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Adjuvant Carboplatin, Paclitaxel and Vaginal Cuff Brachytherapy for Stage III Endometrial Cancer: Analysis of outcomes and patterns of recurrence based on pathologic characteristics

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Abstract

Objective—To evaluate outcomes of patients with stage III endometrial adenocarcinoma treated with surgery followed by adjuvant chemotherapy and vaginal cuff brachytherapy.

Methods—We retrospectively identified 83 patients treated for 1988 FIGO stage III endometrial adenocarcinoma at our institution between 2003 and 2010. All patients underwent comprehensive surgical staging. Adjuvant therapy was carboplatin and paclitaxel for 6 cycles and vaginal cuff brachytherapy. For analysis, patients were grouped into type I (FIGO grade 1–2 endometrioid histology, n=41) or type 2 (FIGO grade 3, clear cell or papillary serous histology, n=42) disease. Forty-three patients (52%) had node positive disease, with similar node positive rates for type I (n=21, 51.2%) and type II (n=22, 52.4%).

Results—Median follow up was 38.6 months. There were no isolated vaginal failures. Estimated 3-year disease-free (DFS) and overall survival (OS) for type I versus type II were 92.4% vs 58.0% (p = 0.001) and 97.2% vs 65.8% (p = 0.002), respectively. The 3-year DFS and OS for node negative versus node positive were 85.0% vs 63.6 % (p = 0.02) and 84.2% vs 78.0% (p = 0.02), respectively. Associations between type I histology and node negative disease with improved DFS and OS persisted on multivariate analysis.

Conclusions—Our institutional approach of adjuvant chemotherapy and vaginal cuff brachytherapy for stage III endometrial cancer appeared acceptable for patients with low risk histology or node negative disease. In contrast, higher rates of failure among those with high risk histology and/or node positive disease support intensification of therapy in these subsets.

Keywords

Endometrial cancer; adenocarcinoma; vaginal cuff brachytherapy; carboplatin; paclitaxel

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Introduction

In 2014, an estimated 52,630 new cases of endometrial cancer will be diagnosed in the United States, with 8590 deaths.¹ While the majority of patients present with early stage disease and have excellent outcomes, the incidence of stage III disease ranges from 6–12%, with poorer outcomes.^{2, 3} The optimal adjuvant treatment approach for stage III endometrial cancer is uncertain. Over the last several decades, a limited number of studies have sought to address if chemotherapy alone, radiotherapy alone, or combined modality treatment provide superior outcomes.

The results of Gynecologic Oncology Group (GOG) 122 study indicated chemotherapy alone improved disease-free survival (DFS) and overall survival (OS) in comparison to whole abdominal irradiation (WAI) alone in those with stage III and IV endometrial cancer, thereby setting the stage for adjuvant chemotherapy as the primary adjuvant treatment modality for patients with high risk endometrial cancer. However, in GOG 122, recurrence rates were still relatively high, with 5-year DFS of 42% and 38% for chemotherapy versus WAI, respectively. Pattern of initial failure varied, where chemotherapy resulted in decreased distant extra-abdominal relapse from 19% to 10%, but increased pelvic recurrence from 13% to 18% compared to WAI. The high risk of pelvic recurrence among advanced endometrial cancer populations treated with adjuvant chemotherapy alone has been further highlighted in several studies, including a retrospective analysis by Mundt *et al.* which found nearly a 40% pelvic recurrence rate, over 80% of these involving vaginal failure⁴. In a recent multi-institutional study, Secord *et al.* reported stage IIIC patients treated with adjuvant chemotherapy alone were 2 to 7-times more likely to have a vaginal recurrence and twice as likely to develop a pelvic only recurrence compared to those who had radiotherapy as part of their adjuvant treatment⁵. These high rates of pelvic failure with adjuvant chemotherapy alone warrant consideration of locoregional adjuvant radiotherapy. However, radiotherapy alone in stage III disease has a 5-year recurrence rate ranging from 20–60%, albeit with a reduction in pelvic failure^{5–9}. This difference in failure patterns based on treatment modality has generated much interest in combined modality therapy to improve outcomes.

The pooled results of NSGO-EC-9501/EORTC-55991 and MaNGO ILIAD-III showed an improvement in DFS and a trend for improved OS for high risk patients treated with adjuvant sequential chemotherapy and radiotherapy¹⁰. These data are consistent with several retrospective studies that have indicated combined modality therapy increases DFS and OS in some subsets of high risk patients^{5, 11–15}. Despite mounting evidence supporting the use of combined modality treatment in advanced stage endometrial cancer, definitive level I evidence supporting a survival benefit for combine pelvic radiotherapy/chemotherapy as compared to chemotherapy alone has not yet been demonstrated. Thus, presently there remains controversy among the gynecologic oncology community concerning the optimal target for radiotherapy, sequencing with chemotherapy, and tolerability of the combination. Radiotherapy approaches continue to vary by institution, ranging from WAI, to pelvic radiotherapy, to tumor directed therapy (ie extended field radiotherapy) with or without vaginal cuff brachytherapy, all with varying toxicities. While vaginal cuff brachytherapy is often considered in addition to external beam radiotherapy in patients with high risk features for local failure, to our knowledge, there has been no study specifically addressing vaginal

cuff brachytherapy as the sole adjuvant radiotherapy as part of a combined modality approach in stage III endometrial adenocarcinoma.

The purpose of this study is to report a single institution experience of adjuvant carboplatin and paclitaxel chemotherapy concurrently with vaginal cuff brachytherapy (without external beam radiotherapy) for optimally resected patients with 1988 FIGO stage III endometrial adenocarcinoma. This regimen was the adjuvant treatment offered to patients with stage III endometrial cancer at our institution between 2003 and 2010, with the rationale that this concurrent regimen would lead to fewer vaginal failures with little added toxicity compared to a chemotherapy-alone approach. In this report, we aimed to analyze outcomes and patterns of recurrence in this retrospective cohort, as well as identify subsets of patients who may have benefited from this treatment approach.

Methods

Study Design

After obtaining Institution Review Board approval, we retrospectively identified patients diagnosed with FIGO stage III (1988 FIGO grading system) endometrial cancer between January 1, 2003 to December 31, 2010 who had undergone total hysterectomy, bilateral salpingo-oophorectomy, and extended surgical staging, followed by adjuvant carboplatin, paclitaxel, and vaginal cuff brachytherapy without external beam radiotherapy as per our institutional practice during this era for all stage III patients. Clinical data were obtained from the medical record, including clinical notes, pathology reports, operative notes, radiation treatment records, and imaging reports. Inclusion criteria comprised of patients with adenocarcinoma histology, including endometrioid, papillary serous, clear cell and mixed adenocarcinoma (histologic diagnosis of a mixture of endometrioid, papillary serous and/or clear cell, not meeting the diagnosis of one subtype alone). Patients were excluded if there was less than 6 months follow-up, synchronous primary malignancies, prior radiotherapy, carcinosarcoma histology, or residual gross disease.

Surgical methods included total abdominal, laparoscopic, or robotic hysterectomy, peritoneal cytology, with or without pelvic and para-aortic lymph node sampling and omental evaluation. Pelvic and para-aortic lymph node sampling was performed in a majority of cases ($n=81$, 97.6 % and $n=70$, 84.3%, respectively), with a median number removed of 20 (range 2–60) and 4 (range 1–28), respectively. The omentum was evaluated intraoperatively and omental biopsy was performed in 30 patients (36.1%). The intended chemotherapy was carboplatin (AUC = 5) and paclitaxel (175 mg/m²) chemotherapy given every 3 weeks for 6 cycles. A total of 7 patients did not complete 6 cycles of the intended chemotherapy; 5 had poor tolerance of the paclitaxel, thus completed the remainder of chemotherapy with carboplatin alone, 1 underwent carboplatin and topotecan chemotherapy, and one patient had paclitaxel alone due to history of nephrectomy. Vaginal cuff brachytherapy was administered using a vaginal cylinder and high dose rate 192-Ir remote afterloading system, prescribed to a depth 0.5 cm from the vaginal surface to a total of 14 Gy ($n = 60$; 72.3%) or 21 Gy ($n = 22$; 26.5%) in 7 Gy fractions. One patient (1.2%) underwent only 1 brachytherapy treatment due to vaginal cuff dehiscence after 1 fraction.

Following treatment, patients were evaluated every 3 months for the first two years, and every six months thereafter. Routine evaluation included history and physical examination, laboratories, vaginal cytology, and CT chest, abdomen and pelvis.

Data analysis

Kaplan-Meier methods were used to estimate 3-year DFS and OS, and differences were tested using the log-rank test. Time to relapse, death or last follow-up was measured from the date of surgery. Therefore, DFS was defined as the time from date of surgery to the date of first event (progression or death). If recurrence was identified, CT scans were reviewed to identify the recurrence as pelvic, para-aortic, or distant. Those who were alive without progression were censored at the time of last follow-up. OS was calculated from the time of surgery to the time of death from any cause, or censored at the time of last follow-up for those who were still alive.

Univariate analysis of DFS and OS was performed using Cox proportional hazards ratio analysis. The multivariate Cox proportional hazards model was constructed in a stepwise fashion, with variables included if $p < 0.05$ and excluded if $p > 0.10$. When multiple covariates that were significant on univariate analysis were also highly correlated with each other (for example, node positive disease was highly correlated with myometrial invasion, endocervical invasion, and lymphovascular invasion) the variable that resulted in the most significant overall model was included.

Analysis was performed using IBM SPSS (Armonk, NY) and STATA/SE 12 (College Station, TX).

Results

Patient characteristics

A total of 83 patients were identified for inclusion in this study. Table 1 summarizes patient characteristics. Median age at time of surgery was 63 years (range 27 – 89). Nineteen (22.9%) were 70 years or older. Pathologic subtypes were categorized as type I disease including endometrioid histology, FIGO grade 1 or 2 ($n=41$; 49.4%), or type II comprising the more aggressive histologies of endometrioid FIGO grade 3, clear cell, papillary serous, or mixed adenocarcinoma ($n=42$; 50.6%). Forty-three patients (51.8 %) had node positive disease. Rates of node positive disease were similar for type I ($n=21$, 51.2%) and type II ($n=22$, 52.4%) patients. Of all node positive patients, 25 (58.1%) had pelvic lymph node only positive disease, 7 (16.3%) had para-aortic only node positive disease, and the remainder had both positive pelvic and para-aortic node disease ($n = 11$; 25.6%).

During the era in which these patients were treated, the FIGO staging criteria changed. Under the current 2009 FIGO staging criteria, 18 (21.7%) of patients who were previously stage IIIA (1988 FIGO staging criteria), would be re-classified as stage IA ($n = 16$; 19.3%), stage IB ($n = 1$; 1.2%) or II ($n = 1$; 1.2%) as their only high risk criteria was positive peritoneal cytology. Twenty-two patients (26.5%) had 2009 FIGO stage IIIA disease.

Treatment outcomes

Median follow-up was 38.6 months (range 10.1–93.8). The three-year estimated DFS and OS were 75.2% and 80.7%, respectively. Sixty-two patients were alive (74.7%), while 21 (25.3%) were deceased at the time of last follow-up. Median time to death was 27.8 months (range 10.1 – 48.4).

Table 2 summarizes the unadjusted hazard ratios of the pathologic and patient characteristics evaluated in this study. Factors significantly associated with improved DFS on univariate analysis included type I vs type II disease ($p = 0.0005$), negative lymph nodes ($p = 0.009$), myometrial invasion of less than 50% ($p = 0.003$), and absence of endocervical stromal invasion ($p = 0.04$). Factors that predicted for better OS on univariate analysis were younger age ($p = 0.0031$), type I disease ($p = 0.001$), node negative disease ($p = 0.02$), myometrial invasion less than 50% ($p = 0.002$), absence of endocervical stromal invasion ($p = 0.03$), and absence of lymphovascular invasion ($p = 0.02$). Although twenty or more pelvic lymph nodes dissected predicted for improved DFS ($p = 0.02$), it was not associated with OS.

Table 3 summarizes the adjusted hazard ratios on multivariate analysis. Type I disease ($p = 0.005$), lymph node negative disease ($p = 0.033$), and 20 or more pelvic lymph nodes dissected ($p = 0.049$) predicted for improved DFS. Younger age ($p = 0.021$), type I disease ($p = 0.012$), and node negative disease ($p = 0.035$) predicted for better OS.

The 3-year DFS and OS of type I versus type II patients were 92.4% vs 58.0% ($p = 0.001$) and 97.2% vs 65.8% ($p = 0.002$), respectively (Figure 1). The 3-year estimated DFS and OS for node negative versus node positive patients were 85.0% vs 63.6% ($p = 0.02$) and 84.2% vs 78.0% ($p = 0.02$), respectively.

Patterns of Failure

A total of 19 patients (22.9%) had recurrence with median time to failure of 13.1 months (range 4.0–34.6). Of the 21 patients who died in this study, 16 (76.2%) died with disease recurrence and death was attributable to disease progression in all cases. The remaining five patients were disease free at the time of last clinical follow-up, but cause of death was unavailable.

Table 4 summarizes characteristics and location of initial failure for the 19 patients with recurrence. Thirteen (68.4%) were within the pelvis and/or para-aortic regions. One of these pelvic and para-aortic failures also had simultaneous distant failure. The remaining 6 (31.6%) failures were distant-only failures. There were no isolated vaginal recurrences. Only one patient developed a vaginal failure which occurred 10 months after diagnosis of distant metastatic disease.

Recurrence patterns according to stage and histology are shown in Table 5. Of note, no patients with 2009 FIGO stage I–II disease or FIGO grade 1 disease had recurrence. The rate of pelvic recurrence was 14% (6 of 43) for node positive patients compared to 2.5% (1 of 40) in node negative patients.

Discussion

This study reports the outcomes of 83 patients with locally advanced endometrial cancer, defined as 1988 FIGO Stage III disease, treated at our institution between 2003 and 2010. Our main finding of a 3-year DFS and OS of 75.2% and 80.7%, respectively, is in keeping with other retrospective studies of stage III disease^{2, 5–9, 16–18}. A unique feature of this cohort was that adjuvant therapy consisted of carboplatin, paclitaxel and vaginal cuff brachytherapy as the sole radiotherapy modality. The consistent use of this treatment approach at our institution during the time period of this study allowed us to identify prognostic factors associated with outcome as well as analyze patterns of failure, and in particular, rates of locoregional failures in the absence of external beam radiotherapy.

Among the cohort as a whole, histology and nodal status were identified as important independent prognostic factors for both DFS and OS. Type I histology was associated with excellent outcome, with 3 year estimated DFS and OS at 92.4% and 97.2%. Conversely, patients in this study with type II histology had significantly lower 3-year DFS and OS at 58.0% and 65.8% respectively. This is in agreement with several other studies that have identified aggressive histology as a risk factor for disease recurrence and poorer OS in advanced disease^{6, 16, 17, 19}. Papillary serous histology carried the highest risk of recurrence with 10 of 15 (66.7%) patients developing recurrence in this study. The difference in recurrence rates did not appear to correspond to a higher incidence of node positive disease in patients with unfavorable histology, as node positive disease rates were similar between the type I and type II patients at 51.2% and 52.4%, respectively, and type II histology was an independent risk factor for both DFS and OS on the multivariable analysis. Not surprisingly, nodal status emerged as a separate, independent prognostic variable for both DFS and OS. Node negative patients had significantly improved outcomes compared to node positive disease with 3-year DFS of 85.0% vs 63.6% ($p = 0.02$) and OS of 84.2% vs 78.0% ($p = 0.02$), respectively. Based on these findings, and consistent with the literature, it appears that patients with higher risk histologic subtypes and those with node positive disease may be the most likely groups whom would benefit from intensification of therapy. For these patients, strategies which combine chemotherapy and external beam radiotherapy appear promising, particularly in stage IIIC patients, with 3–5 year DFS rates ranging from 73%–79% and OS from 73% – 90%^{5, 6, 11, 15, 20}. For high risk histologies, potential use of systemic targeted agents and small molecules^{21, 22} is being actively investigated at this institution and others.

In the setting of high-risk endometrial cancer, adjuvant systemic therapy versus local radiation therapy have been associated with vastly different patterns of failure in the literature. In the Italian randomized trial of high risk stage I–II and stage III disease (two thirds of patients with stage III disease) to CAP chemotherapy or pelvic RT, PFS was 68% and 69% respectively²³. For those patients with recurrence, first site of recurrence in the chemotherapy alone arm was local only in 34%, distant only in 48%, and distant and local in 14.3% compared to the radiotherapy arm with local only in 18%, distant only in 58%, and distant and local in 15%. This translates to approximately 48% of failures having a local component with chemotherapy alone. In the Japanese randomized trial²⁴, pelvic failure rates in the chemotherapy-alone arm was 7.3%, of which 64% were vaginal only failures. In a large retrospective analysis from the MD Andersen Cancer Center, Klopp *et al* reported

that pelvic and paraortic failures in stage IIIC patients were the site of first recurrence in 69% of failures for those receiving systemic therapy without external beam radiotherapy compared to 22% of failures in the external beam arm⁶. A multi-institutional analysis by Secord *et al.* reported stage IIIC patients treated with adjuvant chemotherapy alone were 2 to 7-times more likely to have a vaginal recurrence and twice as likely to develop a pelvic only recurrence compared to those who had radiotherapy as part of their adjuvant treatment⁵. In our analysis of sites of first failure in our institutional cohort of advanced patients treated with adjuvant chemotherapy and brachytherapy, we found no vaginal failures (0%), 3 isolated pelvic (4%), 5 isolated peri-aortic (4%), 5 pelvic and peri-aortic (6%), and 7 distant (8.4%). While different stages of patients and chemotherapy agents prohibit any direct comparison with the literature, overall these findings suggest a vaginal control benefit with this approach, similar to what would be predicted based on landmark trials in early stage disease^{25, 26}. However, despite notable improvement in vaginal control rates, the dominance of regional failures within the pelvis and/or para-aortic regions (13 of 19 initial failures, 68.4%) suggest an overall similarity of outcome between this approach and adjuvant chemotherapy alone. By contrast, it appears from the literature that approaches which combine pelvic radiotherapy with chemotherapy result in improved locoregional outcomes. The phase II RTOG 9708 trial had shown a 4-year pelvic and regional recurrence of 2% using a regimen of chemotherapy combined with external beam radiotherapy and brachytherapy²⁷. Subgroup analysis of stage III patients showed only a small increase in local recurrence compared to the entire cohort with a local recurrence rate of 8% with a 30% distant metastasis rate. GOG 184 also reported loco-regional versus distant metastasis rates in their higher risk stage III and IV patients receiving combined chemotherapy and external beam radiotherapy, showing of the 40% of patients with any failure, only about 25% of first failures were loco-regional with the remaining distant²⁸. The meta-analysis of NSGO-EC-9501/EORTC-55991 and MaNGO ILIAD-III trials also reported similarly that combined chemotherapy and external radiation resulted in a smaller proportion of recurrences as loco-regional (12%) than we report found in our study¹⁰.

While FIGO stage III endometrial cancer encompasses a heterogeneous mix of pathologic characteristics, they tend to be grouped together for the purpose of clinical trials. As such, not all patients are likely to benefit the same from the addition of adjuvant external beam radiotherapy. One of the advantages to this study was the ability to identify a single cohort of patients treated with a similar treatment paradigm, thus allowing for identification of factors that may predict improved outcomes. This differs from most other retrospective analyses whereby different treatment modalities and radiotherapeutic targets are compared. While this regimen of chemotherapy and vaginal brachytherapy has been described previously for early stage disease^{29–32}, to our knowledge, its application in advanced stage disease has been reported in only a few select cases³¹. In the present study, we were able to identify subsets of patients at our institution who appeared to have acceptable outcomes from a relatively de-intensified chemotherapy-brachytherapy treatment approach although numbers are small, follow up is short, and the limitations of this study preclude ability to draw any absolute conclusions for practice.

Limitations of this study include the retrospective approach, limiting this to a descriptive report without study hypothesis. The sample size is small, and there is heterogeneity of

histologic subtypes included, variation in brachytherapy dose, and has relatively short followup. Although we included patients with at least 6 months follow up, several patients were lost to follow up after a few years, thus all recurrences may not have been captured. Selection bias was somewhat minimized as treatment policy was standardized at our institution during this time period for all stage III patients with little variance, but some patients may not have been captured in our study if not referred for any adjuvant therapy. As our adjuvant therapy was standardized during this era, we lack an internal comparison group to evaluate different outcomes with alternate adjuvant therapy approaches. We were also unable to collect data in relation to treatment toxicity, which could be an important factor given the relative reduction in intensity of this therapy compared with chemotherapy and external beam radiotherapy. The results of our study may underestimate recurrence risk do to variability in use of imaging that would identify recurrence and/or classify true pattern of initial failure, as well as the fact that 18 of 83 (21.7%) patients in our study were stage IIIA by virtue of positive peritoneal cytology alone under FIGO 1988 staging, now considered stage I or II under the revised FIGO 2009 staging criteria.

In summary, we show that the use of adjuvant chemotherapy and vaginal cuff brachytherapy for stage III endometrial cancer at our institution in the years 2003–2010 resulted overall in similar DFS and OS rates as compared to other reported outcomes of adjuvant chemotherapy and/or external beam radiotherapy in the literature from a similar time period. Node negative and type I histology fared well, however, patients with high risk histologies and node positive disease were identified as those likely to derive benefit from more intense treatment programs. Despite excellent vaginal control rates overall, the proportion of pelvic and para-aortic recurrences in our series mirrors that found in descriptive studies of adjuvant chemotherapy alone, although the heterogeneity of study inclusion criteria make any direct comparisons difficult. As controversy continues concerning optimal treatment approach for advanced endometrial cancer, we eagerly await the results of the ongoing prospective, randomized studies.

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Figure 1.

DFS (A and C) and OS (B and D) comparing Type I vs Type II (A and B) and nodal status (C and D). Kaplan Meier methods were used to calculate estimated 3 year DFS and OS. Log-rank test was used to calculate differences.

Table 1

Characteristics of 83 patients included in study.

Characteristic	Number	Percentage (%)
Total	83	100
Age, years		
<50	4	4.8
50–69	60	72.3
70+	19	22.9
Surgery type		
Open	58	70.0
Laparoscopic	13	15.6
Robotic	12	14.4
Total Pelvic Lymph Nodes Sampled		
<20	42	50.6
20+	41	49.4
Histology		
Type I	41	49.4
Endometrioid FIGO 1	17	20.5
Endometrioid FIGO 2	24	28.9
Type II	42	50.6
Endometrioid FIGO 3	13	15.7
Clear Cell	5	6.0
UPSC	15	18.1
Mixed AC	9	10.8
2009 FIGO Stage		
I–II	18	21.7
IIIA	22	26.5
IIIC1	25	30.1
IIIC2	18	21.7
1988 FIGO stage		
IIIA	40	48.2
IIIC	43	51.8
Node Status		
Negative	40	48.2
Positive	43	51.8
<i>Pelvic only</i>	25	30.1
<i>Para-aortic only</i>	7	8.4
<i>Pelvic and paraortic</i>	11	13.3
Peritoneal Cytology		
Negative	54	65.1
Positive	29	34.9
Myometrial Invasion		

Characteristic	Number	Percentage (%)
<50%	46	55.4
50% +	37	44.6
Endocervical Stromal Invasion		
No	59	71.1
Yes	23	27.7
not available	1	1.2
Lymphovascular Invasion		
No	39	47.0
Yes	44	53.0

Abbreviations: FIGO – International Federation of Obstetrics and Gynecology, mixed AC – mixed adenocarcinoma histology

Table 2

Univariate analysis for factors associated with DFS and OS.

All Patients		Disease Free Survival unadjusted		Overall Survival unadjusted	
Variable		HR (95% CI)	p value	HR (95% CI)	p value
Age					
70 + vs <70		2.58 (1.01–6.62)	0.06	4.08 (1.71–9.77)	0.0031 *
Histologic Group					
Type II vs Type I		6.40 (1.86–21.98)	0.0005 *	4.85 (1.63–14.43)	0.001 *
Node Status					
Positive vs Negative		3.78 (1.26–11.4)	0.009 *	3.09 (1.13–8.47)	0.02 *
Total Pelvic Lymph Nodes Sampled					
20+ vs <20		0.33 (0.12–0.91)	0.02 *	0.65 (0.27–1.55)	0.33
Myometrial Invasion					
50% + vs <50%		4.3 (1.54–11.90)	0.003 *	3.97 (1.54–10.25)	0.002 *
Endocervical Stromal Invasion					
Present vs absent		2.7 (1.09–6.65)	0.04 *	2.64 (1.12–6.23)	0.03 *
Lymphovascular Invasion					
Present vs absent		2.11 (0.80–5.55)	0.12	2.93 (1.07–8.01)	0.02 *

Abbreviations: HR - hazard ratio, CI – confidence interval.

* Statistically significant

Table 3

Multivariate analysis for DFS and OS

All patients		Disease Free Survival adjusted		Overall Survival adjusted	
Variable		HR (95% CI)	p value	HR (95% CI)	p value
Age					
(70+ vs < 70)		2.33 (0.88–6.16)	0.089	2.84 (1.17–6.87)	0.021 *
Histologic Group					
(Type II vs Type I)		5.91 (1.71–20.36)	0.005 *	4.11 (1.36–12.38)	0.012 *
Node Status					
(Positive vs. Negative)		3.37 (1.10–10.33)	0.033 *	2.96 (1.08–8.12)	0.035 *
Total Pelvic Lymph Nodes Sampled					
(20+ vs <20)		0.34 (0.12–0.998)	0.049 *	--	--

Abbreviations: HR - hazard ratio, CI – confidence interval.

* statistically significant. Total pelvic lymph nodes not included in final model for overall survival as was not significant on univariate analysis.

Table 4

Characteristics and locations of failures.

Histology	2009 FIGO stage	Extrauterine sites involved at diagnosis	Time to recurrence(mo)	Location of initial failure
Endometrioid, FIGO 2	IIIC1	PVN	19.9	PV, PA
Endometrioid, FIGO 2	IIIC2	PVN, PAN	14.1	PA
Endometrioid, FIGO 2	IIIC2	S, A, PVN, PAN, CYT	11.2	Distant
Endometrioid, FIGO 3	IIIC2	PVN, PAN	8.3	PV
Endometrioid, FIGO 3	IIIC2	S, A, PVN, PAN, CYT	34.6	Distant
Mixed AC	IIIC1	S, A, PVN	5.4	PV, PA
Mixed AC	IIIC1	PVN	27.8	Distant
Mixed AC	IIIC2	PAN	32.1	PA
Clear Cell	IIIA	A	4.0	PA
UPSC	IIIA	A, CYT	11.1	PV
UPSC	IIIA	A	16.9	Distant
UPSC	IIIA	A	14.9	Distant *
UPSC	IIIC1	A, PVN	8.2	PA
UPSC	IIIC1	S, A, PVN	4.8	PV, PA
UPSC	IIIC1	PVN	5.6	PV
UPSC	IIIC1	PVN, CYT	13.1	PA
UPSC	IIIC1	PVN	16.2	Distant, PV, PA
UPSC	IIIC2	PVN, PAN	11.5	PV, PA
UPSC	IIIC2	A, PVN, PAN	31.8	Distant

Abbreviations: Mixed AC- mixed adenocarcinoma histology, PVN – pelvic lymph nodes, PAN – paraaortic lymph nodes, S - serosa, A- adnexa, CYT – positive peritoneal cytology, PV – pelvic, PA- para-aortic.

* Patient developed vaginal apex recurrence 10 months after initial distant disease identified

Table 5

Rate and patterns of failure by site of initial 2009 FIGO stage and histology

	Pelvic only	Para-aortic only	Pelvic and para-aortic	Distant	Total ^(a)
2009 FIGO stage					
I–II	0	0	0	0	0/18 (0%)
IIIA	1 (4.5%)	1 (4.5%)	0	2 (9%)	4/22 (18%)
IIIC1	1 (4%)	3 (12%)	3* (12%)	2* (8%)	8/25 (32%)
IIIC2	1 (5.6%)	2 (11%)	1 (5.6%)	3 (16.7%)	7/18 (38.9%)
Histology					
Endometrioid, FIGO 1	0	0	0	0	0/17 (0%)
Endometrioid, FIGO 2	0	1 (4.2%)	1 (4.2%)	1 (4.2%)	3/24 (12.5%)
Endometrioid, FIGO 3	1 (7.7%)	0	0	1 (7.7%)	2/13 (15.4%)
Mixed AC	0	1 (11.1%)	1 (11.1%)	1 (11.1%)	3/9 (33.3%)
Clear Cell	0	1 (20%)	0	0	1/5 (20%)
UPSC	2 (13.3%)	2 (13.3%)	3* (20%)	4* (26.7%)	10/15 (66.7%)

Abbreviations: mixed AC – mixed adenocarcinoma histology.

^(a) number of patients with treatment failure divided by total number at risk