

Adjuvant Treatment Modalities, Prognostic Predictors and Outcomes of Uterine Carcinosarcomas

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Purpose

The purpose of this study is to evaluate the clinicopathological characteristics, treatment, and prognosis of uterine carcinosarcoma (UC).

Materials and Methods

A retrospective review of three cancer registry databases in Turkey was conducted for identification of patients diagnosed with UC between January 1, 1996, and December 31, 2012. We collected clinicopathological data in order to evaluate factors important in disease-free survival (DFS) and overall survival (OS).

Results

A total of 66 patients with UC with a median age of 65.0 years were included in the analysis. The median survival time of all patients was 37.5 months and the 5-year OS rate was 59.1%. In early stage patients (I-II) who received adjuvant chemotherapy (CT) with radiation therapy (RT), the median DFS and OS was 44 months and 55 months, respectively, compared to 34.5 months and 36 months, respectively, in patients who received adjuvant RT or CT alone (hazard ratio [HR], 1.4; 95% confidence interval [CI], 0.7 to 3.1 for DFS; $p=0.23$ and HR, 2.2; 95% CI, 0.9 to 5.3 for OS; $p=0.03$). In advanced stage patients (III-IV), the median DFS and OS of patients receiving adjuvant RT with CT was 25 months and 38 months, respectively, compared to 23.5 months and 24.5 months, respectively, in patients receiving adjuvant RT or CT alone (HR, 3.1; 95% CI, 0.6 to 16.0 for DFS; $p=0.03$); (HR, 3.3; 95% CI, 0.7 to 15.0 for OS; $p=0.01$). In multivariate analysis, advanced International Federation of Gynecology and Obstetrics (FIGO) stage and suboptimal surgery showed significant association with poor OS.

Conclusion

In patients with early or advanced stage UC, adjuvant CT with RT is associated with improved DFS and OS, as compared to CT or RT alone.

Key words

Carcinosarcoma, Uterine neoplasms,
Adjuvant chemotherapy, Adjuvant radiotherapy

Introduction

Carcinosarcoma of the uterus accounts for 1-5% of all uterine malignancies, with an incidence of $< 2/100,000$ women per year. Uterine carcinosarcomas (UC) are monoclonal tumors classified as malignant mixed müllerian tumors, malignant mesodermal mixed tumors, or metaplastic carcinomas [1,2]. Metastases occur from carcinomatous and sarcomatous elements derived from de-differentiation

of the carcinomatous component [2]. These tumors are highly aggressive and often present with extrauterine-spread at stages III-IV [2]. The overall outcome of these patients is poor, with a 5-year survival ranging from 33-39% [3], accounting for 15 % of deaths related to uterine cancer [4].

The management of UC has been controversial. Surgery is the primary treatment for UC; however, as a result of its rarity, surgical management has not been well-defined [5]. In addition, the high rates of both local and distant recurrence after surgery suggest a need for effective adjuvant

therapies, although the benefit of adjuvant chemotherapy (CT) or radiotherapy (RT) remains to be determined [6].

In this study, we performed a retrospective review of the clinical characteristics, management, and outcomes of 66 patients with UC who were treated at three gynecological oncology departments in Turkey.

Materials and Methods

The databases of three Gynecological Oncology Departments at Izmir Tepecik Education and Research Hospital, Eskisehir Osmangazi University School of Medicine, and Zonguldak Bulent Ecevit University School of Medicine were reviewed in order to identify patients with pathologically diagnosed UC treated between January 1, 1996, and December 31, 2012. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local ethics committees of all institutions.

The following clinical data were collected from patient medical, surgical, pathological, CT and RT reports: demographic characteristics, presenting symptoms, serum cancer antigen 125 (CA-125) level, date and type of surgical procedure, presence or absence of residual tumor after surgery, number of excised and positive lymph nodes, presence or absence of ascites, pathological tumor characteristics (grade and size), histologic type (homologous or heterologous), adjuvant therapy if any, date of recurrence, treatment after recurrence, date of last medical examination, and date of death. International Federation of Gynecology and Obstetrics (FIGO) 2009 staging for endometrial carcinoma was used for all patients. The analysis included patients who received either CT with or without RT or RT alone. Patients who did not receive adjuvant treatment were excluded from the analyses.

Patients were classified without staging if only peritoneal washings, and total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO), with or without infracolic omentectomy, were performed. Partial staging was defined as peritoneal washings, infracolic omentectomy, and bilateral pelvic lymphadenectomy with a TAH and BSO. Complete staging was defined as peritoneal washings, infracolic omentectomy, and bilateral pelvic and para-aortic lymphadenectomy with a TAH and BSO. Optimal debulking was defined as a procedure leaving a maximum residual tumor < 1 cm in diameter.

Although postoperative management was not absolutely consistent, the preferred treatment differed at the three institutions, with one institution preferring CT alone, one

Table 1. Clinical characteristics of the study population

Characteristic	No. (%) (n=66)
Age (yr)	65.0 (43-78)
≤ 60	24 (36.4)
> 60	42 (63.6)
Menopause	55 (60.4)
Symptom	
Abnormal vaginal bleeding / discharge	47 (71.2)
Abdominal pain	22 (33.3)
Palpable mass	7 (10.6)
Combination	18 (27.3)
Presence of ascites	22 (33.3)
CA-125 (U/mL)	22.4 (3.0-447.0)
< 35	25 (37.9)
≥ 35	22 (33.3)
Unknown	19 (28.8)
Stage	
I	30 (45.5)
II	7 (10.6)
III	25 (37.9)
IV	4 (6.1)
Grade	
I	8 (12.1)
II	13 (19.7)
III	34 (51.7)
Unknown	11 (16.7)
Tumor diameter (cm)	4 (1-10)
Histopathological type	
Homologous	33 (50.0)
Heterologous	21 (31.8)
Unknown	12 (18.2)
LVSI	
Yes	31 (47.3)
No	21 (31.8)
Unknown	14 (21.2)
Myometrial invasion	
< 1/2	24 (36.4)
≥ 1/2	34 (51.5)
Unknown	8 (12.1)
Positive peritoneal cytology	
Yes	16 (24.2)
No	44 (66.7)
Unknown	6 (9.1)
Necrosis	
Yes	24 (36.4)
No	29 (43.9)
Unknown	13 (19.7)
Recurrence	21 (31.8)
Duration of follow-up (mo)	37.5 (14-123)
Disease-free survival (mo)	28.5 (11-123)
Overall survival (mo)	37.5 (14-123)

Values are presented as median (range) or number (%). CA-125, cancer antigen 125; LVSI, lymphovascular space invasion.

preferring RT alone, and one preferring CT with RT. Patients received CT with or without RT or RT alone based on stage, age, presence of nodal metastasis, performance status, and medical co-morbidities.

External beam radiotherapy (EBRT) was administered to a median dose of 50.4 Gy (range, 45 to 54 Gy) at 1.8-2.0 Gy per fraction, five days per week. Vaginal vault brachytherapy (VBT) (2×650 cGy, prescribed to 0.5-cm depth) was delivered using a vaginal applicator with high-dose rate Iridium-192 source.

Patients returned for a follow-up evaluation every three months for the first two years, every six months for the next three years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Analysis of survival data was performed in December 2012.

Patients were categorized according to two groups: adjuvant CT with RT group (sequential group) and adjuvant RT or CT alone group (alone group). Staging groups were classified as early FIGO stage (I-II) and advanced stage (III-IV).

Survival analysis was based on the Kaplan-Meier method, and the results were compared using a log-rank test. Disease-free survival (DFS) was defined as the time from the date of primary surgery to detection of recurrence or the latest observation. Overall survival (OS) was defined as the time from the date of primary surgery to death or the latest observation. The χ^2 test and Student's t-test for unpaired data were used for statistical analysis. Cox regression analysis was used to determine factors affecting survival, presented as hazard

ratios (HR). All statistical analyses were performed using Med-Calc software (ver. 11.5 for Windows, MedCalc Software, Mariakerke, Belgium). A $p < 0.05$ was considered to indicate statistical significance.

Results

We identified 68 patients with UC during the study period. Two patients did not receive adjuvant therapy, were lost to follow-up, and were not included in the analysis. The characteristics of the patients are shown in Table 1. None of the patients had a history of pelvic RT.

Forty-one of 66 patients (62.1%) received CT with RT (early stage 20/37 and advanced stage 21/29). Sixteen of 66 patients (24.2%) received RT alone (early stage 14/37 and advanced stage 3/29). Only nine patients (13.6%) received CT alone (early stage 3/37 and advanced stage 6/29). The operative procedures performed are described in detail in Table 2.

Postoperative CT alone consisted of cisplatin+doxorubicin (6/9 patients), paclitaxel+carboplatin (1/9 patients), and vincristine+doxorubicin+cyclophosphamide+mesna (2/9 patients) for 4-6 cycles. In the sequential treatment group, CT consisted of cisplatin+doxorubicin (28/41 patients), cyclophosphamide+doxorubicin+cisplatin (4/41 patients), ifosfamide+doxorubicin+mesna (6/41 patients), cyclophosphamide+doxorubicin (1/41 patients), ifosfamide+etoposide

Table 2. Types of management of the patients

	No. (%)
Surgical procedures	
TAH+BSO+washing cytology	2 (3.0)
TAH+BSO+washing cytology+omentectomy	5 (7.6)
TAH+BSO+washing cytology+PLD+omentectomy	13 (19.7)
TAH+BSO+washing cytology+PPLD+omentectomy	46 (69.7)
Residual tumor at initial surgery (cm)	
≤ 1	50 (75.8)
> 1	16 (24.2)
No. of lymph nodes removed	
Pelvic	12 (2-38)
Para-aortic	5 (1-16)
Adjuvant therapy	
Chemotherapy alone	9 (13.6)
Radiotherapy alone	16 (24.2)
Chemotherapy+radiotherapy	41 (62.1)

Values are presented as number (%) or median (range). TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLD, pelvic lymphadenectomy; PPLD, pelvic and para-aortic lymphadenectomy.

Table 3. Details of adjuvant chemotherapy regimens

Chemotherapy regimen	Dosage
Cisplatin+doxorubicin	100 mg/m ² +25 mg/m ²
Paclitaxel+carboplatin	175 mg/m ² +5-6 AUC
Vincristine+doxorubicin+cyclophosphamide+mesna	1.4 mg/m ² +75 mg/m ² +1,200 mg/m ² +1,200 mg/m ²
Cyclophosphamide+doxorubicin+cisplatin	500 mg/m ² +50 mg/m ² +50 mg/m ²
Ifosfamide+doxorubicin+mesna	1.2 mg/m ² +25 mg/m ² +240 mg/m ²
Cyclophosphamide+doxorubicin	600 mg/m ² +60 mg/m ²
Ifosfamide+etoposide+mesna	1.8 mg/m ² +100 mg/m ² +360 mg/m ²
Ifosfamide+paclitaxel+mesna	1.6 mg/m ² +135 mg/m ² +400 mg/m ²

AUC, area under the curve.

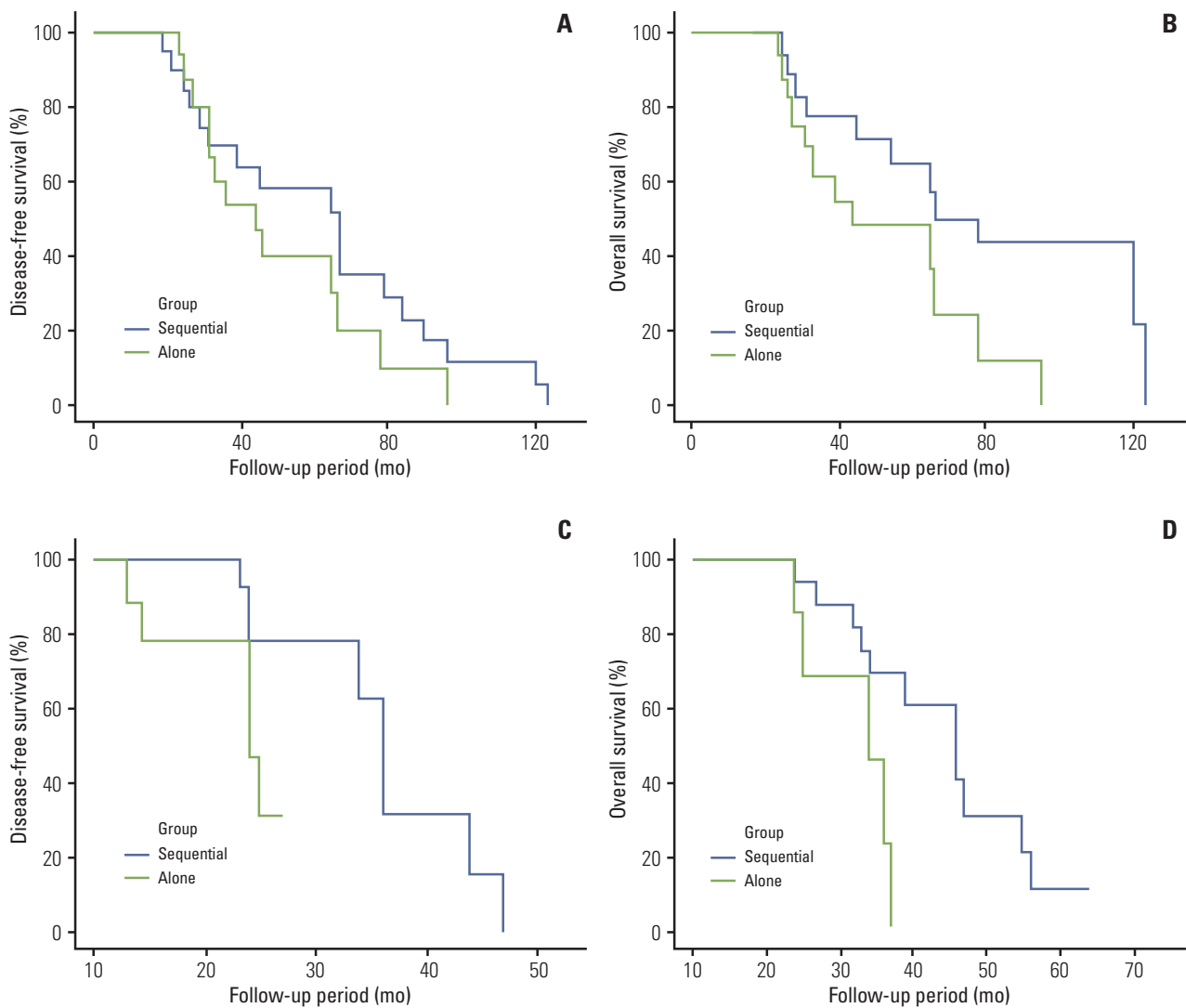


Fig. 1. (A) Disease-free survival curves according to treatment groups in early International Federation of Gynecology and Obstetrics (FIGO) stage (I&II). (B) Overall survival curves according to treatment groups in early FIGO stage (I&II). (C) Disease-free survival curves according to treatment groups in advanced FIGO stage (III&IV). (D) Overall survival curves according to treatment groups in advanced FIGO stage (III&IV).

side+mesna (1/41 patients), and ifosfamide+paclitaxel+mesna (1/41) for 4-6 cycles. Details of adjuvant CT regimens are shown in Table 3. Postoperative RT alone consisted of EBRT (5/16 patients) and EBRT+VBT (11/16 patients). In the sequential treatment group, RT consisted of EBRT (28/41 patients) and EBRT+VBT (13/41 patients).

In early stage disease, the median DFS and OS of patients in the sequential treatment group was 44 months (range, 19 to 123 months) and 55 months (range, 19 to 123 months), respectively, and that of patients receiving RT or CT alone was 34.5 months (range, 17 to 96 months) and 36 months (range, 17 to 96 months), respectively. Results of Kaplan-Meier analysis showed no significant difference in DFS (HR, 1.4; 95% confidence interval [CI], 0.7 to 3.1; $p=0.23$) (Fig. 1A), however, significant difference in OS was observed (HR, 2.2; 95% CI, 0.9 to 5.3; $p=0.03$) (Fig. 1B) between groups.

In advanced stage disease, the median DFS and OS of patients receiving sequential treatment was 25.0 months (range, 13 to 47 months) and 38 months (range, 24 to 64 months), respectively, and that of patients receiving RT or CT alone was 23.5 months (range, 13 to 27 months) and 24.5 months (range, 14 to 37 months), respectively. Results of Kaplan-Meier analysis showed a significant difference in DFS (HR, 3.1; 95% CI, 0.6 to 16.0; $p=0.03$) (Fig. 1C) and OS (HR, 3.3; 95% CI, 0.7 to 15.0; $p=0.01$) (Fig. 1D) between groups.

Disease recurrence occurred in 22 patients (33.3%). The recurrence rate was 88.9% in the no staging group, 50.0% in

the partial staging group, and 24.3% in the complete staging group. Recurrence occurred in 16 patients (72.7%) originally diagnosed in advanced stages and six patients (27.3%) originally diagnosed in early stages. Recurrent disease was located in the pelvis in 11 patients, characterized by distant metastases (lung, liver, or mediastinal lymph nodes) in eight patients, and by peritoneal dissemination in three patients. These patients were managed with CT with/without secondary debulking surgery. The median DFS was 31.0 months (range, 11 to 123 months). The results of univariate and multivariate analyses of DFS are shown in Table 4. In univariate and multivariate analysis, surgical staging type (none or partial), advanced FIGO stage, and suboptimal surgery (residual tumor ≥ 1 cm) were independent prognostic factors for DFS.

The 5-year OS rate was 59.1% and the median duration of survival was 37.5 months (range, 14 to 123 months). The 5-year OS was 11.1% in the no staging group, 50.0% in the partial staging group, and 75.7% in the complete staging group. The results of univariate and multivariate analyses of OS are shown in Table 5. The results of univariate analysis of survival rates showed significant association of myometrial invasion $\geq 1/2$, advanced FIGO stage, suboptimal surgery, surgical staging type (none or partial), tumor size ≥ 2 cm, and heterologous histological subtype with poor OS. In contrast, in multivariate analysis of OS, only advanced FIGO stage and suboptimal surgery showed significant association with poor OS.

Table 4. Results of univariate and multivariate analyses of disease-free survival of patients with uterine carcinosarcoma

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age (< 60 yr vs. ≥ 60 yr)	0.8	0.4-1.6	0.70	1.7	0.5-2.5	0.67
Stage (I/II vs. III/IV)	1.9	1.1-3.3	0.01	3.4	1.2-11.1	0.02
Grade (I vs. II vs. III)	1.3	0.9-1.9	0.11	1.3	0.8-2.0	0.25
Residual tumor size (< 1 cm vs. ≥ 1 cm)	2.6	1.2-5.4	0.04	5.3	1.5-18.5	0.009
Surgical type (none vs. partial vs. complete)	2.3	1.1-4.6	0.01	2.3	1.0-5.6	0.04
CA-125 (< 35 U/mL vs. ≥ 35 U/mL)	1.1	0.6-2.1	0.54	1.7	0.6-4.3	0.26
Histology (homologous vs. heterologous)	1.4	0.7-2.6	0.30	1.3	0.6-3.0	0.45
Presence of ascites	0.6	0.3-1.3	0.20	1.6	0.6-5.0	0.33
LVSI	0.8	0.4-1.5	0.66	1.0	0.5-2.2	0.90
Myometrial invasion (< 1/2 vs. $\geq 1/2$)	0.6	0.3-1.1	0.09	1.7	0.7-4.1	0.20
Positive peritoneal cytology	1.2	0.6-2.2	0.43	1.1	0.5-2.5	0.73
Necrosis	0.8	0.4-1.5	0.49	1.4	0.6-3.4	0.42
Menopause	0.5	0.3-1.0	0.08	1.6	0.3-3.5	0.32
Tumor diameter (< 2 cm vs. ≥ 2 cm)	1.0	0.5-1.8	0.93	1.0	0.4-2.3	0.60

CI, confidence interval; CA-125, cancer antigen 125; LVSI, lymphovascular space invasion.

Table 5. Results of univariate and multivariate analyses of overall survival of patients with uterine carcinosarcoma

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age (< 60 yr vs. ≥ 60 yr)	1.1	0.5-2.1	0.71	1.2	0.5-2.8	0.53
Stage (I/II vs. III/IV)	0.5	0.2-1.0	0.02	3.8	1.0-14.2	0.04
Grade (I vs. II vs. III)	1.2	0.8-1.9	0.24	1.1	0.7-1.8	0.48
Residual tumor size (< 1 cm vs. ≥ 1 cm)	3.4	1.6-7.3	0.02	6.2	1.5-24.7	0.009
Surgical type (none vs. partial vs. complete)	2.0	1.0-4.2	0.04	2.0	0.7-5.7	0.15
CA-125 (< 35 U/mL vs. ≥ 35 U/mL)	1.1	0.6-2.1	0.68	1.0	0.3-3.3	0.91
Histology (homologous vs. heterologous)	2.1	1.1-4.2	0.04	1.7	0.6-4.6	0.29
Presence of ascites	0.6	0.3-1.4	0.27	1.3	0.5-3.3	0.47
LVSI	1.3	0.6-2.4	0.40	1.4	0.6-3.3	0.39
Myometrial invasion (< 1/2 vs. ≥ 1/2)	0.4	0.2-0.9	0.01	1.1	0.5-3.8	0.36
Positive peritoneal cytology	0.9	0.5-1.8	0.89	1.1	0.5-2.5	0.68
Necrosis	1.6	0.8-3.1	0.49	1.4	0.5-3.5	0.42
Menopause	0.7	0.3-1.3	0.32	1.3	0.6-3.7	0.31
Tumor diameter (< 2 cm vs. ≥ 2 cm)	2.0	1.0-3.7	0.03	1.4	0.5-3.6	0.43

CI, confidence interval; CA-125, cancer antigen 125; LVSI, lymphovascular space invasion.

Discussion

In the current study, we performed a retrospective analysis of data from 66 patients with carcinosarcoma of the uterus who were treated with surgery followed by adjuvant therapy at three gynecologic oncology centers in Turkey. Our aim was to describe the demographic and clinical characteristics of UC, to determine the optimal adjuvant therapy strategy according to the early or advanced stage of disease, and to identify variables affecting DFS and OS in patients with this disease.

UC is a rare clinical entity, representing < 5% of uterine cancer cases in most studies [1,2]. Among uterine cancer cases treated in our clinics, 3.3% were diagnosed as UC, which corresponds to previous reports. Patients with prior pelvic RT and use of tamoxifen, reported as risk factors for UC [2,7], were not observed in our cohort. In the literature, the median age of patients with UC is 62 years [8], similar to that in our patient population.

Currently, no national guidelines have been established for management of UC. Surgery is the cornerstone of treatment, although the extent of surgical procedure remains unclear. TAH with BSO is the most common procedure; however, the additive benefit of retroperitoneal lymphadenectomy (RLD) remains undetermined [9]. A recently published article by Vorgias and Fotiou [6] and Park et al. [10] recommended performance of RLD in patients with UC. Nemani et al. [11] reported a significant OS benefit associated with RLD, with a 5-year OS of 49%, compared with 35% for patients who had

not undergone RLD. In our study, the 5-year OS was 11.1% in the no staging group, 50.0% in the partial staging group, and 75.7% in the complete staging group. In addition, the recurrence rate was 88.9% in the no staging group, 50.0% in the partial staging group, and 24.3% in the complete staging group.

There is an ongoing debate regarding the most suitable method for adjuvant treatment of UC [9]. In a series of cases described by Gonzalez Bosquet et al. [12], surgery followed by sequential treatment yielded a significantly longer median DFS versus surgery, RT or CT alone. Menczer et al. [13] published a multicenter retrospective study comparing CT with or without radiation to RT alone in patients who underwent surgical staging for UC. The authors reported that sequential treatment after surgery decreased mortality, as compared to patients taking RT or CT alone [13]. Similarly, Wong et al. [14], who reported a protocol of cisplatin and ifosfamide-based CT along with RT in 43 patients, noted improved survival in patients who received both CT and RT. However, these two studies did not provide separate analysis for early or advanced stages of disease. In our cohort of 66 patients, we showed that surgery followed by a sequential treatment yields a significantly longer median OS versus CT alone or RT alone for early and advanced stage UC.

The 5-year OS rate for all stages of UC varies from 10-69% [10,15], while in our study we reported a rate of 59.1%. Several studies have reported various prognostic factors that predict the outcome of UC, including age, stage, lymphovascular space involvement, tumor histology, elevated preoperative CA-125, residual tumor after surgery, positive

peritoneal cytology, tumor size, and myometrial invasion [16-19]. In our study, advanced FIGO stage, presence of a residual tumor ≥ 1 cm after surgery, and surgical staging type (none or partial) showed significant association with poor DFS in both univariate and multivariate analyses. In addition, myometrial invasion $\geq 1/2$, advanced FIGO stage, suboptimal surgery, surgical staging type (none or partial), tumor size ≥ 2 cm, and heterologous tumor histology showed significant association with poor OS in univariate analysis. Advanced FIGO stage and suboptimal surgery were also independent prognostic factors for OS.

Potential limitations of this study include its retrospective nature, the absence of some data, small sample size, and lack of a standard chemotherapeutic regimen, since selection of the regimen depended on the discretion of the medical oncologists. Despite these limitations, the similarity of demographic characteristics in the study population, availability of good follow-up data, and performance of surgeries in three institutions by the same surgical team increased the validity of results and mitigated weaknesses.

Conclusion

In summary, the three important findings of our study are 1) sequential treatment after surgery decreased mortality in both early and advanced stage disease; 2) performing complete RLD reduces the risk of recurrence and improves OS; 3) advanced FIGO stage and suboptimal surgery were the only significant independent predictors of OS. A multi-center randomized clinical trial including a large series of patients is needed in order to definitively determine optimal management of this rare disease.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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