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Adjuvant paclitaxel and carboplatin chemotherapy interposed with radiotherapy in a "sandwich" protocol for uterine papillary serous carcinoma: a single institution experience and review of literature

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Summary

Aim: The optimal sequence of chemotherapy and radiotherapy for uterine papillary serous carcinoma (UPSC) treatment remains unknown. This study is to evaluate the efficacy and safety in treating UPSC with paclitaxel and carboplatin chemotherapy interposed with radiotherapy in a "sandwich" protocol. *Materials and Methods:* Patients diagnosed with pathologic UPSC (FIGO Stage I-IV) in Beijing Hospital from January 2005 to July 2013 were included. After surgical staging, all patients were treated with three cycles of chemotherapy, radiotherapy, and then three cycles of further chemotherapy. Progression free survival (PFS) and overall survival (OS) were calculated by Kaplan-Meier method. All toxicities and adverse events were recorded. *Results:* Of the 27 eligible patients, 12 patients (44%) were Stage I/II and 15 patients (56%) were Stage III/IV. Histology consisted of pure UPSC in 37% and mixed UPSC in 63%. With a median follow-up time of 49 (range 13-121) months, 11 patients relapsed, and eight patients died of their disease. At three years, the PFS and OS rates for all of the patients were 70% and 82%, for patients with Stage I/II were 75% and 85%, for patients with Stage III/IV were 67% and 80%, respectively. Most of the toxicities were treatable and reversible, with only 26% of patients having Grade 3/4 toxicities. No dose reductions, treatment delays or cessations were recorded. *Conclusions:* The "sandwich" protocol of carboplatin and paclitaxel chemotherapy interposed with radiation therapy is efficacious and safe for UPSC treatment. Larger, prospective, randomized clinical trials should be conducted in future to confirm the results.

Key words: Uterine papillary serous carcinoma; Chemotherapy; Radiotherapy; Uterine cancer.

Introduction

Endometrial cancer is one of the most common gynecologic malignancies worldwide and is separated into type I and type II endometrial cancers according to clinical, pathologic, and molecular behaviors. Type II endometrial cancer is not estrogen related, more aggressive, and of higher mortality, most of which is uterine papillary serous carcinoma (UPSC). UPSC constitutes approximately only 10% of all endometrial cancers but accounts for up to 50% of endometrial cancer-associated relapses and deaths given its tendency to spread outside of uterine [1].

As UPSC is an uncommon type of endometrial cancer, randomized studies aimed at evaluating standard treatments are rare [2]. Consequently, no treatment guidelines for UPSC have been established for now. The standard treatment of UPSC includes hysterectomy, bilateral salpingo-oophorectomy, and surgical staging. However, one challenging aspect in treating UPSC is selecting the optimal adjuvant therapy given the aggressive nature and its frequent systemic spread. To address this question, several studies have provided strong evidence that the combined-modality of chemotherapy and radiotherapy confers prognostic benefit in UPSC [3-9]. The combined-modality hypothetically allows for control of local disease in the pelvis with radiotherapy, while treating distant disease with chemotherapy. However, no treatment modality has been clearly determined to be standard yet. Currently, combined-modality adjuvant therapy is administered using various sequential schedules. These schedules include chemotherapy followed by radiation [10-12], concurrent chemotherapy, and radiation [13, 14], or radiation "sandwiched" between chemotherapy. This latter schedule has been reported to be efficacious and well tolerated in treating advanced endometrial cancer by many studies [15-19]. However, there are few studies regarding the use of combined chemo-radiotherapy in a "sandwich" protocol in treating UPSC.

Commencing in 2005, patients with UPSC in the present hospital underwent surgical staging and received paclitaxel and carboplatin chemotherapy interposed with radiotherapy in a "sandwich" protocol. The current study

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aims to evaluate the efficacy and safety of this therapy. The primary endpoints were the progression free survival (PFS) and overall survival (OS) rates of the UPSC patients treated with this method; the second endpoint was the toxicity in this therapy.

Materials and Methods

After obtaining the approval of institutional review board, all patients diagnosed with pathologic UPSC in Beijing Hospital from January 2005 to July 2013 were retrospectively reviewed. Patients were treated with surgical staging followed by adjuvant chemotherapy, radiotherapy, and additional chemotherapy. Surgical staging consisted of a hysterectomy, bilateral removal of the addenda, bilateral pelvic lymph node dissection, para-aortic lymph node sampling, and peritoneal cytology. Omentum dissection was preferred but not required if no visible omental disease existed. The pathologist reviewed all the pathological materials including initial dilatation and curettage (D&C) specimens, as well as the staging specimens. Patients with any serous component in their specimens were included since these entities have similar clinical course [20, 21]. Patients with the entire sampled tumor showing serous differentiation were identified to be pure UPSCs, otherwise identified to be mixed UPSCs. For differential diagnosis, immunohistochemistry was performed to determine the expression status of ER, PR, p53, Ki-67, and Cerb-2 if necessary. Disease stage was determined by the 2009 International Federation of Gynecology and Obstetrics (FIGO) surgical staging criteria for endometrial cancer. Patients previously treated with pelvic radiation, chemotherapy, or with a history of malignancy within the prior five years were excluded.

Chemotherapy generally commenced within 2~3 weeks after surgery, depending on patient's surgical recovery. According to Chinese body status, paclitaxel at a dose of 135~175 mg/m^2 and carboplatin at an area under the concentration-time curve (AUC) of 5 before radiotherapy and at an AUC of 4 after radiotherapy were administered. Chemotherapy was administrated three-weekly for three cycles prior to radiotherapy. Post-radiation chemotherapy usually commenced within two weeks of completing radiotherapy and consisted of three cycles three-weekly. Prior to each subsequent chemotherapy, adequate hematologic (hemoglobin $\geq$ 10.0 g/dL, WBC $\geq 3.0\times10^9$/L platelets $\geq 100\times10^9$/L, granulocytes $\geq 1.5\times10^9$/L), renal (creatinine $\leq$ 1.5 mg/dL), hepatic (bilirubin$\leq$1.5$\times$ institutional normal value and AST $\leq$ 3$\times$institutional normal value) function and Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 1 were required.Treatment modifications for hematologic toxicities included administration of granulocyte colony-stimulating factor (G-CSF), erythropoietin, and/or thrombopoietin. Dose reductions, treatment delays or cessations were permitted if necessary.

Radiotherapy commenced within 2~3 weeks after the third cycle of chemotherapy when the toxicity recovered to an acceptant level. External beam pelvic radiation therapy (EBRT) was given using a four-field technique, with 1.5 Gy fractions daily, five days per week, for a total dose of 45 Gy. Patients with positive pelvic nodes and negative para-aortic nodes received pelvic radiation only, and those with positive common iliac or para-aortic nodes received extended-field pelvic/para-aortic radiation. High dose rate (HDR) vaginal vault brachytherapy was delivered in all patients. The HDR brachytherapy was administrated to a 5-mm depth of the vaginal surface for a length of 4 cm. All radiation treatments were administered using an accelerator at 8-MV photons and were accomplished in six weeks.

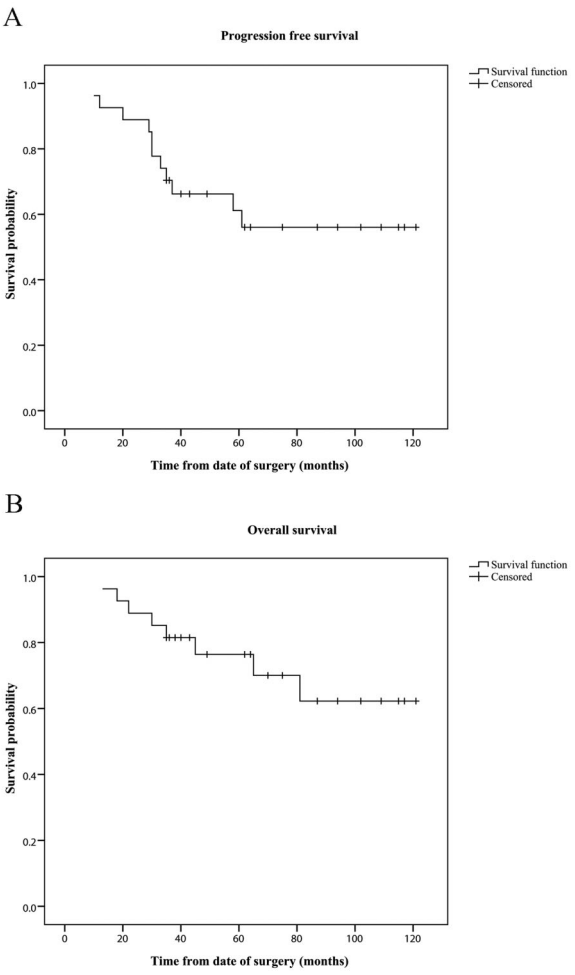

Figure 1. — Kaplan-Meier progression free survival (A) and overall survival (B) analysis in all patients.

Once treatment was completed, patients were followed-up regularly, every three months for two years and every six months thereafter. Upon each time, medical history, a complete physical examination, vagina cytology smear, chest X-ray, CA125, and CA19-9 were performed. Computed tomography (CT) scans of chest, abdomen, and pelvis were performed every six months. Magnetic resonance imaging (MRI) or positron emission tomography (PET) was performed when clinically indicated or the patient was suspicious of relapse. If imaging findings were clear, no histological confirmation was required to identify failure. All toxicities and adverse events were scored using the NCI's Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) [22]. OS was counted from the date of surgery to the date of death or last visit. PFS was defined as the time between the date of surgery and the date of progressive disease, relapse, death or last visit. The curves for PFS and OS were constructed using the Kaplan-Meier method. All analyses were performed using SPSS version16.0, with a $p < 0.05$ considered significant.

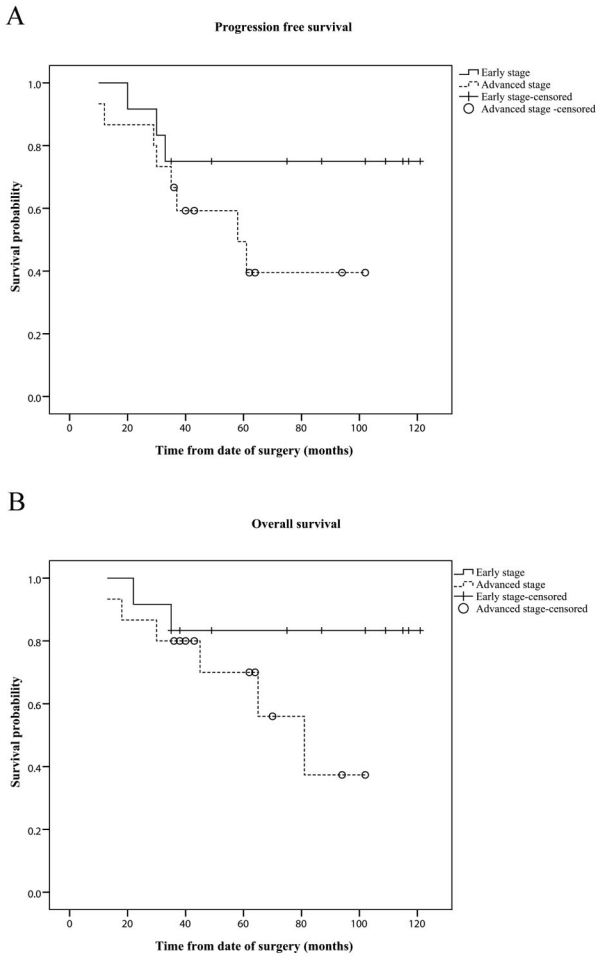

Figure 2. — Kaplan-Meier progression free survival (A) and overall survival (B) analysis according to early and advanced stage.

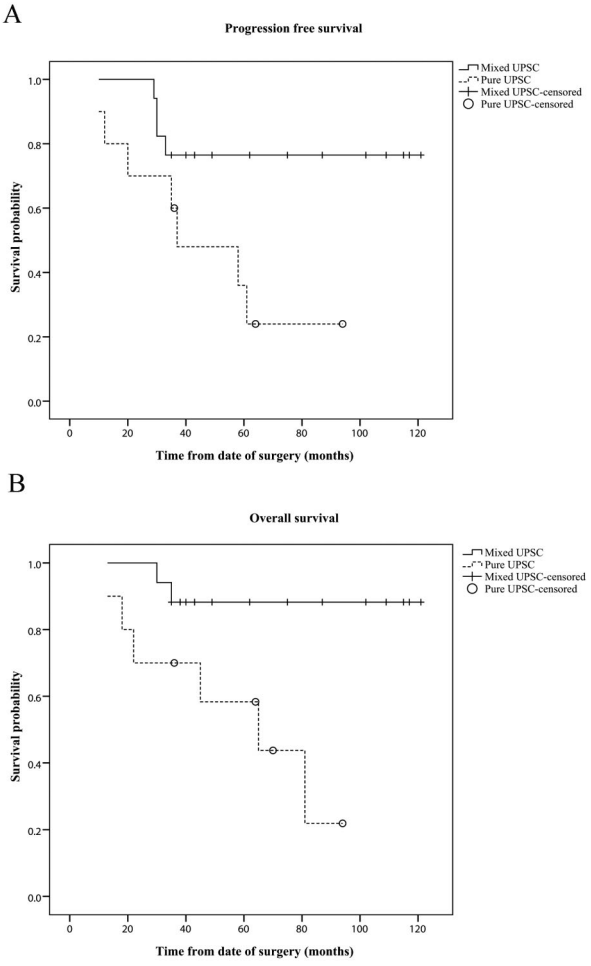

Figure 3. — Kaplan-Meier progression free survival (A) and overall survival (B) analysis of pure and mixed uterine papillary serous carcinoma.

Results

Twenty-seven patients met the inclusion criteria. The median age was 58 (range, 36-72) years. Of the 27 patients, 12 patients (44%) with Stages I and II were assigned into early stage group and 15 patients (56%) with Stages III and IV were assigned into advanced stage group. Histology types consisted of pure UPSC in 37% and mixed UPSC in 63%. Patients' basic characteristics are listed in Table 1.

With a median follow-up time of 49 (range 13-121) months, 11 patients relapsed, and eight patients died of their disease. The three-year PFS and OS rates for the entire group were 70% and 82% (Figure 1). The three-year PFS and OS rates for patients with early stage were 75.0% and 85%, compared to 67% and 80% for patients with advanced stage, with no statistically significant differences ($p = 0.159$ and $p = 0.139$, respectively) (Figure 2). However, the three-year PFS and OS rates for patients with mixed UPSC were 77% and 88%, compared to 60% and 70% for patients with pure UPSC (Figure 3). There were statistically significant differences ($p = 0.009$ and $p = 0.021$, respectively).

Hematologic and non-hematologic toxicities were recorded in all patients (Table 2). Almost all patients had acute toxicities, with only seven patients (26%) having grade 3 toxicities, and no patient had grade 4 toxicities. As for hematologic toxicities, three patients experienced grade 3 neutropenia, two patients experienced grade 3 anemia, and one patient experienced grade 3 thrombocytopenia, respectively. Most of the hematologic toxicities were self-limiting, and when the patient had a grade 3 hematologic toxicity, growth factor support was administrated immediately. Peripheral neuropathy is the most frequent non-hematologic toxicity along with elevation of transaminase, infection, diarrhea, and small bowel obstruction. No dose reductions, treatment delays or cessations were recorded.

Table 1. — *Patient characteristics (n=27).*

Characteristic	n	Percent (%)
Age at diagnosis median (range)(yrs)	58 (36-72)	
Median body mass index (range) (kg/m2)	26.3 (18.1-32.6)	
FIGO Stage (2009)		
I	9	33.3
II	3	11.1
III	14	51.9
IV	1	3.7
Histology		
Pure	10	37.0
Mixed	17	63.0
Grade		
1	2	7.4
2	10	37.0
3	15	55.6
Cytology washings		
Positive	5	18.5
Negative	22	81.5
Optimal cytoreduction		
No	0	0
Yes	27	100
Lymphovascular space invasion		
No	16	59.3
Yes	11	40.7
Lymph node metastasis		
No	12	44.4
Yes	15	55.6

Discussion

Hendrickson *et al.* [23] first described UPSC as a rare aggressive type of endometrial cancer which is inclined to progress rapidly, recur frequently, and have a poor prognosis, resembling serous ovarian cancer [24-25]. Currently, management in patients with this difficult disease is controversial. This study shows that the "sandwich" protocol consisted of three cycles of chemotherapy followed by radiotherapy, and then another three cycles of chemotherapy which is efficacious and well tolerated in patients with UPSC. At three years, the PFS and OS rates for all of the patients were 70% and 82% and for the early-stage disease they were 75% and 85%, and for the advanced-stage disease they were 67% and 80%, respectively. Most of the toxicities were treatable and reversible, with only 26% of patients had Grade 3/4 toxicities. One strength of the present study is that the authors report the highest three-year PFS rate and OS rate in UPSC patients treated with adjuvant chemotherapy and radiotherapy in the "sandwich" protocol.

Due to the rarity of UPSC, there are no large, randomized studies to be based as evidence to formulate management algorithms for UPSC. However, the treatment for UPSC has been evolving. In a multi-institutional retrospective study by the Rare Cancer Network, 129 UPSC patients were examined in three modalities: (1) chemotherapy alone, (2) radiotherapy alone, and (3) combined chemo-radiation. The authors found that adjuvant chemotherapy significantly improved DFS. They also found that radiotherapy offered no significant increase in DFS but offered a statistically significant decrease in pelvic relapse [9]. Results from another retrospective study where 36 patients were only observed, ten patients were prescribed with chemotherapy alone, and 89 patients were prescribed with radiotherapy with or without chemotherapy, suggesting that combined chemo-radiotherapy provided a significant improvement on PFS and OS, and that chemotherapy and radiotherapy should be attempted for both systemic and local control. For now, many studies have addressed the use of multi-modality treatment for this difficult disease [10-14, 26-29] (Table 3). Obermair *et al.* performed a prospective analysis of UPSC patients treated with chemotherapy followed by external beam pelvic radiation therapy, showing a two-year OS of 77.4% for 29 Stage I-IIIA patients [12]. Another prospective trial targeting at concurrent weekly chemotherapy and pelvic radiotherapy followed by chemotherapy obtained a five-year OS of 85% and PFS of 83%, respectively [14]. These data demonstrated that the multi-modal treatment might be feasible and suitable for UPSC patients.

Theoretically, the sequential (chemotherapy followed by radiotherapy or "sandwiched" protocol), rather than concurrent schedule provides maximal therapeutic dosing but results in minimal total toxicity. The potential advantage of the "sandwich" protocol is that chemotherapy first prevents disease progression outside of pelvis while initiation of radiotherapy within 16 weeks after surgery controls local relapse. So far, two trials on treating UPSC patients with combined chemotherapy and radiotherapy in the "sandwich" protocol have been published. Fields *et al.* [26] conducted a prospective trial treating 30 UPSC patients with radiation "sandwiched" between chemotherapy. Their three-year DFS and OS for early stage disease were 69% and 75%, for advanced stage disease were 54% and 52%, respectively, with no significant differences ($p = 0.32$ and $p = 0.34$). Einstein *et al.* [28] conducted a phase II trial on UPSC patients treated with combined chemo-radiotherapy in a "sandwich" protocol, yielding a three-year OS for early stage and advanced stage disease of 85% and 62%, respectively. Although the present study is not prospective, the authors confirm their findings that radiotherapy sandwiched between chemotherapy conferred a preferable outcome in treating UPSC Staged I-IV patients. Survival outcomes in this study were superior to those reported in above studies, which may be attributed to the larger percentage of mixed UPSC patients.

An additional component of the present study was to assess the toxicity of the treatment schedule. Although the occurrence of acute toxicities in this series is high, most of these were treatable and reversible. The occurrence of

Table 2. — *Summary of hematologic and non-hematologic toxicities in 27 patients.*

	Grade 1 (n. patients)	Grade 2 (n. patients)	Grade 3 (n. patients)	Grade 4 (n. patients)
Hematologic toxicities				
Neutropenia	10	9	3	0
Anemia	13	4	2	0
Thrombocytopenia	0	0	1	0
Non-hematologic toxicities				
Peripheral neuropathy	17	3	0	0
Infection(e.g. urinary)	1	2	0	0
Diarrhea	2	0	0	0
Small bowel obstruction	0	0	1	0
Elevation of transaminase (ALT/AST)	3	0	0	0

n.: number of patients experiencing toxicities.

Table 3. — *Review of literature since 2005: multi-modality treatment in patients with uterine papillary serous carcinoma.*

Authors	Country	Year	n.	Stage	Multi-modality treatment	3-year PFS	3-year OS
Fields *et al.* [26]	USA	2008[a]	30	I-IV	Sandwich 3C+R+3C	69% / 54%[b]	75% / 52%[b]
Gellar *et al*. [27]	USA	2010	12	I-IV	Sandwich 3C+R+3C	73%	77%
Einstein *et al* [28]	USA	2012[a]	65	I-IV	Sandwich 3C+R+3C	-	85% / 62%
Low *et al* [10]	Singapore	2005	26	I-I V	Sequential 4C+R	63.3[#]	69.5%[#]
Steed *et al* [11]	Canada	2006	18	I-IV	Sequential 6C+R	70%	81%
Obermain *et al* [12]	Australia	2011[a]	29	I-III	Sequential 4C+R	-	77.4%[#]
Alektiar *et al* [29]	USA	2009	25	I-II	Concurrent C+R	88%*	88%*
Kiess *et al* [13]	USA	2012	41	I-II	Concurrent C+R	85%*	90%*
Jhingran *et al* [14]	USA	2013[a]	30	I-IIIA	Concurrent (C+R)+4C	83%*	85%*
Current study	China	2016	27	I-IV	Sandwich 3C+R+3C	75% / 67%	85% / 80%

C: chemotherapy, R: radiotherapy, PFS: progression free survival, OS: overall survival.
*[a]Prospective study; [b]PFS or OS for early-stage/advanced-stage; #2-year PFS and 2-year OS; *5-year PFS and 5-year OS*

Grade 3/4 toxicities in current study (26%) is lower than reported studies of "sandwich" therapy (31%-48%)[26, 28], and no dose reductions, treatment delays or cessations were recorded in the current study. This may be due to the different clinical practice in dealing with acute toxicity. The present institutional principle is that the authors do not break treatment if side effects can be managed with antiemetics, supportive I.V. hydration, etc. Although no study has demonstrated the addition of G-CSF, erythropoietin and/or thrombopoietin may also be important to decrease dose reductions and treatment delays.

Fotopoulou *et al.* conducted an international survey on systemic management on endometrial cancer; they found that centers from Asia treated endometrial cancer most with adjuvant chemotherapy alone, as opposed to centers in Europe, UK and USA that apply combination chemo-radiotherapy [30]. Consequently, the current study adds to the knowledge of UPSC treated with combination chemo-radiotherapy in Asia in the literature.

This study does have several limitations. First, the retrospective design and the small number of patients that speaks to the paucity of UPSC restricted statistical power. Second, comparisons of "sandwich" protocol versus concurrent or "sandwich" versus chemotherapy followed by radiotherapy were not made. Third, a few mild toxicities of radiotherapy might be missed since the radiotherapy was delivered in the outpatient department. Finally, despite balancing survival outcomes and quality of life for patients is very crucial in delineating the optical schedule, no quality of life components were included in the current study. Thus, the results should be interpreted with caution.

Conclusion

Adjuvant paclitaxel and carboplatin chemotherapy interposed with radiotherapy in a "sandwich" protocol is efficacious and safe for UPSC. Larger, prospective, and randomized clinical trials should be conducted in the future to identify the optimized sequence of chemotherapy and radiotherapy. In addition, patients' quality of life treated with this method should also be addressed.

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