Uterine papillary serous carcinoma (pure and mixed type) compared with moderately and poorly differentiated endometrioid carcinoma. A clinicopathologic study

R. Halperin[1], *M.D., Ph.D.*; **S. Zehavi**[2], *M.D.*; **R. Langer**[1], *M.D.*; **E. Hadas**[3], *Ph.D.*; **I. Bukovsky**[1], *M.D.*; **D. Schneider**[1], *M.D.*

Department of [1]Obstetrics and Gynecology and [2]Pathology, Assaf Harofeh Medical Center, Zerifin, Affiliated with Sackler School of Medicine, Tel-Aviv University, Tel-Aviv [3]Science Based Industrial Park, Ness Ziona (Israel)

Summary

Objective: The aim of this study was to investigate the clinicopathologic features and the outcome in patients with pure and mixed type uterine papillary serous carcinoma (UPSC), and to compare these parameters with those observed in patients with moderately and poorly differentiated endometrioid endometrial carcinoma (MPD-EEC).

Methods: The charts of 34 patients with UPSC and 30 patients with MPD-EEC, operated on between January 1995 and December 2000, were retrospectively reviewed. The UPSC group included ten cases of pure and 24 cases of mixed type UPSC (admixed with endometrioid component). All patients had undergone full surgical staging. Clinical features, surgicopathological findings, recurrence rate and recurrence-free interval were compared between the study groups.

Results: Significantly more patients with MPD-EEC than with UPSC were operated on in FIGO stage I and II ($p = 0.001$). MPD-EEC patients were significantly older and more obese ($p = 0.03$ and $p = 0.01$, respectively) as compared with the UPSC patients. Significantly more patients with MPD-EEC presented with postmenopausal bleeding ($p = 0.02$), had a second primary cancer in the past ($p = 0.03$) and had a first degree relative with history of malignant disease ($p = 0.0001$). Conversely, the rates of positive abdominal cytology and cervical involvement were significantly higher in the group of UPSC ($p = 0.02$ and $p = 0.02$, respectively). Significantly more patients with UPSC were treated with adjuvant therapy ($p = 0.01$). No significant difference between the two study groups was observed comparing the recurrence rate, the recurrence free interval and the 3-year survival.

There was also no significant difference between the pure and the mixed type UPSC, considering the clinical features and the follow-up data.

Conclusion: The current study presented no significant difference in the outcome of MPD-EEC as compared with the pure and the mixed type UPSC, yet prospective studies are needed to evaluate the role of adjuvant therapy in each study group.

Key words: Uterine papillary serous carcinoma; Moderately and poorly differentiated endometrioid endometrial carcinoma; Clinicopathological findings; Survival.

Introduction

The term uterine papillary serous carcinoma (UPSC) was introduced by Hendrickson *et al.* in 1982 [1]. It accounts for 4-10% of all endometrial cancer and histologically resembles papillary serous carcinoma of the ovary [2-5]. Multiple studies have documented the aggressive nature and poor prognosis of women with UPSC [1, 5-9]. Recurrence rates among patients with UPSC are extremely high (50-80%) [5-10], with the majority recurring in the abdomen [5, 10].

Previously, cases of UPSC have been compared with cases of ordinary endometrioid adenocarcinoma [4, 5, 11], consisting mainly of the well differentiated endometrioid adenocarcinomas. A significant difference in recurrence rate was demonstrated comparing patients with endometrioid carcinoma and those with UPSC [4, 12, 13]. The site of recurrence also differed significantly between the two groups, with the abdomen as the most common site among UPSC patients and the vagina among the ordinary adenocarcinoma patients [4, 13, 14]. Still no comparison has been reported between the surgically staged cases of UPSC and those of moderately and poorly differentiated endometrioid endometrial carcinoma (MPD-EEC). In the current study we attempted to compare these two groups with endometrial cancer, differentiating also between the pure UPSC cases and those admixed with areas of endometrioid carcinoma. Our aim was to investigate the clinicopathological features, the outcome and the recurrence pattern in patients with pure and mixed type UPSC, and to compare these parameters with those observed in patients with MPD-EEC.

Materials and Methods

Between January 1995 and December 2000, 34 patients with UPSC and 30 patients with moderately and poorly differentiated endometrioid carcinoma (19 patients with moderately differentiated and 11 patients with poorly differentiated carcinoma) were treated in our department. All these patients were surgically staged according to the FIGO guidelines of 1988 [15], and the charts were retrospectively reviewed. Surgical staging included abdominal washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and

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para-aortic lymph node sampling and omentectomy in cases of UPSC. The FIGO stages of all patients are demonstrated in Table 1. The preoperative endometrial biopsy was evaluated for diagnostic features of UPSC or other types of endometrial carcinoma. The hysterectomy specimens were evaluated for depth of myometrial invasion, lymph vascular space invasion, and for cervical and adnexal invasion by tumor. The UPSC cases were divided into two subgroups: the pure UPSC (10 cases) and the mixed cases, with at least 25% of the tumor being composed of UPSC (24 cases). Patients with the two concomitant primaries (in the uterus and the ovary) were excluded from the study.

Patient records were analyzed for clinical features, histopathologic findings, adjuvant therapy and follow-up. The clinical features included patients' age, gravidity, parity, weight, age of menarche and menopause, presenting symptoms and history of familial cancer.

Statistical analysis

Comparison between the study groups was performed using the two-tailed Student's t-test and Chi-square test for comparison of means and proportions, respectively. Survival curves were generated using the Kaplan-Meier survival analysis, and comparisons of survival were made using the log-rank test.

Differences were considered statistically significant when $p = < 0.05$.

Results

Sixty-five percent of patients with UPSC and 23% of patients with MPD-EEC presented in FIGO stages III and IV (p = 0.001) (Table 1).

There was a significant difference in the mean patients' age comparing the two main study groups: the patients with UPSC (mean 70.1 years, range 54 to 87 years) and the patients with MPD-EEC (mean 61.9 years, range 50-76 years) (p = 0.03). There was no significant difference in the mean patients' age comparing the two subgroups in the UPSC group: the one with pure UPSC and the other with mixed type UPSC, although the patients with the pure UPSC tended to be older (mean age 76.2) (Table 2). There was a significant difference in patients' weight comparing the group with UPSC (66.7±10.6 kg) and the one with MPD-EEC (78.3±16.3) (p = 0.01). There was also a significant difference in patients' weight comparing the subgroups of UPSC (p = 0.03) (Table 2). No significant difference was observed comparing the ages of menarche and monopause, nor gravidity and parity (Table 2).

The most common presenting symptom for all patients was dysfunctional uterine bleeding, being mainly postmenopausal bleeding; yet, while all patients with MPD-EEC presented with dysfuncional uterine bleeding, about 30% of patients with UPSC presented with a pelvic mass and/or abdominal discomfort (p = 0.02) (Table 3). Nevertheless, there was no difference between the sudy groups comparing the duration of bleeding preceeding the diagnosis. We found no significant difference in the rate of background diseases, such as hypertension, diabetes mellitus and ischemic heart disease comparing patients in different study groups, although there was a trend towards a higher rate in the group of MPD-EEC (Table 3). There was a statistically lower rate of second primary malignancies in the past among patients with UPSC as compared to the rate found among patients with MPD-EEC (p = 0.03). Furthermore, the rate of familial cancer (regarding the first-degree relative with a history of malignant disease) was also significantly higher in the group with MPD-EEC as compared to the rate found among patients with UPSC (p = 0.0001).

The comparison of pathological findings, characterizing the different study groups is presented in Table 4. There was a significant difference between the cases of UPSC and those of MPD-EEC regarding the rate of cervical involvement (p = 0.02) and the percentage of positive

Table 1. — *Comparison between the UPSC and the MPD-EEC patients regarding FIGO stages*

FIGO Stage	UPSC (n = 34)		MPD-EEC (n = 30)	
	n	%	n	%
I	8	23.5	22	73.4
II	4	11.8	1	3.3
III	18	52.9	6	20.0
IV	4	11.8	1	3.3

Table 2. — *Patient characteristics*

	UPSC-pure	UPSC-mixed	p[a]	UPSC	MPD-EEC	p[b]
Mean age	76.2	67.6	NS	70.1	61.9	0.03
Weight	57.6	69.1	0.03	66.7	78.3	0.01
Age of menarche	13.0	13.1	NS	13.1	12.8	NS[c]
Gravity	2.8	3.1	NS	2.6	3.4	NS
Parity	2.2	2.4	NS	2.3	2.2	NS
Age of menopause	45.0	51.1	NS	50.3	48	NS

[a]p value between the subgroups of UPSC-pure and UPSC-mixed
[b]p value between the groups of UPSC and MPD-EEC
[c]NS - not significant

Table 3. — *Clinical features*

Presinting symptom	UPSC-pure	UPSC-mixed	p[a]	UPSC	MPD-EEC	p[b]
Dysfunctional uterine bleeding	80%	66.6%	NS	70.5%	100%	0.02
Duration of bleeding (months)	10	4.5	NS	4.5	3.7	NS[c]
Background disease (Hypertension, diabetes mellitus, ischemic heart disease)	60%	36%	NS	56%	73%	NS
Second primary malignancy	0	9%	NS	6.2%	26.6%	0.03
Familial cancer	0	0	NS	0	66.6%	0.0001

[a]p value between the subgroups of UPSC-pure and UPSC-mixed
[b]p value between the groups of UPSC and MPD-EEC
[c]NS - not significant

Table 4. — *Pathologic findings*

	UPSC-pure	UPSC-mixed	p[a]	UPSC	MPD-EEC	p[b]
Preoperative curretage	20%	25%	NS	23.5%	26%	NS[c]
The accuracy in preoperative histological diagnosis	100%	50%	NS	73%	100%	NS
Enlarged uterus	80%	25%	0.03	41%	46%	NS
Positive abdominal cytology	20%	36%	NS	31%	0%	0.02
Deep myometrial invasion	80%	33%	NS	47%	46%	NS
Lymph vascular space invasion	33%	44%	NS	41.6%	40%	NS
Cervical involvement	40%	25%	NS	29.4%	6.6%	0.02
Ovarian metastases	20%	33%	NS	29.4%	13%	NS
Lymph node metastases	60%	30%	NS	40%	21.4%	NS
Omental metastases	40%	9%	0.03	18.7%	0%	NS

[a]p value between the subgroups of UPSC-pure and UPSC-mixed
[b]p value between the groups of UPSC and MPD-EEC
[c]NS - not significant

Table 5. — *Follow-up*

	UPSC-pure	UPSC-mixed	p[a]	UPSC	MPD-EEC	p[b]
Adjuvant therapy	80%	91%	NS	88%	46%	0.01
Recurrence rate	40%	50%	NS	47%	27%	NS[c]
Recurrence-free interval	24±8	20±11	NS	21±10	20±10	NS
Mean follow-up	33±24	26±18	NS	28±19	33±16	NS
Survival	61%	65%	NS	62.5%	80%	NS

[a]p value between the subgroups of UPSC-pure and UPSC-mixed
[b]p value between the groups of UPSC and MPD-EEC
[c]NS - not significant

cytology in peritoneal washings (p = 0.02). No significant difference between these study groups was observed regarding the percentage of patients undergoing complete preoperative curettage, and no difference was observed comparing the accuracy of the diagnosis in the preoperative histological material obtained in each study group. There was also no difference in the rate of enlarged uterus, found intraoperatively, nor in the rate of deep myometrial and lymph vascular space invasion. Moreover, there was no difference in the percentage of ovarian lymph node and omental metastases, comparing the groups of UPSC and MPD-EEC, although there was a trend towards a higher rate of metastases in the group of UPSC (Table 4). Comparing the subgroups of UPSC-pure and UPSC-mixed, a significantly increased percentage of enlarged uterus (p = 0.03) and omental metastases (p = 0.03) was observed in the subgroup of UPSC-pure (Table 4). Significantly more patients with UPSC (88%) than with MPD-EEC (46%) were treated postoperatively with adjuvant therapy (p = 0.01) (Table 5), being mainly radiotherapy in the MPD-EEC group, and the platinum-based combination chemotherapy (commonly combined with taxol) in the UPSC group. The mean follow-up was 28 months for patients with UPSC and 33 months for patients with MPD-EEC (Table 5).

There was no significant difference in the recurrence rate, defined as new evidence of disease following six months of remission, nor in the recurrence-free interval comparing the patients with UPSC and those with MPD-EEC (recurrence rate - 47% and 27%, respectively; recurrence-free interval - 21 and 20 months, respectively). All the recurrences among the UPSC patients and the MPD-EEC patients occurred within 38 and 34 months, respectively. Moreover, no statistical difference in 3-year survival was observed comparing the two main study groups, being 62.5% for UPSC and 80% for MPD-EEC. There were not enough patients to determine the survival according to the different disease stages.

No significant difference in the mean follow-up, in the recurrence rate and recurrence-free interval, nor in survival was observed between the subgroups of UPSC-pure and UPSC-mixed.

Discussion

UPSC is a distinct histologic type of endometrial cancer, associated with a significantly worse prognosis when compared to the endometrioid histology [4, 11]. Yet, no study has been published comparing patients with UPSC, staged surgically according to the criteria used for patients with ovarian carcinoma, and those with MPD-EEC, staged surgically as for endometrial carcinoma.

We decided to compare not only the entire group of UPSC and the group of MPD-EEC patients, but also to focus on a comparison between the subgroups of pure UPSC and the mixed type UPSC, being composed of a serous papillary component admixed with endometrioid carcinoma. The importance of this comparison, on the background of two different types of endometrial carcinoma, is to present the same bad prognosis of the pure and the mixed-type UPSC, as previously reported [8], thus emphasizing the need for precise preoperative diagnosis of the endometrial biopsy, demonstrating even a small focus of a serous papillary component.

According to our data, the mean age of patients with UPSC was significantly higher than the age of patients with MPD-EEC (p = 0.03). Conversely, the patients with UPSC weighed significantly less than those with MPD-EEC (p = 0.01). The only previous publication [4], comparing patients with UPSC and those with endometrioid grade 3 adenocarcinoma, demonstrated no significant dif-

ference in the median age, thus, maybe, alluding to the similarity between these two groups of patients.

Comparing the clinical features of the two study groups, there was no significant difference in the percentage of patients with hypertension, diabetes mellitus and ischemic heart disease. Yet, there was a significant difference in the percentage of patients presenting with postmenopausal uterine bleeding (70.5% of patients with UPSC vs 100% of patients with MPD-EEC) ($p = 0.02$). The incidence of postmenopausal bleeding is in agreement with previously reported data [16].

An interesting finding in the current study, not dealt with previously, is the oncological "tendency", as observed in the group of patients with MPD-EEC (Table 3). The patients in this group had significantly more second primary malignancies in the past ($p = 0.03$), as well as having presented significantly more cases of cancer in their family, compared with the UPSC group ($p = 0.0001$).

This data tends to contradict the possibility of a family-related effect on the incidence of UPSC. These results differ from those presented by Gitsch *et al.* [5], who demonstrated that 50% of women with UPSC have a first-degree relative with a history of malignant disease.

The comparison of pathological findings (Table 4) revealed a significantly higher rate of UPSC cases with positive abdominal cytology ($p = 0.02$), presenting no difference between the cases of pure and mixed type UPSC.

Our data is in agreement with previously reported results, demonstrating the existence of positive abdominal cytology in 11-60% of UPSC cases [5, 11, 16, 17]. This can be explained by the particular propensity of UPSC towards intraperitoneal spread, simulating the behavior of ovarian carcinoma [18].

Although no significant difference between the UPSC and the MPD-EEC patients was observed regarding the different features of tumor spread, an increased number of cases might change the relative incidence of ovarian, lymph node and omental metastases (Table 4). The only significant difference was observed when considering the rate of cervical involvement ($p = 0.02$), being 29.4% in the UPSC group, with no difference from the previously reported rate [8, 9, 16, 19]. It is interesting to note that there has been no case of MPD-EEC with omental metastases, thus emphasizing the different pattern of spread in endometrioid endometrial cancer. Moreover, according to our results, there was a significant increase in the rate of omental metastases in patients with pure as compared with mixed type UPSC ($p = 0.03$). It is reasonable, considering the similar histological type of pure UPSC and ovarian cancer.

We also found significanly more cases of pure than mixed-type UPSC with an enlarged uterus ($p = 0.03$). It might allude to the more aggressive biological behavior of pure UPSC, yet according to our results and those reported previously [8, 9, 19], no difference in survival was observed comparing the pure and mixed-type UPSC.

Our results demonstrated no significant difference in recurrence rate nor in recurrence-free interval comparing the UPSC and the MPD-EEC groups (Table 5). We also found no significant difference in 3-year survival comparing the UPSC and the MPD-EEC cases. Perhaps, a longer follow-up would demonstrate a difference in survival. The only previous publication [4], comparing the different grades of endometrioid endometrial cancer and UPSC, demonstrated recurrence-free intervals and rates of 3-year survival for patients with poorly differentiated EEC and for patients with UPSC, respectively, similar to those presented in the current study. Moreover, all the recurrences among the UPSC patients reported in our study and in the publication of Rosenberg *et al.* [4], occurred within 38 months. The increased number of UPSC cases in advanced stage disease in the current study, as well as in the previously reported study [5], is probably due to the proper surgical staging, performed for all the cases, as approximately 50-70% of UPSC patients with clinical stage I disease are being upstaged with staging laparotomy [8, 20, 21]. It is worthwhile mentioning the fact that previous studies [4, 8, 11] comprised patients with UPSC, treated preoperatively with brachytherapy, as well as undergoing omentectomy only selectively [16, 21]. Further studies, therefore, are needed for comparison of cases undergoing the proper surgical staging.

The current study, similarly to the previous ones [8, 9, 19], found no difference in the outcome of patients with pure UPSC as compared to those presenting the UPSC component in association with endometrioid carcinoma. This data strengthens the importance of proper surgical staging in all cases of mixed type endometrial cancer; even those, containing only foci of serous papillary carcinoma.

According to our results, there was no such significant difference between the UPSC and the MPD-EEC patients as has been reported between the patients with UPSC and well-differentiated EEC [20-21]. Although the UPSC patients were older and weighed less, they had a similar percentage of diseases such as hypertension, diabetes mellitus and ischemic heart disease. Pathologic findings probably point to the more aggressive disease of UPSC (according to the incidence of metastases), yet the number of cases should be increased in order to prove a significant difference. Finally, the recurrence rate, the recurrence-free interval and the 3-year survival demonstrated no difference between the two study groups. Maybe, the same percentage of deep myometrial and lymph vascular space invasion, being well known prognostic factors in ordinary endometrial carcinoma [10, 22], could explain the same outcome in the UPSC and the MPD-EEC groups. This emphasizes the need for thorough surgical staging and aggressive adjuvant treatment in both groups of endometrial cancer. Thus, prospective studies seem to be justified to evaluate the role of chemo and radiotherapy in each study group.

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Address reprint requests to:
R. HALPERIN, M.D., Ph.D.
Department of Obstetrics and Gynecology
Assaf Harofeh Medical Center
Zerifin 70300 (Israel)