Comparing paclitaxel-platinum with ifosfamide-platinum as the front-line chemotherapy for patients with advanced-stage uterine carcinosarcoma

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Abstract

Background: Uterine carcinosarcoma (UCS) is a rare but highly lethal disease. Adjuvant chemotherapy is highly recommended for advanced UCS. To date, the standard chemotherapy regimen is still uncertain, although two regimens as paclitaxel-platinum (PP) and ifosfamide-platinum (IP) regimens are most commonly used. The aims of the current study attempt to compare both regimens in the management of advanced UCS patients.

Methods: We evaluated advanced UCS patients who were treated either with PP or with IP after primary cytoreductive surgery in single institute retrospectively. The clinical-pathological parameters, recurrence, and survival were recorded.

Results: A total of 16 patients were analyzed. Twelve patients received adjuvant PP therapy, and the remaining four patients received IP therapy. The median follow-up time was 28 months, ranging from 3.8 months to 121 months. Disease-related death occurred in 10 patients (62.5%). The median progression-free survival was 4.9 months, ranging from 3.8 months to 36.5 months in IP, and 23.1 months, ranging from 9.3 months to 121 months in PP, with statistically significant difference ($p = 0.04$). The median overall survival was 9.5 months (ranging from 3.8 months to 36.5 months) and 28.7 months (ranging from 10.3 months to 121 months) in IP and PP, respectively, without statistically significant difference ($p = 0.06$). Presence of pelvic and para-aortic lymphadenopathy and deep myometrial invasion (>1/2) were associated with worse prognosis by univariate analysis. No prognostic factor could be identified using multivariate analysis model.

Conclusion: In the current study, due to extremely little number of subjects enrolled, the advantage of using paclitaxel-platinum regimen in the management of advanced UCS was still unclear, although a certain trend of favoring was supposed. We are looking forward to seeing more studies to identify the approximate regimen in the management of this highly lethal disease.

Keywords: Adjuvant therapy; Carcinosarcoma; Chemotherapy; Outcome; Uterine; Uterus

1. INTRODUCTION

Malignant mixed Müllerian tumors (MMMT, carcinosarcomas [CS]) of female genital tract are defined histologically as a biphasic tumor consisting of both carcinoma (malignant epithelial elements) and sarcoma (malignant mesenchymal or stromal elements) components.[1–3] CS usually arises from the uterus but may also rarely appear in the ovary, Fallopian tube, cervix, or peritoneum.[4–6] In the past and traditionally, uterine CS (UCS) has been regarded as a subtype of uterine sarcomas and is often analyzed after grouping other uterine sarcomas, such as undifferentiated uterine sarcoma, endometrial stromal sarcoma, and leiomyosarcoma.[7–10] Recently, clinical, pathologic, and biological evidence has indicated that UCS is a monoclonal origin, which is derived from the Müllerian duct and closely related to high-grade endometrial carcinoma with the driving force to result in sarcomatous transformation (metaplastic carcinoma), and subsequently form the homologous or heterologous groups, depending on the characteristics of the stroma or mesenchymal components of endometrial tissues.[11–13]

Primary complete surgical staging or primary cytoreductive surgery (PCS) is a key factor in the management of women with UCS, based on the studies obtained from the experience for high-grade or advanced endometrial cancer and uterine sarcomas as well as epithelial ovarian cancer, primary peritoneal serous carcinoma, and primary fallopian tube cancers.[10,14–21] PCS includes a total hysterectomy, bilateral salpingo-oophorectomy,

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cytology, retroperitoneal lymph node sampling or dissection, as well as complete resection of the deposit tumors to reach the minimal residual tumor status (optimal debulking surgery) or gross residual tumor status (suboptimal debulking surgery).[18–21] Furthermore, complete resection without any residual tumor, for example, R0 status, may take a better chance to survive.

Although an intensive PCS, as well as complete resection of UCS without residual tumors, was applied in all UCS patients, many of them recur and finally die of diseases, contributing to extremely poor prognosis. Therefore, application of effective therapy is urgently needed. Radiotherapy, chemotherapy, targeted therapy, and some investigated agents, as well as the combination of any of the above-mentioned therapies (called as multimodality treatment), are believed to provide potentially positive impacts on patients with UCS, and this adjuvant therapy is also apparently beneficial in those with an early UCS.[1–3,22–37]

A recent meta-analysis summarizing four studies, which enrolled 2416 patients (939 patients treated with surgery plus postoperative chemotherapy and 1477 patients treated with surgery alone) found that 5-year overall survival (OS) was statistically significantly improved in the combination of surgery and adjuvant chemotherapy group compared to that in the surgery alone group,[23] suggesting that adjuvant chemotherapy should be considered in all UCS patients, regardless of what stages they are. The widely acceptable chemotherapy agents are platinum (either cisplatin or carboplatin), ifosfamide, and paclitaxel.[30–37] To date, the standard or preferred adjuvant chemotherapy regimen and schedule for UCS are still uncertain.[31] Single agent has been frequently used for UCS due to its moderate effect and its tolerable toxicity. Therefore, if any new agent or combination therapy claimed their effect, they should be compared with the above-mentioned single-agent therapy (ifosfamide as the most often used single compound for this purpose). Based on the key role of ifosfamide for the treatment of UCS, nearly all chemotherapy regimens, either single agent or multiagents included ifosfamide, although significant toxicities should be weighted.[2,22,32,33,37]

Paclitaxel is considered as a potential agent for UCS, based on the experience on endometrial cancer. Additionally, combination of paclitaxel and platinum (paclitaxel-platinum regimen: PP) was widely used in the majority of gynecological organ-related cancers.[14,38–41] However, so far, only two studies were attempted to compare the therapeutic outcome between ifosfamide-platinum regimen (IP) and PP for UCS.[42,43] However, both studies included patients with a big range from International Federation of Gynecology and Obstetrics (FIGO) I to IV.[42,43] Therefore, this study was limited to evaluate the effect of both regimens in the management of women with advanced (2009 FIGO stage III and IV) UCS.

2. METHODS

2.1. Patients

This was a single-institution retrospective cohort study with study period between 2009 and 2020. The eligible inclusion criteria were patients with pathologically confirmed UCS who underwent PCS. Patients were excluded if they were early (FIGO I and II); did not have received adjuvant chemotherapy; had received more than one kind of chemotherapy regimens or triple-agent of adjuvant chemotherapy; and had received ifosfamide plus paclitaxel regimen (Fig. 1). This study was approved by the Institutional Review Board (IRB 2016-10-004A).

2.2. Assessments

Data were obtained using both paper and electronic records of the patients. The following parameters were collected, including age, body mass index, date of diagnosis, stage (FIGO stage), PCS status (optimal or suboptimal debulking surgery), pathologically parameters, such as lymphovascular space involvement,

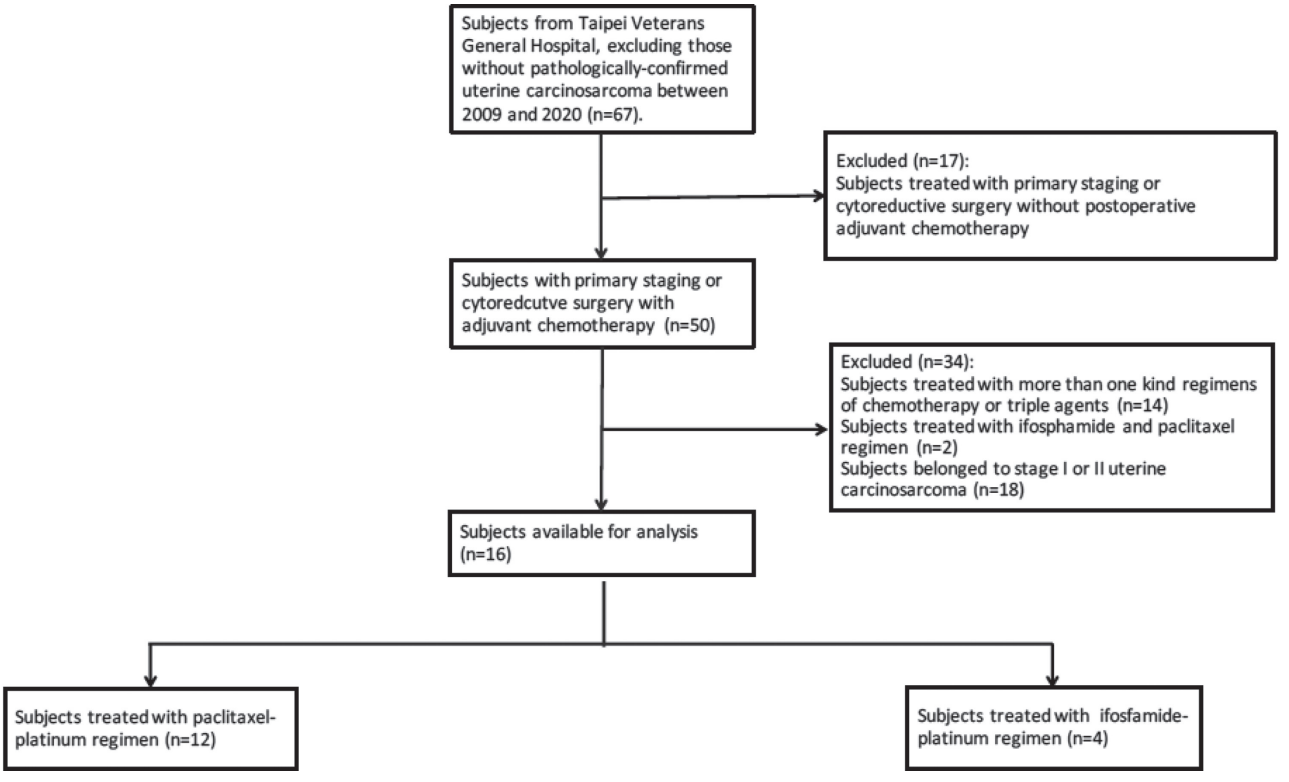

Fig. 1 Cohort flow chart illustrating the inclusion and exclusion of participants in the study.

myometrial invasion, lymph node metastasis, and homologous or heterologous subtypes. Additionally, postoperative radiation therapy was also included for analysis. The primary endpoint was progression-free survival (PFS), defined as the time from the date patients first underwent PCS to the earliest date of disease progression, death from any cause, or the date of the last known follow-up. The secondary endpoint was OS, defined as the time from the date patients first underwent PCS to the date of death from any cause or the date of the last known follow-up.

2.3. Statistical analyses

Descriptive statistics for study groups were presented using mean ± SD or number and percentages as appropriate. We used the Wilcoxon non-parametric test (PROC NPAR1WAY of SAS) procedure to produce all *p*-values for all of the 2 sample tests for location and scale differences. The Kaplan-Meier method was used to generate survival curves, and the generalized Wilcoxon test or Gehan-Breslow test was used to detect the differences between survival curves. Prognostic factors for PFS or OS were evaluated using Cox proportional hazard methods. Multivariate analysis using Cox stepwise forward regression was conducted for the covariates selected in univariate analysis. A p value <0.05 was considered to be statistically significant. All statistical analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC), Stata Statistical Software, version 12.0 (Stata Corporation, College Station, TX), and SPSS v. 24.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. Clinical characteristics and pathological status

Between January 2009 and December 2020, 16 eligible patients were analyzed, including 12 patients treated with PP (platinum, either with carboplatin using area under curve [AUC] 5 or with cisplatin using 50 mg/m^2 and paclitaxel 175 mg/m^2) every three weeks,[35,38] and the remaining four patients treated with IP (ifosfamide 1.5 gm/m^2/day for three days plus platinum 20 mg/m^2/day for three days) every three weeks.[33,37] Mesna was used two grams intravenous during 12 hours beginning 15 minutes before the ifosfamide infusion for three days in patients treated with platinum and ifosfamide.[33,37] Table 1 summarizes the characteristics in each group. The mean age of the whole population was 62.1 years. Optimal PCS was achieved in 81.3% in overall and 91.7% and 50.0% in the PP and IP groups, respectively. Patients in IP seemed to be younger than those in PP, although it did not reach the statistical significance (54.6 vs 61.8 years, p = 0.05). Other parameters, such as body mass index and clinic-pathologic factors, did not reach the statistically significant difference between IP and PP groups.

3.2. Outcomes

During the whole study period with a median follow-up time of 28 months, ranging from 3.8 months to 121 months (at the time of data cutoff on 30 April 2021), disease-related death occurred in 10 patients (62.5%). The median PFS and OS of all 16 patients were 18.3 months, ranging from 4.3 months to 57.4 months and 28.0 months, ranging from 4.3 months to 121 months, respectively. As was presented in Fig. 2, the median PFS was 4.9 months, ranging from 3.8 months to 36.5 months in patients treated with IP, and 23.1 months, ranging from 9.3 months to 121 months in patients treated with PP, with statistically significant difference (p = 0.04).

The median OS was 9.5 months (ranging from 3.8 months to 36.5 months) and 28.7 months (ranging from 10.3 months to 121 months) in patients treated with IP and PP, respectively (Fig. 3). There was also no statistically significant difference between the two groups, although a trend favored the benefit of PP compared to IP (p = 0.06).

Table 1

Demographic and clinicopathological characteristics

Characteristics	PP (n = 12)	PI (n = 4)	*p*
Age (y)	61.73 (53.25-85.86)	54.58 (50.32-55.72)	0.052
Body mass index	24.30 (17.10-38.00)	22.40 (15.50-25.00)	0.275
FIGO stage			>0.999
III	5 (41.7%)	1 (25.0%)	
IV	7 (58.3%)	3 (75.0%)	
Debulking surgery			0.136
Optimal	11 (91.7%)	2 (50.0%)	
Suboptimal	1 (8.3%)	2 (50.0%)	
Histology			0.585
Homologous	6 (50.0%)	1 (25.0%)	
Heterologous	6 (50.0%)	3 (75.0%)	
Myometrial invasion			>0.999
≤1/2	4 (33.3%)	1 (25.0%)	
>1/2	8 (66.7%)	3 (75.0%)	
Lymph node metastases			0.944
None	3 (25.0%)	1 (25.0%)	
Pelvis	4 (33.3%)	1 (25.0%)	
Pelvis and para-aortic area	5 (41.7%)	2 (50.0%)	
Lymphovascular space involvement			>0.999
None	5 (41.7%)	1 (25.0%)	
Yes	7 (58.3%)	3 (75.0%)	
Tumor size			>0.999
≤5 cm	3 (25.0%)	1 (25.0%)	
>5cm	9 (75.0%)	3 (75.0%)	
Radiation therapy			>0.999
None	7 (58.3%)	3 (75.0%)	
Yes	5 (41.7%)	1 (25.0%)	

The data were presented as number (%) or median (range).
FIGO = International Federation of Gynecology and Obstetrics; PP = platinum-paclitaxel regimen; PI = platinum-ifosfamide regimen.

3.3. Prognostic factors

To identify the prognostic factors for OS, a univariate analysis of clinic-pathologic factors showed that myometrial invasion more than 1/2 (hazard ratio [HR], 8.5; 95% CI, 1.0-5.4) and the presence of lymphadenopathy in both pelvic and para-aortic areas (HR, 13.7; 95% CI, 1.2-12.9) were associated with worse prognosis (Table 2). However, both factors did not reach the statistical significance for independent risk factors when using the multivariate analysis model (data not shown). It is interesting to find that some parameters shown in the current study may have the clinical meanings, although all of them did not reach the statistical significance. They were debulking status (suboptimal vs optimal, HR 1.1), lymphovascular space involvement (yes vs no, HR, 3.1), histology type (heterologous vs homologous, HR, 118.7), and radiotherapy (yes vs no, HR, 0.4).

4. DISCUSSION

4.1. Main findings

The main findings of the current study showed that both regimens could be used in the management of patients with advanced (FIGO III and IV) UCS, offering 4.9 months and 23.1 months of median PFS in IP and PP groups, respectively, although the favorable PFS was found in PP (p = 0.04). The median OS was 9.5 months and 28.7 months in IP and PP, respectively, showing the marginal benefits in patients who received PP compared to those treated with IP (p = 0.06).

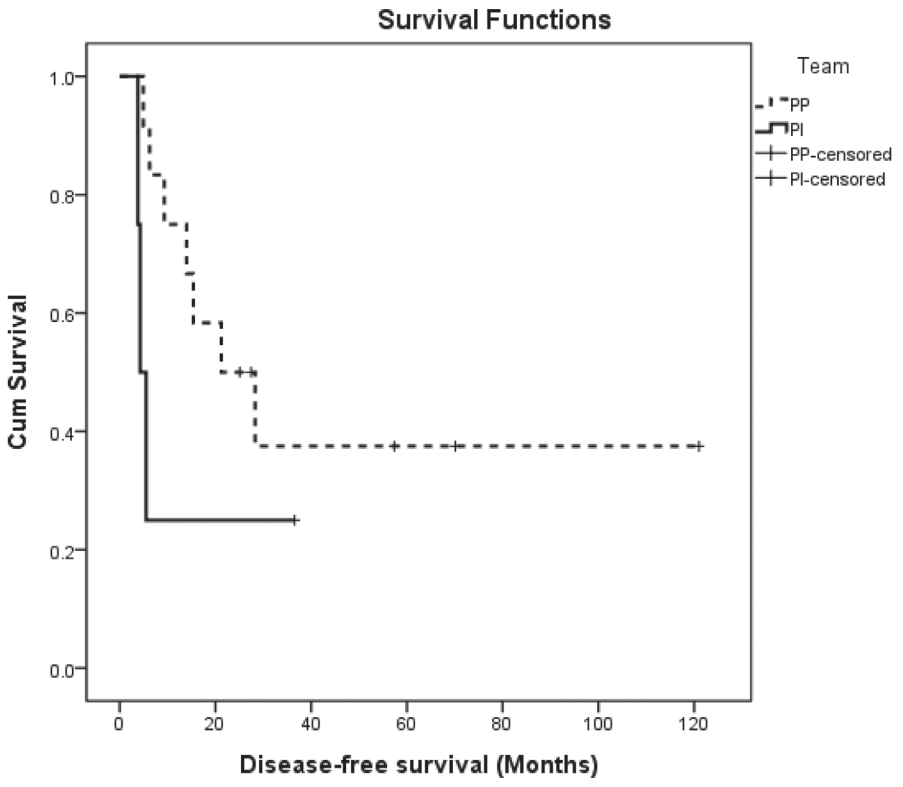

Fig. 2 Disease-free survival (progression-free survival) between paclitaxel-platinum regimen (PP) and ifosfamide-platinum regimen (PI).

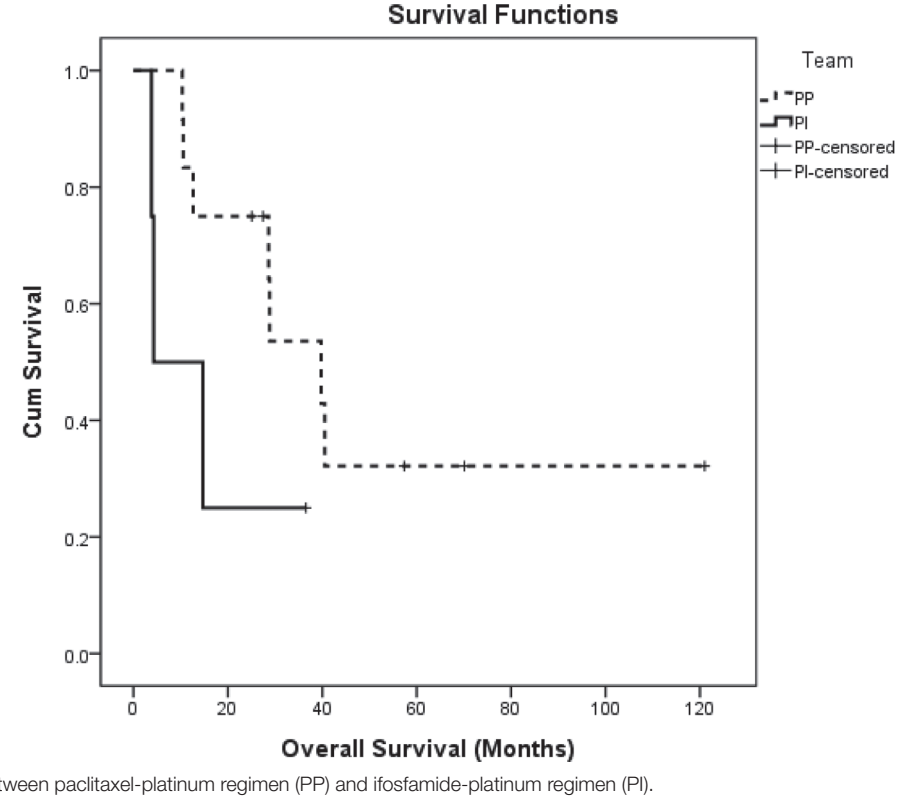

Fig. 3 Overall survival between paclitaxel-platinum regimen (PP) and ifosfamide-platinum regimen (PI).

Table 2

Association between baseline characteristics and overall survival (univariate analysis)

Parameters	Number	HR (95% CI)	*p*
FIGO stage			
III	6	1 (Reference)	
IV	10	0.69 (0.19-2.47)	0.570
Debulking surgery			
Optimal	13	1 (Reference)	
Suboptimal	3	1.08 (0.22-5.36)	0.928
Histology			
Homologous	7	1 (Reference)	
Heterologous	9	118.70 (0.44-31811.32)	0.094
Myometrial invasion			
≤1/2	5	1 (Reference)	
>1/2	11	8.56 (1.04-70.84)	0.046
Lymph node metastases			
None	4	1 (Reference)	
Pelvis	5	0.72 (0.06-8.63)	0.798
Pelvis and para-aortic area	7	13.70 (1.18-158.62)	0.036
Lymphovascular space involvement			
None	6	1 (Reference)	
Yes	10	3.10 (0.75-12.87)	0.119
Tumor size			
≤5 cm	4	1 (Reference)	
>5 cm	12	1.03 (0.26-4.08)	0.962
Radiotherapy			
None	10	1 (Reference)	
Yes	6	0.39 (0.08-1.82)	0.229

FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio.

4.2. Adjuvant therapy

Li et al[44] used the data from the Surveillance, Epidemiology, and End Results (SEER) to evaluate the role of adjuvant radiotherapy, and the results showed that adjuvant radiotherapy after surgery significantly lowered the risk of overall- and cancer-specific mortality in 1069 patients with FIGO stage I to III UCS. By contrast, a meta-analysis showed that radiotherapy alone had no statistical significance in improving PFS (HR, 0.80; 95% CI, 0.49-1.29) and 5-year OS (HR, 0.65 [95% CI, 0.38-1.12) based on 1516 patients in observation group and 750 patients in radiotherapy group.[23] Compared to radiotherapy alone without reaching statistically significant difference, adjuvant chemotherapy or chemoradiotherapy seemed to offer the therapeutic advantages of UCS patients based on the significant reduction of the risk of recurrence (prolonged PFS as HR, 0.59; 95% CI, 0.38-0.91 in the chemotherapy group, and HR, 0.35; 95% CI, 0.24-0.53 in the chemoradiotherapy, respectively) and an improvement of 5-year survival (HR, 0.49; 95% CI, 034-0.71 in the chemotherapy group and HR, 0.46; 95% CI, 0.29-0.72 in the chemoradiotherapy group, respectively) compared to observation.[23,45] Moreover, sequential or combined multimodal adjuvant treatments have been proposed as an alternative choice for advanced UCS.[17,31] Manolitsas et al[46] demonstrated that the sequential treatment with adjuvant radiotherapy and following cisplatin-epirubicin regimen could positively impact survival in patients with stage I and II disease compared to observation group (95 % vs 47 % survival rates, after a median follow-up of 55 months). In 139 cases of stage III UCS, combination of external beam radiotherapy plus chemotherapy was supposed as the best option, leading to a significant improvement of the OS, compared with either chemotherapy (HR, 2.49; 95 % CI, 1.24-4.99) or external radiotherapy alone (HR, 2.53; 95% CI, 1.29-4.97).[47,48] Furthermore, McEachron et al[49] analyzed 148 patients with stage I to IV UCS from multicenters, who were treated with adjuvant therapy either by chemoradiotherapy or by chemotherapy. The results favored the multimodal treatment compared to chemotherapy alone for UCS (PFS: 15 vs 11 months, $p = 0.006$; OS: 26 vs 20 months, $p = 0.018$).[46] In term of 2-year outcome evaluation, chemoradiotherapy was associated with a statistically significant improvement in the 2-year PFS (22.5% vs 13.6%; $p = 0.006$) and OS (50.0% vs 35.6%; $p = 0.018$) compared with chemotherapy alone.[49] Finally, the authors found that the "sandwich as chemotherapy-radiotherapy-chemotherapy" schedule provided a best benefit to patients with UCS because this "sandwich" therapy was associated with longer OS than sequential chemotherapy-radiotherapy and radiotherapy-chemotherapy protocols (34 vs 14 months, $p = 0.038$).[49]

In the current study, our results failed to show the positive impact on prognosis with adding radiotherapy, although many studies, including a recent Taiwan's largest study, favored its additional or synergistic positive effect on survival of UCS.[47–50] To further dissect the potential reason, we analyzed a total of six patients (five in PP and one in IP) who had been treated with radiotherapy as adjuvant therapy. Four patients in PP underwent a "sandwich" therapy and three patients were free of disease (75% survival rate). Another two patients (one in PP and the other one in IP) were treated with combination of chemotherapy and radiotherapy, and both patients died of disease. Taken together, a total survival rate of advanced UCS patients who had been treated with chemotherapy and radiotherapy was 50% (3/6), which may be also better than a 30% survival rate of patients without adding radiotherapy. However, in term of a "sandwich" therapy, the data seemed to support the potential survival benefit of advanced UCS using this strategy. Although no statistical significance was found, it seemed to have a clinically significant benefit when a "sandwich" treatment was applied as adjuvant therapy after PCS for advanced UCS (75% in the sandwich treatment vs 25% in no sandwich treatment). Future study was encouraged to test the reality of a "sandwich" therapy for this highly lethal disease.

4.3. Chemotherapy regimen

As shown in the introduction, it is still uncertain what is the appropriate chemotherapy regimen for UCS. The Gynecology Oncology Group (GOG) 108 study suggested the ifosfamide-platinum offered a small improvement in PFS over ifosfamide alone for advanced UCS.[33] Additionally, the GOG 161 further commented that ifosfamide-paclitaxel regimen should be used for comparison to other promising chemotherapy regimens.[34] Moreover, a retrospective analysis by Dandamudi et al[37] compared different chemotherapy protocols, including single-agent carboplatin, IP, PP, carboplatin-epirubicin, cisplatin-ifosfamide, or doxorubicin-ifosfamide for UCS after surgery. During a median follow-up of 60 months, the authors found the best outcomes (PFS = 35 months, 95 % CI, 0.26-0.43; OS = 47 months, 95 % CI, 0.38-0.56) in women treated with IP.[49] However, recent evidence supports that UCS is various forms of poorly differentiated uterine carcinomas,[1,2,13,17,29–32] contributing to the reconsideration of the use of paclitaxel in place of ifosfamide for UCS.[35,36]

Powell et al[35] conducted a single-arm phase II GOG-232B trial to evaluate the efficacy of PP for recurrent or metastatic UCS to obtain 13% and 41%, of compete and partial response rates, respectively, in 55 advanced UCS (stage III and IV) patients. A total overall response rate was 54% (95% CI, 37%-67%),[35] suggesting the potential vision of using PP for UCS.[35] The feasibility and effectiveness of using PP in the management of women with FIGO stage I to IV UCS was also tested by Japanese Uterine Sarcoma Group and Tohoku Gynecologic Cancer Unit.[36] The authors found there were 78.2% (95% CI, 64.1%-87.3%) of 2-year PFS rate and 87.9% of 2-year OS rate (95% CI, 75.1%-94.4%) as well as 67.9% of 4-year PFS rate

(95% CI, 53.0%-79.0%) and 76.0% of 4-year OS rate (95% CI, 60.5%-86.1%).[36] Other studies also supported the rationale of using PP for UCS based on response rates from 55% to 64% in the upfront and recurrent settings.[51,52] Moreover, although not published yet,[53] the phase III GOG 0261 trial enrolling 537 patients with FIGO stage I to IVB UCS compared adjuvant PP vs paclitaxel-ifosfamide regimen, and the results showed the noninferiority of the PP to the paclitaxel-ifosfamide regimen in the evaluation of OS (median OS: 37 vs 29 months, HR, 0.87; 90% CI, 0.70-1.075) but seemed to offer a better PFS rate in PP (median PFS: 16 vs 12 months; HR 0.73; $p < 0.01$ for noninferiority, $p < 0.01$ for superiority).[43] Compared to IP or paclitaxel-ifosfamide regimen, advantages of the PP are convenience, less bone marrow suppression requiring growth factor support, a better cost profile, and less toxicity.[43,53] In the current study, we did not evaluate the aforementioned potential benefits, such as less myelosuppression, a better cost profile, or less toxicity, but we found that PP may have a possibly better therapeutic effect.

4.4. Clinical-pathological prognostic factors

In the current study, we tried to evaluate the clinical-pathological factors involved in outcome of UCS patients, which included FIGO III vs IV, optimal debulking surgery vs suboptimal debulking surgery, homologous vs heterologous sarcoma component, absence vs presence of deep myometrial invasion, absence vs presence of pelvic or para-aortic lymphadenopathy, absence vs presence of lymphovascular space involvement, small size vs large size of tumor (5 cm as a cutoff value), and use vs nonuse of adjuvant radiotherapy, and found that only presence of deep myometrial invasion (>1/2) and pelvic and para-aortic lymphadenopathy were associated with worse outcome with HR, 8.56 (95% CI, 1.04-70.84) and 13.70 (95% CI, 1.18-158.62), respectively, by univariate analysis. However, multivariate analysis failed to identify any independent prognostic factors associated with worse outcome. Although our findings were significantly influenced by very limited case numbers in the current study, the presence of deep myometrial invasion as a worse prognostic factor was in agreement with previous studies (HR, 2.82; 95% CI, 1.77-4.48).[32,54,55] Moreover, we found the presence of both pelvic and para-aortic lymphadenopathy was associated with a poor outcome, although the presence of pelvic lymphadenopathy but absence of para-aortic lymphadenopathy was not associated with worse prognosis. Previous studies showed the presence of lymph node metastases, regardless of which area involved, was associated with worse 3-year OS (HR, 2.76; 95% CI, 1.64-4.64).[54,55] In the literature review, there are many clinical-pathological factors associated with worse prognosis, including a primary tumor size ≥5 cm (HR, 2.23; 95% CI, 1.32-3.77), the presence of lymphovascular space invasion (HR, 2.11; 95% CI, 1.26-3.52), the rhabdomyoblastic differentiation of sarcomatoid cells (HR, 2.58; 95% CI, 1.30-7.35), and suboptimal debulking surgery (HR, 1.75; 95% CI, 1.07-2.84), were all found to be associated with worse 3-year OS.[54,55] Our study failed to identify these predicting factors associated with worse prognosis, and it may be a result of extremely limited case number. Otherwise, it may also be due to our inclusion criteria. We only evaluated the outcome of patients with FIGO III to IV UCS, compared to other studies enrolling all FIGO I to IV UCS.[32,54,55] Furthermore, consideration of statistical significance or no statistical significance should be carefully interpreted whether this "statistical significance" or "no statistical significance" is clinically meaningful.[56–60] The statistical significance is only a really reflective of the findings of the study based on the reliability of the study results, but it may not be totally presentative of "the extent of change". The change should make a real difference to subject lives, how long the effect remain, consumer acceptability, cost-effectiveness, and ease of implementation.[61–63] In fact, many clinical and pathological parameters were associated with worse prognosis of UCS. Some of them may be a bias inducing unpredicted results. For example, the percentage of patients who underwent optimal debulking surgery in the current study was quite different between these two groups (PP vs IP, 91.7% vs 50%), the trend favoring the therapeutic effect of PP may be influenced by this. It is well known that for UCS treatment, successful PCS is critical for better outcome.[1,2,17,24,26,29–32,64,65] Therefore, the findings of the current study should be interpreted carefully. Indeed, a certain degree of trend showed the following parameters, such as debulking status (suboptimal vs optimal, HR, 1.1), lymphovascular space involvement (yes vs no, HR, 3.1), histology type (heterologous vs homologous, HR, 118.7), and absence of radiotherapy (yes vs no, HR, 0.4) were all associated with worse outcome of advanced UCS, although they did not reach the "statistical significance." We believed that these factors should be kept in mind when we managed these advanced UCS patients.

The main limitation of the current study was a small sample size, and only 16 patients were enrolled. However, in phase II study from Japan, there were only 27 women with advanced uterine CS (FIGO III and IV) in 20 Japanese medical facilities.[36] From data extracted from the SEER database between 1973 and 2010, 27.8% of all UCS patients belonged to FIGO III and IV stage (1031/3706).[26] In Taiwan, a large-scale study showed only 454 UCS cases between 1979 and 2008 (30 years).[66] Although the advanced stage was not mentioned in their study, based on the estimation from majority of previous studies, only 150 advanced-stage UCS cases were proposed. In most recent study from Taiwan Chang Gung Memorial Hospital, 78 patients were FIGO III to IV UCS cases.[50] Second, the study was retrospective in nature, the selection bias should be considered. However, although phase III study has been closed in 2019, there is still absence of final report to compare the effectiveness and safety between PP and IP.[43] All hinted the basic problem of our study should be limited to difficulty of collected data due to extremely limited number cases.

In conclusion, in the current study, we found that presence of both pelvic and para-aortic lymphadenopathy and deep myometrial invasion were associated with worse prognosis. We favored the use of PP for advanced UCS, although evidence is still scarce. Therefore, it is now essential to have the results of the individual patient data meta-analysis (based on prospective, randomized trials) to definitely show clinically relevant benefits of PP therapy in UCS and confirm the independent risk factors associated with worse prognosis of patients with UCS.

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