Adjuvant treatment, tumour recurrence and the survival rate of uterine serous carcinomas: a single-institution review of 62 women

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Abstract

Abstract

***Objectives*:** The aim of this study was to assess our department's management of uterine serous carcinoma (USC) and to determine the correlation of the recurrence and survival rates of stage I-IV patients with different adjuvant treatment modalities.

Design: A retrospective, single-institution, observational cohort study was performed.

Subjects and setting: The study participants were women diagnosed with stage I-IV USC between 1996 and 2012 at the Mercy Hospital for Women, Heidelberg, Australia.

Outcome measures: Outcomes measures were tumour recurrence rates, relapse-free survival and overall survival relating to the different adjuvant treatment modalities.

***Method*:** A retrospective, single-institution study on 62 women with stage I-IV USC diagnosed between 1996 and 2012 was performed.

***Results*:** Thirty patients had stage I, 5 stage II, 16 stage III and 11 stage IV, disease. Twenty patients received no adjuvant treatment, 19 patients adjuvant radiotherapy, 13 adjuvant chemotherapy and 10 adjuvant chemoradiation. Thirty-two (52%) patients experienced a recurrence and 32 patients were deceased, of whom 29 deaths were USC related. Recurrence risk correlated with stage (p-value 0.000). Early-stage (I and II) disease was associated with significant better relapse-free survival and overall survival than advanced-stage (III and IV) disease (p-value 0.000 and p-value 0.001, respectively). Adjuvant treatment significantly improved relapse-free survival and overall survival (p-value 0.008 and p-value 0.020, respectively), compared to no adjuvant treatment. Furthermore, a statistically significant improvement in relapse-free survival (p-value 0.035) and a trend towards better overall survival (p-value 0.064) was demonstrated with chemotherapy.

Conclusion: USC has a high recurrence rate and overall prognosis is poor. The stage of disease seems to be the best predictor of prognosis. This study suggests that even patients with early-stage (I and II) disease, i.e. either pure or mixed USC, should receive adjuvant treatment, as all of these women have a significantly high risk of recurrence. Currently, radiotherapy and chemotherapy are the adjuvant therapies used for USC. Prospective studies may help to determine the most effective adjuvant therapies.

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Introduction

Uterine cancer is the most common gynaecological malignancy in Australia, as in other developed countries. In 2012, more than 2 200 women were diagnosed with uterine cancer, accounting for more than 4% of all female cancer.[1] The incidence rate of uterine cancer in Australia is increasing. However, five-year survival has improved over the last 20 years from 77% to 84%.[2]

Several types of uterine cancer can be classified, i.e. as low- and high-risk tumours, based upon histological appearance. Endometrioid adenocarcinoma is the most common histological type of uterine cancer. These tumours comprise approximately 80% of all endometrial carcinomas. High-risk tumours include grade 3 endometrioid tumours, as well as tumours of non-endometrioid histology, i.e. serous, clear cell and mucinous. They are generally associated with more aggressive clinical behaviour than low-risk endometrial tumours. While they comprise only approximately 10-20% of all endometrial tumours, they account for up to 40% of deaths from the disease.[3-5] This is because they tend to present at an advanced stage. Approximately 50-70% of patients with high-risk uterine cancer present with stage III or IV disease.[6,7] Uterine serous carcinoma (USC) is a high-risk uterine cancer. It has a poorer prognosis because generally, it is a fast-growing tumour, infiltrates deeply in the myometrium, and frequently involves lymphovascular space invasion and distant metastases.[8] By definition, USC is high grade, and frequently presents with upper abdominal spread at the time of diagnosis. As reported in the literature, the five-year overall survival rate for all stages of USC is 43-62%.[6,9-12] Survival varies with each stage, from 45-90% for early-stage (I and II), and 0-30% for advanced stage (III and IV), disease.[6,13-19] These tumours are not well understood owing to the low incidence and limited data published thereon. Surgery is the cornerstone of treatment, but a lack of prospective studies leaves uncertainty as to the role of adjuvant therapy. The aim of this study was to assess our department's management of USC and to investigate relapse-free survival and overall survival in USC patients, with reference to adjuvant treatment modality and stage.

Method

This single-institution cohort study was performed in the Department of Gynaecological Oncology at the Mercy Hospital for Women in Melbourne, Australia, and covered the period from November 1996 to September 2012. Ninety-two patients were diagnosed with USC in this period, of whom 30 were excluded. Eleven patients were lost to follow-up, 10 did not undergo surgery as part of the treatment due to co-morbidities, and nine were excluded because of other histology (sarcomas) or a second primary tumour at the time of the USC diagnosis. Sixty-two of the patients who underwent surgery followed by either observation or adjuvant treatment (radiotherapy or chemotherapy, or both) were reviewed. Each patient with a pure serous histology, or a serous component mixed with endometrioid, clear cell and mucinous tumour types, or a mixture of these histological types, were included.

The hospital medical records of the included patients were reviewed. Data on the surgery, histopathology and tumour characteristics, adjuvant therapy, recurrence and follow-up were collected. The histopathological diagnoses were reviewed by gynaecological pathologists attending the Mercy Hospital for Women, Melbourne, Australia. Staging was based on the 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system. Pure USC was defined as an entire sample showing ≥ 90% serous histology. Mixed USC was defined as a sample with a less than 90%, but more than 5%, component, of serous histology.

Patients were monitored by a gynaecological oncologist, radiation oncologist, medical oncologist or a general practitioner approximately every three months for the first two years, every six months for the next two years, and then annually.

This study was approved by the Mercy Hospital for Women Health Human Research Ethics Committee.

Statistical analysis

Correlation of the recurrence rates at different stages with the different adjuvant treatments was the primary evaluated end-point. Relapse-free survival and overall survival were evaluated as secondary end-points. Correlation between the recurrence rates and different adjuvant treatments was calculated using the chi-square test, and was also examined using a multivariate logistic regression model, while adjusting for demographic and tumour variables. Relapse-free survival was calculated from the date of surgical diagnosis to the date of recurrence. Overall survival was calculated from the date of surgical diagnosis to the last follow-up or the date of death. Relapse-free survival and overall survival were calculated using the Kaplan-Meier method. The effects of age, body mass index (BMI), depth of myometrial invasion, tumour size, lymphovascular space invasion (LVSI), histology, and stage and types of adjuvant treatment on relapse-free survival and overall survival were calculated using the log-rank test and Cox proportional hazard models. SPSS® version 20 software was used for the statistical analyses.

Results

The median age of the patients was 69 years (a range of 44-85), with a median BMI of 29 kg/m^2 (a range of 18-63 kg/m^2). Almost all (60) of the women (97%) were postmenopausal and 12 (21%) had received hormone therapy for breast cancer in the past, or oestrogen supplements for climacteric complaints before the USC was diagnosed. Twelve patients (19%) had a previous history of a second malignancy, of whom 10 (83%) had breast cancer. Fifty-four women (87%) presented with postmenopausal blood loss as a first sign of uterine cancer, and diagnosis was confirmed by curettage and hysterectomy in 56 patients (90%).

All 62 (100%) patients underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Two patients (3%) underwent suboptimal cytoreductive surgery and 30 (48%) had pure serous histology on pathology. The median tumour size was 40 mm (a range of 4-90 mm), the median depth of myometrial invasion and median total thickness of the myometrium was 5 mm (a range of 0-40

Table I: The surgery, pathology and tumour characteristics of the patients

Variable	n (%)
Surgery	
Total abdominal hysterectomy plus bilateral salpingo-oophorectomy	62 (100.0)
Peritoneal cytology	57 (91.9)
Omentectomy	35 (56.5)
Pelvic lymph node dissection	34 (54.8)
Type of surgery*	
Optimal cytoreduction	60 (96.8)
Suboptimal cytoreduction	2 (3.2)
Tumour	
Histology (pure serous)	30 (48.4)
Histology (mixed serous)	32 (51.6)
Median size of the tumour (mm)	40 (range of 4-90)
Median depth of the myometrial invasion (mm)	5 (range of 0-40)
Median total thickness of the myometrium (mm)	15.5 (range of 8-44)
Lymph node metastasis	
Yes	6 (9.7)
No	28 (45.2)
Not performed	28 (45.2)
Lymphovascular space invasion	
None	21 (33.9)
Mild	25 (40.3)
Heavy	16 (25.8)
Stage (pathological)	
I	30 (48.4)
II	5 (8.1)
III	16 (25.8)
IV	11 (17.7)

*: Optimal cytoreduction, i.e. only microscopic lesions or only macroscopic disease ≤ 1 cm; suboptimal cytoreduction, i.e. residual disease > 1 cm

mm) and 16 mm (a range of 8-44 mm), respectively. Lymph node dissection was performed in 34 (60%) of the patients, of whom 6 (10%) had lymph node metastasis, and 41 (66.1%) patients LVSI. Thirty-five (56.5%) of the patients had early-stage (I and II) disease, whereas 27 (43.5%) of the patients had advanced-stage (III and IV) disease (Table I).

The treatment groups were distributed as follows: 20 (32%) of the patients did not receive adjuvant treatment and were observed after surgery, 19 (31%) received radiotherapy, 13 (21%) chemotherapy and 10 (16%) chemotherapy combined with radiotherapy. The patient demographics and clinical variables are shown in Table II. When testing the equality of the group variances, the four adjuvant treatment groups were unequally distributed for pelvic lymph node dissection, histology and stage.

Most patients treated with adjuvant radiotherapy received whole pelvic radiotherapy 15/19 (79%), of whom all received 45-54 Gy in 25-30 fractions. Three (16%) patients received 28-30 Gy vaginal brachytherapy, and one patient received whole pelvic radiotherapy combined with vaginal brachytherapy. All 13 patients who received chemotherapy received ≥ 3 cycles carboplatin as a single (54%) or combination (46%) chemotherapeutic agent. Chemotherapy was started approximately one month after surgery, and all patients who received chemotherapy only had advanced-stage disease. Ten patients were treated with chemotherapy and radiotherapy, of whom all received whole pelvic radiotherapy with carboplatin.

After a median follow-up of 21 months, 32 patients (52%) experienced a recurrence. Recurrences occurred locoregionally in 3 (9%) patients. Twenty-six (81%) patients had a recurrence in their abdomen and/or distant metastases, with or without locoregional recurrence. The most common sites of recurrence were the pelvic or para-aortic lymph nodes (38%), liver (34%), lung (25%), mediastinal lymph nodes (16%) and vagina (9%). Overall, recurrence by stage was 23% (stage I), 40% (stage II), 75% (stage III) and 100% (stage IV). The recurrence rates were higher in the patients who received chemotherapy only (92%).

Recurrence risk correlated with advancing stages of the disease (p-value 0.000). Also, a significant difference in the recurrence rates was shown during a comparison of early- and advanced-stage disease, with an odds ratio (OR) of recurrence of 16.61 [95% confidence interval (CI): 4.51-61.23] for advanced-stage disease, i.e. stage III and IV, compared to that for early-stage disease, i.e. stage I and II (p-value 0.000). There was no significant difference in the recurrence rates by stage when receiving different adjuvant treatment modalities (p-value > 0.100) (Table III). After multivariate logistic regression, in which factors were analysed that could have been associated with the recurrence, only advanced-stage disease was associated with an increased risk of recurrence, with an OR of 34.01 (95% CI: 3.84-301.30), compared to early-stage disease (p-value 0.002). Stage IV disease resulted in a 100% recurrence rate, and the median time to recurrence was 7.5 and 9.0 months for patients treated with chemotherapy and chemoradiation, respectively (p-value 0.480).

Median relapse-free survival and overall survival were 31 and 47 months, respectively, with a five-year overall survival of 41%. Thirty-two patients were deceased, of whom 29 deaths were USC related, and the median time of recurrence to death was 10 months (a range of 1-150). Two patients died of cardiovascular disease and one of lung cancer as a second primary tumour. Twenty-seven patients were alive and free of disease, of whom 23 had early-stage disease (I and II) and four stage III disease. When analysing survival using the FIGO staging, those with early-stage disease had a significantly better relapse-free survival and

Table II: The patient demographics, and clinical and tumour characteristics in the different treatment groups

Variable mean (standard deviation)	Overall (n = 62) n (%)	Observation (n = 20) n (%)	Radiotherapy (n = 19) n (%)	Chemotherapy (n = 13) n (%)	Chemoradiation (n = 10) n (%)	p-value*
Age (mean) (years)	68 (9.2)	69 (9.0)	70 (8.6)	67 (10.6)	63 (7.9)	0.668
Body mass index (kg/m^2)	29 (7.3)	29 (9.5)	29 (5.3)	29 (6.5)	30 (8.3)	0.581
Gravidity	2.5 (1.5)	3.1 (1.7)	2.4 (1.5)	2.2 (1.5)	2.4 (1.5)	0.396
Parity	2.4 (1.5)	2.9 (1.6)	2.3 (1.5)	2.1 (1.5)	2.0 (1.2)	0.533
Malignancy in previous medical history	12 (19.0)	4 (20.0)	4 (21.0)	3 (23.0)	1 (10.0)	0.532
Pelvic lymph node dissection	34 (55)	14 (70.0)	11 (58.0)	2 (15.0)	7 (70.0)	0.012
Depth of myometrial invasion (mm)	7.2 (7.7)	4.8 (5.9)	8.0 (5.8)	10.5 (12.9)	6.3 (3.6)	0.524
Total thickness of the myometrium (mm)	17.6 (7.7)	18.2 (8.3)	17.2 (7.7)	17.9 (9.4)	16.9 (4.6)	0.402
Size of tumour (mm)	37.7 (18.0)	33.2 (17.4)	37.0 (15.4)	40.2 (16.6)	44.2 (24.9)	0.365
Lymphovascular space invasion (positive)	41 (66.0)	10 (50.0)	15 (79.0)	9 (69.0)	7 (70.0)	0.129
Histology (pure, serous)	30 (48.0)	15 (75.0)	6 (32.0)	6 (46.0)	3 (30.0)	0.027
Stage						
I	30 (48.0)	16 (80.0)	11 (58.0)		3 (30.0)	0.000
II	5 (8.0)	2 (10.0)	1 (5.0)		2 (20.0)	
III	16 (26.0)	2 (10.0)	7 (37.0)	4 (31.0)	3 (30.0)	
IV	11 (18.0)			9 (69.0)	2 (20.0)	

*: One-way analysis of variance or chi-square contingency tables

Table III: The recurrence rates for adjuvant treatment modalities sorted according to International Federation of Gynecology and Obstetrics staging

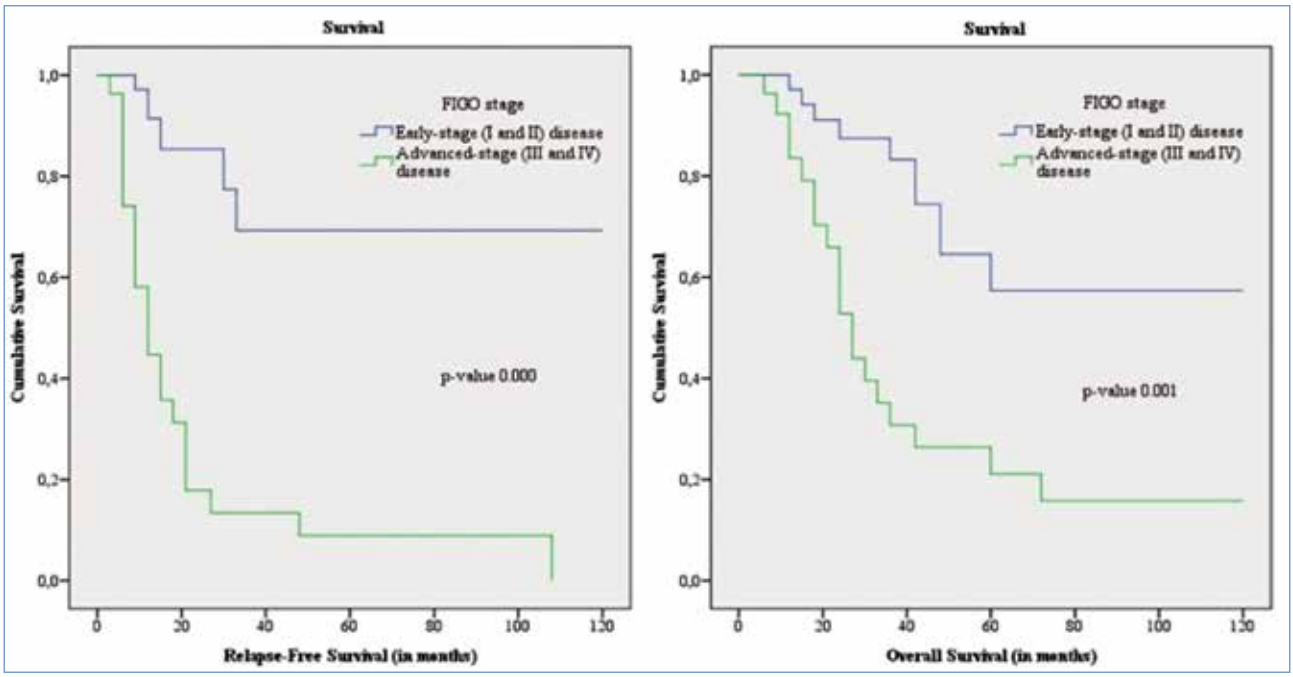
Stage	Observation	Radiotherapy	Chemotherapy	Chemoradiation	Total no of recurrences (by stage)	p-value*,**
I	6/16 (38%)	1/11 (9%)		0/3	7/30 (23%)	0.138
II	1/2 (50%)	0/1		1/2 (50%)	2/5 (40%)	0.659
III	2/2 (100%)	5/7 (71%)	3/4 (75%)	2/3 (67%)	12/16 (75%)	0.843
IV			9/9 (100%)	2/2 (100%)	11/11 (100%)	****
Total	9/20 (45%)	6/19 (32%)	12/13 (92%)	5/10 (50%)	32/62 (52%)***	

*chi-square test
**Recurrence rates for adjuvant treatment modalities by early-stage (p-value 0.164), and advanced-stage (p-value 0.567) disease
***Recurrence rates according to the International Federation of Gynecology and Obstetrics stages I-IV (p-value 0.000). Recurrence rates by early-stage (I and II) [9/35, 26%], versus advanced-stage (III and IV), disease [23/27, 85%], odds ratio 16.61, 95% confidence interval: 4.51-61.23 (p-value 0.000) (univariate logistic regression); and odds ratio 34.01, 95% confidence interval: 3.84-301.30 (p-value 0.002) (multivariate logistic regression)
****The p-value of International Federation of Gynecology and Obstetrics stage IV could not be computed

overall survival than those with advanced-stage disease (p-value 0.000 and p-value 0.001), (Figure 1).

After performing univariate Cox proportional hazard regression to determine the independent variables, relapse-free survival and overall survival were not associated with age, BMI, depth of myometrial invasion, measurement of tumour, LVSI and histology (p-value > 0.100). Relapse-free survival was associated with adjuvant treatment and the FIGO stage (p-value 0.000), and overall survival was only associated with the FIGO stage (p-value 0.001). In addition, multivariate Cox proportional hazard regression showed a significant correlation between adjuvant treatment and the FIGO stage with regard to relapse-free survival (p-value 0.016 and p-value 0.000). The odds of recurrence were less in patients treated with radiotherapy, chemotherapy or chemoradiation, than those in patients without adjuvant treatment, but were increased in patients with more advanced-stage disease. The FIGO stage was correlated significantly with overall survival (p-value 0.001), and there was a trend towards better overall survival in patients who received adjuvant treatment (p-value 0.076) (Table IV).

On multivariate stratified analysis, each treatment at any stage was associated with significantly better relapse-free survival (p-value 0.026) compared to the observation group.



FIGO: The International Federation of Gynecology and Obstetrics

Figure 1: *Kaplan-Meier method:* Relapse-free and overall survival of women with uterine serous carcinoma, according to the International Federation of Gynecology and Obstetrics staging

Table IV: Relapse-free survival and overall survival, using the multivariate Cox proportion hazard regression model

Variable*	Relapse-free survival			Overall survival		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p value
Stage			0.000			0.001
I (reference)	1.00			1.00		
II	2.10	0.24-18.07	0.501	1.42	0.16-12.55	0.755
III	35.66	7.54-168.66	0.000	6.63	1.62-27.20	0.009
IV	175.32	18.44-1 666.72	0.000	75.31	9.10-623.54	0.000
Adjuvant treatment			0.016			0.076
Observation (reference)	1.00			1.00		
Radiotherapy	0.20	0.05-0.82	0.029	0.31	0.07-1.26	0.101
Chemotherapy	0.07	0.01-0.51	0.008	0.07	0.01-0.53	0.010
Chemoradiation	0.06	0.01-0.33	0.002	0.13	0.02-0.73	0.021
Stratified by stage	**Relapse-free survival**			**Overall survival**		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p value**
Adjuvant treatment			0.026			0.054
Observation (reference)	1.00			1.00		
Radiotherapy	0.07	0.01-0.63	0.018	0.24	0.06-1.02	0.053
Chemotherapy	0.03	0.00-0.36	0.007	0.05	0.01-0.47	0.008
Chemoradiation	0.02	0.00-0.25	0.003	0.13	0.02-0.70	0.018
Observation (reference)	1.00			1.00		
Radiotherapy plus chemotherapy plus chemoradiation	0.05	0.01-0.45	0.008	0.18	0.04-0.77	0.020
Observation plus radiotherapy (reference)	1.00			1.00		
Chemotherapy plus chemoradiation	0.24	0.06-0.90	0.035	0.32	0.10-1.07	0.064
Observation plus chemotherapy (reference)	1.00			1.00		
Radiotherapy plus chemoradiation	0.43	0.18-1.07	0.068	0.68	0.28-1.68	0.407

CI: confidence interval

* The following prognostic factors were entered into the Cox proportional hazards model, but are not shown: age, depth of myometrial invasion, lymphovascular space invasion, tumour size and histology (p-value > 0.300)

Furthermore, there was a moderate level of significance (p-value 0.054), showing better overall survival for each adjuvant treatment modality at any stage.

Separate analyses were performed in order to compare survival rates and the different adjuvant treatments stratified by stage relative to one another. Adjuvant treatment significantly improved relapse-free survival (p-value 0.008) and overall survival (p-value 0.020). Moreover, patients who received chemotherapy (chemotherapy or chemoradiation) had a significantly better relapse-free survival (p-value 0.035) and a trend towards better overall survival (p-value 0.064). And finally, a trend towards improved relapse-free survival (p-value 0.068) was indicated with radiotherapy (radiotherapy or chemoradiation), but such a correlation was not found with improved overall survival (p-value 0.407) (Table IV).

Discussion

This study shows that USC patients are at high risk of recurrence, and that even patients with early-stage disease may benefit from adjuvant treatment with respect to relapse-free and overall survival. Adjuvant chemotherapy, traditionally only given to patients with advanced-stage USC, seems to be equally effective or even more effective than radiotherapy in patients with early-stage disease.

In this study, 32 patients experienced a recurrence, with 81% having a recurrence in their upper abdomen and/or distant metastases. This recurrence rate is similar to that reported in other studies.[14-18] The recurrence rates were higher in patients who received chemotherapy only, possibly owing to the fact that only patients with advanced-stage disease (III and IV) received chemotherapy as a single treatment modality. As in other studies, recurrence risk correlated with the stage of disease.[6,13-19] Relapse rates varied from 23% for stage I, to 100% for stage IV, patients. No significant difference could be demonstrated for recurrence rates relating to the adjuvant treatment that patients with different stages of disease received. Thirty-two patients were deceased, of whom 29 deaths were USC related. As in other studies, there was significant correlation between survival and the stage of disease. Five-year overall survival in other studies varied from 45-90% for early-stage (I and II), and 0-30% for advanced-stage (III and IV), disease. We found a five-year overall survival of between 53% and 58% for early-stage, and from 0-39% for advanced-stage (III and IV), disease.[6,13-19]

The median age of our patient with USC at the time of diagnosis was similar to that seen in other studies, but older than the median age of women with endometrioid uterine cancer.[4,6,11,20-22] Abnormal uterine bleeding was the most common clinical presentation with USC, just as it is in endometrioid uterine cancer. However, it was not an early sign as many patients had advanced-stage disease. Likewise, some women presented with abnormal endometrial cells on cervical cytology. Roelofsen et al showed that abnormal endometrial cells on cytology may be found more commonly in patients with USC, than in patients with endometrioid carcinoma, where this is rare.[23]

In accordance with other authors, LVSI, the depth of myometrial invasion and tumour size were not significantly associated with a poor prognosis in USC.[24,25] In our study, more than half of the USCs coexisted with at least one other subtype of uterine cancer (endometrioid, clear cell and mucinous). Slomovitz et al and Fader et al demonstrated that mixed histology and any percentage of USC in a mixed-histology specimen confer a risk for recurrence similar to that in a pure serous tumour.[6,26] We found no difference in prognosis between pure or mixed-histology USCs.

There are conflicting data on adjuvant treatment, and the optimal therapy for this subset of patients has not been defined.[5,6,11,24,27,27] As with most retrospective studies, selection bias with regard to adjuvant treatment is likely. Therefore, we performed a multivariate Cox proportion hazard regression model stratified according to FIGO staging. On the basis of our data and the literature, we recommend adjuvant treatment in each stage of disease since in our study adjuvant treatment significantly improved relapse-free survival and overall survival in each stage, when compared to no adjuvant treatment. Fader et al showed that early-stage patients treated with chemotherapy experienced significantly improved survival compared to patients who were observed or received radiotherapy.[14,15,26] Slomovitz et al reported on improved overall survival in stage III patients treated with chemotherapy.[6] Chemotherapy significantly improved relapse-free survival and overall survival in stage I-IV patients in a review by Roelofsen et al.[28] In addition, we showed that patients treated with chemotherapy (plus radiotherapy) had a significantly better relapse-free survival and a trend towards better overall survival. Similar to that reported by Slomovitz et al, no significantly improved survival for patients treated with radiotherapy was shown by our data.[6]

The limitations of our study, and those referred to in the literature, include their retrospective nature and the relatively small number of patients in each adjuvant treatment group. As a result, it was difficult to draw conclusions about the best adjuvant treatment modality for patients, and particularly the best adjuvant treatment for the different stages of the disease.

Currently, two phase III clinical trials are investigating adjuvant radiotherapy, with or without chemotherapy, for women with high-risk endometrial cancer, including women with serous and clear cell cancer, but also including grade 3 endometrioid carcinomas. The first trial is the Postoperative Radiation Therapy for Endometrial Cancer 3 (PORTEC 3) trial, in which inclusion ended recently, with a final total of 686 patients. The first study results are expected in late 2015.[29] The second trial is the Gynecologic Oncology Group 258 (GOG 258) trial, for which the recruitment of patients

is still in process.[30] These prospective studies may help to allow better evaluation of adjuvant treatment modalities at different stages of USC.

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Declaration

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Conflict of interest

The authors declare no conflict of interest.

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