



## Uterine Papillary Serous Carcinoma: Analysis of 10 Cases

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**Objective:** To establish the prognosis and effect of full surgicopathological staging followed by radiotherapy in patients with uterine papillary serous carcinoma (UPSC).

**Study Design:** Between January 1992 and September 2000, fourteen patients with UPSC were treated. All medical records were reviewed. The 2-year actuarial disease specific survival rate was calculated by using Life-Table. Wilcoxon (Gehan) statistic was used in comparing prognostic factors related with actuarial disease specific survival.

**Results:** The median duration of follow-up was 16 months (range, 4-22 months). The 2-year actuarial disease specific survival rate was found to be 49.3%. The median overall survival was 14.8 months. Wilcoxon (Gehan) statistic revealed that patients with elevated CA-125 levels at diagnosis did significantly better than patients with initial CA-125 levels at normal ranges (p=0.021).

**Conclusion:** Our findings suggest that postoperative treatment with whole pelvic irradiation combined with high dose rate brachytherapy appears to be inadequate in the adjuvant therapy of patients with UPSC.

**Key words:** papillary Serous Carcinoma, Endometrium, Prognosis, Treatment.

### Uterin Papiller Seröz Karsinom: 10 Olgunun Analizi

**Amaç:** Uterin papiller seröz karsinom olgularında cerrahi evrelendirmeyi takiben uygulanan radyoterapinin etkinliğini ve hastalığın prognozunu belirlemek.

**Çalışma Şekli:** Ocak 1992-Eylül 2000 tarihleri arasında uterin papiller seröz karsinom tanısı alan 10 olgu tedavi edildi. Tıbbi kayıtlar incelenerek hastalığa özgü iki yıllık sağ kalım oranı Yaşam Tablosu kullanılarak hesaplandı. Hastalığa özgü iki yıllık sağ kalıma etki eden prognostik faktörler Wilcoxon (Gehan) istatistiği ile belirlendi.

**Bulgular:** Ortanca takip süresinin 16 ay olduğu bulundu (4-22 ay). Hastalığa özgü iki yıllık sağ kalım oranının %49.3 olduğu saptandı. Ortanca sağ kalım süresinin 14.8 ay olduğu belirlendi. Wilcoxon (Gehan) istatistiği, tanı sırasında yüksek CA-125 düzeyi saptanan olgulardaki sonuçların başlangıç CA-125 düzeyi normal sınırlarda olan olgulara göre daha iyi olduğunu ortaya koydu (p=0.021).

**Sonuç:** Bizim bulgularımız, uterin papiller seröz karsinomu olan olgularda, postoperatif adjuvan tedavi olarak pelvik radyasyon ve brakiterapi kombinasyonunun yetersiz olduğuna işaret etmektedir.

**Anahtar kelimeler:** Papiller Seröz Karsinom, Endometrium, Prognoz, Tedavi.

Type II endometrial carcinomas are estrogen-independent and have adverse histologic features and a substantially poorer prognosis. Of those, uterine papillary serous carcinoma (UPSC) is a histologic subtype of endometrial adenocarcinoma that is characterized by its papillary architecture, poor differentiation and advanced stage at initial presentation.<sup>1</sup> Although UPSC represents only 3% to 4% of endometrial cancer cases, it is of particular interest because of the aggressive clinical course and poor prognosis associated with the disease.<sup>2</sup>

UPSC histologically resembles papillary serous carcinoma of the ovary.<sup>3</sup> Unlike typical endometrial carcinoma, patients with UPSC often have extrauterine disease simulating the behaviour of ovarian carcinoma.<sup>4</sup> Recurrence rates among patients with UPSC are extremely high (50-80%) with the majority of tumors recurring in the abdomen.<sup>4</sup>

This report deals with experience at SSK Maternity and Women's Health Teaching Hospital, Ankara, in managing the patient with UPSC. In the current study, we report on the clinical history, treatment and follow-up of ten women with UPSC.

## PATIENTS AND METHODS

A total of 653 patients with endometrial carcinoma were recorded at SSK Maternity and Women's Health Teaching Hospital, Ankara, between January 1992 and September 2000; fourteen (2.1%) were diagnosed to have UPSC.

### Clinical Features

Medical records were abstracted for age, reproductive history, history of diabetes mellitus, hypertension, obesity (defined as  $BMI \geq 29 \text{ kg/m}^2$ ), surgical stage, persistent, recurrent or metastatic disease.

Surgical staging was performed according to the criteria adopted by the International Federation of Obstetrics and Gynecology (FIGO) (5). All patients were operated on and staged surgically.

### Histopathology

All pathologic slides were reviewed by the same pathologist (Ö.A) and confirmed to be UPSC according to the criteria defined previously (6,7). All hysterectomy materials were evaluated for the depth of myometrial infiltration, vessel invasion, cervical, adnexial and lymph node involvement. The depth of myometrial infiltration was classified as 1) intramucosal, 2) less than half of the myometrium, 3) more than half of the myometrium. Vessel invasion was considered positive when tumor cells were found within spaces lined by endothelium.

### Treatment

Total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic and paraaortic lymphadenectomy was performed for all patients. Infracolic omentectomy was routinely performed and peritoneal washings were obtained from every patient. Surgery was followed by vaginal and pelvic irradiation. At the time of relapse, treatment was individualized and patients were treated with cisplatin-based chemotherapy.

### Follow-up

Follow-up examinations were performed at SSK Maternity and Women's Health Teaching Hospital, Ankara, Department of Gynecological Oncology. After the initial operation, patients were followed-up

every three months for two years. If dead, the cause of death was defined and was recorded as either death from endometrial carcinoma or death from intercurrent disease.

Four patients were excluded from the study; one patient was lost to follow-up, two patients having been operated at other centers referring to our institution afterwards and one woman because of being medically inoperable who underwent primary radiotherapy. The diagnosis of recurrent disease was based on clinical and radiologic examinations.

### Survival and Statistical Analysis

Actuarial disease specific survival rate was calculated by Life-Table with the help of a commercially available programme based on SPSS 9.01 for Windows. Wilcoxon (Gehan) statistic was performed for comparing prognostic factors related with actuarial disease specific survival.

## RESULTS

### Patient Characteristics

The mean age of patients at the time of diagnosis was found to be 60.5 years (range, 50 to 72 years). The presenting symptom was postmenopausal bleeding in nine of ten women. One patient was on hypertensive medication but with normal blood pressure at the time of diagnosis while two were with pre-existing insulin-dependent diabetes mellitus. Five patients were identified to be obese with a BMI more than  $29 \text{ kg/m}^2$ . Two patients were nulliparous, others had more than one child. The mean number of parities for all patients included was found to be  $4.5 \pm 3.2$  (range, 0-10). CA-125 determination at admission revealed a level of  $CA-125 \geq 35 \text{ U/ml}$  in five women. The demographic characteristics of patients are shown in Table 1.

Eight patients (80%) had FIGO Stage III and IV disease whereas two patients showed Stage II tumors. Of eight patients with advanced disease, three were assigned to Stage IIIA because of positive peritoneal cytology and three were assigned to Stage IIIC on the basis of retroperitoneal lymph node involvement. Two patients were staged as Stage IVB because of the macroscopic disease detected in omentum. The surgicopathological stage and morphologic features are shown in Table 2.

### Treatment and Outcome

Diagnosis was established by dilatation and curettage in all women. All patients underwent total abdominal

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**Table 1.** Demographic characteristics of patients with UPSC versus relapse rate.

Characteristic	No	(%)	Relapse	(%)
<b>Age (years)</b>				
<61	7	(70)	4	(57.1)
61-72	3	(30)	1	(33.3)
<b>Parity</b>				
Nulliparous	2	(20)	0	(0)
Multiparous	8	(80)	5	(62.5)
<b>Presenting symptom</b>				
Postmenopausal bleeding	9	(90)	4	(44.4)
Abdominal pain	1	(10)	1	(100)
<b>Diabetes Mellitus</b>				
Yes	2	(20)	1	(50)
No	8	(80)	4	(50)
<b>Hypertension</b>				
Yes	1	(0)	0	(0)
No	9	(90)	5	(55.5)
<b>Obesity</b>				
Yes	5	(50)	2	(40)
No	5	(50)	1	(20)
<b>Initial CA-125 level</b>				
≥35 U/ml	5	(50)	4	(80)
<35 U/ml	5	(50)	1	(20)

**Table 2.** The morphologic features of the patients with UPSC versus relapse rate.

Characteristic	No	(%)	Relapse	(%)
<b>Surgical Stage</b>				
Stage IIB	2	(20)	2	(100)
Stage IIIA	3	(30)	2	(66.6)
Stage IIIC	3	(30)	0	(0)
Stage IVB	2	(20)	1	(50)
<b>Myometrial invasion</b>				
None	0	(0)	0	(0)
<1/2	2	(20)	1	(50)
>1/2	8	(80)	4	(50)
<b>Vessel invasion</b>				
Yes	9	(90)	4	(44.4)
No	1	(10)	1	(100)
<b>Cervical involvement</b>				
Yes	7	(70)	3	(42.8)
No	3	(30)	2	(66.6)
<b>Adnexial metastasis</b>				
Yes	6	(60)	2	(33.3)
No	4	(40)	3	(75)
<b>Peritoneal washing</b>				
Positive	6	(60)	3	(50)
Negative	4	(40)	2	(50)
<b>Lymph node involvement</b>				
None	6	(60)	4	(66.6)
Pelvic and paraaortic	4	(40)	1	(25)

hysterectomy and bilateral salpingo-oophorectomy with pelvic and paraaortic lymphadenectomy combined with infracolic omentectomy. In four of these patients (40%) positive lymph nodes were found. After surgery, eight women were macroscopically free of disease. In one woman, residual disease was > 2 cm and in one woman it was < 2 cm.

A total dose of 5000 cGy external beam irradiation (ERT) of the pelvis in daily fractions of 200 cGy combined with a total dose of 3000 cGy high dose rate brachytherapy (HDRB) was performed for all patients following surgery (three fractions of HDRB with one week intervals, where the fraction dose was 1000 cGy). Five patients had recurrent disease (defined as new evidence of disease 6 months or

**Table 3.** The site and time of recurrent disease in patients with UPSC.

No	Site of recurrence	Time of recurrence	Status
1	Abdominal mass between transverse colon and stomach (abdomen)	16 months	Alive with tumor
2	Ascites (abdomen)	9 months	Dead of cancer
3	Spleen (abdomen)	19 months	Alive with tumor
4	Suprarenal gland (retroperitoneum)	8 months	Alive with tumor
5	Ascites (abdomen)	11 months	Alive with tumor

**Table 4.** The 2-year actuarial disease specific survival in various clinical and histopathological features of UPSC.

Characteristic	n	2-year actuarial disease specific survival (%)	Wilcoxon (Gehan) p value
FIGO Stage			
II	2	50	
III and IV	8	51.4	1.0
Myometrial Invasion			
<1/2	2	33.3	
>1/2	8	51.4	0.58
LVSI			
Yes	9	41.6	
No	1	100	0.33
Cervical involvement			
Yes	7	30.4	
No	3	100	0.15
Adnexial metastasis			
Yes	6	50	
No	4	50	0.46
Peritoneal washing			
Positive	6	60	
Negative	4	35.7	0.24
Initial CA-125 level			
≥ 35 U/ml	5	100	
< 35 U/ml	5	0	<b>0.021</b>
Retroperitoneal lymph node involvement			
Yes	4	35.7	
No	6	60	0.55

more after termination of initial treatment) following irradiation. Those patients experiencing recurrent disease were treated with intravenous cisplatin (50 mg/m<sup>2</sup>) and doxorubicin (50 mg/m<sup>2</sup>) every three weeks for six courses. The site and time of recurrent disease is shown in Table 3.

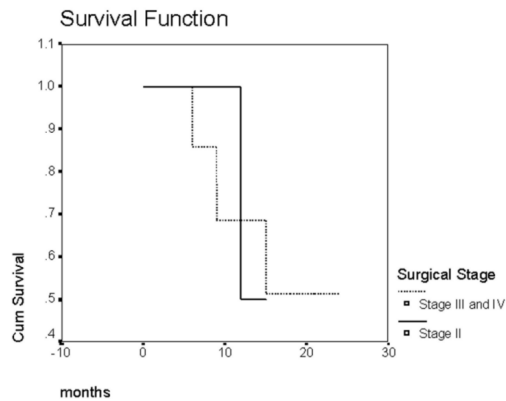
The median duration of follow-up was 16 months (range, 4-22 months). The 2-year actuarial disease specific survival rate was found to be 49.3%. The median overall survival was 14.8 months. The 2-year actuarial disease specific survival according to pathologic stage is demonstrated in Figure 1. At the time of reporting, two patients are alive with no evidence of disease while four are alive with tumor. However, four women are dead of disease.

The 2-year actuarial disease specific survival as related to surgical stage, myometrial infiltration, vessel

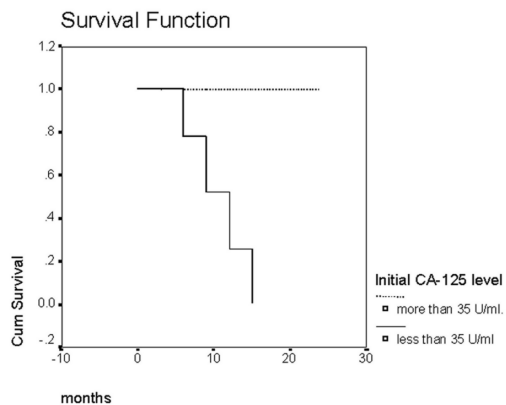
invasion, cervical involvement, adnexial metastasis, peritoneal washings and retroperitoneal lymph node involvement by Wilcoxon (Gehan) statistic is shown in Table 4. The 2-year actuarial disease specific survival according to initial CA-125 antigen level is shown in Figure 2.

## DISCUSSION

UPSC is a highly aggressive type of endometrial cancer that occurs in the absence of hyperestrogenism and endometrial hyperplasia.<sup>8</sup> Biologically, UPSC belongs to a distinct group of aggressive neoplasms of the extended Mullerian epithelium that are characterized by hypoestrogenism, advanced disease at diagnosis, a serous papillary histotype and a dismal prognosis.<sup>8</sup> UPSC has been associated with an increased propensity for extrauterine spread.<sup>9</sup> Even when the primary lesion is small, it exhibits a propensity for



**Figure 1.** The 2-year actuarial disease specific survival according to early and advanced disease.



**Figure 2.** The 2-year actuarial disease specific survival according to initial CA-125 level.

early myometrial invasion, lymph-vascular space involvement and metastatic intraabdominal and lymphatic spread.<sup>10</sup> Survival rates of not more than 50% are commonly reported even for tumors which appear to be confined to the uterus.<sup>9</sup>

The reported frequency of UPSC varies from 3% to 10% of all endometrial carcinomas.<sup>1-3,6,11</sup> Our finding of 2.1% is significantly lower than the previously reported incidences.

The mean age of patients with UPSC is reported to be relatively high. Bancher-Todesa et al.<sup>4</sup> reported the mean age of patients with UPSC to be 72.4 years. The mean age at UPSC at diagnosis was reported to be 69 years by Rosenberg et al.<sup>12</sup> The mean age of the patients was 60.5 years in our series. Our finding of

60.5 years appears to be almost a decade younger when compared with previous reports.

Postmenopausal bleeding is reported to be the most frequent symptom in UPSC.<sup>13</sup> In nine of ten patients, postmenopausal bleeding led to the diagnosis in our series whereas 20 of 23 patients in the series of Bancher-Todesca et al.<sup>4</sup> presented with postmenopausal bleeding. However, obesity, diabetes and hypertension are not as closely related to UPSC as they are to the usual endometrioid adenocarcinoma.

In the present study, the 2-year actuarial disease specific survival rate in UPSC was found to be 49.3%. The 5-year overall survival probability for patients with FIGO Stage III, IV UPSC was reported to be 22.4%<sup>4</sup> while Rosenberg et al.<sup>14</sup> reported that 52% of Stage I UPSC patients were dead of their disease. The median overall survival was 14.8 months in our series. Ho et al.<sup>15</sup> reported the overall survival as 15 months in a series of 19 cases with UPSC.

Cirisano et al.<sup>16</sup> reported that when UPSC was confined to the endometrium, paraaortic metastases occurred in 13% of cases while extrauterine metastases occurred in 55% of UPSC tumors confined to the inner one-half of myometrium.<sup>16</sup> It was reported that the 5-year overall survival probability decreased as FIGO Stage and the presence of lymph node metastases increased.<sup>4</sup>

We were unable to define the depth of myometrial infiltration, vessel invasion, cervical involvement, adnexial metastasis, positive peritoneal washing, retroperitoneal lymph node involvement as prognostic factors by Wilcoxon statistic (Table 4). Interestingly, Wilcoxon statistic revealed that patients with elevated CA-125 levels at diagnosis did better than patients with initial CA-125 levels at normal ranges. Abramovich et al.<sup>16</sup> reported that 13 of 16 patients with UPSC were with elevated CA 125 levels prior to chemotherapy and concluded CA-125 antigen level to be a useful indicator of disease response or progression in women with UPSC. However, no relationship between initial CA-125 level and prognosis was reported in the study of Abramovich et al.<sup>16</sup> Although all patients in our series with elevated CA-125 levels at diagnosis experienced recurrences, the 2-year disease specific survival was significantly better in these patients when compared to patients with normal CA-125 antigen levels at diagnosis. In spite of the fact that the number of patients in our series is very limited, we

suggest that elevated CA-125 antigen levels at diagnosis of UPSC might be a marker of recurrent disease as well as an indicator of response to cisplatin-based chemotherapy. It should be emphasized that these preliminary results should be interpreted cautiously and should be confirmed in larger studies.

Because even the earliest stage of disease is associated with a poor prognosis, a case can be made for offering adjuvant therapy to all patients diagnosed with UPSC.<sup>17</sup> The effect of postoperative adjuvant therapy on the outcome of patients with papillary serous carcinoma has been controversial.<sup>1</sup> Several authors have described a complete response to cisplatin-based chemotherapy, whereas others have reported UPSC to be relatively resistant to chemotherapy.<sup>1,10,18</sup> However, the results of chemotherapy as treatment in a recurrent disease setting have been disappointing.<sup>4</sup> Minimal overall response rates on the order of 20% have been reported in most series.<sup>13,18,19</sup> However, all patients experiencing recurrences in our series were treated with cisplatin and doxorubicin. Of those, one is alive with no evidence of disease, three are alive with the tumor and one is dead of the disease.

Although radiation therapy has been the mainstay of adjuvant therapy in endometrial carcinoma, the results of this treatment modality in UPSC have been diverse.<sup>20-22</sup> Bancher-Todesca et al.<sup>4</sup> reported the 5-year overall survival probability to be 30% for patients with UPSC treated with radiotherapy alone. Only two of five patients treated with adjuvant radiotherapy are alive in our series. It should be emphasized that patients with recurrent disease who were treated with cisplatin-based chemotherapy are not evaluated in this concept. Regarding to these results, we consider that whole pelvic irradiation combined with HDRB appears to be inadequate in the adjuvant therapy of UPSC.

On the other hand, Mallipeddi et al.<sup>23</sup> reported a 50% survival rate in 10 patients treated with whole-abdomen radiation therapy (WART). In contrast, Frank et al.<sup>24</sup> reported no benefit from WART. In both of these studies the patients who survived had early-stage tumors.

Rosenberg et al.<sup>14</sup> reported the recurrence rate to be 31% among patients with Stage I UPSC. The recurrence rate was found to be 50% in our study. The most common site of recurrence was reported to be abdomen (46%) by Rosenberg et al.<sup>14</sup> whereas

four of the five recurrences in our series located in the abdominal cavity (Table 3). More than 80% of relapses have been reported to occur within 25 months.<sup>23,24</sup> Our results are consistent with the latter finding (Table 3).

Although our study is of limited numbers, we want to point out the probability of initial CA-125 antigen level to serve as an indicator of recurrent disease and potential response to chemotherapy in UPSC. Larger studies concerning with full surgicopathological staging are needed in order to confirm these preliminary data.

Our results indicate that postoperative treatment with whole pelvic irradiation combined with HDRB appears to be inadequate in the adjuvant therapy of patients with UPSC. Further improvement in treatment regimens is required to effectively alter the poor prognosis associated with this condition.

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