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Prognostic factors in endometrial cancer Stages III and IV: a single academic institution experience of 49 patients

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Summary

Background: To evaluate the clinical and pathologic factors associated with survival in patients with advanced staged endometrial carcinoma. *Matreials and Methods:* Between 2005 and 2017 all patients with endometrial carcinoma type I were identified from tumor registry databases at this Academic hospital. The impact of clinical and pathologic risk factors on the survival of patients with endometrial carcinoma was evaluated using Kaplan-Meier life table analyses and log-rank tests. *Results:* Forty-nine patients with advanced endometrial cancer were collected. The median progression-free survival (PFS) for all patients was 42 months whereas the median overall survival (OS) was 69 months for all patients. Univariate analysis was extended to all prognostic factors for all stages showed as statistically significant positive cytology and cervical invasion, whereas for Stage III only cervical invasion. For Stage IIIA the prognostic factors statistically significant were cervical invasion and lymphovascular space invasion (LVSI). Furthermore, prognosis was worse in tumors belonging to Stage IV with positive cytology. *Conclusion:* Prognostic factors related to a lower survival rate in advanced stages of endometrial cancer are represented by cervical invasion, LVSI, and positive peritoneal cytology. These factors with respect to LVSI and positive peritoneal cytology should be included in FIGO 2009 surgical staging system because associated to a poor prognosis.

Key words: Prognostic Factors; Uterine carcinoma; Endometrial carcinoma.

Introduction

Endometrial cancer is the most frequent malignancy of the female genital tract in all countries, and accounts for about 6% of all newly diagnosed cancer and for about 3% of cancer deaths [1]. Since vaginal bleeding is commonly associated to the presence of disease, more than 75% of endometrial cancer cases are diagnosed at early stage, resulting in overall favourable prognosis, with a five–year overall survival (OS) and cancer-specific survival rates of 80% to 85% and 90%, to 95 %, respectively [2, 3].

Only 5%–10% of endometrial cancer patients had Stage III-IV disease. For those patients, the prognosis remains poor and the optimal adjuvant therapy is yet to be established [2]. Therefore, advanced endometrial cancer provides a therapeutic challenge for the oncologist. A subset of these patients may benefit from hormonal manipulation, systemic chemotherapies, or combination treatment with volume-directed radiotherapy and systemic chemotherapy. The choice of therapy depends on the extent of residual disease after initial surgery, and the intent of treatment, is if it should be curative or palliative. Given the poor prognosis, it is important to identify prognostic factors responsible for survival in an effort to improve treatment strategies.

In this current series of patients with endometrial cancer Stages III and IV the authors identified the clinical and pathologic prognostic factors responsible for survival. Furthermore, various therapeutic strategies in the treatment of this aggressive cancer were investigated.

Materials and Methods

Between 2005 and 2017, all endometrial cancer type I patients Stages IIIA-IVB (according to FIGO 2009 staging system) were collected retrospectively. Endometrial carcinoma type 1 such as endometrioid, mucinous, and adenosquamous histotypes were included in the study.

Clinical data were collected from patient medical records and official reports which included age at the time of diagnosis, comorbidity, Eastern Cooperative Oncology Group (ECOG) performance status, Ca125 serum marker value at the time of diagnosis, radiologic evaluations as CT scan, MRI, PET, histology tumor type, and surgical and adjuvant treatments. Progression-free survival (PFS) was defined as the interval between surgery and recurrence of disease confirmed by clinical-instrumental evaluation or the interval between surgery and last follow up. OS was defined as the interval between diagnosis and death, or interval between diagnosis and last follow up in survived patients.

The software used for the survival analysis was XLSTAT. Kaplan-Meier analyses were used to determine OS and PFS. Differences in OS and PFS were tested by log-rank tests. All tests with p values less than 0.05 were considered significant. Multivariate analyses were performed with the use of Cox proportional hazards regression. A two-sided probability value less of 0.05 was considered to be significant.

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Table 1. — *Patient characteristics.*

	Number	Percentage
Performance status (PS, ECOG)		
0	16	33%
1	28	57%
2	5	10%
Ca 125		
Negative	13	27%
Positive	36	73%
Comorbidity		
Hypertension	18	37%
Diabetes	7	14%
Hypercholesterolemia	4	8%
Tumor familiarity		
Enodmetrial cancer	3	6%
Breast	1	2%
Others	5	10%
FIGO Stage		
IIIA	22	45%
IIIB	4	8%
IIIC1	6	12%
IIIC2	4	8%
IVA	1	2%
IVB	12	25%
Histological type		
Endometrioid	40	82%
Mucinous	1	2%
Adenosquamous	8	16%
Grading		
G1	14	28%
G2	15	31%
G3	20	42%
Myometrial invasion		
< 50%	11	22%
> 50%	38	78%
Serous invasion		
Si	36	73%
No	13	27%
Ovarian metastasis		
Bilateral	8	16%
Monolateral	11	23%
Negative	30	61%
Tubaric metastasis		
Bilateral	5	10%
Monolateral	11	23%
Negative	33	67%
Cervical invasion		
Yes	27	55%
No	22	45%
Vaginal invasion		
Yes	5	10%
No	44	90%
Parametrial invasion		
Yes	7	14%
No	42	86%
LSVI		
Yes	25	51%
No	24	50%
Cytology		
Not performed	9	18%
Performed	40	82%
Positive cytology		
Yes	7	17%
No	33	83%
Pelvic lymphadenectomy		
Not performed	28	57%
Performed	21	43%
Pelvic lymph nodes		
Negative	13	26,0%
Positive	8	74,0%
Surgical procedures		
HBSO	14	29%
HBSO+LFN	5	10%
HBSO+LFN+OMENT	6	12%
HBSO+LFN+PERIT	2	4%
HBSO+LFN+PERIT+OMENT	5	10%
HBSO+OMENT	5	10%
HBSO+PERIT	3	6%
HBSO+PERIT+OMENT	9	19%
Adjuvant therapy		
CT	27	56%
RT	11	23%
CT+RT	10	21%

HBSO = abdominal hysterectomy and bilateral salpingo-oophorectomy, LFN = lymphadenectomy, OMENT = omentectomy, PERIT = peritonectomy, CT = chemotherapy, RT = radiotherapy.

Results

Forty-nine patients with diagnosis of advanced endometrial cancer type 1 were collected. The median age at diagnosis was 62 years (range 19-84). Performance Status, according to life quality index of ECOG was 0 in 16 (33%), one in 28 (57%), and two in five (10%) patients. Ca125 serum marker value was within normal limit in 13 (27%) patients, whereas 36 (73%) had values between 54 U.I./ml and 11436 U.I./ml. Almost all women underwent cytoreductive primary surgery: 29% (n=14) of them underwent abdominal hysterectomy (LH) and bilateral salpingo-oophorectomy (BSO), 10% (n=5) of patients underwent LH, BSO, and lymphadenectomy, 12% (n=6) LH, BSO, lymphadenectomy and omentectomy, 4% (n=2) LH, BSO, lymphadenectomy and peritonectomy, 10% (n=5) LH, BSO, lymphadenectomy, peritonectomy, and omentectomy, 10% (n=5) LH, BSO and omentectomy, 6% (n=3) LH, BSO and peritonectomy and 19% (n=9) LH, peritonectomy. and omentectomy. Only one patient underwent neoadjuvant chemotherapy because the tumor was evaluated as unresectable by the present surgical team that considered an optimal cytoreduction not safely feasible with standard surgical procedures based on CT scan evaluation.

Regarding tumor staging, at time of diagnosis, 36 patients (73%) had tumor belonging to Stage III [IIIA: n= 22 (45%), IIIB: n= 4 (8%), IIIC1: n= 6 (12%), IIIC2: n= 4 (8%)], and 13 patients (27%) Stage IV [IVA: n=1 (2%), IVB: n= 12 (25%)] according to FIGO 2009 staging system.

Regarding histologic evaluation, 40 (82%) had endometrioid cell type, eight (16%) adenosquamous type, and only one (2%) patient a mucinous one. The 28% (n=14) of

Table 2. — *Univariate analysis of survival based on clinical and pathologic factors.*

Prognostic Factors	Median survival	*p* value
Performance status (PS)		
0	Undefined	0.3564
1	61	
2	35	
PS		
0 – 1	75	0.3
2	35	
Ca 125		
Negative	69	0.7397
Positive	75	
Histological type		
Endometrioid	75	0.7858
Non-endometrioid	61	
Grading		
G1	Undefined	0.1808
G2	38	
G3	61	
Stage		
III A	69	0.3196
III B	75	
III C1	Undefined	
III C2	90	
IV A	9	
IV B	24	
Stages III		
IIIA	69	0.8913
IIIB	75	
IIIC	85	
Stages III – IV		
III	75	0.2003
IV	24	
Cytology		
Negative	61	< 0.0015
Positive	8.5	
Cervical involvement		
Negative	Undefined	< 0.0036
Positive	35	
LVSI		
Negative	168	0.0623
Positive	39	
LFN pelvic + LA		
Negative	Undefined	0.7018
Positive	Undefined	
Parametrium		
Negative	69	0,5619
Positive	75	
Ovaries		
Negative	75	0.4885
Positive	61	
Fallopian tubes		
Negative	69	0,3122
Positive	168	

the tumors were well differentiated (G1), 31% (n=15) moderately differentiated (G2), and 42% (n=20) poorly differentiated (G3). Thirty-eight (78%) tumors had myometrial

Table 3. — *Univariate analysis of survival in Stage III and IV patients based on clinical and pathologic factors.*

Prognostic Factors	Median survival	*p* value
Cytological Stage III		
Negative	61	0.2106
Positive	12	
Cytological Stage IV		
Negative	24	<0.0004
Positive	6	
Myometrial Stage III		
< 50 %	168	0.0754
> 50 %	61	
Serous Stage III		
Negative	Undefined	0.3096
Positive	75	
Cervical Stage III		
Negative	Undefined	<0.0116
Positive	51	
LSVI Stage III		
Negative	168	0.0623
Positive	39	
LFN Stage III		
Negative	Undefined	0.6919
Positive	Undefined	
Parametrial Stage III		
Negative	69	0.8275
Positive	75	
Ovarian Stage III		
Negative	75	0.9789
Positive	Undefined	
Adjuvant treatment Stage III		
CT	69	0.1823
RT	78	
CT + RT	85	

Table 4. — *Univariate analysis of survival in Stage IIIA patients based on clinical and pathologic factors.*

Prognostic factors	Median survival	*p* value
Cytological Stage III A		
Negative	39	0.4078
Positive	Undefined	
Myometrial Stage IIIA		
< 50 %	168	0.0851
> 50 %	38	
Serous Stage IIIA		
Negative	Undefined	0.2101
Positive	61	
Cervical Stage IIIA		
Negative	Undefined	<0.0351
Positive	35	
LSVI Stage IIIA		
Negative	168	<0.0469
Positive	38	
Ovarian Stage IIIA		
Negative	168	0.4705
Positive	61	
Adjuvant treatment Stage III A		
CT	76	0.5390
RT	65	
CT + RT	89	

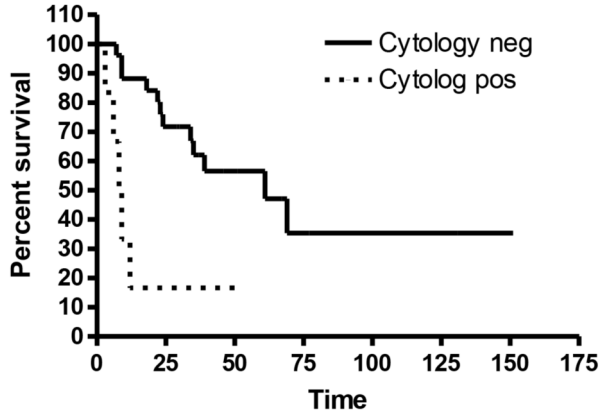

Figure 1. — Kaplan-Meier survival analysis based on cytology.

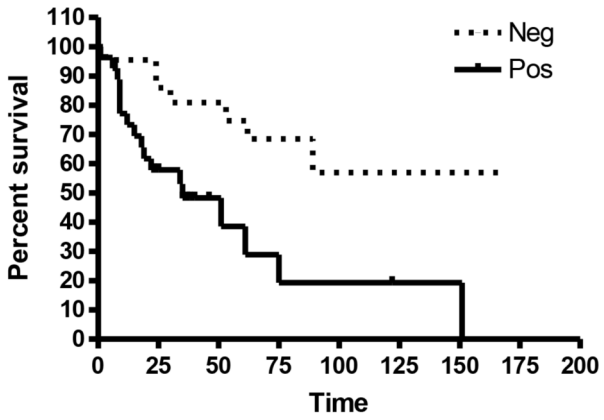

Figure 2. — Kaplan-Meier survival analysis based on cervical involvement.

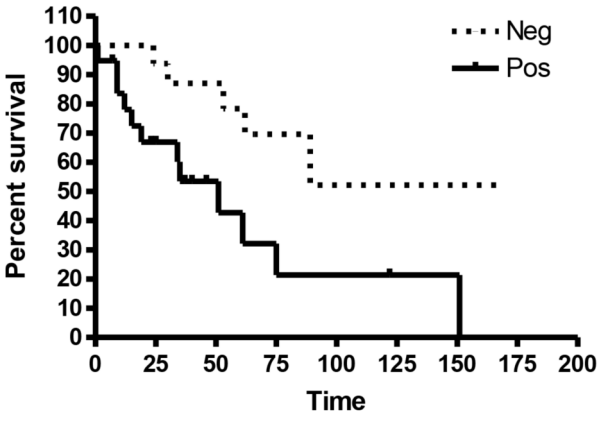

Figure 3. — Kaplan-Meier survival analysis based on cervical involvement in Stage III.

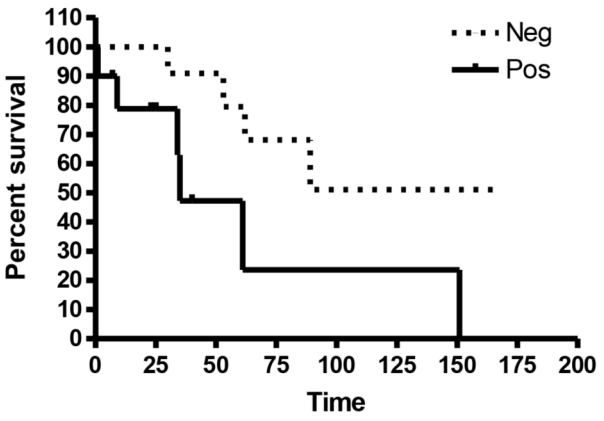

Figure 4. — Kaplan-Meier survival analysis based on cervical involvement in Stage IIIA.

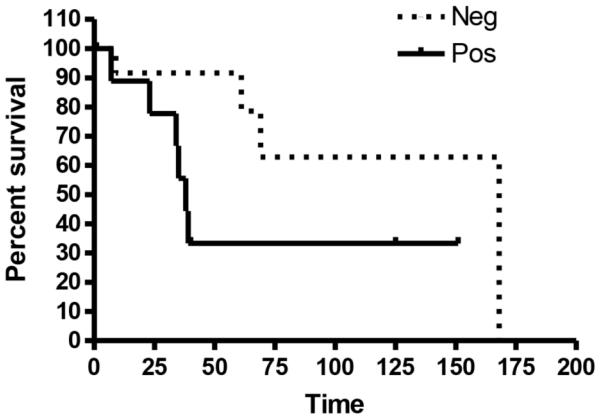

Figure 5. — Kaplan-Meier survival analysis based on LVSI in Stage IIIA.

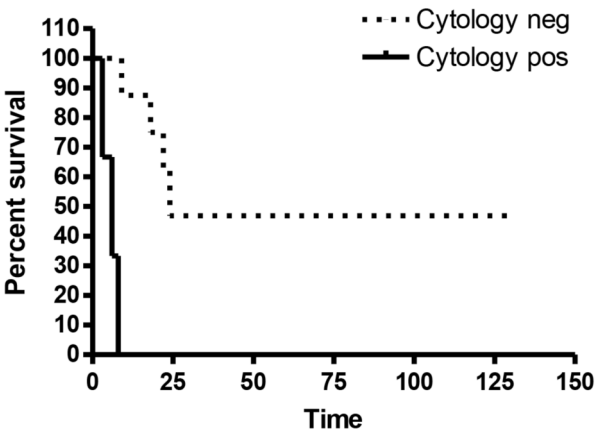

Figure 6. — Kaplan-Meier survival analysis based on cytology in Stage IV.

involvement greater than 50%, whereas only 11 (22%) had myometrial involvement lower than 50%. Furthermore, 36 (73%) had serous involvement. The cervix was involved by the tumor in 27 (55%) cases, whereas ovarian involvement was present in 19 patients: 11 (23%) had an unilateral ovarian involvement whereas eight (16%) had a bilateral one. Fallopian tubes were positive with unilateral involvement in the 23% of cases (n=11) and positive with bilateral one in the remaining 10% (n=5). In addition, five (10%) cases had vaginal invasion, and seven (14%) had parametrial infiltration. Lymphovascular space invasion (LVSI) was identified in the 51% (n= 25) of cases. Peritoneal washing was performed in 40 patients during surgery. Seven of them showed a positive cytology. Lymph nodes dissection was performed in 21 (44%) patients, with eight (38%) of them showing lymph nodes metastases. Only two cases of them showed tumor invasion of both pelvic and aortic lymph nodes.

Adjuvant treatment consisting in chemotherapy, radiotherapy or chemoradiation was suggested in all patients that underwent surgical treatment, but was refused in only one case. More specifically, chemotherapy based on carboplatin and paclitaxel was administered in the 56% (n=27), radiotherapy in the 23% (n=11), chemoradiation in the remaining 21% (n=10) of patients (Figure 1). Recurrences was observed in 13 (27%) of patients. Among the patients who recurred, 10% (n=5) of them had local disease recurrence, whereas 12% (n=6) had distance recurrence, and 4% (n= 2) had both local and distance disease.

The median PFS for all patients was 42 months in an interval time between one and 168 months. The median PFS of patients in Stage III was 45 (range 0-168) months, whereas the median PFS of patients in Stage IV was 33 (range 1-131) months.

The median OS was 69 months for all patients, in a time interval between one and 168 months. Univariate analysis considered ECOG performance status, Ca125 value, histotype, tumor grading, stage of disease, positive cytology, cervical invasion, LVSI, lymph nodes status (both for pelvic and aortic lymph nodes), parametrial involvement, and ovarian and tubal metastases was performed in order to determine the significance of these prognotic factors (Tables 2-4). Positive cytology (Figure 1) and cervical invasion (Figure 2) was found to be prognostic factors in all stages. However, stratified for stages, the authors found that cervical invasion was the only prognostic factor for patients in Stage III (Figure 3), whereas for Stage IIIA cervical invasion (Figure 4), and LVSI (Figure 5). Furthermore, prognosis was worse in tumors belonging to Stage IV with positive cytology (Figure 6). A positive trend, even if not strictly statistically significant, was observed for myometrial invasion > 50% and for LVSI in all tumors belonging to Stage III. To examine the variables identified as important in univariate analyses further, a multivariate analysis was performed. Positive cytology and cervical invasion remained in all stages as a significant independent poor prognostic factor for survival in the present patient population.

Discussion

Endometrial cancer is the most common female genital cancer [1, 2]. Most women are diagnosed in an early stage because of abnormal vaginal bleeding, which is the most common early symptom [3].

Although the prognosis of endometrial cancer is generally favourable, the disease can behave differently, it can have an excellent prognosis, and high curability or can be aggressive with poor outcomes [4-7]. It is thought that endometrial cancer can be treated and/or controlled by adequate primary surgery, due to a generally prompt diagnosis that allows to detect and treat the tumor in an early stage, as suggested by the analysis of the Surveillance, Epidemiology and End Results (SEER) data [8]. However, data showed that mortality rate of endometrial cancer has increased more rapidly than its incidence. There are many reasons that contribute to the increased mortality, such as an increased rate of advanced stage cancers, high-risk histotypes, and diagnosis in old age [7, 8].

Advanced endometrial cancer is relatively uncommon and accounts for fewer than 20% of all patients with endometrial cancer [8, 9]. Prognostic factors for endometrial cancer include stage, histotype, myometrial invasion, cervical involvement, and lymph node metastases [10-14], but these parameters are insufficient to accurately predict endometrial cancer prognosis. Results of the present study showed that disease prognosis in patients with advanced endometrial cancer is considerably worse in case of positive cytology obtained through peritoneal washing during surgery, cervical invasion, and LVSI.

In particular, positive cytology, globally considered in Stages III and IV, and exclusively considered in Stage IV, is a predictor of a poor prognosis; this is probably related to the frequent association between positive cytology and abdominal metastases found in an advanced stage disease.

Results obtained in more than 50 reports in the literature regarding the significance of positive peritoneal cytology in endometrial cancer have been published: several reports showed the increase of recurrence rates and the decrease of survival ones suggesting, on these bases, an adequate treatment in case of positive cytology [15-23]. These findings showed that, even if peritoneal cytology is not yet included in FIGO surgical staging system, it represents a very important prognostic factor related to a poor prognosis. Thus, based on the present results, the authors' recommendation is to include cytology in the FIGO staging system for endometrial cancer. Furthermore, in this study the importance of cervical invasion emerged, representing itself a statistically significant prognostic factor in all analyzed disease stages. The importance of cervical invasion, according to data of the literature, has never been related to advanced

stages of endometrial cancer. Therefore, based on the present results the authors suggest that cervical invasion in advanced stage would be an important evaluation that may help the physician in the choice of adjuvant treatment.

LVSI resulted statistically significant in Stage IIIA, with a positive trend even if not significant in Stage III. This is a known risk factor in endometrial cancer both in early- and advanced-stage disease that has been previously described [13]. LVSI is not yet included in FIGO surgical staging system as prognostic factor [11], even if same authors described LVSI as a predictor factor for the presence of lymph nodal metastases [24].

In addition, the present authors evaluated myometrial invasion more than 50% as prognostic factor and they found that this factor is related to a poor prognosis, even if not statistically significant by test of equality ($p > 0.05$), probably due to the necessity of expanding the sample group. In fact, a limitation of this study was the small number of patients. However, based on these analyses, the authors believe that these results should be evaluated in a global perspective, as support of what is yet described in the literature. For this reason, information regarding peritoneal cytology is still important in the diagnosis of endometrial cancer based on its role as independent prognostic factor. Therefore, the present authors believe that studies with larger number of patients are necessary in order to establish a possible role of this prognostic factor in the FIGO staging system for endometrial cancer.

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