Uterine Papillary Serous Carcinoma—The KK Hospital Experience

T H Ho,*MBBS, M Med (O & G), FRCOG, T L W Lim,**MBBS, H S Khoo Tan,***MBBS, FRCR

Abstract

A review of 355 cases of endometrial cancer treated at the KK Gynaecological Cancer Centre from June 1987 to June 1997 revealed 19 cases (5.3%) of uterine papillary serous carcinoma (UPSC), a clinically aggressive and pathologically distinct variant of adenocarcinoma which closely resembles ovarian papillary serous carcinoma. The majority of UPSC presented as late stage disease with 79% showing extrauterine disease. Twelve of 15 patients also had lymphovascular space invasion. Of the 19 cases, 15 had total hysterectomy and bilateral salpingo-oophorectomy with or without omentectomy and lymphadenectomy. Two had omental biopsy only and another 2 had dilatation and curettage only. The overall median survival in the series was 15 months. Twelve patients had died of disease (67%). Early stage disease seemed to confer a better prognosis. The poor prognosis is frequently ascribed to its tendency to present at a late stage.

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Key words: Chemotherapy, Endometrial carcinoma, Median survival, Pelvic irradiation, Total hysterectomy and bilateral salpingo-oophorectomy.

Introduction

Endometrial carcinoma comprises a morphologically heterogeneous group of tumours. Several authors during the 1960s and 1970s described an unusual variant of endometrial cancer containing psammoma bodies.[1-4] Some of these cases possessed a prominent papillary pattern and were unusually virulent with a propensity for early myometrial invasion and metastatic spread, often in a manner similar to that of ovarian papillary serous carcinoma.

Uterine papillary serous carcinoma (UPSC) was established as a distinct type of endometrial carcinoma by Lauchlan[5] and Hendrickson et al[6] in 1982. They identified a papillary architecture supported by a fibrovascular framework identical to that seen in ovarian serous carcinomas. The stroma of the papillae was oedematous or abundant, and was covered by highly pleomorphic cells containing hyperchromatic nuclei. The majority of cases demonstrated marked anaplasia and very prominent nuclei.

Christopherson et al[7] reviewed 46 cases of papillary adenocarcinoma of the endometrium and highlighted other features including multiple papillary arborisations, cellular stratification, desquamation of cells, and variation in nuclear morphology.

Chen et al[8] in 1985 reviewed all papillary neoplasms of the endometrium at the University of Florida. They divided them into UPSC as defined by Hendrickson et al and well-differentiated adenocarcinoma of the endometrium with papillary features characterised by elongated, slender papillae covered by relatively uniform neoplastic epithelial cells. UPSC differentiated a group of poor prognosis patients from patients who had well-differentiated adenocarcinoma with papillary features.

Although relatively rare in occurrence compared to that of endometrioid carcinoma, UPSC however contributes significant mortality and together with other aggressive variants such as clear cell and squamous cell carcinoma, makes endometrial cancer as a whole a gynaecological cancer with significant mortality.

In this report, we reviewed our institutional experience with UPSC with regards to clinico-pathological features and the prognostic factors influencing survival.

* *Head and Senior Consultant*
** *Medical Trainee*
KK Gynaecological Cancer Centre
Department of Gynaecologic Oncology and Urogynaecology
KK Women's and Children's Hospital, Singapore
*** *Consultant*
Department of Therapeutic Radiology
National Cancer Centre, Singapore
Address for Reprints: Dr Ho Tew Hong, Department of Gynaecologic Oncology and Urogynaecology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Patients and Methods

Three hundred and fifty cases of endometrial carcinoma managed at our centre between June 1987 and June 1997 were identified from our tumour registry using the SGO (Society of Gynaecologic Oncologists) database programme. Nineteen cases of UPSC were identified. The histopathological slides of these 19 cases were reviewed and the pathological diagnosis was classified according to published criteria by Hendrickson et al.[9]

The stages of tumours whenever possible were reassigned according to FIGO[10] 1988 classification after systemic review of records. Patients' data were analysed to determine the association among demographic, pathologic and prognostic factors. Patients' survival rates were calculated using the Kaplan-Meier method.[11]

Results

Nineteen cases of UPSC were identified from 355 endometrial cancers managed at the KK Gynaecological Cancer Centre, KK Women's and Children's Hospital. This accounted for 5.3% of all cases of endometrial carcinoma seen from June 1987 to June 1997.

The ages of patients with UPSC ranged from 45 to 78 years with a median of 64 years. This was in contrast to a median of 54 years for patients with endometrial carcinoma reported in another study from the same institution from 1991 to 1994.[12] This is consistent with the finding of UPSC patients being older by about 10 years.

Seventeen of the patients were postmenopausal. The commonest presenting symptom was postmenopausal bleeding in 15 patients (79%), 2 presented with irregular menses and 2 patients with abdominal distension and pelvi-abdominal mass.

Preoperative cervical cytology was available in 12 patients ; 5 were normal, 4 showed atypical / dysplastic cells and 3 revealed grossly malignant cells. The 4 showing dysplastic or atypical cells on cytology were proven not to have dysplasia of the cervix.

The diagnosis of UPSC was made by tissues obtained from dilatation and curettage in 15 (79%), endometrial sampling in 1 (5%), after laparotomy in 2 (11%) and in 1 (5%) case after radical hysterectomy for an initial diagnosis of a poorly-differentiated squamous cell carcinoma on cervical biopsy. In the latter case following review of the uterine specimen, a diagnosis of UPSC with involvement of the cervix was made.

A total of 17 cases underwent laparotomy. Two of the 17 however had inoperable cancer and only omental biopsies were taken. Both omental biopsies were positive. The remaining 15 had total hysterectomy and bilateral salpingo-oophorectomy done. In another 2 cases only dilatation and curettage was performed.

Of the 19 cases, 3 were assigned as stage I, 1 was stage II, 10 were stage III and 5 were stage IV (Table I). Of the 10 patients assigned as stage III, 3 were assigned stage IIIC on account of the positive retroperitoneal nodes, 6 were IIIA due to positive washings and the other as IIIB because of a vaginal metastasis. There were 5 with stage IV disease. The majority of 15 patients (79%) therefore were in an advanced stage of the disease when diagnosed. Extrauterine disease was found in 15 of 19 cases (79%).

Of the 15 patients who had total hysterectomy and bilateral salpingo-oophorectomy (THBSO), 10 additionally had pelvic lymph node evaluation, either node

TABLE I: STAGE DISTRIBUTION
n = 19

Stage		Number		%
Stage	I	3	3	16
	IA	0		
	IB	3		
Stage	II	1	1	5
	IIA	1		
	IIB	0		
Stage	III	10	10	53
	IIIA	6		
	IIIB	1*		
	IIIC	3		
Stage	IV	5	5	26
	IVA	0		
	IVB	5*		

* D&C only was performed in 1 case of IIIB and 1 case of IVB

TABLE II: TYPES OF SURGERY

Patient Number	Stage	Surgery
1.	I B	THBSO
2.	II A	THBSO
3.	IV B	Omental biopsy / PC positive
4.	III B	EUA / Clinical staging
5.	III A	THBSO + LN + Omentectomy / PC positive
6.	I B	THBSO + LN / PC negative
7.	III A	THBSO + LN / PC positive
8.	IV B	THBSO + Omentectomy / PC positive
9.	IV B	Omental biopsy / PC positive
10.	III A	THBSO + PC positive
11.	IV B	THBSO + LN + Omentectomy
12.	III A	THBSO + LN + Omentectomy / PC positive
13.	III A	THBSO + LN + Omentectomy / PC positive
14.	III A	THBSO + PC positive
15.	I B	THBSO + LN + Omentectomy / PC negative
16.	III C	Radical hysterectomy + LN
17.	III C	THBSO + LN + Omentectomy / PC positive
18.	IV B	EUA / Clinical staging
19.	III C	THBSO + LN / PC negative

EUA: examination under anaesthesia;
LN: lymph nodes sampling/dissection; PC: peritoneal cytology;
THBSO: total hysterectomy, bilateral salpingo-oophorectomy

sampling or dissection and 7 had omentectomy. Three of the 10 with nodal assessment had positive nodes. Eleven of the 15 cases had peritoneal cytology taken (Table II). Two patients who had omentectomy revealed malignant deposits. Eight patients were positive for malignant cells on peritoneal cytology.

In 15 patients who had THBSO, 3 had inner half myometrial invasion (20%) and 12 had outer half involvement (80%); of the latter, 10 had extrauterine disease. In 12 patients with lymphovascular space involvement in the uterine specimens, 10 had extrauterine disease.

Of the 15 who underwent THBSO, 7 cases had adjuvant platinum-based chemotherapy followed by pelvic irradiation, 6 cases had only adjuvant pelvic irradiation and 1 each had hormonal treatment and the other only chemotherapy. Chemotherapy consisted mainly of a combination of cisplatin and epirubicin (50 mg / m^2 body surface area of each drug at 28-day intervals). Two patients who were inoperable received platinum-based chemotherapy. One of 5 patients with stage IVB disease had a combination of cisplatin and epirubicin followed by pelvic irradiation (Table III).

Follow-up data were available for 18 of the 19 patients, a single patient was lost to follow up as she returned to her home country. The duration of follow up ranged from 2 to 120 months. Twelve patients (67%) have died of their disease and 6 (33%) patients are still alive at the time of writing. Of these, 4 had no evidence of disease but 2 had disease during follow up at 2 to 13 months. Of

TABLE III: DISEASE STAGE, THERAPY AND SURVIVAL STATUS

Patient number	Stage	Status	Survival (mo)	Treatment	
				Chemotherapy	RT
1.	I B	ANED	120	-	WPRT
2.	II A	ANED	108	-	WPRT
3.	IV B	DOD	7	Cisplatin Epirubicin	-
4.	III B	Lost to FU	-	-	-
5.	III A	DOD	8	-	WPRT
6.	I B	DOD	53	-	WPRT
7.	III A	DOD	42	-	WPRT
8.	IV B	DOD	10	Carboplatin	WPRT
9.	IV B	DOD	16	Cisplatin Cyclophosphamide	-
10.	III A	DOD	9	Cisplatin Cyclophosphamide	-
11.	IV B	DOD	14	MPA	-
12.	III A	DOD	24	-	WPRT
13.	III A	DOD	10	Cisplatin Epirubicin	WPRT
14.	III A	ANED	39	Carboplatin → Cisplatin / Cyclophosphamide → Cisplatin / Epirubicin	WPRT
15.	I B	ANED	34	Cisplatin Epirubicin	WPRT
16.	III C	DOD	20	Cisplatin Epirubicin	WPRT
17.	III C	AWD	13	Cisplatin Epirubicin	WPRT
18.	IV B	AWD	2	Cisplatin Epirubicin	WPRT
19.	III C	DOD	13	Cisplatin Epirubicin	WPRT

ANED: alive with no evidence of disease; AWD: alive with disease; DOD: died of disease;
MPA: medroxyprogesterone acetate; RT: radiotherapy; WPRT: whole pelvic radiotherapy

the 12 who died of their disease, the median follow-up period was 13.5 months (range 7 to 53 months). The overall median survival was 15 months. The 5-year survival for this group of patient with UPSC was less than 20% (Fig. 1).

Of the 4 cases with early disease (stage I / II), 3 were alive without disease and the other survived for 53 months before she succumbed to her disease. However, as there was no agreed protocol of management of these patients, it is difficult to ascribe the success or failure to a particular mode of therapy.

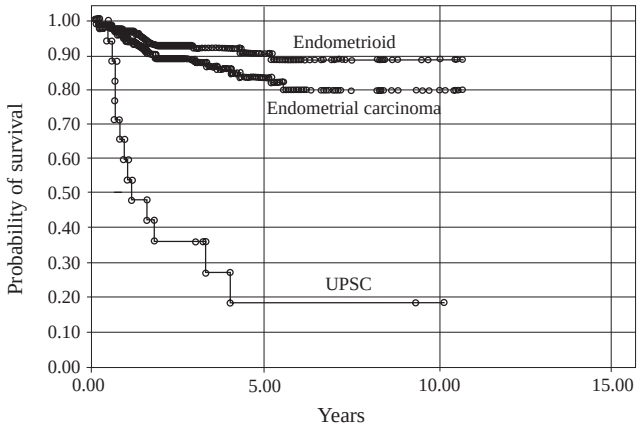

Fig. 1. Comparison of survival of histologic types.

Discussion

UPSC is a distinct histologic subtype of endometrial cancer associated with a significantly poorer prognosis when compared to endometrioid histology.[8-9,13-16] Patients with this histological type account for a disproportionate number of intra-abdominal failures among patients with endometrial carcinoma. UPSC has accounted for 50% of the treatment failures reported in the series by Hendrickson et al.[9]

Postmenopausal bleeding is the most common presenting symptom in our series as in most other series.[17] Other clinical presentations include abdominal or pelvic mass and pain. Patients with UPSC are generally older by about 10 years when compared to patients with endometrioid carcinoma. In our series, 19 of 355 (5.3%) women with endometrial cancer were found to have UPSC. Percentages reported in the literature range from 1% to 10%.[17,18]

The disease has to be staged surgically as in the case of ovarian cancer paying extra attention to extrauterine disease. Lymphovascular invasion is a predictor of extrauterine disease and correlates with a poorer prognosis.[19,20]

Multiple therapeutic modalities have been used to manage the disease. Levenback et al[21] treated 19 patients with cisplatin, adriamycin and cyclophosphamide (CAP) and 58% were alive without evidence of disease after 24 months. The recognition of UPSC as a distinct histologic subtype with an aggressive behaviour and high relapse rate has lead to attempts at aggressive treatment including the use of whole abdominal radiation therapy[22,23] (WART) and chemotherapy.[24] Attempts at treating the disease utilising platinum-based[21,24] combination therapy have met with mixed results.

Rosenberg et al[24] treated 10 patients with clinical stage I UPSC with radical hysterectomy, whole pelvic radiation 45 Gy, and four cycles of cisplatin (50 mg / m^2) and epirubicin (50 mg / m^2). With a median follow up of 32 months, there were no recurrences.

In our institution, we are still evaluating the use of the combination of epirubicin and platinum followed by whole pelvic irradiation in a group of patients who have adequate surgical staging including THBSO, omentectomy and complete pelvic lymph node dissection.

Whole abdominal radiation therapy has also been advocated by several authors[22,23] but others have not found it to be a effective adjuvant therapy.[25]

In a study by Kato et al[18] evaluating 30 cases of UPSC, the authors found a favourable 5-year survival of 79% for surgical stage I and II disease in patients primarily treated with surgery and adjuvant radiation. Similar results were obtained by Grice et al[26] who were able to show that women who have undergone meticulous surgical staging and found to have disease confined to the uterus (stage I / II), the prognosis was similar to that of high grade endometrioid tumours confined to the uterus.

Of the 4 patients with early stage disease in our series, 3 are still alive without disease at the time of writing. One patient with stage IB disease survived for 53 months. Two of the four patients had THBSO with pelvic radiation and the other 2 had THBSO with chemotherapy and pelvic radiation.

The treatment of UPSC should include THBSO with debulking surgery and some form of adjuvant therapy. Despite the histopathological similarities between ovarian serous carcinoma and UPSC, the systemic cisplatin-based combination chemotherapy that has proved successful in inducing remissions in women with ovarian epithelial malignancies appears to be of limited use in patients with UPSC. More recently, the use of paclitaxel-containing chemotherapy has been advocated for UPSC.[27]

UPSC demonstrated a poorer survival outcome compared with that for endometrioid carcinoma. Overall, the survival curve for endometrial cancer in general is lowered because of the inclusion of such "bad actors" as clear cell, mucinous and squamous cell carcinoma (Fig. 1).

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