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Prospective, Non-Randomized Phase 2 Clinical Trial of Carboplatin plus Paclitaxel with Sequential Radical Pelvic Radiotherapy for Uterine Serous Papillary Cancer

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Abstract

Objective

Uterine Papillary Serous Carcinoma (UPSC) is uncommon and accounts for less than 5% of all uterine cancers. Therefore the majority of evidence about the benefits of adjuvant treatment comes from retrospective case series. We conducted a prospective multi-centre non-randomized phase 2 clinical trial using four cycles of adjuvant paclitaxel plus carboplatin chemotherapy followed by pelvic radiotherapy, in order to evaluate the tolerability and safety of this approach.

Methods

This trial enrolled patients with newly diagnosed, previously untreated patients with stage 1b-4 (FIGO-1988) UPSC with a serous-papillary component of at least 30%. Paclitaxel (175 mg/m^2) and carboplatin (AUC 6) were administered on day 1 of each 3-week cycle for 4 cycles. Chemotherapy was followed by external beam radiotherapy to the whole pelvis (50.4 Gy over 5.5 weeks). Completion and toxicity of treatment (Common Toxicity Criteria, CTC) and quality of life measures were the primary outcome indicators.

Results

Twenty-nine of 31 patients completed treatment as planned. Dose reduction was needed in 9 patients (29%), treatment delay in 7 (23%), and treatment cessation in 2 patients (6.5%). Hematologic toxicity, grade 3 or 4 occurred in 19% (6/31) of patients. Patients' self-reported quality of life remained stable throughout treatment. Thirteen of the 29 patients with stage 1-3 disease (44.8%) recurred (average follow-up 28.1 months, range 8-60 months).

Conclusion

This multimodal treatment is feasible, safe and tolerated reasonably well and would be suitable for use in multi-institutional prospective randomized clinical trials incorporating novel therapies in patients with UPSC.

Introduction

Uterine papillary serous carcinoma (UPSC) is an aggressive histological subtype of endometrial cancer, accounting for less than 5% of its incidence, but 40% of its mortality [1]. Compared to those with endometrioid endometrial cancers, women with UPSC are more often non-obese, parous and older [2, 3].

UPSC has a higher propensity for lymphovascular space invasion (LVSI), and intraperitoneal as well as extra-abdominal spread, than other endometrioid cancers [4-9]. Depth of myometrial invasion does not correlate with the likelihood of extrauterine disease and approximately two-thirds of women with UPSC have disease outside of the uterus at diagnosis [4, 9].

Recurrence and mortality rates are high for all stages of this disease. Even for stage 1 UPSC, the survival probability at 5 years is only 72% [10]. Established prognostic factors include lymph node involvement, LVSI and deep myometrial invasion [4, 11].

Given the poor prognosis, most clinicians argue for adjuvant treatment for early-stages of UPSC, but there is no standardized post-operative treatment. Because of its rarity, the majority of evidence is derived from retrospective studies. Few prospective (non-randomized) phase II trials have been reported to date [12, 13], suggesting that a combination of adjuvant chemotherapy and radiotherapy may improve survival in this patient group.

Therefore, we conducted this prospective, multi-centre, non-randomized phase II clinical trial of a triple treatment regimen consisting of radical pelvic surgery, followed by systemic combination chemotherapy with carboplatin plus paclitaxel plus sequential radical pelvic radiotherapy. The primary objective was to assess the safety and feasibility of delivering that regimen. Secondary objectives were to assess the

patterns of disease recurrence, the impact of the treatment on patient quality of life (QoL) and overall survival, and to compare survival of pts on trial with a historical control group.

Patients and Methods

Study Setting

This trial was conducted at four tertiary referral sites for gynaecological cancer in Australia and New Zealand. The study was approved by the Human Research Ethics Committee at all participating hospitals. Written informed consent was obtained from patients prior to the commencement of any study-related procedure.

Patients were screened for eligibility after surgery when histopathological results were available. The inclusion and exclusion criteria are illustrated in Table 1. The trial was registered with the Protocol Registration System of the National Institutes of Health and the Therapeutic Goods Administration (TGA) under the Clinical Trial Notification Scheme (CTN) (Protocol Number: 2003/200, Trial Number: 2004/531).

Treatment

Standard surgical treatment consisted of at least total hysterectomy to confirm the histological diagnosis of UPSC. Treatment also included bilateral salpingo-oophorectomy, bilateral pelvic and aortic lymph node dissection (at the discretion of the treating surgeon), omentectomy, and peritoneal cytology for apparent early disease (FIGO stages 1 or 2) or surgical cytoreduction of macroscopic tumor for advanced stages of disease (FIGO stages 3 and 4).

Chemotherapy commenced at the clinicians' discretion but generally 2-4 weeks postoperatively depending on patient's surgical recovery. All patients received four

cycles of i.v. chemotherapy every 3 weeks. Paclitaxel 175mg/m^2 and carboplatin (at a dose of AUC 6) were administered on the first day of each cycle. After the fourth cycle patients with stage 4 disease were to continue with chemotherapy to a total of 6 cycles. Pelvic radiotherapy was given only to patients with stage 1 to 3 disease, and commenced after hematological count recovery from the last cycle of chemotherapy (usually 4-6 weeks after chemotherapy). Pelvic radiotherapy was administered at a dose of 50.4 Gy in 28 fractions over 5.5 weeks (1.8 Gy per fraction) for five days per week using a four field technique. If aortic nodal metastases were confirmed, patients also received aortic-field radiotherapy (45Gy -50.4 Gy in 25 - 28 fractions) depending on the site and volume of nodes and patient's tolerance. Because of increased risks of hematologic toxicity, concurrent chemotherapy (as radio-sensitizer) was avoided. Vaginal vault brachytherapy boost was allowed at clinicians' discretion following pelvic radiotherapy.

Evaluation of patients including quality of life assessment

At trial entry (post-surgery) all patients had full blood count, biochemistry, liver functions tests and CA125, a chest x-ray and ECG. A baseline CT of chest to pelvis was to be performed for all patients thought to have any type of residual disease, and repeated after 3 and 6 cycles of chemotherapy if residual disease was suspected. Blood counts were repeated prior to each cycle of chemotherapy and prior to start of radiotherapy. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events (AE), version 3.0 prior to each cycle of chemotherapy and weekly during radiotherapy. Patients were followed-up clinically at three month intervals. Recurrence of tumor was confirmed histologically whenever possible and or by radiological imaging.

Three different reliable and validated scales were used to assess quality of life (QoL) outcomes prior to each cycle of chemotherapy, and at the start and end of radiotherapy. The Hospital Anxiety and Depression Scale's (HADS) anxiety and depression subscale scores varied from 0-21. HADS scores between 0-7 were classed as 'normal', 8-10 as 'doubtful cases', and 11 or higher as 'likely anxiety/depression cases' [14]. The Center for Epidemiologic Studies Depression Scale (CES-D) scores (which range from 0-60) of 16 or higher were considered indicative of depression [15]. The Functional Assessment of Cancer Therapy (FACT-G) accompanied by a disease specific endometrial cancer subscale (FACT-en) was used to assess patient's global and disease-related QoL. FACT-G provides a maximum score of 108 when all the four subscales are combined: 0-28 for each of physical, social and functional well-being and, 0-24 for emotional well-being [16]. FACT-en scores could vary from 0 to 64. The treatment outcome index (TOI) was calculated by adding up the physical, functional and endometrial subscales (possible range: 0-120). Higher scores on all subscales indicate better QoL [17].

Statistical analysis

A pragmatic sample size of 30 patients was chosen based on predicted recruitment within the participating centers. The regimen was considered feasible and tolerable if 80% of patients could complete the planned treatment without requiring treatment cessation. . Morbidity and QoL analyses were performed for all recruited patients (n=31).

Adverse events: Adverse events (AE) were classified and graded by CTC categories, and collapsed into 'low' grade (grades 1 and 2) and 'high' grade (grades 3 and or 4). Descriptive statistics were used to present the number of patients and percent of patients by AE categories and grade.

Quality of Life: Descriptive statistics were used to summarize patients' QoL scores over time and unadjusted results are presented. A change of 2 points in the QoL scores was considered clinically significant for the FACT-G subscales, 4 points for the FACT-en subscale and 5 points for the FACT-G summary score and TOI, and a change of one third of a standard deviation was defined as clinically significant for HADS and CES-D [18-21]. Linear mixed models were used to evaluate changes in QoL over time.

Survival: Overall survival (OS) was calculated from date of surgery to date of death or date of last follow-up if censored. The Kaplan Meier method was used to compare survival among patients with stage 1b to stage 3 in this study (n=29) with those of matched historical controls.

Historical Controls: Thirty-seven patients who received treatment for UPSC at the Queensland Centre for Gynaecological Cancer between September 1999 and August 2004 represented the historical controls. They were selected on the basis of stage (1b to 3c) (FIGO 1988) and age (age <80 years at the time of diagnosis). Patients received a variety of postoperative treatment regimens. Seven patients received chemotherapy only, 3 patients received external beam radiotherapy only and 5 patients were treated with a combination of chemo and external beam radiotherapy. The remainder either received no treatment after surgical staging (n=10), brachytherapy only (n=4) or other combinations of treatment alternatives (n=8)[radiotherapy and brachytherapy (n=3), chemo- and brachytherapy (n=1), chemo-, radio- and brachytherapy (n=1), hormone replacement therapy only (n=1), chemo- and radiotherapy in combination with hormone replacement therapy (n=1), or chemo-, radio- and brachytherapy in combination with hormone replacement therapy (n=1)].

Results

Patient characteristics

Thirty-one patients from four participating institutions in Australia and New Zealand were registered between September 2004 and February 2008. Patients' median age was 63 years (range 37-77). Twenty-seven patients (93%) had ECOG status zero or one; two patients (7%) had ECOG status 2. Twelve patients (41%) had tumors that invaded the Lympho Vascular Space (LVSI+).

One patient with UPSC confined to the endometrium but with extensive LVSI (non-invasive) throughout the myometrium, who had to be regarded as stage 1A according to the FIGO 1988 staging classification was registered and treated. The distribution of FIGO (1988) stages is shown in Table 2.

Treatment received

Twenty nine out of the 31 patients enrolled, completed their treatment (93.5% completion rate, 95% CI: 80.9%-98.6%). Of the 29 patients with stages 1-3C who were planned to receive chemotherapy plus sequential radiotherapy, two patients (6.9%) received only two cycles of chemotherapy due to toxicity (grade 3 peripheral neuropathy and depression (n=1); grade 3 neutropenia (n=1)). All 29 patients received pelvic radiotherapy as planned, and eight patients (27.6%) also had a vaginal vault brachytherapy boost to the top 3 cm of the vagina. The two patients with stage 4 disease completed all 6 cycles of planned chemotherapy. Chemotherapy dose reduction was needed in 9 (29%), treatment delay in 7 (23%), and treatment cessation in 2 patients (6.5%). Radiotherapy was delivered as planned for all patients.

Toxicity

All patients had at least one grade 1 or 2 adverse event (AE), with 15 patients (48%) experiencing at least one high grade (3 or 4) AE (Table 3). AEs were related more commonly to the gastrointestinal system (e.g., nausea, vomiting), closely followed by pain (e.g., myalgia), neurological issues (e.g., peripheral neuropathy) and constitutional symptoms (e.g., fatigue). Fourteen patients (45%) experienced at least one high grade, non-hematologic toxicity and six patients (19%) experienced at least one, high-grade, hematologic toxicity. Five of the six patients who experienced high grade hematologic toxicity also experienced high grade non-hematologic toxicity. Peripheral neuropathy (grades 3 and 4) was noticed in 2 patients (6%). Five patients (16%) experienced grade 3 or 4 neutropenia with two patients (6%) exhibiting febrile neutropenia. Toxicities were appropriately managed and no treatment-related deaths occurred.

Quality of life

Overall, patients' QoL remained largely stable over the course of the treatment (Table 4). Compared to the baseline assessment after surgery, scores for anxiety (HADS, anxiety) and depression (HADS, depression and CES-D) improved after the first cycle of chemotherapy, worsened slightly at the commencement of radiotherapy and subsequently improved again. FACT-G scores remained largely unchanged between commencement and completion of treatment. The FACT-en and TOI scores showed a small, decline in QoL throughout the treatment period, but these changes did not reach clinical significance. Most of the QoL variables showed non-linear or no clear trend over the specified time points with the exception of Endometrial Wellbeing (EnWB) which showed a linear downward trend ($P<0.05$).

Recurrence and Survival

After a median follow-up of 28.1 months (range 8-60 months), thirteen of the 29 patients with stage 1-3 disease (44.8%) recurred. The site of recurrence was pelvis (n=2), abdomen (n=2), distant (n=5) or multiple sites (n=4). Nine (31%) patients died due to progressive disease (n=8) or unknown cause (n=1). The two patients with stage 4 disease relapsed at multiple sites.

Characteristics of patients that recurred are illustrated in Table 5. Disease recurrence was seen in 3 of the 10 stage 1 patients (30%), 2 of the 5 stage 2 (40%) and 8 of the 14 stage 3 (57%) patients. Overall survival probability was 77.4% at two years. The two-year survival probability was 85.6% for stage 1 or 2 patients and 68.8% for stage 3 patients.

Historical Controls

Distribution of stages of patients in the historical controls is illustrated in Table 2. Patients within the historical cohort were older on average and included a higher proportion of patients with earlier stage of disease compared to the trial cohort. Their median follow-up was 40.9 months (range: 2.8-114.7 months) and overall survival probability was 75.7% at two years. Kaplan-Meier curves comparing overall survival of patients in this study with that of the historical controls is shown in Figure 1.

Discussion

This non-randomized Phase II clinical trial evaluated the tolerability and safety of four cycles of carboplatin and paclitaxel combination chemotherapy plus sequential pelvic radiotherapy in the postoperative setting for patients with UPSC. This treatment regimen was generally well-tolerated with 29 of 31 patients (93.5%) completing treatment as scheduled.

Survival of patients with stage 1 and 2 UPSC without adequate staging and / or adjuvant treatment is poor. From early retrospective data it became clear that meticulous surgical staging provides useful information on the extent of disease, thus impacting on the postoperative treatment plan in patients with early stage UPSC. However, generating evidence on treatment of UPSC is challenging due to low incidence rates resulting in few prospective trials. Several groups have presented retrospective data on the outcomes of treatment with the inevitable inherent selection bias [22]. The interpretation of these retrospective studies is controversial because of the use of multiple adjuvant treatment regimens and heterogeneous patient groups probably similar to our historical control group. Some publications favor radiotherapy while others recommend chemotherapy or a combination of both in patients with UPSC [3, 23, 24].

The role of whole abdominal radiotherapy (WART) was evaluated in GOG 94 [25]. This study enrolled 21 patients with clinical stage 1 or 2 UPSC. Patients had radical surgery followed by (WART) with a pelvic boost. Five year progression free survival was 38%. The majority of treatment failures were within the radiation field, which led to the conclusion that a combination of chemotherapy and radiotherapy may improve survival outcomes. However, the combination of systemic chemotherapy and pelvic radiotherapy, its tolerability and safety profile in the setting of previous radical pelvic surgery had not been examined prior to the time of the writing of this study protocol.

In our study, non-hematologic toxicity grade 3 or 4 was recorded in 45% of patients, and hematologic toxicity grade 3 or 4 was documented in 19%. No case of radiation-associated fistula or bowel obstruction requiring intervention was recorded. All but two patients completed the treatment according to the study protocol. The prospective

clinical trial by Fields and colleagues [12] evaluated pelvic radiation treatment 'sandwiched' between six cycles of paclitaxel/platinum chemotherapy in 30 patients with stage 1 to 4 UPSC and found similar outcomes. All but one patient completed treatment as per protocol. Of 177 chemotherapy cycles administered they observed grade 3 or 4 neutropenia, thrombocytopenia and anemia in 42%, 3% and 1%, respectively [12]. Distribution of chemotherapy toxicity was similar in cycles of chemotherapy given before and after radiotherapy. In comparison, the Hoosier Oncology Group reported outcomes of a phase 2 study on 21 patients with stage 1 and 2 UPSC. Patients received intraperitoneal radioactive phosphorus and vaginal brachytherapy to the whole vagina. The treatment was extremely well tolerated, with minimal low-grade toxicity and no grade 2, 3 or 4 toxicities [13]. Two of these three studies used radiotherapy to the whole pelvis and it seems that hematologic and non-hematologic toxicity was distinctly more common and severe in those studies [12, 25]. Therefore, it seems that the external beam radiotherapy component may account for a large part of the incidence and severity of toxicity observed in our trial.

The sample size of this phase II trial did not allow for extensive statistical analysis of QoL data. Patients' QoL remained acceptable throughout treatment. These QoL outcomes are consistent with the encouraging toxicity outcomes and support the use of this treatment combination. Unfortunately, none of the previous prospective clinical trials on UPSC has QoL available for comparison. However, in a published review, while gynecological cancer patients appear to have worse QoL during treatment compared to for example breast cancer patients, the majority seem to cope well with treatment and return to QoL comparable to norms shortly after cessation of treatment [26]. Carter et al studied gynecological cancer patients undergoing intensive chemotherapy and found little difference in QoL across cycles [27]. In contrast,

Lutgendorf et al described lower physical, emotional and functional wellbeing, but no difference in anxiety and depression between more extensively treated gynecological cancer patients or those receiving surgery only [28].

The two year survival probabilities of 85.6% for patients with stage 1 or 2 disease and 68.8% for patients with stage 3 disease, is comparable to previous prospective studies. After a median follow up of 28.1 months, thirteen of the 29 patients with stage 1-3 (44.8%) disease experienced recurrence with the majority of recurrences occurring outside the pelvis. Fields et al. reporting on radiation "sandwiched" between combination chemotherapy reported an overall survival of 75% for patients for stage 1 and 2 UPSC and 52% for advanced disease (stages 3 and 4) at two years [12]. The Hoosier Oncology Group evaluating intraperitoneal phosphorus plus vaginal brachytherapy reported an overall two-year survival 93.3% (n=17) for patients with stage 1 or 2 UPSC [13]. Survival in the GOG 94 study after WART was poor [25].

We compared overall survival of our study group with historical controls from a three year time period immediately prior to this trial. The number of patients available for analysis was similar for both the time periods but patients in the historical control group were older and more likely to be diagnosed with stage 1 disease. Even though such an imbalance should favor outcomes for historical controls, when compared to those who participated in this study, the survival outcomes were similar (Figure 1). It should also be noted that not all the patients in this trial underwent surgical staging and patients may have been assigned a stage lower than their actual stage.

Recently, a consortium of 10 gynecologic oncology units presented a retrospective analysis of data on 55 patients with stage 2 UPSC [29]. Patients who received chemotherapy ± radiotherapy (CT±RT) had a longer progression free survival and a

lower risk of recurrence (11%) than the radiotherapy (RT) alone group (50%). Of the 19 patients in the CT±RT group, all patients had platinum/taxane combination chemotherapy and 12 of the 19 patients had radiotherapy. The same group has more recently published similar results for a cohort of stage 1 patients, suggesting a survival benefit and lower relapse rate in patients treated with platinum-taxane based chemotherapy [29]. However, another recently published retrospective series of 58 stage 1 and IIA UPSC patients showed no significant difference in overall survival between those patients who received carboplatin and paclitaxel chemotherapy and those that did not. In contrast, a survival benefit was suggested for those patients who received adjuvant radiation [30]. Unfortunately the selection bias inherent in these retrospective studies is a major confounder and only a randomized controlled trial will be able to report on treatment efficacy.

In summary, our data support the feasibility and safety of multimodal therapy as an emerging treatment concept for UPSC. Triple treatment consisting of surgery, chemotherapy and radiotherapycan be offered to patients less than 80 years of age, with histologically confirmed and myoinvasive UPSC. Patients with other high-risk uterine cancers, such as clear cell cancers or malignant mixed mullerian tumours may also benefit from this treatment regimen. Nevertheless, the generally poor results that are seen in patients with UPSC and the conflicting data from the available literature, mandate the need for international collaboration in order to perform prospective randomized trials incorporating novel therapeutic approaches to improve patient outcomes.

Conflict of interest statement:

This clinical trial was supported in part by Bristol Myers Squibb. All the authors have declared that there are no conflicts of interest.

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Table 1: Inclusion and exclusion criteria for eligibility in study

Inclusion criteria:

- Histologically confirmed primary diagnosis of UPSC (serous-papillary component of ≥ 30% on a hysterectomy specimen)
- Stage 1b-4 disease
- Chemonaive for UPSC
- Females between 18-80 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Adequate bone marrow, renal, hepatic and neurologic function (ANC ≥ 1,500/ul, Platelets ≥ 100,000/ul, Creatinine ≤ 1.5 x ULN, Bilirubin ≤ 1.5 x ULN, Neuropathy ≤ CTC Grade 1)
- Written informed consent

Exclusion criteria:

- Presence of other histological type than UPSC or endometrioid
- Personal history of malignancy and disease-free for less than 5 years
- Uncontrolled hypertension (>180mmHg/100mmHg), cardiac arrhythmia or diabetes mellitus
- History of another malignancy within the last 5 years that could affect the diagnosis or assessment of UPSC
- Estimated life expectancy of less than 6 months
- History of serious cardiac disease within the last 6 months
- Active serious infection or underlying medical condition impairing protocol treatment
- Medical or psychiatric illness, dementia or altered mental status impairing informed consent
- History of severe allergic reactions to drugs containing cremophor or hypersensitivity to paclitaxel, carboplatin or cremophor EL
- Previous radiotherapy to the whole pelvis
- Uncontrolled pelvic inflammatory disease contraindicating pelvic radiotherapy
- Breast-feeding
- Other concurrent investigational therapy

Table 2: Patient and Disease Characteristics of patients enrolled in our study and of the historical control at baseline

Characteristic	All patients (this study)		Historical control	
	N	%	N	%
Age at baseline in years, median (range)	63 (37-77)		68 (41-80)	
Total	31	100	37	100
Prognostic factors at baseline				
Stage				
1a	1	3.3	0	0
1b	4	12.9	13	35.1
1c	5	16.1	6	16.2
2a	1	3.3	3	8.1
2b	4	12.9	1	2.7
3a-c	14	45.1	14	37.8
4	2	6.4	0	0

Table 3. Summary of adverse events for 31eligible patients by CTC category (v. 3.0) and grade

	CTC grades (Patients)					
Categories	**1 and 2**	**%**	**3 and 4**	**%**	**Total**	**%**
Allergy/Immunology	1	3.2%	0	0.0%	1	3.2%
Blood/Bone marrow	**23**	**74.2%**	**6**	**19.4%**	**23**	**74.2%**
Cardiac general	1	3.2%	2	6.5%	3	9.7%
Constitutional symptoms	24	77.4%	4	12.9%	24	77.4%
Dermatology/Skin	22	71.0%	0	0.0%	22	71.0%
Gastrointestinal	30	96.8%	2	6.5%	30	96.8%
Hemorrhage/Bleeding	4	12.9%	0	0.0%	4	12.9%
Infection	5	16.1%	0	0.0%	5	16.1%
Lymphatics	6	19.4%	2	6.5%	8	25.8%
Metabolic/Laboratory	3	9.7%	4	12.9%	6	19.4%
Musculoskeletal/Soft tissue	2	6.5%	0	0.0%	2	6.5%
Neurology	23	74.2%	2	6.5%	25	80.6%
Pain	29	93.5%	4	12.9%	29	93.5%
Pulmonary/Upper respiratory	5	16.1%	0	0.0%	5	16.1%
Renal/Genitourinary	2	6.5%	0	0.0%	2	6.5%
Sexual/Reproductive function	1	3.2%	0	0.0%	1	3.2%
Syndromes	2	6.5%	0	0.0%	2	6.5%
Vascular	1	3.2%	2	6.5%	3	9.7%
Total	31	100%	15	48.4%	31	100.0%

Table 4: Quality of life outcomes for each treatment time point (n=31 patients)

Scale, Mean (SD)	Chemotherapy				Radiotherapy	
	Cycle 1	*Cycle 2*	*Cycle 3*	*Cycle 4*	*Start*	*End*
HADS, anxiety*	5.71 (3.02)	3.88 (3.24)	3.12 (2.58)	3.54 (3.35)	3.85 (2.90)	2.96 (2.80)
No. patients	28	26	25	26	26	25
HADS, depression*	2.25 (3.00)	2.35 (2.46)	2.04 (2.28)	2.12 (2.69)	2.46 (3.10)	2.76 (3.53)
No. patients	28	26	25	26	26	25
CES-D*	12.32 (6.14)	10.74 (9.24)	11.76 (8.26)	8.29 (6.69)	8.96 (7.60)	7.48 (8.52)
No. patients	25	23	25	28	25	25
FACT-G**	91.08 (13.69)	92.56 (13.95)	93.01 (10.60)	92.59 (14.24)	92.07 (13.24)	91.28 (16.03)
No. patients	28	26	25	26	24	25
FACT-en**	59.21 (4.61)	57.08 (6.29)	57.52 (5.51)	57.49 (6.27)	57.99 (4.93)	56.08 (6.81)
No. patients	29	26	26	25	26	25
FACT-all**	149.08 (17.49)	149.61 (18.82)	150.31 (15.35)	148.38 (19.35)	149.73 (17.28)	147.36 (21.47)
No. patients	29	26	25	23	24	25
TOI**	105.07 (12.14)	103.47 (15.91)	103.43 (12.98)	102.40 (16.92)	103.43 (13.34)	100.32 (17.51)
No. patients	28	26	25	24	24	25

* higher scores indicate greater symptoms

** higher scores indicate better quality of life

Table 5: Characteristics of patients who recurred (13/29 patients with disease stage 1-3)

Patients with recurrence (n=13)

Patient	Age at diagnosis	Stage	Surgery Type	Treatment	DFS, months	Recurrence site	FU, months
201001	54	3A	TAHBSO, washings, omentectomy	4 X Carbo/Tax + EBRT	6	Distant	8 (died)
301001	54	4B	TAHBSO, bilateral Pel+PA LND, omentectomy, washings	6 Carbo/Tax	8	Multiple: brain & liver	11 (died)
301002	71	1B	TAHBSO, bilateral Pel+PA LND, omentectomy, washings	4 X Carbo/Tax +EBRT+ VVBT	23	Distant	28 (died)
401007	60	3C	TAHBSO, bilateral Pel+PA LND, omentectomy, washings	4 X Carbo/Tax + EBRT	11	Abdomen	20 (died)
401008	62	2B	TAHBSO, washings	4 X Carbo/Tax +EBRT+ VVBT	12	Multiple	20 (died)
401011	68	3B	TAHBSO, omentectomy	4 X Carbo/Tax + EBRT	13	Distant	36 (died)
401012	63	3C	TAHBSO, bilateral Pel+PA LND, omentectomy, washings	4 X Carbo/Tax + EBRT	16	Distant	21 (died)
401016	77	3C	TAHBSO, bilateral Pel+PA LND, washings	4 X Carbo/Tax + EBRT	32	Distant	37
401018	72	3A	TAHBSO, bilateral Pel+PA LND, omentectomy, washings	4 X Carbo/Tax +EBRT+ VVBT	25	Multiple: thoracic & abdominal	28
901001	65	1C	TAHBSO, bilateral Pel+PA LND, washings	4 X Carbo/Tax + EBRT	15	Multiple	16 (died)
901002	77	1C	TAHBSO, bilateral Pel+PA LND, washings	4 X Carbo/Tax + EBRT	33	Pelvis	40 (died)
901003	50	3C	TAHBSO, bilateral Pel+PA LND, omentectomy, washings	5 X Carbo/Tax + EBRT	16	Pelvis	23
901004	65	2B	TAHBSO	4 X Carbo/Tax +EBRT+ VVBT	17	Abdomen	26

TAHBSO: Total Abdominal Hysterectomy and Bilateral Salpingo Oophorectomy; Pel+PA LND: Pelvic and Para-aortic Lymph Node Dissection; EBRT: External Beam Radiotherapy; VVBT: Vaginal Vault Brachytherapy; DFS: Disease-free Survival; FU: Follow-up

Figure **1**: Kaplan-Meier overall survival curves of patients in this UPSC trial (stages 1b-3C) compared with historical control (n=37)