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Retrospective Analysis of Adjuvant Therapy in Intermediate and High Risk Endometrial Cancer Patients

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Abstract

Introduction: Endometrial cancer is the most common gynecologic malignancy in developed countries. The most significant prognostic factors are tumor stage, histological grade and type, depth of myometrial invasion, lympho-vascular space or nodal involvement. The optimal adjuvant therapy in high and intermediate risk endometrial cancer is still controversial. Aim of the work: Evaluating the impact of adjuvant chemotherapy in addition to radiotherapy on prognosis of high and intermediate risk endometrial cancer. Patients and methods: Forty six patients with high and intermediate risk endometrial cancer presenting to Kuwait Cancer Control Center (KCCC) underwent total abdominal hysterectomy, bilateral salpingo-ophorectomy, and 18 patients underwent lymphadenectomy (39.1%). All patients received adjuvant chemotherapy followed by adjuvant radiotherapy. According to GOG risk stratification, 28 patients (60.9%) were high risk, 6 (13%) high intermediate and 12 (26.1%) low intermediate. At the end of follow up period, 34.71% of patients relapsed, 21.71% locally and 13% systemic. Median PFS was 38.06 months(ms) (95% CI 36.94 - 39.18 ms). There was a statistically significant effect of lympho-vascular space invasion (LVSI), grade and near statistically significant effect of patients age on PFS (p = 0.01, 0.05, 0.06 respectively). Median OS for all patients was not reached; estimated survival at 3 years was 87.5%. There was no statistically significant effect of age, pathological subtype, grade, LVSI on survival (p = 0.35, 0.95, 0.53 and 0.09 respectively). On stratifying patients into high and intermediate risk based on GOG risk stratification, there was a statistically significant difference on PFS and near statistically significant difference on OS between those groups (p = 0.02 and 0.09 respectively). Conclusion: The most effective adjuvant treatment regimen for patients with intermediate and high risk endometrial cancer is still an area of controversy. Sequential chemotherapy and radiotherapy is

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both efficacious and well tolerated. Large-scale randomized controlled trials are necessary in the future.

Keywords

Endometrial Cancer, Adjuvant, High Risk, Intermediate Risk

1. Introduction

Endometrial Cancer (EC) is the most common gynecologic malignancy in developed countries [1]. The most important prognostic factors are tumor stage [2], histological grade and type, depth of myometrial invasion and LVSI or nodal involvement [3]. Women with a high risk EC, as stage I grade 3 with deep myometrial invasion, stages II and III are at high risk of both pelvic and distant recurrences and consequently death [4]-[8].

Uterine serous and clear cell carcinomas are more aggressive histologic types. This was demonstrated in a Surveillance, Epidemiology, and End Results study of cases diagnosed from 1998 to 2001. The five-year survival rate stratified by histologic type was 45, 65, and 91 percent for serous, clear cell, and endometrioid adenocarcinomas, respectively [8].

Patients with surgical and pathologic stage III endometrial cancer have a lower five-year survival rate (60 versus 97 and 80 percent for stage I and II, respectively) [3]. However, outcomes appear to differ based on grade. Among women with stage III disease, those with grade 1 adenocarcinoma have a higher five-year survival rate (83 versus 68 and 48 percent for women with grade 2 or 3 tumors, respectively).

Cooperative groups, like Gynecologic Oncology Group (GOG) include women with intermediate-risk EC in clinical trials of high-risk endometrial cancer based on three tumor-associated risk factors: grade 2 or 3 histology, outer-third myometrial invasion, or LVSI.

The combination of chemotherapy and postoperative radiotherapy has been actively used in the treatment of advanced endometrial cancer and it could probably slow the disease progression and improve the overall survival [9] [10]. However, there is still no clearly determined standard treatment modality

2. Patients and Methods

Data of 46 patients with high and intermediate risk EC according to GOG risk stratification [11] presenting to KCCC were retrospectively analyzed, all slides were reviewed by a dedicated experienced pathologist to confirm diagnosis and patients with synchronous ovarian cancer were excluded from this analysis. A written informed consent was approved by the Institutional Review board (IRB) ethical committee of the KCCC.

All patients underwent total abdominal hysterectomy and bilateral salping oophorectomy ± pelvic lymphadenectomy followed by adjuvant chemotherapy and radiotherapy.

Patients treated with EBRT (external beam radiotherapy) received 45 - 50.4 Greys (Gy) in 25 - 28 daily fractions of 1.8 Gy given in 5 - 5.5 weeks. Those who received vaginal vault brachytherapy as boost after EBRT for cervical involvement were treated with HDR (high dose radiotherapy) 5.5 Gy in 2 fractions at 0.5 cm from the surface of the applicator given at least a week apart.

Chemotherapy consisted of carboplatin area under curve (AUC5) and paclitaxel 175 mg/m^2 every 3 weeks for a total of six cycles. In case of adjuvant sequential chemoradiotherapy, according to our protocol, chemotherapy was administered for 6 cycles before radiotherapy.

After the surgery and adjuvant treatments, all patients were followed with symptom review, symptom-directed physical exam and pelvic examination every 3 months during the first two years, then every 6 months after. CT scan chest, abdomen and pelvis annually.

Statistical Methods

Data management and analysis was performed using SPSS, version 20. Categorical data were summarized as percentages; numerical data were summarized using means and standard deviation or medians and ranges. Overall survival (OS) was defined as the time from diagnosis to the time of death from any cause. Patients who

were alive on the date of last follow-up were censored on that date. Progression free survival (PFS) was defined as the time from starting therapy until documented progression or death. For patients without disease progression (DP) at the time of analysis, the date of last follow-up was considered right-censored. OS and PFS were estimated using the Kaplan-Meier analysis. Log rank test was used to compare survival curves. All tests of hypotheses were conducted at the alpha of 0.05 Level, with a 95% confidence interval.

3. Results

Forty six patients with high and intermediate risk endometrial cancer presenting to KCCC underwent surgery then received adjuvant chemotherapy followed by radiotherapy. Patient's demographic characters are shown in **Table 1** and **Table 2**.

Table 1. Patients characteristics.

Patients Characteristics	frequencies	
	n	%
Mean age	60.35	±1.79
Age groups		
<60	18	39.1%
≥60	28	60.9%
PS		
0	18	39.1%
1	26	56.5%
2	2	4.3%
Pathological subtype		
Endometrioid	24	52,2%
Serous	16	34.8%
Clear	4	8.7%
Others	3	4.3%
Grade		
I	2	4.3%
II	4	8.7%
III	40	87%
LV invasion		
Yes	24	52.2%
No	22	47.8%
Myometrial infiltration		
<50%	16	34.8%
≥50	30	65.2%
Stage at diagnosis		
I	8	17.4%
II	18	39.2%
III	16	34.8%
Iva	4	8.7%
Risk stratification		
High risk	28	60.9
High intermediate	6	13
Low intermediate	12	26.1

Table 2. Effect of risk factors on PFS* and OS*.

	PFS*	95% CI	P value	0S*	95% CI	p value
Age			0.06			0.35
<60	Not reached			Not reached		
≥60	37.77	34.20 - 41.34		43.81	43.76 - 43.87	
Pathological type			0.08			0.94
endometrioid	38.80			Not reached		
Serous and clear	37.77	31.72 - 43.82		43.78	23.28 - 64.29	
Pathological grade			0.05			0.53
I & II	Not reached			Not reached		
III	Not reached			45.13	42.53 - 47.73	
Myometrial infiltration			0.58			0.15
<50%	38.45	37.47 - 39.44		Not reached		
≥50	37.74	28.18 - 47.29		43.82	23.1 - 64.48	
lV infiltration			0.01			0.09
Present	37.74	34.37 - 41.11		43.81	43.75 - 43.88	
Absent	Not reached			Not reached		
Risk stratification			0.02			0.09
Intermediate risk	Not reached			Not reached		
High risk	37.74	34.37 - 41.11		43.82	43.75 - 43.88	
lymphadenectomy			0.35			0.69
done	38.06	34.14 - 41.98		43.78	23.22 - 64.34	
Not done	38	36.11 - 41.48		Not reached		

PFS: Progression free survival; OS: Overall survival.

According to GOG risk stratification; 28 patients (60.9%) were high risk, 6 (13%) high intermediate and 12 (26.1%) low intermediate. According to 2009 FIGO staging system, Stages I, II, III and IV are presented 17.4%, 39.2%, 34.8% and 8.7% of our patients respectively. 87% presented with grade 3 tumors. 65.2% had > 50% myometrial invasion. LVSI was found in 52.2% of cases. Endometrioid adenocarcinoma was reported in 52.2%, serous in 34.8% and clear in 8.7% of patients.

All patient underwent total abdominal hysterectomy, bilateral salpingo-ophorectomy, 18 patients underwent lymphadenectomy (39.1%). All patients received adjuvant chemotherapy followed by radiotherapy. Median number of chemotherapy cycles was 5.7 ± 0.19.

Median duration of follow up was 29 ms (range 5.2 - 77.8 ms). At the end of follow up period, 16 (34.71%) patients relapsed; 10 (21.71%) locally and 6 (13%) systemic. Median PFS was 38.06 ms (95% CI 36.94 - 39.18 ms). 71.4% were relapse free at 36 ms.

There was a statistically significant effect of LVSI and grade on PFS (p = 0.01, 0.05 respectively). No statistically significant differences in PFS as regard age, depth of myometrial infiltration, pathological type and whether the patient did lymphadenectomy or not (p = 0.06, 0.58, 0.08, 0.35 respectively) (**Table 2**).

Median overall survival (OS) for all patients was not reached; estimated survival at 3 years was 87.5%. There was no statistically significant effect of age, pathological subtype, grade, LVSI on OS (p = 0.35, 0.95, 0.53 and 0.09 respectively) (**Table 2**).

On stratifying patients into high and intermediate risk based on GOG risk stratification there was a statistically significant difference on PFS and near statistically significant difference on OS between those groups (p = 0.02 and 0.09 respectively) (**Figure 1** and **Figure 2**).

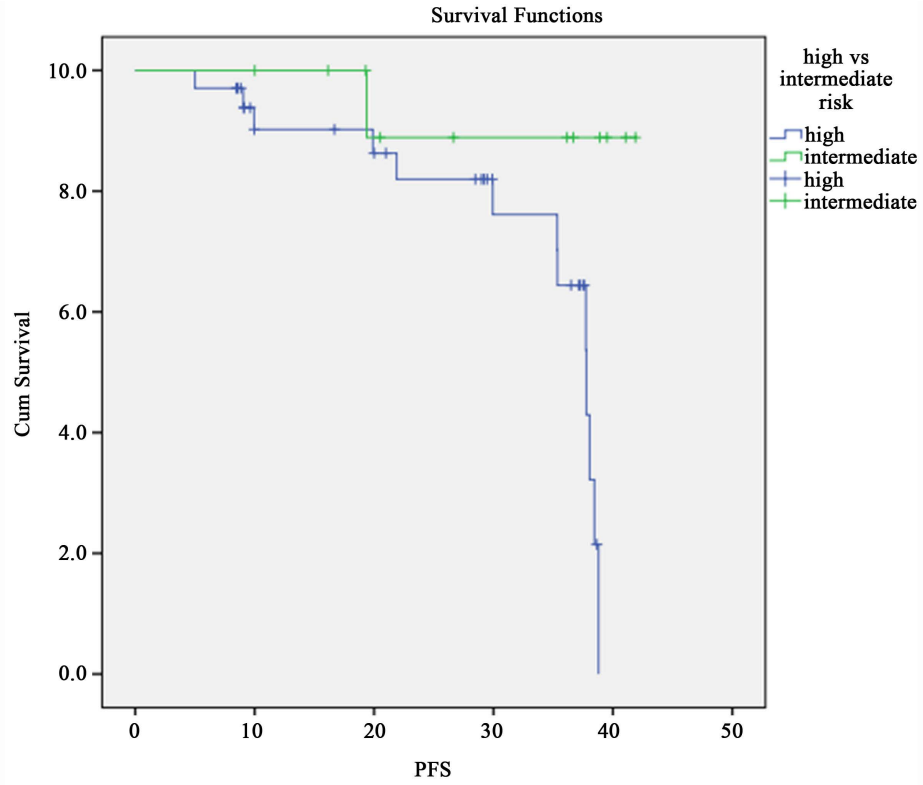

Figure 1. PFS for patient with high risk versus intermediate risk EC.

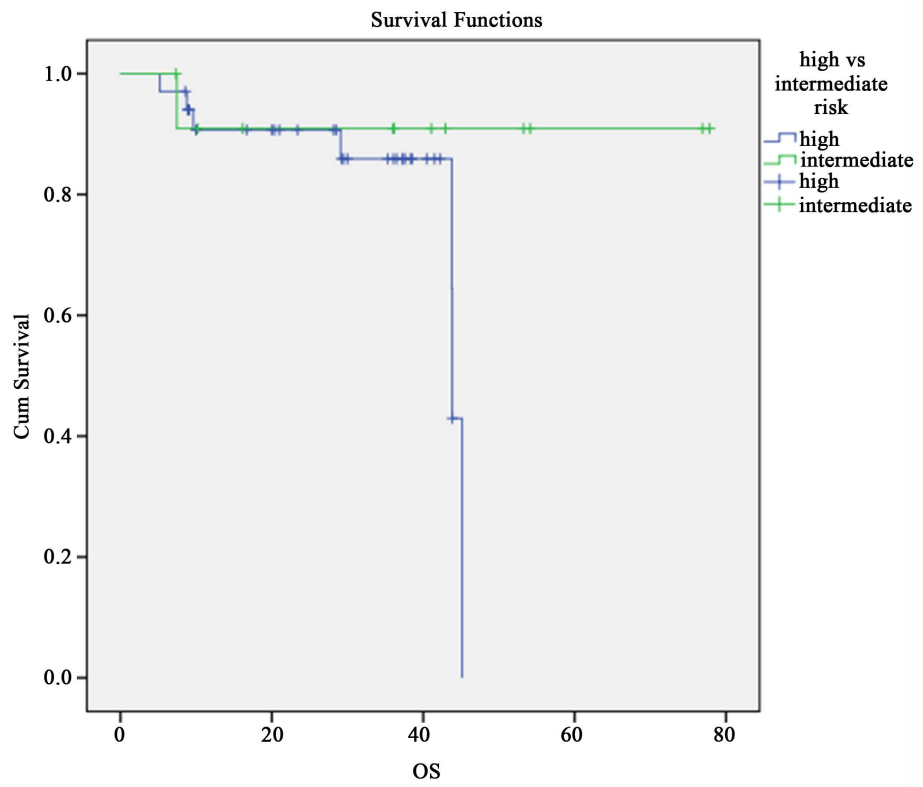

Figure 2. OS for patient with high risk versus intermediate risk EC.

4. Discussion

Our single institution retrospective analysis for outcome of patients with intermediate and high risk endometrial cancer receiving adjuvant chemotherapy followed by radiotherapy showed a 34.7% relapse rate; 21.7% pelvic and 13% systemic at a median follow up duration of 29 months. Median PFS was 38.06 ms (95% CI 36.94 - 39.18 ms). 71.4% were relapse free at 36 months. Median OS for all patients was not reached; estimated survival at 3 years was 87.5%.

Mauro *et al.* did a study on 254 women with stage IB grade 3, II and III EC (2009 FIGO staging). 42 (16.5%) of them received sequential chemoradiotherapy, out of which 7 patients relapsed (16.6%); he found that Sequential chemoradiotherapy improved both disease free survival (DFS) ($p = 0.015$) and OS ($p = 0.014$) in stage III, while only a trend was found for DFS ($p = 0.210$) and OS ($p = 0.102$) in stage I-II EC. In the multivariate analysis, only age (≤65 years) and sequential chemoradiotherapy were statistically related to the outcome [12].

Similar results were reported in the NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III clinical trial. The NSGO/EORTC-trial initially included patients with FIGO stage I disease, but later included stage II and III. The MaNGO-trial included patients with more advanced stage disease (FIGO stage II-III). Serous/clear cell carcinomas were included in the NSGO/EORTC-trial and excluded in ILIADE. An overall 16% relapse rate was described in the chemoradiotherapy arm, of which 2% pelvic and 13% distant, in the pooled data, there was a significant 45 % risk reduction when looking at cancer-specific survival [13].

In MSKCC data of patients with stage III (FIGO 2009) endometrial cancer who underwent total hysterectomy and bilateral salpingo-ophorectomy followed by adjuvant RT/cisplatin, then carboplatin/paclitaxel were retrospectively analyzed. The 5-year rate of recurrence was reported as 6% local and 25% distant metastases in stage III disease showing a very favorable 5-year DFS and OS of 79% and 85% [14].

The combined concomitant and sequential chemoradiotherapy was also evaluated by the phase II RTOG 9708 study. Seventeen stage I-II and 27 stage IIIA-C patients, were treated with EBRT with concomitant triweekly cisplatin, followed by 4 cycles of adjuvant cisplatin-paclitaxel based chemotherapy. At four years pelvic, regional and distant recurrence rate were 2%, 2%, and 19% respectively. OS and DFS of 85% and 81% at 4 years, respectively [15].

On comparing our relapse rates to other trials we found that our rate of distant relapse is comparable to or even less than other trials this may be attributed to the fact that our patients received 6 cycles of systemic chemotherapy (carboplatin/paclitaxel), however the local control in our patients series was less than that reported in other trials.

A supportive Cox analysis of the pooled material from the NSGO/EORTC and MaNGO showed that the treatment effect on PFS remained unaffected with age, stage, grade, pathological subtype, and lumphadenectomy no/yes as covariates. In our patient's series PFS was affected only by LVSI and grade.

Park *et al.* performed a meta-analysis in 2013 enrolled 6 articles suggested that the chemotherapy plus radiotherapy group had a more significant survival benefit compared to that of the radiotherapy group in advanced stage EC with the OS hazard ratios (HR) 0.53 and PFS HR 0.54 [11] The sandwich protocol has also been reported with favorable survival outcomes in several recent studies. Geller et al reported a 3-year PFS and OS of 80% and 88%, respectively, on patients with stage II-IV endometrial cancer [16]. In a retrospective analysis, Secord et al indicated that patients with stage III-IV who received the sandwich protocol had 3-year PFS (69%) and OS (91%) [17].

At 3 years 71.4% of our patients were relapse free and 87.5% were still surviving, data which is consistent with that reported by Geller *et al*. and Second *et al*., however these values were less than the values reported by MSKCC and the RTOG 9708.

Our study has limitations due to its retrospective nature and the small number of patients due to the small country population.

Two randomized trials are ongoing to clarify the role of combined-versus single-modality therapy. The PORTEC-3 trial is evaluating the role of concomitant chemo and radiotherapy followed by 4 cycles of carboplatin-paclitaxel with EBRT only, while the GOG 258 trial is comparing the same experimental treatment with 6 cycles of chemotherapy for stage III or IV.

5. Conclusion

In conclusion, until results of the ongoing randomized trials are available, sequential chemo and radiotherapy should be strongly considered for the treatment of this subset of patients.

References

[1] Seigel, R., Naishadham, D. and Jemal, A. (2013) Cancer Statistics. *CA*: *A Cancer Journal for Clinicians*, **63**, 11-30. http://dx.doi.org/10.3322/caac.21166

[2] Creasman, W. (2009) Revised FIGO Staging for Carcinoma of the Endometrium. *International Journal of Gynecology & Obstetrics*, **105**, 109. http://dx.doi.org/10.1016/j.ijgo.2009.02.010

[3] Guntupalli, S.R., Zighelboim, I., Kizer, N.T., Zhang, Q., Powell, M.A., Thaker, P.H., *et al.* (2012) Lymphovascular Space Invasion Is an Independent Risk Factor for Nodal Disease and Poor Outcomes in Endometrioid Endometrial Cancer. *Gynecologic Oncology*, **124**, 31-35. http://dx.doi.org/10.1016/j.ygyno.2011.09.017

[4] Creutzberg, C.L., van Putten, W.L., Warlam-Rodenhuis, C.C., van den Bergh, A.C., de Winter, K.A., Koper, P.C., *et al.* (2004) Outcome of High-Risk Stage IC, Grade 3, Compared with Stage I Endometrial Carcinoma Patients: The Postoperative Radiation Therapy in Endometrial Carcinoma Trial. *Journal of Clinical Oncology*, **22**, 1234-1241. http://dx.doi.org/10.1200/JCO.2004.08.159

[5] Long, K.C., Zhou, Q., Hensley, M.L., Alektiar, K.M., Gomez, J., Gardner, G.J., *et al.* (2012) Patterns of Recurrence in 1988 FIGO Stage IC Endometrioid Endometrial Cancer. *Gynecologic Oncology*, **125**, 99-102. http://dx.doi.org/10.1016/j.ygyno.2011.11.020

[6] Tewari, K.S., Filiaci, V.L., Spirtos, N.M., Mannel, R.S., Thigpen, J.T., Cibull, M.L., *et al.* (2012) Association of Number of Positive Nodes and Cervical Stroma Invasion with Outcome of Advanced Endometrial Cancer Treated with Chemotherapy or Whole Abdominal Irradiation: A Gynecologic Oncology Group Study. *Gynecologic Oncology*, **125**, 87-93. http://dx.doi.org/10.1016/j.ygyno.2011.12.414

[7] Hoekstra, A.V., Kim, R.J., Small Jr, W., Rademaker, A.W., Helenowski, I.B., Singh, D.K., *et al.* (2009) FIGO Stage IIIC Endometrial Carcinoma: Prognostic Factors and Outcomes. *Gynecologic Oncology*, **114**, 273-278. http://dx.doi.org/10.1016/j.ygyno.2009.04.013

[8] Bakkum-Gamez, J.N., Mariani, A., Dowdy, S.C., Weaver, A.L., McGree, M.E., Martin, J.R., *et al.* (2014) Efficacy of Contemporary Chemotherapy in Stage IIIC Endometrial Cancer: A Histologic Dichotomy. *Gynecologic Oncology*, **132**, 578-584. http://dx.doi.org/10.1016/j.ygyno.2014.01.007

[9] Kosary, C. (2007) Cancer of the Corpus Uteri. In SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. NCI, SEER Program, National Cancer Institute; Bethesda, MD.

[10] Bruzzone, M., Miglietta, L., Franzone, P., *et al.* (2004) Combined Treatment with Chemotherapy and Radiotherapy in High-Risk FIGO Stage III-IV Endometrial Cancer Patients. *Gynecologic Oncology*, **93**, 345-352. http://dx.doi.org/10.1016/j.ygyno.2004.02.008

[11] Park, H.J., Nam, E.J., Kim, S., *et al.* (2013) The Benefit of Adjuvant Chemotherapy Combined with Postoperative Radiotherapy for Endometrial Cancer: A Meta-Analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **170**, 39-44. http://dx.doi.org/10.1016/j.ejogrb.2013.06.009

[12] Keys, H.M., Roberts, J.A., Brunetto, V.L., *et al.* (2004) A Phase III Trial of Surgery with or without Adjunctive External Pelvic Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma: A Gynecologic Oncology Group Study. *Gynecologic Oncology*, **92**, 744. http://dx.doi.org/10.1016/j.ygyno.2003.11.048

[13] Signorelli, M., Lissoni, A.A., De Ponti, E., Grassi, T., Ponti, S. and Fruscio, R. (2015) Adjuvant Sequential Chemo and Radiotherapy Improves the Oncological Outcome in High Risk Endometrial Cancer. *Journal of Gynecologic Oncology*, **26**, 284-292. http://dx.doi.org/10.3802/jgo.2015.26.4.284

[14] Hogberg, T., Signorelli, M., de Oliveira, C.F., Fossati, R., Lissoni, A.A., Sorbe, B., *et al.* (2010) Sequential Adjuvant Chemotherapy and Radiotherapy in Endometrial Cancer: Results from Two Randomised Studies. *European Journal of Cancer*, **46**, 2422-2431. http://dx.doi.org/10.1016/j.ejca.2010.06.002

[15] Milgrom, S.A., Kollmeier, M.A., Abu-Rustum, N.R., Tew, W.P., Sonoda, Y., Barakat, R.R., *et al.* (2013) Postoperative External Beam Radiation Therapy and Concurrent Cisplatin Followed by Carboplatin/Paclitaxel for Stage III (FIGO 2009) Endometrial Cancer. *Gynecologic Oncology*, **130**, 436-440. http://dx.doi.org/10.1016/j.ygyno.2013.06.024

[16] Greven, K., Winter, K., Underhill, K., Fontenesci, J., Cooper, J. and Burke, T. (2006) Final Analysis of RTOG 9708: Adjuvant Postoperative Irradiation Combined with Cisplatin/Paclitaxel Chemotherapy Following Surgery for Patients with High-Risk Endometrial Cancer. *Gynecologic Oncology*, **103**, 155-159. http://dx.doi.org/10.1016/j.ygyno.2006.02.007

[17] Geller, M.A., Ivy, J., Dusenbery, K.E., *et al.* (2010) A Single Institution Experience Using Sequential Multi-Modality Adjuvant Chemotherapy and Radiation in the "Sandwich" Method for High Risk Endometrial Carcinoma. *Gynecologic Oncology*, **118**, 19-23. http://dx.doi.org/10.1016/j.ygyno.2009.11.025

[18] Alvarez Secord, A., Havrilesky, L.J., Bae-Jump, V., *et al.* (2007) The Role of Multi-Modality Adjuvant Chemotherapy and Radiation in Women with Advanced Stage Endometrial Cancer. *Gynecologic Oncology*, **107**, 285-291. http://dx.doi.org/10.1016/j.ygyno.2007.06.014