

Evaluation of adjuvant therapy in women with uterine papillary serous cancer

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BACKGROUND AND OBJECTIVE: Uterine papillary serous cancer (UPSC) represents only 10% of all uterine cancers and is associated with a significantly worse prognosis compared with other histological types of endometrial cancers. It closely resembles the behavior of ovarian carcinoma.

DESIGN AND SETTING: Retrospective study in a referral center covering period from February 1989 to January 2009.

PATIENTS AND METHODS: Eighteen patients who underwent definitive surgery followed by adjuvant therapy—platinum-based chemotherapy, radiotherapy, or both—were reviewed. Median age was 62 years (range, 52-76 years). All patients underwent total abdominal hysterectomy and salpingo-oophorectomy. Positive lymph nodes were found in 4 of 7 patients who underwent lymph node sampling/dissection. Seven patients had stage I/II disease, whereas 11 patients had stage III disease. Six patients received chemotherapy, 5 patients received radiation therapy, while 7 patients received both chemotherapy and radiation therapy.

RESULT: Median follow-up was 27 months. The median survival and relapse-free survival were 33 and 23 months, respectively. Eight patients were alive and free of disease, of whom 5 patients were stage I/II and 4 patients were stage III. Distant metastasis was the most common site of relapse. Early stage (I/II) was associated with significant improvement in relapse-free survival (RFS) and overall survival (OS) ($P=.004$ and $P=.05$, respectively). The combined-modality treatment including chemotherapy-radiotherapy showed statistically significant improvement in RFS ($P=.012$), while the improvement in OS did not reach statistical significance ($P=.12$).

CONCLUSION: This study indicates that postoperative combined treatment with chemotherapy and radiation therapy plays a role in the management of UPSC by improving RFS. Distant metastasis remains the major site of relapse. Future studies using combined-modality therapy are needed to improve the outcome in patients with UPSC.

Uterine papillary serous cancer (UPSC) is an uncommon histological type that accounts for only 10% of all uterine cancers.^{1,2} UPSC has a propensity for deep myometrial invasion and lymphatic vascular invasion (LVI) and often presents in an advanced stage.^{3,4} Relapse rates are extremely high (50%-80%), with a high incidence of upper abdominal metastasis and dissemination that closely resembles the behavior of ovarian carcinoma.⁵ UPSC has a significantly worse prognosis compared with other histological types of endometrial cancers.

Even among women with stage I disease, the 5-year survival rates for UPSC were reported to be 72%, compared with 89% for endometrioid cancers.⁶ Because

of its aggressive behavior and poor clinical outcome, treatment with surgery alone is not sufficient.⁷ There is a lack of consensus on the optimum management of women with UPSC, especially in an adjuvant setting. There are no randomized, controlled trials.^{7,8} Studies have shown that radiotherapy alone for the treatment of UPSC is inadequate and have pointed toward a more aggressive approach, viz, postoperative combination of chemotherapy and radiation.

PATIENTS AND METHODS

This was a retrospective study covering the period February 1989 to January 2009. Eighteen patients who underwent definitive surgery followed by adju-

vant therapy—either platinum-based chemotherapy, radiotherapy, or both—were reviewed. Patients who had developed metastatic disease at presentation or had suboptimal surgery with residual disease were excluded. The hospital records were reviewed, and data on both the patient and tumor characteristics (histology, lymphovascular invasion, and lymph node involvement) were collected. The staging system of the International Federation of Gynecology and Obstetrics from the AJCC Cancer Staging Manual, Sixth Edition, was adopted for staging. Pure UPSCs were defined as an entire sample showing UPSC or in which any other component was less than 10% of the tumor sampled. Mixed UPSCs were defined as those in which the minor components of a mixed tumor, serous or other, constituted 10% or more of the tumor sampled.

Data on treatment modalities, adverse events associated with therapy, time to recurrence, and overall survival were collected. Relapse-free survival (RFS) was calculated from date of surgery to relapse of disease or death from any cause. Overall survival (OS) was calculated from date of surgery to last follow-up or the date of death. RFS and OS were calculated using the Kaplan-Meier curves. The effects of age, stage, LVI, and treatment modality on RFS and OS were calculated using the Cox proportional hazard models with significance at values of $P < .05$.

RESULTS

The median age of the patients was 62 years (range, 52-76 years). All patients underwent total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Eleven patients had peritoneal fluid washing. Omentectomy was done in 5 patients, and 7 patients underwent lymph node sampling/dissection. Fifteen (83%) patients had pure UPSC. Seven (39%) patients had stage I/II disease, whereas 11 (61%) patients had stage III disease. Positive lymph nodes were found in 4 of 7 patients who underwent lymph node sampling/dissection (Table 1).

Adjuvant therapy was given to all patients, including the following: 6 (33%) patients received chemotherapy, 5 (28%) patients received radiation therapy alone, while 7 (39%) patients received both chemotherapy and radiation therapy (Table 2). Chemotherapy, which was started approximately 4 weeks after surgery, consisted of cisplatin and cyclophosphamide (Cytosan) (before the year 2000) or carboplatin and paclitaxel (after the year 2000). Ten (77%) patients received carboplatin and paclitaxel, while 3 (23%) patients received cisplatin and cyclophosphamide. The median number of chemotherapy cycles was 3. Only 1 patient received neoadjuvant chemotherapy (carboplatin and paclitaxel, 3 cycles), followed by

Table 1. Patient characteristics.

Variable	Number (%)
Median age	62 (range, 52-76)
Surgery	
TAH + BSO	18 (100)
Lymph node	7 (39)
Sampling/dissection	5 (28)
Omentectomy	11 (61)
Peritoneal washing	
Stage	
IA	1 (5.5)
IB	1 (5.5)
1C	1 (5.5)
IIA	3 (17)
IIB	1 (5.5)
IIIA	6 (33)
IIIC	5 (28)
Histology	
Pure	15 (83)
Mixed	3 (17)
Lymphovascular invasion	
Yes	5 (28)
No	5 (28)
Unknown	8 (44)
Lymph node metastasis	
Yes	4 (22)
No	3 (17)
Not done	11 (61)
Peritoneal washing	
Positive	3 (17)
Negative	8 (44)
Not done	7 (39)

TAH: Total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy

6 cycles after surgery. One patient experienced grade 3 vomiting during chemotherapy.

All 12 (67%) patients who received radiation therapy were given external-beam radiation to the whole pelvis. It usually started 3 to 4 weeks after surgery or on completion of chemotherapy. Six (50%) patients received 45 Gy

Table 2. Type of adjuvant therapy administered.

Variable	Number (%)
Chemotherapy	6 (33)
Radiation	5 (28)
Chemotherapy and radiation	7 (39)
Type of chemotherapy	
Carboplatin and paclitaxel	10 (77)
Cisplatin and cyclophosphamide	3 (23)
No. of cycles	
≤3	7 (54)
>3	5 (38)
Unknown	1 (8)
Type of radiation	
Pelvic radiotherapy	2 (17)
Pelvic + brachytherapy	9 (75)
Unknown	1 (8)

in 25 fractions, 2 (17%) patients received 50 Gy in 25 fractions, and 3 (25%) patients received 50.4 Gy in 28 fractions. This was followed by high-dose-rate brachytherapy in 9 (75%) patients. A brachytherapy dose of 5 Gy in 2 fractions was given to 2 patients; 10 Gy in 4 fractions was given to 4 patients; and 25 Gy was given to 2 patients. Patients receiving combined chemotherapy-radiotherapy (7 patients) received chemotherapy followed by radiation therapy.

The median follow-up was 27 months. The median OS and median RFS were 33 months (95% CI, 18.7-46.6 months) and 23 months (95% CI, 12.6-33.3 months), respectively. Eight (44%) patients were alive and free of disease, of whom 5 patients were stage I/II and 3 patients were stage III. Seven (39%) patients were alive with recurrence, while 2 (11%) patients were not alive at the time of last follow-up. One patient had died without evidence of recurrence.

Eight (44%) patients developed recurrence, and all had distant metastasis at the time of relapse. The most common sites of relapse were the lung (3 patients) and peritoneum (2 patients), followed by the liver, brain, and mediastinal lymphnodes (1 patient each). Locoregional recurrence occurred in 7 patients, and the most common site was abdominopelvic lymph nodes (6 patients), followed by the vaginal vault (1 patient). The percentages of recurrence were higher in patients who received chemotherapy alone (4 patients, 50%) or radiation therapy

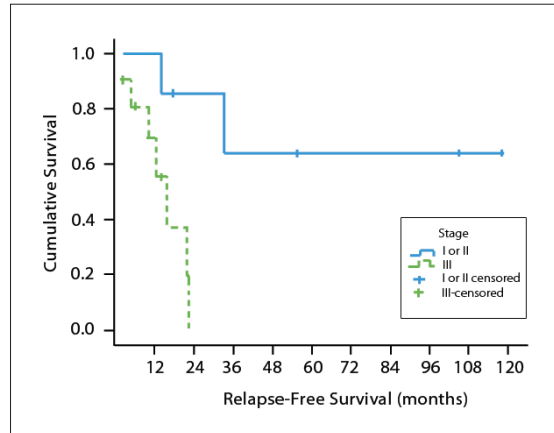


Figure 1. Kaplan-Meier relapse-free survival analysis for women with uterine papillary serous carcinoma by stage.

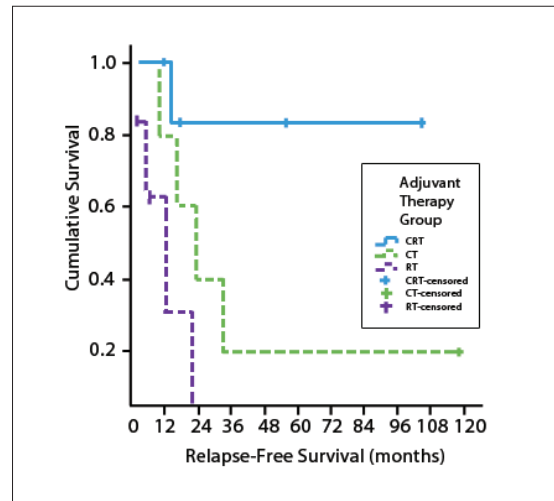


Figure 2. Kaplan-Meier relapse-free survival analysis for women with uterine papillary serous carcinoma by adjuvant therapy group. CRT: chemoradiotherapy, RT: radiotherapy

alone (3 patients, 37.5%) compared with the patient who received both chemotherapy and radiation (1 patient, 12.5%).

Early stage (I/II) was associated with significant improvement in RFS (3-year RFS, 64.3% vs 0% for stage III; $P=.004$) (Figure 1). Three-year OS was marginally significant in patients with stage I/II compared with patients with stage III (64.3% vs 19.4%; $P=.05$). The combined-modality treatment, including both chemotherapy and radiation, resulted in a statistically significant improvement in RFS (3-year RFS, 83.3% vs 0% with chemotherapy and 20% with radiation; $P=.012$) (Figure 2), while the improvement in OS did not reach statistical significance ($P=.12$).

DISCUSSION

UPSC is a rare variant of endometrial cancer; it is associated with a poor prognosis. It frequently presents at an advanced age and has aggressive behavior, with a propensity for deep myometrial invasion, lymphovascular space invasion, and upper abdominal metastasis. Its clinical behavior resembles that of an ovarian papillary serous cancer. Optimal cytoreduction surgery should be considered with the aim of leaving no macroscopic disease at the end of operation. Macroscopic residual disease was a significant prognostic factor that was associated with worse OS.⁹

Relapse rates as high as 50% to 80% have been reported even in early-stage disease. Because of poor outcome, treatment with surgery alone is inadequate even for patients with stage I disease, and there is need for further adjuvant therapy to improve the overall result. In our study, 11 (61%) of the patients presented with advanced stage III disease. The relapse rate was high (44%), and all patients with recurrence developed distant metastasis at the time of relapse. Patients with early stage (I/II) showed significant improvement in RFS and OS compared with patients with advanced stage ($P=.004$ and $P=.05$, respectively).

Because of the rarity of UPSC, there is no randomized trial; and there is a lack of consensus on the optimum management of women with UPSC, especially in the adjuvant setting. The role of adjuvant radiation therapy is controversial. Many studies have shown that adjuvant pelvic radiotherapy may reduce the risk of locoregional failure postsurgery.^{10,11} Attention has been focused on whole abdominal radiation therapy (WART) because of the propensity of UPSC for relapse in the abdomen. However, the results of published reports are conflicting. Lim et al¹² showed a significant improvement in 5-year disease-specific survival in patients who received WART in comparison with patients who did not, but they also showed the majority of relapses were in the pelvis and abdomen despite receiving WART. Frank et al¹³ reported no benefit from WART. Other studies also showed that the majority of recurrences occurred within the radiated field.^{14,15}

Adjuvant chemotherapy is a logical choice of treatment for UPSC because of the similarity in behavior between UPSC and ovarian cancer. The majority of

studies were retrospective reviews. They demonstrated that patients treated with platinum-based chemotherapy have an improved outcome compared with early-stage patients who undergo observation or radiation alone postsurgery.¹⁶⁻¹⁹ A recent retrospective review showed that chemotherapy significantly affected progression-free survival and OS, based on a multivariate analysis.²⁰

In our series, the median survival and RFS were 33 and 22 months, respectively. The combined multimodality therapy with adjuvant chemotherapy and radiation showed significant improvement in RFS compared with either modality alone ($P=.012$). Our present study is the first one from Arab countries, and its data are consistent with those of other studies. A retrospective review of 23 women with UPSC showed higher overall survival in patients treated with chemotherapy and radiation compared with those treated with radiation alone.²¹ Another report of 26 patients treated with adjuvant platinum-based chemotherapy followed by radiation for stages I to IV UPSC showed better local control, and 14 (54%) patients were alive and disease free.²² Similar conclusions were reached when a retrospective series compared 18 patients treated with chemotherapy and WART with 55 patients treated with WART alone. It showed significantly worse progression-free survival and OS with WART compared with multimodality therapy.²³

In a pilot phase II trial, 30 women with UPSC were treated after surgery with 3 cycles of paclitaxel/platinum chemotherapy followed by pelvic radiation and then three additional chemotherapy cycles. Three-year disease-free survival and OS with stage I/II disease were 69% and 75%, respectively, and with stage III/IV disease were 54% and 52%, respectively. While these results seem better than those reported by other series, in this trial, there was no control group for comparison.²⁴

In conclusion, patients with UPSC have a poor prognosis because of a high risk of recurrence, with a high incidence of upper abdominal and distant metastases. The combined-modality therapy with adjuvant chemotherapy and radiation may improve survival compared with either modality alone. Future prospective studies using multimodality therapy are needed to confirm this hypothesis.

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