Published in final edited form as:

Eur J Surg Oncol. 2010 December ; 36(12): 1195–1201. doi:10.1016/j.ejso.2010.09.010.

Prognostic factors in stages II/III/IV and stages III/IV endometrioid and serous adenocarcinoma of the endometrium

P. Mhawech-Fauceglia^{a,b,*}, R.F. Herrmann^d, J. Kesterson^c, I. Izevbaye^{a,b}, S. Lele^c, and K. Odunsi^c

^aDepartment of Pathology, Roswell Park Cancer Institute, Buffalo, NY, USA ^bDepartment of Laboratory Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA ^cDepartment of Gynecology-Oncologic Surgery, Roswell Park Cancer Institute, Buffalo, NY, USA ^dGeneva University Hospitals, Department of Rehabilitation and Geriatrics, Geneva, Switzerland

Abstract

Aims—To explore and to compare the outcome of patients diagnosed with stage II/III/IV and stage III/IV endometrioid adenocarcinoma (EAC) with their serous carcinoma (USC) counterparts.

Materials and methods—A total of 107 patients (73 EAC and 34 USC) were evaluated. For statistical analysis, the following baseline variables were considered for their prognostic value: the patient's age at presentation, the tumor size, the depth of myometrial invasion (MI), the lympho-vascular involvement (LVI) and the USC and the EAC subtypes (considered as binary variables). Disease free survival (DFS), death of disease (DOD) and overall survival (OS) were assessed using univariate and multiple Cox proportional hazards models.

Results—In univariate analysis, USC tends to recur more frequently than EAC ($p = 0.004$), a finding that disappeared in multivariate analysis. Furthermore, tumor histology had no significance in predicting the tumor outcomes. Among all of the prognostic factors and after adjusting for the aforementioned variables, MI 50% was the only independent factor in predicting DOD in stages II/III/IV ($p = 0.009$) and in stages III/IV ($p = 0.004$). MI was also an independent predictive factor

*Corresponding author. Roswell Park Cancer Institute, Department of Pathology, Elm and Carlton Street, Buffalo, NY 14263, USA. Tel.: +1 716 845 3204; fax: +1 716 845 3427. pmhawech1@yahoo.com, Paulette.mhawech-fauceglia@roswellpark.org (P. Mhawech-Fauceglia).

Contributors

Contribution of each of the authors: Paulette Mhawech-Fauceglia: Designed the study and wrote the manuscript. Francois R. Herrmann: performed the statistical analysis and reviewed the manuscript. Joshua Kesterson: collecting the follow-up and treatment modalities and he also corrected the manuscript. Iyare Izevbaye: collected the slides and reviewed the slides and he also corrected the manuscript. Shashikant Lele: helped in designing the project. Kunle Odunsi: corrected the manuscript and he was mentor on this project.

Conflict of interest

This manuscript is an original contribution not previously published in any form and not under consideration for publication elsewhere. All authors, Drs. Mhawech-Fauceglia, Kesterson, Izevbaye, Lele and Odunsi, have participated in the study to a significant extent. We are unaware of any conflicts of interest or any ethical issues.

The Health Sciences Institutional Review Board (HSIRB) of Roswell Park Cancer Institute has authorized this research. We have adhered strictly to the Human Research Protections Program and we have followed the authorization template for the use and disclosure of identifiable health information for research purposes.

The corresponding author has no other investments or sources of income or alliances.

for OS ($p = 0.02$) and early recurrences in stages III/IV. LVI was the only independent factor in predicting recurrences ($p = 0.004$) in stages II/III/IV but not in stages III/IV.

Conclusion—Based on our study, tumor histology was not a significant factor in predicting disease outcome in stages II/III/IV and II/IV. Despite our limited sample size, we believe that our findings provide meaningful insights into the clinical study of endometrial cancer patients which in turn warrants further investigation.

Keywords

Endometrioid adenocarcinoma; Uterine serous carcinoma; Prognostic factor; Disease outcome

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries, with an estimated incidence occurrence of 39,080 new women that are affected annually and claiming approximately 7400 of life every year.¹ Based on the clinico-pathologic and molecular data, endometrial adenocarcinomas are dichotomized in to two types; type I (endometrioid and mucinous adenocarcinoma) and type II (serous and clear cell carcinoma). Endometrioid adenocarcinoma (EACs) are the most frequent subtype and they account for more than 80% of all endometrial adenocarcinoma cases. They are most often associated with obesity and exogenous hormonal therapy and they tend to present as low grade and low stage tumors with a good cure rate. However, approximately 16% of women with EAC will present with stage III and stage IV disease with 5-year survival rate of 30–89% and 0–10% respectively.^{2,3} EAC are often associated with PTEN (phosphatase and tensin homologue) inactivation. Complete surgical staging followed by local or regional therapy and chemotherapy is usually reserved to patients with advanced stage disease, high International Federation of Gynecology and Obstetrics (FIGO) grading, distant metastasis or disease recurrences.^{3,4} Uterine serous carcinoma (USCs) account for 3–10% of all endometrial carcinomas. They are high grade tumors and they are likely to present with deep myometrial invasion and lympho-vascular involvement. In most cases, by the time of USC is diagnosed, it presents as disseminated disease.^{2–6} USCs are usually associated with p53 abnormalities rather than PTEN abnormalities. Because of the high risk of extra uterine spreading, women with USC stage II are usually treated with chemotherapy with or without local or regional radiation after a complete staging procedure.^{7–9} Furthermore, the overall survival (OS) rate in women diagnosed with USC tends to be less than women that are diagnosed with EAC.^{10,11} The known prognostic factors for predicting disease outcome in endometrial carcinoma are defined by the patient age at diagnosis, the tumor subtypes, the tumor grade, the tumor stage, the myometrial invasion (MI), and the lympho-vascular involvement (LVI).^{12–14} Recently, numerous articles have been published, exploring the risk factors for early recurrence and survival rate in early stage Type I and Type II endometrial carcinoma or in Types II uterine carcinoma and G3-EAC.^{15–17} However, the difference in tumor outcome and the potential prognostic predictive factors in pure EAC and USC cases which the disease extends beyond the endometrial cavity are yet to be explored.

The purpose of our study is to investigate the risk factors when predicting disease outcome in advanced stages (stage II/III/IV and stage III/IV) USC and EAC in a series of properly stages, uniformed treated patients with consistent follow-up in a single given Institution.

Materials and methods

Patient selection and data collection

EAC and USC cases that were diagnosed at RPCI, Buffalo-NY between January 2000 and December 2007 were pulled from the archive department. A retrospective chart review was conducted with the extraction of clinical information including the age of the patients, at the time of diagnosis, the surgical procedure, the tumor staging, the post-operative therapy, the disease free survival (DFS), the overall survival (OS), The site of recurrence and the time before recurrence, the death of disease (DOD) and the death from unrelated causes. Follow-up data was also retrieved from the tumor registry when it was required. The International Federation of Gynecology and Obstetrics (FIGO) system was used for the tumor grade and the stage.¹⁸ All of the cases were evaluated by one Pathologist expert in Gynecologic Oncology to confirm the tumor type, the tumor size, the tumor grade, the percentage of MI and the presence of LVI. Hundred and seven of 245 patients had a diagnosis of pure EAC or USC stage II/III/IV disease and proper staging were included in the study. These cases were included in our study.

Patient treatment

All patients in our study underwent a surgical staging procedure including an abdominal hysterectomy with bilateral salpingo-oophorectomy, a pelvic and para-aortic lymph nodes dissection and a pelvic washing. Additional vaginal brachytherapy and/or external body radiation therapy (EBRT) were administrated to patients with stage II EAC, EBRT with or without chemotherapy or chemotherapy only to patients with stage III/IV EAC. On the other hand, patients with stage II USC were given EBRT and chemotherapy and patients with stage III/IV USC were given chemotherapy. Chemotherapy consisted of doxorubicin/ cisplatin/paclitaxel.

Statistical methods

For statistical analysis, the following baseline variables were considered for the patient's prognostic value: the age at presentation, the tumor size, MI and LVI; USC and EAC subtypes (considered as binary variables). Associations between categorical variables were studied using the Fisher's exact tests. Recurrence free, persistence of disease, progression free survival and overall survival rate, were assessed using univariate and multiple Cox proportional hazards models. The results were expressed as a hazard ratio, which was derived from the estimated regression coefficients along with their 95% confidence intervals. A *p* value of less than 0.05 was considered statistically significant. Statistics were performed using the STATA Statistical Software, release 11.0.

Results

Patients with stage II, III and IV

Clinical and pathologic features—Table 1 summarizes the clinical and pathologic features of all 107 patients that were evaluated for this study. LVI was significantly associated with tumor grade $p = 0.0001$ but it was not associated with tumor stage $p = 0.07$. There was no significant difference in DOD between EAC and USC patients ($p = 0.216$). The OS was significantly better for EAC 62.7% than for USC 37.2% with p value of 0.04. The time of relapse ranged from 0.0 to 107.4 with a median of 15.9 months. The pattern of relapse of EAC was as follows; 4 patients were in stage IV (1 grade 2, and 3 grade 3), 10 in stage III (2 grade 2, and 8 grade 3) and 3 in stage II (all grade 2). The sites of recurrences included the vagina ($n = 2$), pelvis ($n = 6$), and distant metastasis ($n = 9$). The median time from diagnosis to relapse was 21.0 months. The pattern of relapse for USC cases was; 7 patients in stage IV, 5 in stage III and 3 in stage II. The site of recurrences included the vagina ($n = 5$), the pelvis ($n = 2$) and distant metastasis ($n = 8$). The median time from diagnosis to relapse was 5.8 months.

Predictive factors and tumor outcomes—Table 2 summarizes the predictive factors of disease in univariate and multivariate analysis of the 107 patients. Predictive factors for recurrence and tumor subtypes had proven to have an effect as patients diagnosed with USC recurred more quickly than patients diagnosed with EAC ($p = 0.004$) in univariate analysis. However, when compared to other parameters such as age of patients at diagnosis, the tumor size, MI and LVI, tumor subtypes lost its predictive factor for early recurrence ($p = 0.245$). Among all other clinico-pathologic parameters, LVI was the only independent factor when predicting early recurrence and any poor outcome such as persistence, progression or recurrence $p = 0.004$ and 0.006 respectively. In addition, among all of the parameters, only EAC with high tumor grade and MI $>50\%$ revealed to be an independent factor when predicting poor outcome $p = 0.016$ [HR 2.25; 95% CI 1.16–4.34]. Tumor subtypes did not have any significant value when predicting DOD ($p = 0.243$). Again, only high tumor grade and depth of invasion had an independent factor when predicting DOD $p = 0.004$ [HR 1.015–95% CI 1.00–1.02]. MI and patient age, both had an independent predictive value to predict OS with $p < 0.001$ [HR 3.51–95% CI 1.80–6.83] and $p = 0.029$ [HR 1.025–95% CI 1.00–1.04] respectively.

Patients with advanced stage III and IV

Clinical and pathologic features—The clinical data is summarized in Table 3. There was no significant difference in recurrence rate between EAC and USC patients ($p = 0.669$). 22 patients with EAC and 13 USC had died of disease ($p = 0.704$) at a 28.1 month average interval after diagnosis. The OS rate was somewhat better in patients diagnosed with EAC (61.3%) than those with USC (38.6%), however, it did not reach a significant value with $p = 0.544$.

Predictive factors and tumor outcomes—The predictive factors for disease outcome in univariate and multivariate analysis are summarized in Table 4. In advanced stage disease, tumor subtype failed to predict recurrence in univariate and multivariate analysis $p = 0.206$

and $p = 0.906$ respectively. MI >50% seemed to be an independent predictive factor for early recurrence in EAC and USC with $p = 0.021$ [HR 3.80; 95% CI 1.22–11.78]. Also, MI had independent value in OS $p = 0.02$ [HR 1.016; 95% CI 1.006–1.027]. Tumor subtypes did not have any value in predicting DOD $p = 0.163$. MI was an independent predictive value for DOD $p = 0.004$ [HR 3.64; 95% CI 1.51–8.78]. All other parameters such as the patient age, and the tumor size, did not demonstrate any predictive value for the patients' outcome.

Discussion

This is a retrospective study that has been carried out on a series of 107 patients during a seven year period within a single Institution where the patients were properly staged and uniformly managed. The patient's age, the tumor grade, MI, and LVI have proven to be significant predictive factors in stage I endometrial cancer. However, the literature is very limited when evaluating the prognostic factors in late stage endometrial cancer.^{19,20} Presumably, could be due to low survival rate and poor outcome despite aggressive therapy in these patients with late stages tumors. Our study is among the very few that has focused on evaluating the clinico-pathologic risk factors in endometrial cancer extending beyond the uterine cavity.^{19,20} To prevent any bias or interference with the results of this study, we disregarded subtypes other than endometrioid and serous carcinoma as well as any mixed tumor subtypes.

Consistent with previous reports,^{3–6} USC stage II/III/IV had a higher recurrence rate in comparison to stage-matched EAC (40% Vs 22%), as well, a shorter time to relapse (5.8 months for USC vs 15.9 months for EAC). Additionally, patients with USC had worse OS of 37.2% compared to EAC 62.7%.^{21,22} However, we did not find a significant difference in the DOD rate between USC and EAC patients. On the other hand, when we analyzed patients with advanced stage disease (III/IV), there were no significant differences in recurrences, OS and DOD between USC and EAC. These findings indicate that whenever the tumor has already metastasized, tumor histological subtypes did not influence the disease outcomes.

Evaluating the clinical and histopathological risk factors in EAC and USC was our primary goal. In univariate analysis, serous carcinoma has a higher early recurrence rate in stage II/III/IV disease, in comparison to EAC. However, this value disappeared when we adjusted to other variables such as the patients' age, the tumor stage, MI and LVI. This suggests that the poor prognosis in these patients should not be attributed to histologic subtype, but rather to the more advanced stage at the time of diagnosis. Similarly, in advanced stage diseases, tumor subtype did not appear to have any independent value in predicting outcomes such as recurrence, DOD or OS. Additionally, Cirisano et al. found that USC and Clear Cell Carcinoma (CCC) to be significant factors in predicting poor survival rates when in comparing EAC in univariate analysis.¹⁵ Corn et al. identified that USC or CCC versus EAC to correlate with 5 year rate free distant relapse in univariate analysis.²³ However, these findings failed prove any significance in multivariate analysis.

The role of LVI in EAC is known to be correlated with early tumor recurrence and to predict poor outcome, especially in early stage disease.²⁴ However, the role of LVI in USC is somewhat controversial and it is widely unknown in late stages.^{14,16} In our study, we

concluded that LVI was an independent predictor for early recurrence and any poor outcome in stage II/III/IV disease. This finding led us to believe that the presence of the LVI status should be of major importance in the surgical pathology reports and the use of immunohistochemistry for lympho-vascular space identification should be performed when necessary. Similar to other studies, the patient's age was proven to have an independent prognostic significance in predicting OS.²⁵ Shorter OS in older women may be related to more frequent concomitant medical conditions that often occur in the elderly.

MI was proven to be the most predictive uterine factor for extra uterine metastasis in endometrial tumors. In a large Gynecologic Oncology Group (GOG) clinical trial, Creasman et al. demonstrated that the incidence of lymph node metastasis increased with the depth of MI.²¹ However, in this study USC patients were excluded. Additionally, and in another GOG study, Morrow et al found that the rates of relapse in patients with no MI or deep MI were 13% and 16% respectively.¹² However, others did not find similar results.²⁰ In a recent study, Cirisano et al. found that depth of invasion correlated with survival rate in USC/CCC and EAC in early stages I and II disease.¹⁵ Benito et al analyzed USC tumors and found that the depth of invasion had an independent influence on OS in multivariate analysis.⁶ In our series, depth of MI was the single most important factor in uterine carcinoma. MI of >50% was an independent factor in predicting DOD, OS and any poor outcome (recurrence, progression or persistence of disease) in stage II/III/IV cancer. Furthermore, MI proved to be an independent predictive factor for early recurrence, OS and DOD in both advanced stage EAC and USC. These results concluded that MI is of vital importance for prognosis in patients with late stage disease and it could be used as an additional factor in the patients' assessment.

Shortcomings of this study include the limited number of stage III/IV patients. This was due to a small percentage of advanced stage endometrioid adenocarcinoma at first presentation as seen in the literature. Thus, this leads us to believe that a multicenter study is necessary to reach sufficient numbers and to confirm our results. Nevertheless, despite our limited sample size, we conclude that our findings have meaningful insights into the clinical study of endometrial cancer patients which warrant further investigation.

Acknowledgments

We would like to thank Mr. Timothy Dolan for his archives search. We also thank Heidi Wagner for editing the manuscript.

Funding

There was no funding provided for this study for any of the co-authors.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. CA Cancer J Clin. 2007; 57:43–66. [PubMed: 17237035]
2. Soslow RA, Bissonnette JP, Wilton A, et al. Clinicopathologic analysis of 187 high-grade endometrial carcinomas of different histologic subtypes: similar outcomes belie distinctive biologic differences. Am J Surg Pathol. 2007; 31:979–87. [PubMed: 17592263]

3. Kitchener HC, Trimble EL, Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial cancer state of the science meeting. *Int J Gynecol Cancer*. 2009; 19:134–40. [PubMed: 19258955]
4. Sutton G, Axelrod JH, Bundy BN, et al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: a gynecologic oncology group study. *Gynecol Oncol*. 2005; 97:755–63. [PubMed: 15913742]
5. Naumann RW. Uterine papillary serous carcinoma state of the state. *Curr Oncol Rep*. 2008; 10:505–11. [PubMed: 18928665]
6. Benito V, Lubrano A, Arencibia O, et al. Pure papillary serous tumors of the endometrium. A clinicopathological analysis of 61 cases from a single institution. *Int J Gynecol Cancer*. 2009; 19:1364–9. [PubMed: 20009891]
7. Faratian D, Stillie A, Busby-Earle RM, Cowie VJ, Monaghan H. A review of the pathology and management of uterine papillary serous carcinoma and correlation with outcome. *Int J Gynecol Cancer*. 2006; 16:972–8. [PubMed: 16803471]
8. Boruta DM II, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a society of gynecologic oncology (SGO) review. *Gynecol Oncol*. 2009; 115:142–53. [PubMed: 19592079]
9. Tchabo NE, McCloskey S, Mashtare TL, et al. Treatment of early-stage uterine papillary serous carcinoma at Roswell Park Cancer Institute, 1992–2006. *Gynecol Oncol*. 2009; 115:249–56. [PubMed: 19692115]
10. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poor survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer*. 2006; 94:642–6. [PubMed: 16495918]
11. Fader AN, Starks D, Gehrig PA, et al. An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC). *Gynecol Oncol*. 2009; 115:244–8. [PubMed: 19712966]
12. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathologic risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1991; 40:55–65. [PubMed: 1989916]
13. FIGO DC, Otton PM, Tamimi HK, Greer BE. Treatment variables in the management of endometrial cancer. *Am J Obstet Gynecol*. 1983; 146:495–500. [PubMed: 6859175]
14. Sagr ER, Denschlag D, Kerim-Dikeni A, Stanimir G, Gitsch G, Gilbert L. Prognostic factors and treatment-related outcome in patients with uterine papillary serous carcinoma. *Anticancer Res*. 2007; 27:1213–8. [PubMed: 17465265]
15. Cirisano FD, Robboy SJ, Dodge RK, et al. The outcome of stage I–II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. *Gynecol Oncol*. 2000; 77:55–65. [PubMed: 10739691]
16. Alektiar KM, McKee A, Lin O, et al. Is there a difference in outcome between stage I–II endometrial cancer of papillary serous/clear cell and endometrioid FIGO grade 3 cancer? *Int J Radiat Oncol Biol Phys*. 2002; 54:79–85. [PubMed: 12182977]
17. Boruto DM II, Gehrig PA, Groben PA, et al. Uterine serous and grade 3 endometrioid carcinomas. Is there a survival difference? *Cancer*. 2004; 101:2214–21. [PubMed: 15452833]
18. Creasman WT. Revision in classification by international federation of gynecology and obstetrics. *Am J Obstet Gynecol*. 1992; 167:857. [PubMed: 1326895]
19. Van Wijk FH, Huiseshoven FJ, Abdulkadir L, Ewing PC, Burger CW. Stage III and IV endometrial cancer: a 20-year review of patients. *Int J Gynecol Cancer*. 2006; 16:1648–55. [PubMed: 16884379]
20. Goff BA, Goodman A, Muntz HG, Fuller AF Jr, Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. *Gynecol Oncol*. 1994; 52:237–40. [PubMed: 8314145]
21. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical spread patterns of endometrial cancer. A Gynecologic Oncology Group study. *Cancer*. 1987; 60:2035–41. [PubMed: 3652025]
22. Goff BA, Kato D, Schmidt RA, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol*. 1994; 54:264–8. [PubMed: 8088602]

23. Corn BW, Lanciano RM, D'Agostino R, et al. The relationship of local and distant failure of endometrial adenocarcinoma: defining a clinical paradigm. *Gynecol Oncol.* 1997; 66:411–6. [PubMed: 9299254]
24. Nofech-Mozes S, Ackerman I, Ghorab Z, et al. Lymphovascular invasion is a significant predictor for distant recurrence in patients with early-stage endometrial endometrioid adenocarcinoma. *Am J Clin Pathol.* 2008; 129:912–7. [PubMed: 18480008]
25. Vaknin Z, Ben-Ami I, Schneider D, Pansky M, Halperin R. A comparison of perioperative morbidity, perioperative mortality, and disease-specific survival in elderly women (≥ 70 years) versus younger women (<70 years) with endometrioid endometrial cancer. *Int J Gynecol Cancer.* 2009; 19:879–83. [PubMed: 19574777]

Table 1

Clinical and pathologic features of the 107 patients.

Characteristic	Endometrioid adenocarcinoma (EAC)	Uterine serous carcinoma (USC)	Total	Range
<i>N</i>	73	34	107	
<i>Stage</i>				
II	29	9	38	
III	32	16	48	
IV	12	9	21	
<i>Grade FIGO</i>				
G1	26	0	26	
G2	23	0	23	
G3	24	34	58	
Lympho-vascular involvement (LVI)	39	24	63	
<i>Treatment</i>				
None	5	8	13	
Brachytherapy	35	5	40	
Chemotherapy	32	21	40	
Megace	3	1	4	
EBRT	38	6	44	
<i>Outcomes</i>				
No recurrence	46	12	58	
Recurrence	16	14	30	
Persistent	9	5	14	
Progression	2	3	5	
<i>Status at end of follow-up</i>				
ANED (alive no evidence of disease)	29	7	36	
AWD (alive with disease)	6	4	10	
DOD (dead of disease)	29	17	46	
DUC (dead unknown cause)	8	6	14	
LFU (lost for follow-up)	1	0	1	
<i>Status (synthesis)</i>				
With disease	35	21	56	
Dead	37	23	60	
<i>Tumor size [cm] – mean</i>	5.7	4.5	5.3	
<i>Depth of invasion % – mean</i>	64.6	55.3	61.6	
<i>Mean age [yrs] – mean</i>	66.3	74.4	68.9	30–97
<i>Median follow-up (IQR) [months] – median (IQR)</i>	31.6	12.9	25.1	0.4–107.4

Table 2

Uni and multiple Cox regression analysis of the prediction for recurrence and any poor outcome.

Characteristics	N = 107			
	HR (Hazard ratio)			
	Crude	Adjusted	HR	p
Recurrence				
Subtype	2.87	0.004	1.83	0.245
Age	1.01	0.498	0.99	0.721
Tumor size	1.05	0.306	1.04	0.488
Depth of invasion (>50%)	2.10	0.066	1.91	0.151
Grade FIGO	1.00		1.00	
	G1			
	G2	3.12	0.164	1.59 0.584
	G3	8.50	0.004	4.25 0.078
Stage	II	1.00		1.00
	III	1.71	0.250	0.72 0.505
	IV	4.31	0.004	1.99 0.205
Lympho-vascular involvement (LVI)	7.72	<0.001	5.36	0.004
<i>Any bad outcome</i>				
Subtype	1.96	0.016	0.91	0.798
Age	1.01	0.236	1.01	0.470
Tumor size	1.01	0.842	1.00	0.980
Depth of invasion (>50%)	2.44	0.003	2.25	0.016
Grade FIGO	1.00		1.00	
	G1			
	G2	1.51	0.400	0.85 0.758
	G3	4.62	<0.001	3.40 0.010
Stage	II	1.00		1.00
	III	1.85	0.069	1.07 0.859
	IV	4.49	<0.001	2.71 0.013
Lympho-vascular involvement (LVI)	4.45	<0.001	2.74	0.006
<i>Dead of disease</i>				
Subtype	1.65	0.111	0.64	0.243

Characteristics	N = 107	HR (Hazard ratio)			
		Crude		Adjusted	
		HR	p	HR	p
Age		1.01	0.258	1.02	0.264
Tumor size		1.01	0.797	1.01	0.789
Depth of invasion (>50%)		2.51	0.008	2.64	0.009
Grade FIGO	G1	1.00		1.00	
	G2	1.96	0.272	1.19	0.784
	G3	5.47	0.001	5.11	0.006
Stage	II	1.00		1.00	
	III	1.69	0.162	1.01	0.972
	IV	3.38	0.003	1.78	0.195
Lympho-vascular involvement (LVI)		3.47	0.001	1.70	0.184

Bad outcome is defined as recurrence, persistent or progression of the disease.

Table 3

Clinical and pathologic features of the 69 patients of stage III and IV.

Characteristic	Endometrioid adenocarcinoma (EAC)	Uterine serous carcinoma (USC)	Total	Range
<i>N</i>	44	25	69	
<i>Stage</i>				
III	32	16	48	
IV	12	9	21	
<i>Grade FIGO</i>				
G1	12	0	12	
G2	11	0	11	
G3	21	25	46	
<i>Lympho-vascular involvement (LVI)</i>	31	17	48	
<i>Treatment</i>				
None	3	4	7	
Brachytherapy	15	3	18	
Chemotherapy	28	18	46	
Megace	1	0	1	
EBRT	21	5	26	
<i>Outcome</i>				
No recurrence	21	9	30	
Recurrence	13	10	23	
Persistent	8	4	12	
Progression	2	2	4	
<i>Status at end of follow-up</i>				
ANED (alive no evidence of disease)	11	5	16	
AWD (alive with disease)	6	2	8	
DOD (dead of disease)	22	13	35	
DUC (dead unknown cause)	5	5	10	
<i>Status (synthesis)</i>				
With disease	28	15	43	
Dead	27	18	45	
<i>Tumor size [cm] – mean</i>	6.2	5.1	5.8	
<i>Depth of invasion % – mean</i>	72.7	57.3	67	
<i>Mean age [yrs] – mean</i>	65.1	73.8	68.2	60–97
<i>Median follow-up (IQR) [months] – median (IQR)</i>	19.7	23	20.4	0.4–107.4

Table 4

Uni and multiple Cox regression analysis in predicting recurrence and any poor outcome.

Characteristics	N = 69 patients of stage III and IV		HR (Hazard ratio)	
	Crude	Adjusted	HR	p
<i>Recurrence</i>				
Subtype	1.71	1.07	0.206	0.906
Age	1.01	1.01	0.393	0.658
Tumor size	1.02	1.09	0.635	0.180
Depth of invasion (>50%)	2.40	3.80	0.070	0.021
Grade FIGO	1.00	1.00		
	G1			
	G2	0.30	0.662	0.272
	G3	3.57	0.065	0.124
Stage	1.00	1.00		
	III			
	IV	3.56	0.020	0.013
Lympho-vascular involvement (LVI)	5.26	3.11	0.008	0.105
<i>Any bad outcome</i>				
Subtype	1.15	0.61	0.667	0.244
Age	1.01	1.02	0.219	0.222
Tumor size	0.98	1.03	0.593	0.537
Depth of invasion (>50%)	2.35	3.07	0.015	0.006
Grade FIGO	1.00	1.00		
	G1			
	G2	0.31	0.997	0.085
	G3	2.60	0.056	0.060
Stage	1.00	1.00		
	III			
	IV	2.91	0.004	0.003
Lympho-vascular involvement (LVI)	2.62	1.55	0.008	0.292
<i>Dead of disease</i>				
Subtype	1.08	0.54	0.825	0.163
Age	1.01	1.01	0.427	0.492
Tumor size	0.97	1.02	0.563	0.728

Characteristics	N = 69 patients of stage III and IV	HR (Hazard ratio)			
		Crude		Adjusted	
		HR	p	HR	p
Depth of invasion (>50%)		2.48	0.025	3.64	0.004
Grade FIGO	G1	1.00		1.00	
	G2	1.27	0.751	0.51	0.425
	G3	3.04	0.068	3.59	0.052
Stage	III	1.00		1.00	
	IV	1.99	0.050	1.94	0.077
Lympho-vascular involvement (LVI)		1.84	0.134	0.84	0.714

Bad outcome is defined as any recurrences, persistent or progression of the disease.