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PHASE II TRIAL OF VAGINAL CUFF BRACHYTHERAPY FOLLOWED BY ADJUVANT CHEMOTHERAPY WITH CARBOPLATIN AND DOSE DENSE (Dd) PACLITAXEL IN PATIENTS WITH HIGH-RISK ENDOMETRIAL CANCER

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SCHEMA

Clinical Stage I-II endometrial cancer
Surgery

↓

Stage I endometrioid with 3 high-intermediate risk (H-IR) features
OR
Stage II any histology
OR
Stage I-II Serous or Clear Cell

↓

Vaginal cuff brachytherapy

↓

Followed by
Carboplatin (AUC 6) on day 1and Paclitaxel
80 mg/m2 IV over 1 hour days 1, 8, and 15
X 3 total cycles

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1.0 OBJECTIVES

1.1 Primary objectives

1.11 To determine the *feasibility* of treatment in patients with high risk endometrial cancer treated by vaginal cuff brachytherapy followed by 3 cycles of dose dense paclitaxel and carboplatin chemotherapy.

1.2 Secondary objectives

1.2.1 To determine the *toxicity* of vaginal cuff brachytherapy followed by carboplatin and dose dense paclitaxel chemotherapy.

1.2.2 To describe *sites of failure*.

1.2.3 To determine recurrence-free survival for patients treated with the proposed study

1.2.4 To determine the contributing cause of death for patients with high risk endometrial cancer

1.2.5 To determine overall survival

2.0 BACKGROUND AND RATIONALE

At the State of the Science in Endometrial Cancer Meeting in Manchester, England (Nov 2006), sponsored by the NCI, an international group of investigators was charged with defining what would be considered standard therapies and potential investigational therapies that could be explored in the management of early stage endometrial cancer with high risk features for recurrence. Because of that meeting, a randomized phase III trial, GOG #249 was developed and conducted comparing pelvic radiation therapy versus vaginal cuff brachytherapy (VCB) followed by 3 cycles paclitaxel/carboplatin (q 21 day, standard dosing) chemotherapy. The population evaluated included a broad group of "high-intermediate risk" patients based on prior experience with GOG #99 and PORTEC1. The initial results of GOG #249 have suggested that VCB + chemotherapy (VCB/C) is not superior to pelvic radiation alone[1]. In addition, the study also helped to further define subpopulations at risk for recurrence.

The GOG #99 previously compared pelvic radiation therapy (PXRT) to observation in a group of intermediate risk, stage I-II patients with endometrial cancer with pathologic negative lymph nodes.[2] A multi-institutional Dutch group evaluated the same two treatments in a group of intermediate risk (defined by tumor grade and depth of myometrial invasion) stage I-II patients who had not undergone a lymphadenectomy (PORTEC trial).[3] In both studies, PXRT reduced recurrences (principally by reducing pelvic failures), but did not statistically improve survival. One hypothesis generated from GOG #99 was that a higher intermediate risk (H-IR) patient population could be identified which accounted for 2/3 of the recurrences, and for whom PXRT should be considered. Similarly, PORTEC trial suggested that older patients and those with grade 3 tumors accounted for the highest risk of recurrence. Many have suggested that the patient populations in general enrolled in GOG #99 and PORTEC were at too low of a risk to demonstrate improved survival with radiation. For example, in GOG #99 only 1/3 of patients enrolled had H-IR features. Additionally, intercurrent deaths on both arms had an impact on the ability to detect differences in survival.

GOG #249 demonstrated no difference between PXRT and VCB/C in a 600 patient randomized controlled trial. There was no difference in recurrence free survival (RFS) (82% vs. 84%) or overall survival (OS) (93% vs 92%) at the 24 month interval. There was however a change in the patterns of failure. Those receiving PXRT had excellent local control, with ~2.5% pelvic failure rate and nearly 11% distant failure rate, while the VCB/C arm had a ~7.5% pelvic failure rate and only 8% had distant failure. There were similar rates of non-hematologic toxicities, while the VCB/C as expected had significantly more grade 3/4 hematologic toxicity. There were no treatment related deaths in either arm and completion of either regimen was high VCB/C-87% and PXRT 91%. Another important finding of GOG #249 was that most patients in this enriched population were at low risk for recurrence. Only those of with serous or clear cell carcinoma, stage II, or patients of any age with all 3 risk factors had a >15% chance of recurrence. In this population, neither therapy was effective in decreasing recurrences, suggesting this is a population who would benefit from a new strategy.

Several studies have looked at the potential benefit of weekly dose dense paclitaxel compared to q21 day infusions with promising results. GOG protocol #262 and #252 are both evaluating a Dd regimen in patients with ovarian cancer and a Dd regimen was demonstrated to be feasible in a cohort of patients with advanced endometrial cancer.[4] Similar studies on ovarian cancer have shown controversial results. Katsumata et al. reported that dose-dense treatment of paclitaxel plus carboplatin offers better survival than conventional treatment and is a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer[5]. A large phase 3 randomized trial reported that patients randomized to the weekly group had less frequency of grade 3-4 neutropenia, febrile neutropenia and thrombocytopenia when compared to those allocated paclitaxel plus carboplatin every 3 weeks[6]. A recent report showed that patients treated with weekly paclitaxel had a higher rate of grade 3 or 4 anemia and grade 2 to 4 sensory neuropathy but a lower rate of grade 3 or 4 neutropenia than did those treated with paclitaxel every 3 weeks[7].

This phase II trial attempts to build on evolving knowledge related to manipulations of paclitaxel/carboplatin backbone. Using a dose dense (Dd) strategy, we propose to conduct a pilot trial to evaluate the feasibility of carboplatin + Dd paclitaxel in this population of patients in an effort to understand ability to successfully complete the regimen, identify toxicity, and finally, assess efficacy. A piloted regimen which demonstrated feasibility could be advanced as an experimental arm into a larger cooperative group based clinical trial.

A high risk population of early stage endometrial cancer patients exists: Despite the ability for surgical staging to define a low risk patient population for most patients with negative pelvic and para-aortic lymph nodes, certain subgroups of patients with stage I-II endometrial cancer have been shown to have a higher risk of recurrence. These patients may benefit from some form of post-operative adjuvant therapy. For example, in GOG #99 a subgroup of patients with "high-intermediate risk" (H-IR) could be defined which accounted for 66% of recurrences and cancer-related deaths. Risk criteria included grade 2-3 tumors, presence of lymphovascular space involvement (LVSI), and outer 1/3 myometrial invasion.[2] Patients were classified as H-IR if they were at least 70 years with any one factor, at least 50 years with any 2 factors, or any age with all 3 factors. The cumulative risk of recurrence without therapy at 48 months was 27% for this group. Similarly, the PORTEC trial suggested that patients 60 years and older and those with grade 3 lesions had a higher hazard ratio for cancer related death (HR 3.1, p=0.02, HR 4.9, p= 0.0008, respectively).[8] Patients with early staged uterine papillary serous (UPSC) or clear cell (CC) tumors also appear to have an elevated risk for recurrence.[9] Huh reported on 60 patients with Stage I PS tumors who underwent complete surgical staging. Of the 40 patients who did not receive adjuvant therapy, the 5-yr disease-free survival rate was 66%.[10] In GOG #94, for stage I-II patients treated with whole abdominal radiation therapy (WART), 5-yr PFS was 38% for UPSC patients, and 54% for CC patients.[11] Creasman reported on data from FIGO that for stage I patients, 5-year survival (for surgery alone) was comparable between UPSC/CC (66%/77%) and grade 3 tumors (68%).[12] Given the comparable outcomes between the patient

populations, patients with high risk endometrioid tumors will be combined with patients with UPSC/CC tumors.

Unstaged patients may be included into high-risk, early stage models: In an effort to foster enrollment in clinical trials, the GOG has been charged by the Gynecologic Cancer Steering Committee reviewers to broaden eligibility in endometrial cancer clinical trials. The GOG has traditionally required comprehensive surgical staging for eligibility. Since gynecologic oncologists treat less than 1/3 of endometrial cancer patients, and most patients with endometrial cancer do not undergo complete surgical staging with assessment of pelvic and para-aortic nodes, a large pool of unstaged patients with H-IR features may exist, and who could be considered eligible for enrollment. The PORTEC trial, including a patient population considered to have low risk of nodal disease, found that in patients without nodal dissection, PXRT improved local control but did not impact survival. Many now consider patients with grade 1-2 tumors with < 50% invasion (and undissected nodes) to be at sufficiently low risk that routine adjuvant therapy is not recommended.[13] Unstaged patients with grade 3 tumors or > 50% invasion are typically perceived to be at higher risk for recurrence, and are commonly offered PXRT to treat potential unrecognized nodal disease. For example, a review of the SEER data from a group of 21,249 patients with stage IA-IC endometrial cancer, of which only 43% had some form of nodal sampling, showed that 43% of patients with grade 3 tumors and 57% of stage IC patients received some form of post-operative radiation therapy.[14] The potential for extrauterine disease spread is not insignificant in this patient population. For example, the GOG (GOG #33) found that 18% of grade 3 tumors and 25% of tumors with invasion into the outer 1/3 myometrium had pelvic nodal metastases.[15] Clinically, the outcomes of unstaged patients with high risk factors have been reported in a subset analysis of patients registered and followed (but not eligible) within the PORTEC trial. Ninety-nine patients with stage IC, grade 3 endometrial cancers were treated with PXRT, and followed. Data showed local-regional failures occurred in 14% of patients (compared to 1-3% who were enrolled in the PORTEC trial), and distant failures occurred in 31% (compared to 3-8% who were enrolled in the PORTEC trial). While PXRT appears to improve local control in these cases (compared to no therapy), distant failures remain frequent and the authors concluded, “novel strategies for adjuvant therapy should be explored”. More recently, results of a randomized trial (ASTEC) comparing surgical to clinical evaluation of nodal status have suggested a limited value of routine pelvic lymphadenectomy, particularly when patients receive post-operative PXRT regardless of node status (pathologically vs. clinically negative).[16]

Hendrickson first reported the histologic criteria distinguishing UPSC from endometrioid variants in 1982.[17] Since this time several investigators have reported their experiences with UPSC and demonstrated that this histologic type behaves differently than the more common endometrioid adenocarcinoma.[18,19] Subsequent studies have classified CC tumors into a more aggressive subgroup as well.[12] These two histologic variants are associated with a higher frequency of extrauterine disease spread, different patterns of failure, and poorer survival versus endometrioid types in most series.[9,12,20] Both early staged and advanced

disease states appear to behave aggressively. In GOG #249 the UPSC/CC cohort accounted for 30% of the total PFS events with 22% of patients having an event. While patients with all 3 risk factors accounted for nearly half of the recurrence events in the study, with 18% (18/98) patients having an event.

For patients with early stage disease, considerable controversy exists as to the optimal management of UPSC and CC tumors. A variety of treatments have been proposed for high-risk histologies. Patients with surgically staged Stage I UPSC/CC have been treated with no further therapy, WART, PXRT, radiation (pelvic or vaginal cuff) followed by chemotherapy, and chemotherapy alone. Retrospective studies have been inconsistent in reporting both high and low rates of recurrences in patients receiving no or a variety of adjuvant therapies. GOG #94 was a phase II study of patients with high risk endometrial cancers (Stage I-IV) treated by WART. Data from the subgroup of 49 patients with Stage I-II UPSC/CC tumors, reporting on one of the largest surgically staged series of Stage I-II UPSC/CC patients, showed five- year disease-free survival (DFS) was only 35 %.[11] By comparison, Stage I patients with endometrioid histologies in GOG #99, had two-year DFS between 86-92%, depending on the use of PXRT.[9] Data from the annual FIGO report for Stage I uterine cancers (based on 148 UPSC, 59 CC tumors) for five-year DFS is shown below:

Stage	UPSC	CC
Ia	74%	83%
Ib	74%	67%
Ic	46%	64%

Relatively few series reported in the literature have specifically evaluated surgically staged patients with UPSC/CC tumors. Most series describing patterns of failure or survival have come from groups of patients with and without complete staging procedures. Goff and colleagues demonstrated that when patients with UPSC cancers were surgically staged, 72% were found to have extrauterine disease at laparotomy.[19] GOG #33 demonstrated that para-aortic nodal disease was more common in patients with UPSC/CC tumors. The inclusion of unstaged patients into series of "early staged" UPSC patients reported in the literature has made it difficult to assess patterns of failure and determine appropriate therapies. In an effort to study a defined relatively homogenous patient population, all patients in this study must have complete surgical staging.

The patterns of failure for Stage I-II UPSC/CC patients following whole abdominal radiation were described in GOG #94.[11] The majority of failures occurred within the abdomen and pelvis, but distant failures were not uncommon. These findings indicate that radiation therapy alone has a limited role in the management of UPSC/CC. It is unclear to what extent complete surgical staging can define patterns of failure for Stage I-II patients. For patients with early staged endometrioid histologies, GOG #99 and the PORTEC trial showed that pelvic failure was the most common site, and could be reduced by the addition of pelvic radiation therapy. In the PORTEC study, pelvic radiation therapy led to a significant reduction in locoregional failures (4% vs 14%), but without improvement in overall survival.[2,13] Radiation therapy seemed to impact vaginal recurrence risk more than pelvic

recurrence. The authors speculated that vaginal cuff brachytherapy might have controlled 30/40 locoregional recurrences. In GOG #99, surgically staged patients with myometrial invasion were randomized to PXRT or no further therapy (NFT).This study found that PXRT significantly reduced pelvic failures. It was interesting to note however, that in the NFT group, 16/42 (38%) of failures were vaginal alone raising the suspicion that VCB may be a reasonable alternative. It remains to be seen whether similar patterns of failure would also be seen in patients with UPSC/CC tumors. As the data seem to suggest that post operative PXRT is most effective in controlling vaginal failures, it is hypothesized that VCB could do the same and with less morbidity. Data from GOG #99 and PORTEC1 are shown below:

STUDY	GOG #99 (NFT vs XRT)	PORTEC (NFT vs XRT)
Site of Failure		
Vagina	7.4% vs 1.6%	10.2% vs 2.3 %
Pelvis	4.0% vs 0.5%	3.4% vs 2.0 %
Distant	5.5% vs 4.0%	7.0% vs 7.9%

Adjuvant treatment modalities should be based on risk and patterns of failure. Without adjuvant therapies, patterns of failure for surgically stage I endometrioid uterine cancers are predominantly in the vaginal cuff and at distant sites. Therapies, which address both local and systemic disease, may have the best chance to improve outcomes. In GOG #99, of 202 patients who received no adjuvant therapy, recurrences were in the vaginal cuff (6.4%), pelvis (2.4%), and at distant sites (6.4%). Both the PORTEC and GOG #99 trials suggested that the primary benefit of PXRT is in its ability to reduce vaginal cuff failures. Indeed the conclusions of both studies suggested that similar reductions in risk might be obtained by substituting VCB for PXRT. The tolerability and lower toxicity compared to PXRT or WART is also desirable. Several studies have shown efficacy of VCB. Pearcey reviewed 1800 cases with low-intermediate risk endometrial cancer treated with high dose VCB and reported a 99.3% vaginal control rate.[21] Patients with higher risk stage I disease have also been treated with VCB. Chadha reported on 124 surgically staged patients with stage Ib/Grade 3, Ic, and occult II endometrial cancer and found no vaginal failures, and 3 extra-pelvic failures (two abdomen, one abdomen + lung).[13] No grade 3-4 bowel toxicity was reported, and two patients developed complete vaginal stenosis. Ng reported on 77 patients with Ib/Grade 3 and Ic patients treated by surgical staging and post-operative VCB. Median follow-up was 37 months and 11 patients (14%) have recurred including three distant failures.[22]

While it is clear that these tumors are at an increased risk, no definite standard of care exists by which to manage them. It has been suggested that UPSC/CC tumors more closely resemble ovarian cancers than endometrial cancers. The high rates of intra-abdominal

disease spread and intra-abdominal failures reported support this concept, and have lead to the use of ovarian cancer-based chemotherapy regimens or WART as a treatment. It is interesting to note that regardless of the chemotherapy used, most regimens selected mirrored what was considered standard for ovarian cancer at that time. As more effective chemotherapeutic agents have been identified in endometrial cancer, combination regimens have demonstrated improved responses, and at least in populations with advanced disease, chemotherapy has shown superiority to radiation alone (GOG #122), chemotherapy as a front line treatment in endometrial cancer is supported.[23]

Role of Chemotherapy

The GOG and others have studied a variety of endometrial cancer patient populations in clinical trials utilizing chemotherapy. In GOG #34, surgically staged patients with high- risk factors (defined by positive adnexa, nodes, cervical extension or >50% myometrial invasion) were randomized to PXRT with or without post radiation adriamycin.[24] The study found no difference in DFS or overall survival with the addition of adriamycin. The study evaluated a small group of patients with Stages I-III disease and lacked power to detect the magnitude of difference which was proposed. Chemotherapy alone in the management of early staged endometrial cancer has been evaluated. Burke reported on the 62 patients with high-risk endometrial cancer (21% with UPSC or CC histologies), including 33 patients with Stage I-IIa disease treated with cisplatin, adriamycin, and cyclophosphamide following surgical staging.[25] Three-year survival was 82% in patients without extrauterine disease. Levenback described 20 patients with UPSC, including 11 clinical stage I patients, treated with PAC chemotherapy and reported a 5 yr survival of 23%.[26] Paclitaxel has demonstrated significant activity in endometrial cancer patients with advanced or recurrent disease in two GOG phase II studies (GOG #86-O, #129- C).[27,28] Its combination with cisplatin and adriamycin was studied in GOG #177, and is now being evaluated sequentially with radiation in GOG#184, and is being compared to paclitaxel/carboplatin in GOG#209.[29]

Paclitaxel has demonstrated activity in UPSC tumors as reported by Ramondetta and colleagues from the M.D. Anderson Cancer Center. They reported a 77% objective response rate in a small series of patients with advanced disease.[30] Hoskins reported experience using paclitaxel and carboplatin with and without radiation in 63 patients with advanced and recurrent endometrial cancer. In a subgroup of 15 patients with advanced UPSC tumors, the response rate was 60%, and 2/4 patients with recurrent disease responded to the regimen.[31] Carboplatin has demonstrated comparable activity to cisplatin in most gynecologic malignancies, including endometrial cancer. Substituting carboplatin for cisplatin appears to reduce toxicity and increase ease of administration.

Recently, the Japan Gynecologic Oncology Group (JGOG) presented results of a phase III trial comparing whole pelvic irradiation to cyclophosphamide-doxorubicin-CDDP (CAP) chemotherapy in women with endometrial carcinoma with deeper than 50% myometrial

invasion.[32] Of 385 eligible patients, 75% had surgical stage IC-IIB disease. There were no statistically significant differences in PFS and OS between the 2 regimens. For all patients treated with CAP, only 3.7% recurred in the vaginal cuff. For stage IC patients, 5 yr survival was 89% in both treatment groups. The investigators suggested that adjuvant cisplatin-based combined chemotherapy might have potential as an alternative to radiotherapy for intermediate risk endometrial cancer. Aoki evaluated 34 patients with stage I-II endometrial cancer who had 2 or more risk factors (grade 3, outer ½ DOI, LVSI, and cervix involvement).[32] Of 26 patients treated with 3 cycles of CAP, 5 yr PFS and OS were 86% and 95% respectively. Of the 8 other patients treated by surgery alone, 5 yr PFS was 50%. By combining therapies (VCB/C), it is hoped to improve both local and distant control.

Study	Arms	PFS Events	OS Events
Maggi 2006	Chemo PXRT	66 59	59 59
Susumu 2008	Chemo PXRT	30 33	22 26
GOG 249	VCB/C PXRT	43 44	23 18
Totals	**Chemo** **PXRT**	**139/666= 20.8%** **136/660= 20.1%**	**104/666= 15.6%** **103/660= 15.5%**

Japanese GOG presented their randomized controlled trial (JGOG 3016) at ASCO 2008, #550621 comparing paclitaxel 180 mg/m2 over 3 hours IV and carboplatin AUC 6 IV with weekly paclitaxel 80 mg/m2 days 1, 8, and 15 and carboplatin AUC 6 in ovarian cancer patients stages II-IV. The PFS was 17.2 months for the three week schedule and 28 months for the weekly schedule (p=0.0015 HR=0.714 [0.58) 1-0.879]). The two-year overall survival is 77.7% for the three-week schedule and 83.6% for the weekly schedule p=0.496 HR=0.735 [0.540-1.0]). This data is encouraging for the weekly regimen, but there was only a 56% objective response in patients with measurable disease, only 47% completed 6 cycles, and 68 patients went off study for hematologic toxicity. The hematologic toxicity includes 44% grade 3-4 thrombocytopenia, and 9% febrile neutropenia. There were 48% of dose dense participants who had at least one dose reduction and 76% who had at least one cycle

delay. Carboplatin dose was reduced for hematologic toxicity and paclitaxel dose was reduced only for neurotoxicity or abnormal liver functions.

There is considerable support for weekly paclitaxel over the three-week schedule in the breast cancer literature. Sparano reported on the superiority of weekly paclitaxel for node positive or high risk node negative breast cancer patients with a HR=1.32 (p=0.01) when compared to every three week paclitaxel.[33] CALGB23 protocol 9840 also demonstrated an advantage for weekly paclitaxel with response rate of 42% compared to 29% for the every three week schedule in breast cancer patients with metastatic disease. Neuropathy was more common in the weekly schedule (24% vs 12%).

GOG #99 showed pelvic radiation was effective at reducing vaginal failures, with distant failures occurring in ~6% of patients. Radiation therapy as a single modality is thought to be less effective in a population enriched for risk for distant failure including only H-IR patients, those with stage II disease, or those with UPSC/CC histologies. For this reason chemotherapy is combined with radiation. The results of GOG #150, which included patients with Stage I-IV carcinosarcoma of the uterus, demonstrated better outcomes with 3 cycles of chemotherapy versus WART suggesting that an abbreviated course of chemotherapy may be adequate.[34] Similarly, the median number of chemotherapy cycles used in the JGOG study was 3.[35] Maggi et al reported no differences in survival of patients with high-risk endometrial carcinoma who were randomized to receive either pelvic radiation or 5 cycles of chemotherapy.[36] Given the added expense, toxicity, and time to complete therapies with 6 versus 3 cycles of therapy, the costs of extending the duration of chemotherapy to 6 cycles is balanced if 6 cycles results in superior RFS. If the risk of recurrence is not reduced by >/= 40% with the use of 6 versus 3 cycles of therapy, then the value of additional chemotherapy will be judged to be not clinically relevant. This level of risk reduction is well within limits previously tested by the GOG.

A phase II study evaluating surgically staged, stage I-II UPSC/CC and stage I-II endometrial carcinoma with high-intermediate features treated by VCB followed by three cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 6) was performed. This regimen was well tolerated with 19/23 patients completing all prescribed therapy and 91% progression free at 24 months.[37] This led to GOG protocol #249 which randomized patients to VCB/C or PXRT in protocol. A total of 601 pts were accrued; PXRT was assigned to 301 (18 did not receive study treatment) and VCB/C to 300 (9 did not receive study treatment). The median age was 63 years, 74% had stage I disease, and 89% underwent lymphadenectomy. Histology included 71% with endometrioid type, 15% UPSC, and 5% CC. Nearly all pts completed the prescribed therapy (91% PXRT, 87% VCB/C). Acute toxicity was more common with VCB/C. Recurrence sites totaled to 5 vs 3 vaginal, 2 vs 19 pelvic, and 32 vs 24 distant failures with PXRT vs VCB/C. With a median follow-up of 24 months, the 24 month RFS was 82% vs 84% for PXRT and VCB/C and treatment hazard ratio was 0.97 (95% CI 0.635-1.43) (VCB/C relative to PXRT). The 24 month survival was 93% vs 92% for PXRT and VCB/C and treatment hazard ratio was1.28 (95% CI 0.689- 2.36) (VCB/C relative to PXRT).

There was no statistically significant treatment effect heterogeneity with respect to RFS among clinical- pathologic variables evaluated. Of interest, the group receiving VCB/C had more pelvic recurrences 19 vs 2, fewer distant failures 24 vs 32, while vaginal control was excellent for both 5 vs 3. GOG #249 also allowed further discrimination of patients at risk for recurrence, patients having grade 3 tumors or patients with outer half invasion, >70yo, and LVSI were at highest risk for recurrence.[34] Recently, weekly paclitaxel in combination with tri-weekly carboplatin has demonstrated acceptable toxicity in patients with endometrial cancer, and is being evaluated in the phase III setting for ovarian cancer in GOG 252 and 262[32]. Combining a dose dense paclitaxel regimen with VCB presents an ideal combination for achieving distant control while maintaining excellent vaginal control.

2.1 Inclusion of Women and Minorities

The Stephenson Cancer center will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire endometrial cancer population treated.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Inclusion Criteria

3.11 All patients must have undergone hysterectomy. Bilateral salpingooophorectomy is stronglyencouraged but not mandatory.

3.12 Pelvic and para-aortic lymphadenectomy are optional, but strongly encouraged. Peritoneal washing are optional.

The hysterectomy may be performed as per the surgeon's preference including vaginally, laparoscopically, robotic, or open. A specific number of lymph nodes removed will not be utilized for eligibility, but the operative report should reflect that the procedure performed was consistent with the procedures described in the GOG Surgical Manual.

3.13 If either a bilateral salpingo-oophorectomy or nodal dissection was not performed, post-operative pre-treatment CT/MRI is required and must not demonstrate evidence suggestive of metastatic disease (adnexa, nodes, intraperitoneal disease). Post-operative, pre-treatment CT/MRI must be performed if a pelvic and para-aortic nodal dissection was not performed.

3.14 All patients will be staged according to the FIGO 2009 staging system and with endometrial carcinoma (endometrioid types) confined to the corpus uteri or with endocervical glandular involvement fitting one of the following high-intermediate risk factor categories:

- age ≥18 years with 3 risk factors
- Risk factors:

a) Grade 2 or 3 tumor, (+) lymphovascular space invasion, outer ½ myometrial invasion. Patients with these risk criteria may be enrolled with either positive or negative cytology.

b) Patients with Stage II endometrial carcinoma (any histology) with cervical stromal invasion (occult or gross involvement), with or without high- intermediate risk factors.

c) Patients with serous or clear cell histology (with or without other high- intermediate risk factors) are eligible provided the disease is uterine- confined (with or without cervical stromal invasion or endocervical glandular involvement).

3.15 Patients must have GOG performance status 0, 1, or 2.

3.16 Patients must have adequate:

3.181 Bone Marrow Function:
Absolute neutrophil count (ANC) ≥ 1,500/mcl [equivalent to Common Toxicity Criteria (CTCAE v4.0) Grade 1]. Platelets ≥

100,000/mcl (CTCAE v4.0 Grade 0).

3.182 Renal Function:
Serum creatinine ≤ institutional upper limit normal (ULN), CTCAE v 4.0 Grade 0.
Note: If serum creatinine > ULN, a 24-hour creatinine clearance must be collected and must be >50 mL/min.

3.183 Hepatic Function:
Bilirubin ≤ 1.5 x ULN (CTCAE v4.0 Grade 0). SGOT and alkaline phosphatase ≤ 2.5 x ULN (CTCAE v4.0 Grade 0).

3.184 Neurologic Function: Neuropathy (sensory and motor) ≤CTCAE v4.0 Grade 1.

3.17 Patients who have met the pre-entry requirements specified in Section 7.0; testing values/results must meet eligibility criteria specified in Section 3.1.

3.18 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.2 Exclusion Criteria:

Patients who meet any of the following criteria will not be eligible for this study:

3.21 Patients with recurrent disease.

3.22 Patients with GOG performance status of 3 or 4

3.23 Greater than 12 weeks elapsed from surgery to enrollment

3.24 Patients have prior pelvic or abdominal radiation therapy

3.25 Known hypersensitivity to any component of study treatments that resulted in drug discontinuation

3.26 Significant intercurrent illness including, but not limited to, unstable angina pectoris, and cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements

3.27 Active pregnancy or lactation

3.28 Prior malignancy requiring treatment within the last 3 years

4.0 STUDY MODALITIES

4.1 Surgery

Surgical therapy is an entry criterion, and not part of the experimental design of the study (See Sections 3.11-3.12).

4.2 Vaginal cuff brachytherapy (VCB)

All patients will be assigned to VCB and chemotherapy; treatment will be delivered either by LDR or HDR brachytherapy. Treatment should commence within 12 weeks of the surgery/hysterectomy. Chemotherapy should start within 3 weeks of initiating brachytherapy.

4.21 Intravaginal brachytherapy should be delivered with a vaginal cylinder (HDR or LDR) or colpostats (LDR). Given the variation in practice patterns and prescription routines, the treating physician must choose one of the following:

A) HDR 6-7 Gy x 3 fractions, weekly, prescribed at a depth of 0.5 cm from the surface of the vagina. Dose optimization should be used in an effort to create reasonable homogeneity of dose at a depth of 5 mm from the surface of the applicator.

B) HDR 10-10.5 Gy, x 3 fractions, weekly, prescribed at the vaginal surface. Dose optimization should be used in an effort to create reasonable homogeneity of dose around the surface of the applicator.

C) HDR 6 Gy x 5 fractions, weekly, prescribed at the vaginal surface. Dose optimization should be used in an effort to create reasonable homogeneity of dose around the surface of the applicator.

D) LDR 6500-7000 cGy prescribed at the vaginal surface in 1-2 insertions at a dose rate of 40-100 cGy/hr.

4.22 The minimum vaginal length treated (length of the relevant isodose) is 3 cm. The entire vagina is not required to be treated.

4.23 Expected Radiation Toxicities: Acute toxicity (occurring </= 30 days from completion of radiation) and Chronic toxicity (occurring > 30 days from completion of radiation) will be graded by the CTCAE v4.0.

4.231 Expected short-term toxicities from brachytherapy include fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, vaginal mucosal and vulvar irritation, and rarely urinary tract infection.

4.232 Possible long-term side effects may include shortening of the vagina, vaginal fibrosis, vaginal vault necrosis dyspareunia, rectal ulceration, dysuria, hematuria, bowel obstruction, chronic malabsorption, and fistula formation between pelvic tissues.

Brachytherapy-related toxicities and time of onset will be recorded on data collection forms. Treatment delays and their reason must be documented.

4.24 Protocol Compliance: Minor violation includes a deviation of the intracavitary radiation dose of more than 15%, but less than 25%. A major deviation is defined as (1) a deviation of the intracavitary radiation dose of more than 25% from the protocol dose; (2) use of interstitial therapy, or brachytherapy applicators other than those specified by the protocol.

4.3 Chemotherapy:

4.31 Paclitaxel (Taxol®, NSC #673089)

4.311 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. It is also available in 100 and 300 mg vials.

4.312 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) to a final concentration of 0.3 to 1.2 mg/ml. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In- line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate

formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

4.313 Storage: The intact vials can be stored in a temperature range between 20° – 25° C (68 – 77° F), protected from light.

4.314 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable **at room temperature (25° C)** for 27 hours.

4.315 Supplier: Commercially available from Bristol-Myers Squibb Company as well as generic manufacturers.

4.316 Administration: Paclitaxel 80 mg/m2 IV over approximately 1 hour days 1, 8, and 15 of a 21 day cycle x 3 total cycles will be given to all patients. Paclitaxel will be administered prior to carboplatin on day 1 of the infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) that are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. See section 5.46.

4.317 Adverse Effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)
Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, injection-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin, alkaline phosphatase and triglycerides, hepatic failure, hepatic necrosis

Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, headaches
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata
*See FDA- approved package insert for a comprehensive list of adverse events associated with paclitaxel.

4.32 Carboplatin (Paraplatin®, NSC # 241240)

4.321 Formulation: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL or 600mg/60mL of carblplatin.

4.322 Solution Preparation

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

4.323 Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

4.324 Stability: When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

4.325 Supplier: Commercially available from Bristol-Myers Squibb Company as well as generic manufacturers.

4.326 Administration: Carboplatin IV will be administered over approximately 30 minutes at an AUC 6 q 21 days (Day1 of 21 day cycle). See Section 5.224.

4.327 Adverse effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, constipation
Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms
Renal: Abnormal renal function test results including serum creatinine, blood urea nitrogen, and creatinine clearance
Hepatic: Abnormal liver function tests including bilirubin, SGOT, and alkaline phosphatase
Electrolyte Changes: Abnormally decreased serum electrolyte

values reported for sodium, potassium, calcium, and magnesium.
Allergic Reactions: Rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.
Injection Site Reactions: Redness, swelling, pain; necrosis associated with extravasation has been reported.
Other: Pain, asthenia, alopecia. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of patients and did not appear to be related to chemotherapy. Cancer- associated hemolytic-uremic syndrome has been reported rarely.
Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

5.1 Treatment Plan

Patients with endometrial cancer meeting eligibility criteria will receive vaginal cuff brachytherapy followed by three cycles of chemotherapy with carboplatin and paclitaxel. Either LDR or HDR brachytherapy will be permitted, but must be specified at enrollment.

5.21 Radiation Therapy: Within 12 weeks of surgery (within 2 weeks of enrollment) all patients must start vaginal cuff brachytherapy. The use of LDR or HDR therapy must be specified at enrollment.

5.22 Chemotherapy: Carboplatin IV, AUC 6, on day 1 of a 21 day cycle and Paclitaxel 80 mg/m2 IV days 1, 8, and 15 (of a 21 day cycle) x 3 cycles will be given to all patients. Chemotherapy will begin within 3 weeks of completion of brachytherapy.

5.221 Methods of Chemotherapy Administration

Maximum body surface area used for dose calculations will be 2.0 m^2.
The dose will be based on the patient's actual weight at baseline

(Day 1 of Cycle 1). It is not necessary to recalculate the dose unless the patient has ≥10% weight changes during the study.

5.222 Sequence and timing of drug administration:

Paclitaxel will be administered per institution guidelines over approximately 1 hour. Paclitaxel will be administered prior to carboplatin.
All patients should be pre-medicated per institution standard practice. See Section 5.223.
Carboplatin will be administered per institution guidelines over approximately 30 minutes. Carboplatin will be infused after Paclitaxel.

5.223 Antiemetic Regimens: It is anticipated that nausea and vomiting may be a significant side effect of chemotherapy. It is recommended to administer prophylactic anti-emetics per institution standard practice. For all courses where paclitaxel is administered, it is recommended that a preparative regimen be employed prior to the treatment regimen, to reduce the risk associated with hypersensitivity reactions to this drug. This regimen may include standard dose(s) of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an equivalent dose of an alternate H1 blocker such as loratadine or fexofenadine), and a standard dose of anti-histamine H2 IV (such as cimetidine, ranitidine, or famotidine).

5.224 **Dosing of Carboplatin:**
The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula. The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol. Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline. In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment. For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher)

baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR + 25)
NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.
The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg
For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of
Cockcroft-Gault using the following formula:
Creatinine Clearance (mL/min) = {[140-Age (years)] x Weight (kg) x 0.85} / [72 x serum creatinine (mg/dl)]
Notes:
1) Weight in kilograms (kg):
a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight
e. If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.
2) The Cockcroft-Gault formula above is specifically for women (it includes the
0.85 factor).
At the time of a dose modification for toxicity:
1) If the creatinine at the time of a dose modification is lower than the creatinine used to
calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine.

This will ensure that the patient is actually receiving a dose reduction.

6.0 TREATMENT MODIFICATIONS

6.1 Radiotherapy Procedures: There will be no modifications for radiotherapy.

6.2 Chemotherapy Modifications: Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

6.21 **Chemotherapy** – **Day 1** of a subsequent cycle of cytotoxic chemotherapy will not be administered until the ANC is ≥ 1,000 cells/mcl and the platelet count is ≥ 75,000/mcl. All treatment will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive protocol-directed cytotoxic therapy.

6.22 **Chemotherapy- Day 8 and 15 paclitaxel** dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is at least 50,000/mcl. If not given, these doses are omitted and not made up.

6.23 Use of Hematopoietic Cytokines and Protective Agents: It is anticipated that myelosuppression may be a significant side effect of dose dense chemotherapy. Myeloid growth factors can be used (it is recommended that NCCN and/or ASCO guidelines be consulted)[38]. If myeloid growth factors are used, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery Administration of growth factors on the same day as chemotherapy is not recommended. Pegfilgrastim is not recommended for chemotherapy regimens given less than every 2 weeks.

6.3 Modifications for Hematologic Toxicity (Nadirs)

6.31 Initial occurrence of dose-limiting neutropenia (defined in 6.32) or dose limiting thrombocytopenia (defined in 6.33) will be handled according to Tables A

6.32 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of

- febrile neutropenia(disorder characterized by an ANC <1000/mcl and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour)
- Grade 4 neutropenia persisting ≥ 7 days,
- delay of treatment for more than 7 days because of neutropenia,
- ANC<1000cells/mcl on day 1,
- or omission of day 8 or day 15 paclitaxel because of neutropenia.

6.33 Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of: Grade 4 thrombocytopenia (<25,000/mcl)

- bleeding associated with Grade 3 thrombocytopenia (25,000 to
- <50,000/mcl),
- delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia,
- platelet count of <75,000/mcl on day 1,
- or inability to give day 8 or day 15 paclitaxel on Regimen II due to thrombocytopenia.

There will be no modifications for uncomplicated Grade 3 thrombocytopenia except as above.

Table A: Modification Instructions for Dose-Limiting Hematologic Toxicity Regimen

DLT ANC	DLT PLT	First Occurrence	Second Occurrence (06/20/2011)	Third Occurrence
Yes	**No**	Reduce carboplatin one AUC unit	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel	Reduce caboplatin one AUC, and give G-CSF after day 8 paclitaxel. Fourth occurrence: Discontinue Part A Protocol Directed Cytotoxic Therapy.
Yes	**Yes**	Reduce carboplatin one AUC unit	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel	Discontinue Part A Protocol-Directed Cytotoxic Therapy**

6.4 Non-hematologic Toxicity: Patients, whose treatment is delayed > 21 days because of toxicity should have protocol therapy discontinued.

6.41 Table B should be used for dose level modifications for non-hematologic toxicity only as indicated specifically in the sections below.

6.42 Paclitaxel hypersensitivity reaction: If hypersensitivity to paclitaxel or its vehicle Cremophor occurs, it will usually be during the first few minutes of infusion. **If severe hypersensitivity occurs, stop infusion and do not rechallenge. Minor hypersensitivity reactions (such as flushing, skin reactions, dyspnea, hypotension, or tachycardia) do not require interruption of treatment.** However appropriate symptomatic therapy should be given; patients must be cautioned about potential recurrences of the reaction. Should the patient decide to continue with treatment, it is preferable that this be done on the same day of occurrence and re-titrated. A suggested procedure would be to administer the drug first with 1 cc of the original IV solution diluted in 100 cc over one hour, then 5 cc in 100 cc over one hour, then 10 cc in 100 cc over one hour, and finally, the original solution at original speed. Patients who elect not to have continued treatment with paclitaxel after experiencing a hypersensitivity reaction will discontinue study treatment, and be treated according to the physician's recommendations.

6.43 Neuropathy. Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, or recurs, then the patient will be discontinued from study.

6.44 Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, defined by serum creatinine greater than 1.5 x institutional upper limit normal (ULN).

6.45 Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

6.46 There will be no dose modifications for alopecia, nausea, or constipation. It is recommended that routine medical measures be employed to manage nausea, constipation. Grade 3 diarrhea on day of planned treatment will require holding of paclitaxel in patients on weekly paclitaxel. Any grade 3 diarrhea in patients on weekly paclitaxel will mandate a one dose level reduction of paclitaxel in future cycles. If the diarrhea is clearly infectious and has resolved, the above

mandated dose reductions do not apply.

Table B: Modifications for Non-Hematologic Toxicity			
Drug	**Regimen Starting Dose**	**Regimen -1 Level**	**Regimen -2 level**
Paclitaxel (weekly)	80 mg/m2	70 mg/m2	60 mg/m2
Carboplatin	6.0	5.0	4.0

7.0 STUDY PARAMETERS

7.1 Observations and Tests- The following observations and tests are to be performed and recorded on the appropriate form(s).

Parameter	Pre-Therapy (within 14 days of start) (see Section 3.1 for specific eligibility criteria)	Weekly	Prior to Each Cycle	Following completion of therapy
History & Physical	X		X	X[1]
ECOG PS	X		X	X
Toxicity Assessment	X	X	X	X[4]
CBC/Differential/Platelets	X	X	X	X
Electrolytes, BUN, creatinine, calcium (Ca), magnesium (Mg), phosphate (PO_4), Urinalysis	X		X	X
Bilirubin, SGOT, SGPT, Alkaline Phosphatase	X		X	
Chest x-ray (CT of chest should be obtained if CXR is abnormal/suspicious)	X[2]			X[4]
CT scan abdomen/pelvis	X[3]			X[4]

1 Follow up starts within 4 weeks after completing or discontinuing study therapy, then every 3 months to assess for survival status until death, withdrawal of consent, or until 2 years from the date of registration.
2 Within 28 days prior to enrollment.
3 Patients who did not have a bilateral pelvic and para-aortic lymphadenectomy performed must have a pretreatment (within 28 days prior to initiating treatment) CT/MRI demonstrating negative/non-suspicious lymph nodes. It is suggested that for CT scans, a spiral CT with an

intravenous/oral contrast and ≤ 5mm slice thickness be used where possible. MRI should be performed with gadolinium and include both T2W and T1W sequences; the minimum possible slice should be obtained for all sequences, depending on the size of the patient.

4 Within 4 weeks after completing or discontinuing study therapy.

8.0 EVALUATION CRITERIA

8.1 Objective Response

The major parameters of response to be assessed include Progression-Free Interval, Overall Survival, documentation of Sites of Recurrence, and Treatment Related Toxicity.

8.11 Measurable Lesions- All patients in this study will have completely resected disease at enrollment. Response rate will not be measured.

8.12 Progression-Free Interval will be defined as date from entry to a particular protocol to date of reappearance or increasing parameters of disease or to date of last contact.

8.13 Survival will be defined as observed length of life from entry to a particular protocol to death or, for living patients, date of last contact (regardless of whether or not this contact is on a subsequent protocol).

8.14 Sites of Recurrence will be assessed. Any clinical or radiological evidence for new tumor, preferably confirmed by pathology, will be considered as a recurrence. . Pattern of relapse to be noted:
8.14.1 Pelvic (peritoneal, nodal)
8.14.2 Abdominal (peritoneal, nodal, visceral, ascites)
8.14.3 Diaphragmatic
8.14.4 Distant (nodal, parenchymal)
8.14.5 Omental
8.14.6 Effusions (pleural, ascites)

8.15 Treatment Toxicity: The grade level of the various toxicities will be classified using the Common Toxicity Criteria, version 4 (CTCAE v.4) guidelines. Acute toxicities will be scored if occurring </= 30 days from treatment completion, and chronic if > 30 days. Frequency and duration of treatment interruptions due to the treatment toxicity will be assessed.

9.0 DURATION OF STUDY

9.1 This treatment of this study is approximately 4 months.

9.2 Following completion of therapy, the patient will be followed and data captured every 3 months to assess for survival status until death, withdrawal of consent, or until 2 years from the date of registration.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 Safety oversight will be performed by Stephenson Cancer Center's (SCC) internal Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "*NIH Policy for Data and Safety Monitoring*," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

Under the direction of the DSMC chair, a full board meeting is convened on a biannual basis to review the accumulated safety data, accrual information, and additional information as stated in the DSMC plan.

DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC, either through the formal audit report provided by the external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

Using the existing DSMC structure of the SCC, a DSMC will be conveyed (using the SCC CTO SOP's) to assess toxicity. We will review cohorts of 5 patients enrolled for frequency and severity of grade 2-3-4 toxicities and compare to data reported for standard regimens. Following a review of the DSMC meetings, information will be provided to the IRB.

10.2 A patient consent form must be signed by the patient or guardian prior to study entry.

10.3 ADVERSE EVENT REPORTING FOR COMMERCIAL DRUG STUDIES

This study will utilize the CTCAE v4.0 for toxicity and Adverse Event Reporting.

Toxicity Grade	**Type[a]**	**OUHSC IRB** via mail
4,5	Unknown	Yes
5	Known	No
2,3	Unknown	No
4 (non-myelo)	Known	No
4 (myelo[b])	Known	No

* If clearly related to the commercial agent(s)

[a] Type (Known or unknown) is based on toxicities included in the package insert or literature of known toxicities associated with the study drug(s).

[b] Myelosuppression, which includes neutropenia, anemia, thrombocytopenia

10.31 AE will be reported to the IRB as per policy.
A serious adverse event (SAE) is any sign, symptom or medical condition that emerges during treatment or during 30 days post-treatment follow-up period that was not present at the start of treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs should be recorded on SAE report Form and reported to: Dr. Lisa Landrum, Principal Investigator
Contact Information phone # (405) 271-8707 and fax # (405)-271-6275

AND:
IRB Contact information phone # (405) 271-2045 and fax # (405) 271-1677

11.0 STATISTICAL CONSIDERATIONS

11.1 **Study design overview and registration**: This study is designed as a phase II clinical trial. This design will provide a direct assessment of the feasibility associated with 3 cycles of adjuvant combination carboplatin and Dd paclitaxel chemotherapy and VCB compared to historically demonstrated outcomes of surgery followed by pelvic radiation therapy in patients with high-risk early stage endometrial carcinoma.

11.2 **Data collection**: The principal parameters to be collected, analyzed and reported to determine the relative therapeutic effect of the two treatment regimens are:

11.21 **Outcome variables**

11.211 Primary: Completion of 3 cycles of chemotherapy and VCB

11.212 Secondary: duration of recurrence-free survival, toxicity related to vaginal brachytherapy and combination carboplatin and paclitaxel, sites of failure, contributing cause of death, overall survival.

11.22 **Tumor characteristics:** FIGO stage determined after definitive surgery, histologic cell type, tumor grade, depth of myometrial invasion, lymphatic- vascular space involvement (LVSI) of tumor.

11.23 **Host characteristics:** age at entry, performance status, and race.

11.24 **Adverse effects:** frequency and severity of adverse effects graded by CTCAE v 4.0.

11.25 **Treatment:** total dose of radiation received; the number of cycles and total dose of protocol directed therapy administered; for those not completing study therapy, the reason for not completing the assigned treatment

Accrual:

Based on the experience with GOG 249 (randomized trial), 46 patients from the Stephenson Cancer Center were enrolled over a 5 year period. Of the total patients enrolled in GOG 249, the eligibility criteria as restricted in this study would account for

73% of the total number of patients with recurrence.

A similar investigator initiated pilot study (single arm) conducted at the Stephenson Cancer Center enrolled 23 patients in 2 years.[37] Based on our prior experience with this population we anticipate enrollment of 10 patients per year.

11.3 **Hypotheses and sample size:**

Primary Hypothesis: This study will evaluate the effect of vaginal brachytherapy and 3 cycles of carboplatin and Dd paclitaxel following surgery verses historical controls who underwent surgery followed by pelvic radiation therapy. The primary endpoint for this evaluation is recurrence-free survival. The design of this study will provide evidence of benefit with regard to recurrence-free survival. The type I error level will be set at 0.05 (one tail test).

Assumptions: It is anticipated based on available data from the recently completed prospective study GOG, patients treated with surgery and pelvic radiation (control arm of GOG 249):
18% of patients with stage I endometrioid tumors and 3+ risk factors recurred, and 36 mo PFS was 75%
15% of patients with patients with stage II endometrioid tumors with or without other risk factors recurred, and 36 mo PFS was 80%
22% of patients with patients with stage I-II serous or clear cell tumors with or without other risk factors recurred and 36 mo PFS was 70%.
These 3 patient populations accounted for 73% of all recurrences/deaths in the study.

Sample Size: It is anticipated that 10 patients per year will be accrued for a total of 46 patients in a 5 year period. Based on the 87% and 91% completion of therapy rates in the GOG 249 protocol arms, the regimen will be considered feasible if 85% of enrolled patients complete the study, or 39/46. [35]

11.4 **Study Duration:** The planned sample size is 46 patients. It is anticipated that this study will require approximately 60 months of accrual assuming a uniform accrual rate of 10 patients per year.

11.5 **Interim Analyses:** There will be one planned interim analysis of recurrence-free survival data. The planned interim analysis will occur when at least 20 failures (recurrence or death) have been reported. A log rank test will be used to test the independence of treatment and recurrence-free survival. The type I error spent at the interim analysis will be 0.005. If additional interim analyses are warranted, then the error spent at each interim analysis will be 0.005. The number of patients with UPSC/CC histology that have been included in the study

will also be determined at this time. It may be necessary to accrue more patients than originally anticipated in order to ensure that adequate numbers of patients with UPSC/CC histology are included.

Additionally, a futility analysis will be carried out. If the observed recurrence or death rate of the experimental arm is greater than the observed recurrence or death rate of the control arm, then accrual termination will be considered (if still active) with a conclusion that an advantage for the experimental arm has not been established. The increase in type II error due to this interim analysis is negligible. Under the null hypothesis, this procedure has a 50% chance of resulting in early termination.

12.0 BIBLIOGRAPHY

1. Suh DH, Lee KH, Kim K, Kang S, Kim JW. Major clinical research advances in gynecologic cancer in 2014. *Journal of gynecologic oncology.* Apr 2015;26(2):156-167.
2. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* Mar 2004;92(3):744-751.
3. Carcangiu ML, Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. *Gynecol Oncol.* Dec 1992;47(3):298-305.
4. Ito K, Tsubamoto H, Itani Y, et al. A feasibility study of carboplatin and weekly paclitaxel combination chemotherapy in endometrial cancer: a Kansai Clinical Oncology Group study (KCOG0015 trial). *Gynecol Oncol.* Feb 2011;120(2):193-197.
5. Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *The Lancet. Oncology.* Sep 2013;14(10):1020-1026.
6. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *The Lancet. Oncology.* Apr 2014;15(4):396-405.
7. Chan JK, Brady MF, Penson RT, et al. Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. *The New England journal of medicine.* Feb 25 2016;374(8):738-748.
8. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. *J Clin Oncol.* Apr 1 2004;22(7):1234-1241.
9. Grice J, Ek M, Greer B, et al. Uterine papillary serous carcinoma: evaluation of long-term survival in surgically staged patients. *Gynecol Oncol.* Apr 1998;69(1):69-73.
10. Huh WK, Powell M, Leath CA, 3rd, et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical Stage I patients with and without adjuvant therapy. *Gynecol Oncol.* Dec2003;91(3):470-475.
11. Sutton G, Axelrod JH, Bundy BN, et al. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* Feb 2006;100(2):349-354.
12. Creasman WT, Kohler MF, Odicino F, Maisonneuve P, Boyle P. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. *Gynecol Oncol.* Dec 2004;95(3):593-596.
13. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet.* Apr 22 2000;355(9213):1404-1411.
14. Kong A, Johnson N, Cornes P, et al. Adjuvant radiotherapy for stage I endometrial cancer. *The Cochrane database of systematic reviews.* 2007(2):CD003916.
15. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer.* Oct 15 1987;60(8 Suppl):2035-2041.
16. group As, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet.* Jan 10 2009;373(9658):125-136.
17. Hendrickson M, Ross J, Eifel PJ, Cox RS, Martinez A, Kempson R. Adenocarcinoma of the endometrium: analysis of 256 cases with carcinoma limited to the uterine corpus. Pathology review and analysis of prognostic variables. *Gynecol Oncol.* Jun 1982;13(3):373-392.
18. Gallion HH, van Nagell JR, Jr., Powell DF, et al. Stage I serous papillary carcinoma of the endometrium. *Cancer.* Jun 1 1989;63(11):2224-2228.
19. Goff BA, Kato D, Schmidt RA, et al. Uterine papillary serous carcinoma: patterns ofmetastatic spread. *Gynecol Oncol.* Sep 1994;54(3):264-268.

20. Cirisano FD, Jr., 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.* Apr 2000;77(1):55-65.
21. Pearcey RG, Petereit DG. Post-operative high dose rate brachytherapy in patients with low to intermediate risk endometrial cancer. *Radiother Oncol.* Jul 2000;56(1):17-22.
22. Ng TY, Perrin LC, Nicklin JL, Cheuk R, Crandon AJ. Local recurrence in high-risk node-negative stage I endometrial carcinoma treated with postoperative vaginal vault brachytherapy. *Gynecol Oncol.* Dec 2000;79(3):490-494.
23. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* Jan 1 2006;24(1):36-44.
24. Morrow CP, Bundy BN, Homesley HD, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study. *Gynecol Oncol.* Feb 1990;36(2):166-171.
25. Burke TW, Gershenson DM, Morris M, et al. Postoperative adjuvant cisplatin, doxorubicin, and cyclophosphamide (PAC) chemotherapy in women with high-risk endometrial carcinoma. *Gynecol Oncol.* Oct 1994;55(1):47-50.
26. Levenback C, Burke TW, Silva E, et al. Uterine papillary serous carcinoma (UPSC) treated with cisplatin, doxorubicin, and cyclophosphamide (PAC). *Gynecol Oncol.* Sep 1992;46(3):317-321.
27. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol.* Aug 1996;62(2):278-281.
28. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* Mar 2003;88(3):277-281.
29. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* Jun 1 2004;22(11):2159-2166.
30. Ramondetta L, Burke TW, Levenback C, Bevers M, Bodurka-Bevers D, Gershenson DM. Treatment of uterine papillary serous carcinoma with paclitaxel. *Gynecol Oncol.* Jul 2001;82(1):156-161.
31. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol.* Oct 15 2001;19(20):4048-4053.
32. Aoki Y, Watanabe M, Amikura T, et al. Adjuvant chemotherapy as treatment of high-risk stage I and II endometrial cancer. *Gynecol Oncol.* Aug 2004;94(2):333-339.
33. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *The New England journal of medicine.* Apr 17 2008;358(16):1663-1671.
34. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. *Gynecologic oncology.* Nov 2007;107(2):177-185.
35. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. *Gynecol Oncol.* Jan 2008;108(1):226-233.
36. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer.* Aug 7 2006;95(3):266-271.
37. Landrum LM, Nugent EK, Zuna RE, et al. Phase II trial of vaginal cuff brachytherapy followed by chemotherapy in early stage endometrial cancer patients with high-intermediate risk factors. *Gynecologic oncology.* Jan 2014;132(1):50-54.
38. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jul 01 2006;24(19):3187-3205.