Original Article

Tumor Recurrence Rate and Survival Outcomes of Uterine Serous Carcinoma after Surgical Treatment

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Background: Uterine serous carcinoma is a rare histologic subtype of endometrial cancer. Oncologic outcomes for this disease are sparsely reported, and adjuvant therapy after surgery is considerably heterogeneous.

Objective: To determine the 2-year recurrence rate, recurrence-free survival, overall survival, and associated factors among patients with uterine serous carcinoma after surgical treatment at Siriraj Hospital.

Materials and Methods: One hundred thirty uterine serous carcinoma patients diagnosed between December 2007 and June 2015 were enrolled. Patients who did not undergo surgery as a primary treatment or not achieve clinically complete response were excluded. Pathological slides were reviewed. Data were retrieved from the medical records including gynecologic data, surgical and pathological results, post-operative treatment, response status, recurrence status, and follow-up data. The recurrence rate at two years was calculated. Recurrence-free survival and overall survival were analyzed, and various characteristics were used to determine associated treatment outcomes.

Results: One hundred nine patients were analyzed, 50 in stage I, 15 in stage II, 38 in stage III, and six in stage IV. Median follow-up time was 23 months. At two years, the recurrence rate was 35.8%. Post-operative treatment was performed in 91.7%, and chemotherapy was the most common modality used. Eleven patients (16.9%) in early-stage and twenty-five patients (56.8%) in the advanced stage had disease recurrence. Thirty patients (83.3%) had disease recurrence intra-abdominal or multiple metastases. No patient in stage I that received adjuvant chemotherapy had relapsed disease. Two-year recurrence-free survival and 2-year overall survival were 71.2% and 83.4%, respectively. FIGO staging was the only factor associated with recurrence-free survival.

Conclusion: Uterine serous carcinoma represents a rare disease with a high recurrence rate and poor prognosis. FIGO staging is related to recurrence-free survival. Adjuvant chemotherapy showed survival benefits in early-stage uterine serous carcinoma.

Keywords: Uterine serous carcinoma, Adjuvant therapy, Recurrence, Survival

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Uterine cancer is the fifth most common cancer in women next to breast cancer, colon cancer, cervical cancer, and lung cancer[1]. The age-standardized incidence rate of uterine cancer is 8.2 per 100,000. In terms of mortality, the rate is quite high (1.8 per 100,000). Uterine cancer is also the third most common gynecologic cancer in Thailand. The age-standardized incidence and mortality rate are 3.9 and 1.1 per 100,000, respectively.

Endometrioid adenocarcinoma is the most common histologic subtype, which accounts for 75% to 80%. Serous carcinoma accounts for approximately 10%[2] and tends to be more aggressive, with higher recurrence and death. The other types, mucinous, clear cell, and squamous carcinoma are rare entities.

Surgery is the mainstay of endometrial cancer treatment. Radiotherapy and chemotherapy are the adjuvant options with risk factors for recurrences. The prognosis depends on the stages of the disease

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and histopathologic cell types. For early-stage endometrioid adenocarcinoma, the five-year overall survival rate is 75% to 87%[3]. In contrast, early-stage serous carcinoma has reported lower survival rate, approximately 44% to 72%[4,5], and the recurrence rate is as high as 50% to 80% for all stages. Moreover, uterine serous carcinoma is frequently associated with distance spread at the time of diagnosis.

The heterogeneity is often detected in uterine serous carcinoma, pure serous, and mixed serous carcinoma. The etiology, pathogenesis, and clinical behavior of these different types are not well-understood. A similar prognosis and risk for metastasis had been reported[6]. On the other hand, some studies demonstrated a favorable outcome for mixed serous carcinoma patients compared with pure serous carcinoma[4,7].

Owing to low incidence and lack of optimal data of this aggressive cancer, the primary objective of the present study was to determine the 2-year recurrence rate, recurrence-free survival, overall survival, and associated factors for recurrence-free survival among patients with uterine serous carcinoma after surgical treatment at Siriraj Hospital.

Materials and Methods

After ethical approval from the Siriraj Institutional Review Board (SIRB) (Si076/2016), a retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital.

Patients diagnosed with uterine serous carcinoma between December 2007 and June 2015 were enrolled. The patients who did not undergo surgery or did not have available data from the operative records were excluded. The sample size was calculated based on the recurrence rate, an estimated 52%, at a median follow-up of 21 months from the previous study[8]. At least 119 patients were required to achieve a 95% confidence level.

One hundred thirty uterine serous carcinoma patients were enrolled. Information was retrieved from the medical records. Pathological slides were review by a pathologist. Data from patients who achieved complete response were analyzed. The primary endpoint of the present study was a 2-year recurrence rate. The secondary endpoints were recurrence-free survival and overall survival at two years, and associated factors for recurrence-free survival were also evaluated.

Complete response was defined as no evidence of disease at the time of last treatment, including 1) no gross residual tumor after surgery with or without adjuvant therapy, and 2) negative imaging after adjuvant therapy in a patient with the gross residual tumor. Patients were follow-up by gynecologic oncologists every three to four months for two years, every six months for the next three years, and then annually. During each visit, careful history taking, physical examination, and pelvic examination were performed. Computed tomography (CT) scan was evaluated after clinically suspected tumor recurrence. Recurrence-free survival was defined as the time from a complete response to the first recurrence of endometrial cancer. Overall survival was defined as the time from a complete response to death from any cause.

Statistical analysis

Descriptive statistics were used to assess patients' baseline characteristics, operational data, histo-pathology, post-operative treatments, response status, recurrence status, and follow-up data. Survival curves were performed by the Kaplan-Meier method and were compared by the log-rank test. Cox proportional hazards regression model was used to determine the association for each potential factor. A p-value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using PASW Statistics, version 18 (SPSS Inc., Chicago, IL, USA).

Results

One hundred thirty uterine serous carcinoma patients treated at Siriraj Hospital were included. Six patients did not receive complete treatment, fourteen patients did not achieve a complete response, and one patient was lost to follow-up. Thus, 109 patients were assessed. The mean age was 62.3 years and 23.9% were nulliparous. Fifty-six patients (51.5%) were overweight or obese. Seven patients (6%) were diagnosed with breast cancer concurrently or after the diagnosis of uterine serous carcinoma.

Table 1 summarizes the operative and pathological findings. All women had a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Omentectomy was performed in 66 patients (60.6%), and histologically proven omental metastases were found in three patients (4.5%). Pure serous carcinoma accounted for 67.9%. The patients were in early-stage disease (stage I and II) and advanced disease (stage III and IV), 59.7% and 40.3%, respectively. Complete surgical staging without a gross residual tumor was achieved in 79.5% of the advanced stage patients. Lymphadenectomy was

Table 1. Surgical, pathological and tumor characteristics

Characteristics	n (%)
Surgery (109 cases)	
Hysterectomy	109 (100)
Bilateral salpingo-oophorectomy	109 (100)
Pelvic lymphadenectomy	101 (92.7)
Para-aortic lymph node sampling	64 (58.7)
Omentectomy	66 (60.6)
Surgical outcomes in patients with advanced-stage (44 cases)	
Without gross residual tumor	35 (79.5)
Histology (109 cases)	
Serous	74 (67.9)
Serous + endometrioid	31 (28.5)
Serous + clear cell	2 (1.8)
Serous + endometrioid + clear cell	2 (1.8)
Lymph nodes status (101 cases)	
Pelvic nodes metastasis	21 (20.8)
Para-aortic nodes metastasis	2 (2.0)
Pelvic and para-aortic nodes metastasis	6 (5.9)
Lymph-vascular space invasion (109 cases)	
Yes	45 (41.3)
Omental metastasis (66 cases)	
Yes	3 (4.5)
FIGO staging	
IA	35 (32.1)
IB	15 (13.8)
II	15 (13.8)
IIIA	9 (8.3)
IIIB	1 (0.9)
IIIC1	20 (18.3)
IIIC2	8 (7.3)
IVA	0 (0.0)
IVB	6 (5.5)
Adjuvant treatment (109 cases)	
Observation	9 (8.3)
Radiotherapy	19 (17.4)
Chemotherapy	51 (46.8)
Combined chemotherapy and radiation	30 (27.5)

FIGO=International Federation of Gynecology and Obstetrics

performed in 92.7% (101 cases). The median numbers of harvested pelvic and paraaortic lymph nodes were 15 (6 to 47) and six (1 to 9), respectively. Lymph nodes metastasis was detected in 28.7% of the patients who underwent lymphadenectomy. Two cases in this group had isolated paraaortic lymph node metastasis.

Post-operative adjuvant treatment was obtained in 91.7%, and chemotherapy was the most common treatment modality. All patients in the chemotherapy group received a platinum-based regimen. Carboplatin plus paclitaxel was the most common regimen used. Radiotherapy consisted of external pelvic beam radiation or brachytherapy, or both.

According to the International Federation of Gynecology and Obstetrics (FIGO) staging, as shown in Table 2, of the 65 patients with stage I and II, 17 patients (26.1%) received adjuvant radiotherapy, 25 patients (38.5%) received adjuvant chemotherapy, 15 patients (23.1%) received combined chemotherapy and radiation, and eight patients (12.3%) did not receive adjuvant treatment. Eleven patients (16.9%) in early-stage had disease recurrence. No patient in stage I that submitted to chemotherapy had disease recurrence.

Of the 44 patients with stage III and IV, two patients (4.5%) received adjuvant radiotherapy, 26 patients (59.1%) received adjuvant chemotherapy, 15 patients (34.1%) received combined chemotherapy and radiation, and one patient (2.3%) received no adjuvant treatment. Twenty-five patients (56.8%) in the advanced stage had disease recurrence. For disease recurrence, despite no statistically significant correlation between FIGO staging and adjuvant therapy, the authors observed that patients in stage I cancer had less recurrence rate among chemotherapy and combined chemotherapy and radiation groups.

Median follow-up time was 23 months. Eighty-one patients were followed up at least 24 months. There were 29 patients from 81 patients with recurrent disease (35.8%, 95% CI 26.2 to 46.7) at 2-year. However, there were 36 recurrences cases from 109 cases (33%, 95% CI 24.9 to 42.3) during the follow-up time. The tumor recurred locoregionally in six patients (16.7%). Thirty patients (83.3%) had a recurrence in the abdomen or multiple metastases. Treatment at recurrence was surgery in one patient, radiotherapy in five patients, chemotherapy in 15 patients, multi-modality in five patients, and best supportive care in 10 patients. There were 20 deaths during the study period.

Figure 1 shows the 2-year recurrence-free survival and the 2-year overall survival of uterine serous carcinoma patients at 71.2% and 83.4%, respectively. The survival in Figure 2 was significantly better in early-stage cancer than in the advanced stage ($p<0.001$). Mixed and pure serous carcinoma histology had no significant impact on recurrence-free survival ($p=0.081$). It was observed that the pure

Table 2. Recurrence rates stratified by adjuvant treatment and FIGO staging

Stage	Observation n (%)	Radiotherapy n (%)	Chemotherapy n (%)	Combination n (%)	No. of recurrences n (%)	p-value
I	2/8 (25.0)	3/11 (27.2)	0/20 (0.0)	1/11 (9.0)	6/50 (12.0)	0.089
II	-	2/6 (33.3)	2/5 (40.0)	1/4 (25.0)	5/15 (33.3)	0.894
III	1/1 (100)	1/2 (50.0)	10/20 (50.0)	9/15 (60.0)	21/38 (55.3)	0.755
IV	-	-	4/6 (66.7)	-	4/6 (66.7)	*
Total	3/9 (33.3)	6/19 (31.6)	16/51 (31.4)	11/30 (36.7)	36/109 (33.0)	0.967

FIGO=International Federation of Gynecology and Obstetrics

* The p-value could not be computed

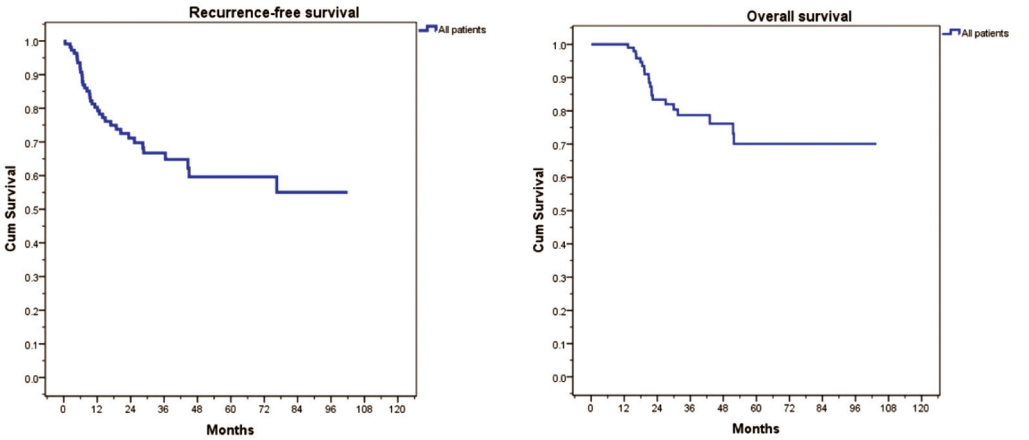

Figure 1. Recurrence-free survival and overall survival of uterine serous carcinoma patients.

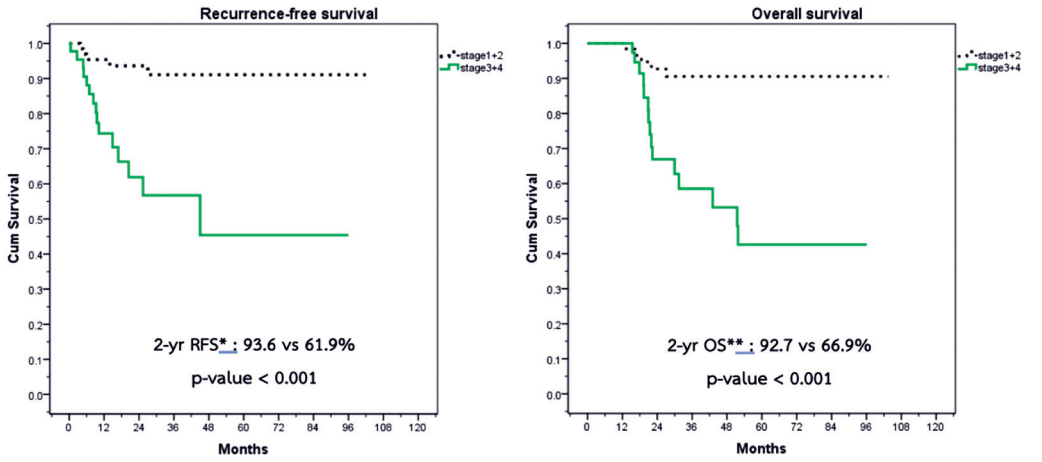

Figure 2. Recurrence-free survival and overall survival, according to FIGO staging.

* RFS=recurrence-free survival, ** OS=overall survival

serous carcinoma patients had lower 2-year overall survival than the mixed type carcinoma (p=0.014), as shown in Figure 3.

Associated factors for recurrence-free survival were advanced-stage cancer, lymph node metastasis, and lymph-vascular invasion. They were significantly

Table 3. Univariate and multivariate analysis for recurrence-free survival

	Univariate analysis	Multivariate analysis	
	p-value	HR (95% CI)	p-value
Mixed type histology	0.087*	0.64 (0.25 to 1.61)	0.343
Lymph-vascular space invasion	0.003*	1.32 (0.54 to 3.18)	0.543
Lymph node metastasis	<0.0001*	0.99 (0.38 to 2.65)	0.996
Advanced stage (III-IV)	<0.0001*	4.05 (1.32 to 12.41)	0.014*

HR=hazard ratio; CI=confidence interval

* p<0.05 is statistically significant

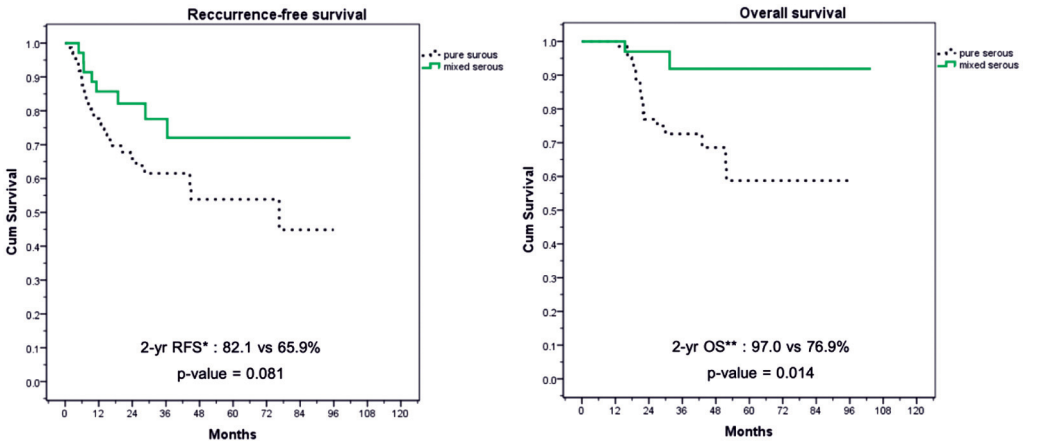

Figure 3. Recurrence-free survival and overall survival, according to histology, pure serous carcinoma and mixed type.

* RFS=recurrence-free survival, ** OS=overall survival

correlated with a higher risk of relapse. Table 3 represents the multivariate analyses adjusting for histology (pure and mixed serous carcinoma), lymph-vascular invasion, lymph node metastasis, and FIGO staging. Only FIGO staging was an independent predictor of recurrence-free survival (p=0.014).

Discussion

Uterine serous carcinoma is commonly reported in older patients. The mean age of patients in the present study was 62.3 years, which was similar to other studies[9,10]. The incidence of uterine serous carcinoma in patients with a history of breast cancer was 4.6% to 25%, which was higher than the endometrioid subtype[11,12]. Tamoxifen therapy and uterine serous carcinoma were in conflict, which supported the association[13,14]. In the present study, the correlation between breast cancer, tamoxifen therapy, and uterine serous carcinoma cannot be concluded owing to a small number of patients in this particular group.

Comprehensive surgical staging is the mainstay of uterine serous carcinoma treatment. Lymphadenectomy may improve survival in the high-risk endometrial cancer group[15,16]. In the present study, lymph node metastasis was detected in 28.7%, almost equivalent to 29% from the Surveillance, Epidemiology and End-Results (SEER) database[17]. Owing to 58.7% of paraaortic lymph node evaluation in the present study, paraaortic lymph node metastasis (7.9%) was less than the SEER database (13.3%). Therefore, systematic pelvic and paraaortic lymphadenectomy should be performed in all patients with serous carcinoma. Omental metastasis was demonstrated in only 4.5% of the patients. This is different than previous studies (25% to 34.6%)[18,19]. However, omentectomy should be considered, but not strongly recommended in the surgical staging for uterine serous carcinoma. Gehrig et al[19] reported that microscopic omental metastasis was rare, and they concluded that omental sampling should not be included in routine surgical staging.

Most of the recurrence were identified outside of the pelvis, particularly in multiple sites. In the present study, there was 36 cases (33%) of recurrences, which was similar to previous studies (37%)[20,21]. A higher rate of recurrence (52%) was reported in Pol et al[8]. This result could be explained in the present study as only patients who achieved a complete response, more early-stage patients, and fewer patients without adjuvant treatment were included. Although adjuvant therapy was not associated with a significant improvement in recurrence, no patient in stage I who received chemotherapy had disease relapse. This result follows on the previous studies[22-24] that adjuvant chemotherapy has a survival benefit, particularly in early-stage uterine serous carcinoma.

Several studies presented the correlation between early-stage disease and favorable outcomes[20,25,26]. The present study affirmed that FIGO staging was significantly associated with recurrence-free survival ($p<0.001$) and overall survival ($p<0.001$). In terms of histology, patients with mixed serous carcinoma had significantly longer overall survival ($p=0.014$) than pure serous carcinoma, although recurrence-free survival was not significantly longer ($p=0.081$). Mixed serous carcinoma consisted of an endometrioid component, which demonstrated a better prognosis, and may explain such a result. A similar prognosis and risk for metastasis of these two different histologic subtypes had also been reported in the previous study[6]. In contrast, Roelofsen et al[7] concluded that patients with pure serous carcinoma had a 2.9 and 2.6-times higher risk for recurrence and death, respectively, than those with mixed-type carcinoma. However, the etiology and clinical behavior of these different subtypes are not well-understood. It could be expected that the etiology and pathogenesis were different between these two subtypes.

Nowadays, the optimal post-operative treatment of uterine serous carcinoma is still controversial. Many studies supported the survival benefit in adjuvant therapy for each stage[8,24,25]. Although the correlation between adjuvant therapy and recurrence-free survival was not observed in the present study multivariate analysis, there was a trend of lower recurrence in chemotherapy and combined chemotherapy and radiation groups for stage I disease.

There are some limitations to the present study. Firstly, the analyses were affected by a small sample size that limited the ability to detect the survival difference among post-operative treatment modalities. Stratifying the results by treatment groups cannot be estimated owing to the small number of patients in each group. Secondly, not only the retrospective and non-randomized design of the study were resulting in the incomplete data collection, it was also lowering an accuracy of some specific information. Lastly, the authors institute's oldest computer database is limited to January 2007, which limits the number of enrolled patients who follow-up at least 24 months, thus was less than previously expected.

Conclusion

Uterine serous carcinoma represents a rare disease with a high recurrence rate and poor prognosis. FIGO staging is related to recurrence-free survival and overall survival. In stage I, patients tend to have less relapse in the adjuvant chemotherapy group. Future trials are needed to assess appropriate treatment, and the role of targeted therapy, optimized sequence, and schedule.

What is already known on this topic?

Uterine serous carcinoma is a rare histopathology with a high recurrence rate and poor prognosis. Regarding the rarity and lack of optimal data of this specific subtype, particularly in the Asian population, adjuvant therapy after surgery is inconsistent among institutions. Moreover, recurrence and survival outcomes in such patients are sparsely reported.

What this study adds?

FIGO staging is related to recurrence-free survival in patients with uterine serous carcinoma. Adjuvant chemotherapy may have survival benefits in early-stage patients with this specific histologic subtype. The results of this study presented the data of treatment outcomes in such patients and help tailoring adjuvant therapy after surgery to decrease recurrence and increase survival benefits.

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Authors' contributions

Kuljarusnont S designed the study and critically revised the final draft of the manuscript. Pradyachaipimol A collected and analyzed the data and helped preparing the manuscript. Yotchai W reviewed pathology specimens. Ketthong J collected the chemotherapy data. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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