing to poor results with surgery alone, both radiotherapy (RT) and chemotherapy have been investigated postoperatively in women with both early- and advanced-stage disease in an effort to improve outcomes. However, the benefit of these modalities, as well as the optimal treatment for each disease stage, remains unclear. RT is often utilized to achieve local disease control or to treat locoregional recurrences, while chemotherapy is used to treat systemic or metastatic disease. In women with stage I endometrioid adenocarcinoma, 5-year survival is approximately 80–90%, but only 50–80% of women with stage I UPSC experience similar survival rates. Furthermore, in women with UPSC, disease relapse commonly occurs outside the pelvis, limiting the ability of RT as a single modality to be delivered with curative intent (Figure:2).

Figure:2 UPSC Management Algorithm



Surgical Management

Recurrence patterns (particularly for UPSC) are more similar to that of epithelial ovarian carcinoma

(EOC) than they are to endometrial cancer As such, surgical therapy should parallel that of EOC, and

serum CA-125 levels provide a good marker of disease activity

Meticulous staging is important to exclude the presence of extrauterine disease, which portends a poor prognosis and influences the postoperative management plan. Approximately 70 percent of patients with UPSC will be found to have macroscopic or clinically occult stage III or IV disease. Therefore, women with UPSC and clear cell cancers should undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), pelvic/paraortic dissection (and not just sampling, omentectomy, assessment of the peritoneal cavity including pelvic and diaphragmatic cytology, and resection of gross metastases. If possible, these women should be referred to gynecologic oncologists for surgical management. The strongest predictor of overall survival is the amount of residual disease following surgery. In two series totaling 83 patients, as an example, women with optimal cytoreduction (ie, residual disease less than or equal to 1 cm in maximal diameter) had longer median survival than those left with suboptimal residual disease (26 versus 10 months and 15 versus 8 months. In another report from the Gynecologic Oncology Group (GOG), there were no long-term survivors among those left with gross residual disease following surgery.

Because of poor results with surgery alone, even for patients with stage I disease, both radiation therapy (RT) and chemotherapy have been added postoperatively in an attempt to improve outcomes. However, the benefit of these approaches as well as the optimal treatment for each stage of disease remain unclear. Randomized controlled trials are not available, and interpretation of the majority of retrospective series is compromised by the use of a variety of adjuvant strategies, and the heterogeneity of the treated population⁷. Most reports include incompletely surgically staged women (with some notable exceptions whose disease stage ranges from I to IV. This renders the results virtually uninterpretable.

Adjuvant Radiation Therapy

The role of adjuvant RT in women with UPSC and/or clear cell endometrial carcinomas is controversial. Traditionally, such patients have been treated with adjuvant RT, typically pelvic RT with or without vaginal brachytherapy. Since the initial observation of the propensity of UPSC to relapse in

the abdomen however, attention has been primarily focused on adjuvant whole abdominal RT (WART). Despite the popularity of this approach, no prospective phase III clinical trials have been conducted evaluating the role of WART in UPSC and/or clear cell cancer; as a result, its true benefit remains unproven⁸. Published retrospective series report large variations in disease-free survival and overall survival following WART

In a series of 28 patients, three-year disease-free and overall survival rates following adjuvant WART were 87 and 87 percent for women with stage I to II disease, and 32 and 61 percent for patients with stage III to IV disease, respectively. Only three women recurred in the upper abdomen.

Of the 58 women treated with postoperative WART in a second series, 11 of the 21 relapses were in the abdomen or pelvis. Ten-year disease-free and cause-specific overall survival rates were 35 and 74 percent, respectively.

A single arm study from the GOG (GOG 94) which included 180 surgically staged and optimally debulked women with stage III or IV disease, the three-year disease-free survival and overall survival rates after adjuvant WART were 27 and 35 percent, respectively

The future of WART in stage III to IV UPSC and/or clear cell carcinoma is uncertain given the results of GOG 122. In this trial, optimally debulked (less than or equal to 2 cm residual) women with stage III to IVa endometrial cancer were randomly assigned to WART with a pelvic boost or eight cycles of chemotherapy with cisplatin and doxorubicin. Chemotherapy proved to be superior to WART in terms of two-year overall survival and progression-free survival (PFS). Twenty percent of the enrolled patients had UPSC, and response to treatment was the same for both endometrioid and UPSC tumors. It is likely that few, if any, patients with stage III or IV UPSC and/or clear cell cancer will undergo WART as the sole adjuvant therapy at most institutions in the future.

The benefit of WART is particularly unclear for stage I-II tumors evidenced by the following:

- In a review of 193 women with stage I-II UPSC from nine published studies, abdominal failures occurred in 6 of 68 patients (9 percent) treated with WART versus 10 of 125 patients (8 percent) treated without WART. The use of pelvic and/or

vaginal irradiation was beneficial in terms of pelvic control, however.

- In the only prospective study evaluating WART in women with all stages of UPSC (GOG 94), there was only a 35 percent five-year PFS rate for 31 women with surgical stage I UPSC. These data have only been reported in abstract form, although the results in patients with stage III and IV UPSC have been published.

There is a stronger rationale to support the use of adjuvant pelvic RT for patients with stage I or II disease. In one review, pelvic recurrences occurred in substantially fewer women who received pelvic RT compared to those who did not (11 versus 27 percent, respectively).

The utility of pelvic RT has been challenged in patients with stage I to II disease who undergo complete surgical staging⁹. At least in one report of 60 women with stage I UPSC after complete surgical staging which included complete lymph node dissection, the recurrence rate was similar among the 20 patients who received adjuvant therapy (12 of whom had pelvic RT) and the 40 who did not (16 versus 17 percent). In particular, pelvic sidewall failures were not observed despite the lack of adjuvant pelvic RT.

While an argument can be made for withholding adjuvant pelvic RT for patients with stage I to II disease who undergo complete surgical staging, no degree of lymph node dissection addresses the vaginal cuff. Thus, even complete staging does not obviate the need for vaginal brachytherapy in these patients. In a review of surgical stage I UPSC patients (of whom 48 percent received adjuvant chemotherapy), vaginal recurrences were noted in none of 43 patients who received vaginal brachytherapy versus 6 of 31 patients (19 percent) who did not. These results support the use of vaginal brachytherapy in patients with early stage UPSC who are completely surgically staged.

Even more limited data are available regarding the role of adjuvant RT in patients with clear cell tumors. Unfortunately, most investigators simply group these tumors together with UPSC; as a result, the benefit of adjuvant RT for clear cell tumors has not been adequately defined. The largest study to date focusing on adjuvant RT reviewed outcomes of 38 clear cell patients treated with primary surgery. Pelvic recurrences were seen in 0 of 22 treated patients versus 8 of 16 patients treated without adjuvant RT. Corresponding pelvic recurrence rates

for stage I-II patients with and without adjuvant RT were 0 of 16 versus 5 of 6. Of note, although no women received WART, only one (2 percent) failed in the upper abdomen¹⁰. These results suggest that the optimal adjuvant RT approach for these women is pelvic RT. It remains unclear whether vaginal brachytherapy is sufficient for patients with surgically completely staged clear cell cancer.

CONCLUSION

UPSC is the most aggressive endometrial cancer, representing less than 10% of all cases, a disproportionate number of deaths and a poor 5-year overall survival of 55%. With such a dismal prognosis, these patients should be treated aggressively. Patients should receive complete surgical staging. Those who are identified to have residual UPSC in the uterus at the time of surgery should receive adjuvant carboplatin and paclitaxel chemotherapy, and a strong consideration should be given for vaginal cuff brachytherapy. In patients who present with advanced and/or recurrent chemotherapy-resistant disease, we expect whole-genome sequencing to soon represent a critical tool for the identification and rational design of targeted therapies in women diagnosed with UPSC. Prospective trials incorporating targeted therapies are warranted to define the optimal management approach for women with this biologically aggressive variant of endometrial cancer. Despite the lack of randomized trials on uterine papillary serous carcinoma, several recent reports have provided insight into the diagnosis, surgical management, and adjuvant treatment of this high-risk endometrial cancer.

REFERENCES

1. Bellone S, Black J, English DP, Schwab CL, Lopez S, Cocco E, et al. Solitomab, an EpCAM/CD3 bispecific antibody construct (BiTE), is highly active against primary uterine serous papillary carcinoma cell lines in vitro. *Am J Obstet Gynecol.* 2016;214(1):99 e1-8.
2. Damast S, Higgins SA, Ratner E, De Leon MC, Mani S, Silasi DA, et al. High-dose-rate vaginal brachytherapy with chemotherapy for surgically staged localized Uterine Papillary serous carcinoma. *J Contemp Brachytherapy.* 2015;7(1):35-40.
3. Annunziata CM, Kotz HL. Uterine papillary serous carcinoma: a new paradigm for treatment? *Cancer.* 2009;115(16):3594-6.

4. Dewdney SB, Kizer NT, Andaya AA, Babb SA, Luo J, Mutch DG, et al. Uterine Papillary serous carcinoma: increased familial risk for lynch-associated malignancies. *Cancer Prev Res (Phila)*. 2012;5(3):435-43.
5. El-Sahwi KS, Schwartz PE, Santin AD. Development of targeted therapy in Uterine Papillary serous carcinoma, a biologically aggressive variant of endometrial cancer. *Expert Rev Anticancer Ther*. 2012;12(1):41-9.
6. Black JD, English DP, Roque DM, Santin AD. Targeted therapy in Uterine Papillary serous carcinoma: an aggressive variant of endometrial cancer. *Womens Health (Lond)*. 2014;10(1):45-57.
7. Kawano K, Ushijima K, Yokomine M, Fukui A, Ijichi M, Kamura T. A case of minimal Uterine Papillary serous carcinoma with distant lymph node metastasis without peritoneal dissemination. *J Gynecol Oncol*. 2011;22(1):53-6.
8. Singh Lubana S, Singh N, Tuli SS, Seligman B. Adrenal Metastasis from Uterine Papillary Serous Carcinoma. *Am J Case Rep*. 2016;17:289-94.
9. Cantu de Leon D, Perez Montiel D, Tabarez A, Martinez RM, Cetina L. Serous adenocarcinoma of the fallopian tube, associated with verrucous carcinoma of the uterine cervix: a case report of synchronic rare gynecological tumors. *World J Surg Oncol*. 2009;7:20.
10. Chiu IH, Ho WJ, Wu RC, Chao A. Successful multidisciplinary treatment of Uterine Papillary serous carcinoma in a patient who had previously undergone renal transplantation. *Taiwan J Obstet Gynecol*. 2018;57(4):601-4.

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