A Pilot Phase II Trial of Intravenous Paclitaxel and Intraperitoneal Carboplatin/Taxol Followed by Radiation in Patients with Advanced Stage Uterine Serous Carcinoma

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SCHEMA

Weeks 1-18

Paclitaxel 135 mg/m2 over 3 hrs on day 1
Carboplatin IP (AUC= 6.0) on day 1
Paclitaxel 60 mg/m2 IP on Day 8
Repeat q 21 days x 6 cycles
CT Imaging after chemotherapy

Weeks 19-23 **

Pelvic 6MV Photon Beam Energy, or IMRT where appropriate
1.8 Gy Dose/FX Total Dose 45 Gy

Weeks 24-26 **

High Dose Radiation (HDR) x 3, or IMRT where appropriate
5 Gy to 0.5cm Depth from the Vaginal Cylinder Surface
Total Dose 15 Gy

* Disease surveillance with CT imaging should be performed after six cycles of chemotherapy, prior to radiation. CT after 3 cycles of chemotherapy is permitted, depending upon physician's discretion.
** Radiotherapy is given to eligible patients who have not had prior radiation exposure radiation in the abdomen and pelvis.
Quality of Life (QOL) surveys to be obtained at 3 time points
Baseline (after surgery, prior to initiating first cycle)
Completion of chemotherapy (18 weeks after Cycle 1 Day 1 if patient is no longer on protocol-directed treatment)
Completion of radiation therapy (26 weeks after Cycle 1 Day 1 if patient is no longer on protocol-directed treatment)
Two years post diagnosis, if feasible.

BACKGROUND

Uterine corpus cancer is the most common gynecologic malignancy in the United States. If diagnosed at an early stage, it is associated with good prognosis, after surgery and adjuvant radiation +/- chemotherapy. However patients with high risk endometrial carcinoma have a significant risk for recurrent disease and mortality. [1-3] High risk features associated with poor prognosis include distinct histologic cell types (clear cell, serous and carcinosarcoma), grade (2 or 3), and advanced stage. Uterine serous carcinoma (USC) is an uncommon, but aggressive variant of endometrial carcinoma that has poor response to standard therapy. In addition, it has a propensity for pelvic as well as abdominal recurrences and peritoneal carcinomatosis, similar to serous carcinoma of the ovary. In fact, many patients with disease apparently confined to the uterus will have microscopic intra-abdominal spread at the time of diagnosis. [4-8] After staging and surgical cytoreduction of gross disease, adjuvant radiation therapy is recommended to treat patients at high risk for recurrence. [9-20] The Gynecologic Oncology Group (GOG 94) evaluated patients with high risk endometrial cancer treated with whole abdominal and pelvic radiation, which included 103 patients with stage III/IV high risk uterine cancer subtypes such as clear cell carcinoma and USC. The overall recurrence rates were 67% at 3 years for these patients, and 21% occurred within the abdomen.[21] In another study detailing 21 patients with stage I/II USC, more than half of recurrences were within the radiation field. [22] Thus, it appears that while pelvic radiation can limit local recurrences, a significant percentage of patients, approximately 25-30%, with high-risk features will recur with distant metastases after

radiation therapy (RT). Even patients treated with whole abdominal irradiation are at risk for extra-abdominal recurrences with progression-free intervals of 7 to 8 months. [23-25] Chemotherapy is expected to control pelvic as well as distant sites of failures in advanced or recurrent endometrial carcinoma. There have been several randomized trials addressing the efficacy of optimal chemotherapy regimen. Doxorubicin, in combination with platinum, has a 42% response rate, and a survival advantage against whole abdominal radiation. [26, 27] Paclitaxel has an overall response rate of 36% in patients with advanced and recurrent endometrial cancer. [28] In combination with doxorubicin and cisplatin, paclitaxel has been shown to have a superior survival advantage. However, due to the high rate of toxicity of this intense regimen, a review of literature shows most practicing gynecologic oncologists use a modified regimen of carboplatin and paclitaxel in the adjuvant setting instead. [29, 30]. Due to the propensity for systemic metastasis and recurrence in high risk uterine cancers, several studies have studied the combination of chemotherapy and radiation. Carboplatin and paclitaxel followed by pelvic RT in patients with advanced endometrial cancer, including patients with USC, appear to have acceptable toxicity profile and favorable survival. [31-34] More specifically, in a large prospective phase II trial of USC patients receiving RT 'sandwiched' between six cycles of carboplatin and paclitaxel, excellent survival was observed in the entire cohort, with 3-year probability of survival for advanced stage (III/IV) patients being 50%. In patients who completed the entire treatment course, their 3-year survival was 65%. This compares favorably with published existing literature for USC, and is associated with limited, manageable toxicities.[35]

Recent phase III trials in ovarian cancer have shown the longest survival advantage (median 65 months) when intraperitoneal (IP) cisplatin and paclitaxel, plus intravenous (IV) paclitaxel were utilized for optimally debulked ovarian cancer (GOG 172). The relative risk of progression was 0.80 (95% CI 0.64, 1.00) for the intraperitoneal group ($p=0.05$, two-sided log-rank test). [36] To date, no trials utilizing intraperitoneal therapy for uterine cancer have been reported. In advances stage and recurrent setting, high risk uterine cancer mirrors ovarian cancer with it spread patterns and response to therapy. Based on these findings and the similarities as well as the clinical success of paclitaxel with IP platinum therapy in patients with ovarian serous carcinoma, we propose to prospectively assess IV/IP therapy in patients with advanced stage and recurrent USC. In GOG 172, patients in the IP arm experienced significantly worse quality of life (QoL) prior to cycle 4 ($p<0.0001$), and worse QoL 3-6 weeks post treatment ($p=0.0035$). However QoL differences resolved one year post-treatment.[36] Only 42% of patients in the IP group completed 6 cycles of chemotherapy, and 49% received 3 or fewer cycles. The main reasons for discontinuing IP chemotherapy were 1) catheter complications 2) intolerance of high dose cisplatin with nausea, renal dysfunction and electrolyte disturbances 3) intolerance of distention from IP infusion. Since GOG 172, it has been shown in a number of IP therapy trials in ovarian cancer that implementation of strict pre and post hydration schedules, routine utilization of anti-emetics, and substitution of carboplatin for cisplatin would improve adherence (due to its improved toxicity profile and less need for hydration).[37, 38] GOG is currently conducting a Phase III trial in ovarian cancer that includes comparison of intraperitoneal cisplatin 75 mg/m2 IP to carboplatin AUC 6 IP (GOG 252). Preliminary data indicated no difference in PFS in patients receiving IV or IP chemotherapy, however, it was limited given all arms of the trial received Avastin. Data from the Japanese GOG (JGOG 3016), suggests the superiority of weekly dose dense paclitaxel, IV 80mg/m2 administered compared to paclitaxel IV given every three

weeks.[39] The PFS was 17.2 months for the three week schedule and 28 months for the weekly schedule (p=0.0015 HR=0.714 (0.581-0.879). The 2-year overall survival was 77.7% for the three-week schedule and 83.6% for the weekly regimen (p=0.496 HR 0.735: 0.54-1.0). MITO-7 is a randomized multicenter phase III trial. Weekly paclitaxel had similar PFS and no difference in estimated probability of survival, as well as lower rates of toxicity. [40] In addition, there is also support for a weekly schedule over an every 3-week in the breast cancer literature. The superiority of weekly paclitaxel in node positive, or high risk node-negative breast cancer was reported by Sparano et al (HR 1.32, p=0.01).[41] The existing literature supports the superiority of weekly paclitaxel regimen, and GOG 252 has included a confirmatory arm of dose-dense weekly paclitaxel, 80 mg/m2 versus paclitaxel 135 mg/m2 every three weeks for treatment of epithelial ovarian cancer. GOG 9920 is a phase I study that evaluated the toxicity associated with modified paclitaxel/doxorubicin/cisplatin regimen followed by IP cisplatin/paclitaxel for patients with advanced endometrial cancer. Most patients had stage IV disease and the majority (59%) had serous/clear cell histology. At median followup of 22 months, 46% of patients remained progression free. [42]Building on the success of some recent trials and what is now considered standard of care for serous ovarian cancer, we propose a safety and feasibility study using for adjuvant therapy in women with advanced stage USC.

2.0 OBJECTIVES

Primary Objectives

2.11 To evaluate the toxicity (as defined by NCI Common Toxicity Criteria v. 4.0) of IP carboplatin/IV paclitaxel followed by Day 8 IP paclitaxel chemotherapy given in 3 week cycles, followed by RT in patients with advanced stage USC.

2.12 To determine the feasibility of this regimen in women with advanced stage USC. Feasibility will be assessed by: Treatment completion proportion – the proportion of participants who complete the IV paclitaxel/IP carboplatin followed by IP paclitaxel/RT regimen
Screening ratio – the number of potential participants screened per enrolled participant

Secondary Objectives
2.21 To assess the frequency and the reasons for early discontinuation of the study treatments.
2.22 To describe patient-reported quality of life parameters at specified time points during the study using validated questionnaires:
EORTC QLQ-C30 and QLQ-OV28

Exploratory Objectives
2.31 To define patterns of recurrence (e.g. local versus distant) and progression-free survival in patients with advanced and recurrent USC treated with IV paclitaxel/ IP carboplatin therapy and IP paclitaxel.
2.32 To correlate surrogate endpoint biomarkers that is performed in standard histology processing (Estrogen receptor and Progesterone receptor status as well as Her2/ *neu* status, p53 status) with progression-free survival and prognosis.

2.33 To assess the potential late effects of combined IP chemotherapy and radiotherapy on the gastrointestinal, genito-urinary, bone marrow and other body systems beginning at 6 months post treatment completion during routine office visits.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria
Patients may be included in the study if all of the following criteria are met:

- Histological/cytologically documented primary FIGO Stage IIIA, IIIB, IIIC1, IIIC2, IVA, and IVB uterine serous carcinoma.
- Patients with stage IVB disease include abdominal metastasis only
- Primary surgery with residual disease ≤ 1cm by surgeon report.

b. All patients must have a procedure for determining the definitive diagnosis of USC. At the discretion of the surgeon, complete surgical staging should include: total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, omental biopsy and lymph node evaluation.
c. Age > 18 years.
d. ECOG performance status of ≤ 2.
e. Written voluntary informed consent.
3.2 Exclusion Criteria
Exclusion from the study will be required if any of the following criteria are met:
a. Distant metastasis to the lung, bone or brain. Typically, most stage 4 USC is confined to the abdomen on presentation.
b. Patient has impairment of hepatic, renal or hematologic function as defined by the following baseline laboratory values:
Serum SGOT and /or SGPT > 2.5 times the institutional upper limit of normal (ULN)
Total serum bilirubin > 1.5 mg/dl
Serum creatinine > 2.0 mg/dl
Platelets < 100,000/mm3
Absolute neutrophil count (ANC) < 1500/mm3
Hemoglobin < 8.0 g/dl (the patient may be transfused prior to study entry)
c. History of abdominal/pelvic radiation therapy.
d. Severe or uncontrolled, concurrent medical disease (e.g. uncontrolled diabetes, unstable angina, myocardial infarction within 6 months, congestive heart failure, etc.)
e. Patients with dementia or altered mental status that would prohibit the giving and understanding of informed consent at the time of study entry.

4.0 REGISTRATION PROCEDURES

All patients must be registered. Any questions regarding eligibility should be addressed with the P.I. or the research coordinator.

5.0 TREATMENT PLAN

5.1 Dosing Guidelines
5.1.1 Chemotherapy

Paclitaxel is available commercially. Paclitaxel 135mg/m2 will be given over 1 hour in 250-500 ml of 5% dextrose or normal saline. Premedication for prevention of anaphylactic reactions with anti-histamines and/or steroids should be administered as per standard practice. Paclitaxel should be given first given the risk of immediate drug sensitivity reaction. Following on Day 8 of the cycle, paclitaxel will be given IP at 60mg/m2. After infusion the patient will be asked to change position at 15-minute intervals for two hours to ensure adequate intra-abdominal distribution. No attempt will be made to retrieve the infusate, however if a large amount of ascites is present, ascites may be drained by paracentesis or accessed port prior to instillation of drug.
Carboplatin is available commercially. Carboplatin should be reconstituted in 500-1000cc of normal saline warmed to 37 °C (when feasible) and infused through a peritoneal catheter as rapidly as possible. It is preferred that an additional 1000 ml of warm saline is infused after IP Carboplatin, or 500ml of warmed normal saline infused before and after IP Carboplatin to help with drug dispersion throughout the peritoneal cavity, for a total volume of approximately two liters. After infusion the patient will be asked to change position at 15-minute intervals for two hours to ensure adequate intra-abdominal distribution. No attempt will be made to retrieve the infusate, however if a large amount of ascites is present, ascites may be drained by paracentesis or accessed port prior to instillation of drug. Carboplatin at an AUC of 6.0 will be administered intraperitoneally (if there is a prior history of radiotherapy, AUC of 5 would be used). AUC based dosing as described by Calvert et al. will be according to the following formula: **Dose (mg) = AUC x (GFR + 25).**
The initial GOG trial using combination paclitaxel and carboplatin therapy was performed on patients with optimally debulked ovarian epithelial carcinoma.[43] At that time, the carboplatin dose was an AUC of 7.5. Since then, multiple large cooperative trials have been performed using AUCs of 6.0 and even 5.0. The lower dosage of carboplatin does not appear to compromise the efficacy of the drugs, and is associated with less toxicity.[44-46]
Where AUC is as stated above and GFR is the calculated renal function according to the method of Cockcroft and Gault: **GFR (ml/min) = 0.85 x {(140-age)/Scr)} x {wt(kg)/72}.**
Where Scr is the serum creatinine level. We will use GFR of 125ml/min as cutoff as per NCI guidelines.
Following 6 cycles of IV/IP chemotherapy, a CT of chest, abdomen and pelvis should be obtained for disease surveillance prior to proceeding with radiotherapy (See section 5.4). If clinically indicated, the primary oncologist may have the option to proceed with the CT imaging after 3 cycles of chemotherapy.
5.1.2 Antiemetic Regimens
Nausea and vomiting is anticipated as a side effect. The following representative antiemetic regimen is suggested:

Ondansetron 8-32 mg IV or PO 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV or PO 30 minutes prior to drug administration.
Aprepitant 125 mg PO one hour prior to chemotherapy on day 1 and 80 mg daily PO on days 2 & 3 for patients having nausea or vomiting with carboplatin (the intravenous formulations may be substituted when available).
Granisetron 10 mcg/kg IV (or 2mg PO) 30 minutes prior to chemotherapy, dexamethasone 10-20 mg IV 30 minutes prior to chemotherapy
5.2 Intraperitoneal device specifications:
Insertion of peritoneal catheter may be done by the following procedures as listed below: 1) at time of original laparotomy 2) laparoscopic placement 3) interventional radiology guided placement. Silicone catheters are preferred. Controversy exists between the use of venous 9.6 silicone catheters or silicone IP ports with fenestrations. Bardport silicone peritoneal catheter 14.3 Fr (Reorder number 0603006) is the preferred catheter. This has been FDA approved for IP therapy. The 9.6 Fr single lumen IV access device is also acceptable. Equivalent or similar devices are acceptable if silicone large enough not to kink and without a Dacron cuff.

Procedure at time of original laparotomy:
1) At the completion of the laparotomy just prior to closing the incision, make a 3-4 centimeter incision over the lower costal margin on the side where the catheter is to be placed. The incision is carried down to the fascia using blunt and sharp dissection.
2) A subcutaneous pocket superior to the incision is fashioned slightly larger than the diameter of the portal.
3) Select an area several centimeters below and lateral to the umbilicus as the peritoneal entrance site of the catheter. Prepare a subcutaneous tunnel from the portal pocket to the site in the peritoneal cavity you want the catheter to enter the abdomen and draw the catheter through the subcutaneous tissue into the abdomen using a tunneling device.
4) Attach the catheter to the portal as per manufacturer's instructions and suture the portal in place with permanent suture (i.e. 2-0 prolene) to the fascia overlying the rib cage. Be sure the chemotherapy nurses will be able to feel the port and stabilize it on the chest wall for easy access with Huber needle in the future. Be sure the Huber needle will not have to go through the wound to access the port; the port should lie superior to the port incision site.
5) After flushing the system with heparin 100 units per ml to determine that flow is not obstructed and no leaks exist, place the distal end of the catheter to the desired infusion site, with at least 10 cm of free catheter in the abdomen. Do not allow the catheter to be long enough to reach the bladder, vagina or rectum.
6) Close incisions and place a Huber needle trans-dermally into the portal if the catheter is going to be irrigated in the immediate postoperative period. Wait a minimum of 24 hours prior to treating patient after IP port placement, and wait for return of gastrointestinal function (regular diet tolerated and normal bowel movement) after major laparotomy.

Postoperative procedure with mini laparotomy (video available at SGO.org and GOG.org)
1) Select a site several centimeters below and lateral to the umbilicus and make an incision through skin, subcutaneous tissue and fascia. Separate rectus muscle and enter peritoneum. Knowledge of the previous surgical resections and current anatomy will assist in choosing location.

2) Pull the catheter from subcutaneous tissue into the peritoneal cavity through the full thickness of the abdominal wall (fascia, muscle, peritoneum) from an adjacent location (not through the incision) while under direct visualization to prevent injury to bowel. This can be accomplished with a tonsil clamp or tunneling device.
3) The catheter must be left in the abdominal cavity at least 10 cm to prevent migration out of the peritoneal cavity.
4) The opposite end of the catheter is tunneled up to the costal margin where it is attached to an implanted port as described above. The catheter is left long enough to not retract, but not long enough to reach vagina, rectum or bladder. It is generally left at least 10 cm into the peritoneal cavity.

Post-operative laparoscopically assisted surgical implantation of Port

1) Laparoscopic placement of an IP catheter is usually feasible from a left upper quadrant approach. Knowledge of the previous procedures performed (i.e. bowel resections and anastomosis sites) and location of the tumor will inform the surgeon as to the best approach and what locations to avoid.
2) Once the peritoneal cavity can be visualized, a second puncture can be used to gain access to the peritoneal cavity and then the catheter is tunneled in the subcutaneous tissues to the planned Port pocket.

Port placement under Interventional Radiologic guidance

Interventional radiology may also place IP catheters, if preferred by treating provider. Knowledge of anatomy and the best sites for placement should be communicated between the primary provider or surgeon and the radiologist. CT or ultrasound can allow direct access to peritoneal cavity, followed by subcutaneous tunneling to the anterior chest wall for appropriate port placement and catheter attachment.

Radiation:

Radiation therapy will be delivered at provider discretion after the 6th cycle of chemotherapy.
Physical Factors: All treatment will be delivered by megavoltage equipment ranging from 6 MV to a maximum of 25 MV photons. Cobalt-60 equipment will not be acceptable for treatment on this protocol. Tomotherapy is allowed.
Localization and Simulation Methods: Localization images taken on the conventional or CT-simulator will be necessary in all cases.
Treatment Plan and Dose Specification: Patients may be treated with either conventional radiation therapy approaches or with IMRT. The use of individualized custom blocking is required.
Daily Tumor Dose, Total Dose, and Overall Treatment Time: A daily tumor dose of 180 cGy per day will be given to a total dose of 4500 cGy (180 cGy *x* 25 treatments) in approximately five weeks. Treatment will be given 5 days a week, from Monday through Friday
Dose Distribution (Site): Dose to the CTV should not vary by more than +/- 5% from the prescribed dosage for 3D conformal plans. The use of tissue wedges and/or compensating filters

may be necessary to accomplish this goal. As a general rule, only pelvic radiation therapy will be given, unless there is imaging, intra-operative, histologic, or other evidence of para-aortic node involvement
.
If there is tumor extension into the vagina, the external beam fields will be modified to include the disease volume with at least a 2 cm margin. For involvement of the distal 1/3 of the vagina, inguino-femoral nodes should also be covered in the external beam RT ports. If the patient's tumor extends into the cervix, or invades deeply and extends into the lower uterine segment, or if there is lymph-vascular space invasion by tumor, or if the tumor has extended into the vagina, such a patient will receive intravaginal boost brachytherapy

Radiation Therapy Volumes and Technique

Pelvic field: 3D Conformal
Portal and Treatment Volume Definition:
The boundaries are as follows:
AP/PA Fields: Cephalad Border:
A transverse line drawn within 2 cm of the L5-S1 interspace or higher if necessary to include known areas of lymph node involvement by tumor.

AP/PA Fields: Caudal Border:
The mid-portion of the obturator foramen or a minimum of 4 cm margin on the vaginal cuff, preferably defined by marker seed placement or by placement of a vaginal swab at the time of simulation.
Lateral Borders: >1 cm beyond the lateral margin of the true pelvis at its widest points. Alternatively, use of a CT scan to outline the target vessels with a border of at least 1 cm is acceptable.
Lateral Pelvic Fields:
The cephalad and caudal borders are same as above.
Anterior Border:
A horizontal line drawn anterior to the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodal regions or, in the absence or radiographic documentation, the line should pass at least 1.5 cm anterior to the L5 vertebral body. Individualized custom blocks can be used to achieve this goal.
Posterior Border:
A cephalo-caudal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm.

IMRT
Patient Immobilization: Prior to simulation, it is recommended that radiopaque marker be inserted into the vaginal apex to help to identify the area by CT scan. Patients are to be immobilized in the supine position in an immobilization device. Patients are to be treated in the

immobilization device. CT scan thickness should be 3 mm or smaller through the region that contains the PTV, extending from at least L3-4 level to below the perineum.
Simulation: CT simulation is required to define clinical target volume (CTV) and planning target volume (PTV). The CT scan should be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast are highly recommended for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation, as well as small bowel contouring, respectively.
Contouring the Target volumes:
Please refer to the RTOG Gynecological Atlas for volume specification. The atlas may be accessed on the RTOG website at: http://www.rtog.org/gynatlas/main.html
The Clinical Target Volume (CTV) is defined as the vaginal apex in addition to pelvic nodal regions lying within the field borders given in Section 4.61. If gas/stool distends the rectum, the CTV is to be expanded to include the anterior half of the rectum to account for evacuation of the rectum. The nodal portion of the CTV should include the internal (hypogastric and obturator), and external iliac lymph node regions. The CTV should be delineated using the contrast enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 6 mm axial margin around the vessels). Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 6 mm margin around the vessels). Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) may be added to the CTV for adequate coverage of pre-sacral nodes, although this is optional and at the discretion of the treating radiation oncologist. In addition the most antero-lateral margin of the external iliac nodes that lie just proximal to the inguinal canal should be excluded from the CTV (nodal CTV should stop at the femoral head). Proximally, the CTV should end 7 mm from the L5-S1 interspace to account for the PTV. The CTV should include the inguino-femoral nodes if the distal one-third of the vagina is involved with tumor.
The PTV should provide a 7 mm-1 cm margin in all directions around the CTV.
The definitions of volumes will be in accordance with the 1993 ICRU report #50. Prescribing, recording and reporting photon beam therapy and 1999 ICRU report #62.
Critical normal surrounding structures:
Bladder will be contoured in each slice in which it appears.
Rectum will be contoured in each slice in which it appears. As a general guideline, the radiation oncologist can consider the maximum caudal extent of the rectum to lie 1.5-2.0 cm from the bottom of the ischial tuberosities. Superiorly, judgment will be required to establish where the rectum ends and the sigmoid colon begins. The transition to the sigmoid colon is marked by increased curvature and tortuosity in its path. Bowel will be contoured in each slice in which it appears, 2 cm above the PTV as bowel bag and inferiorly to the rectosigmoid junction.
Femoral heads will be contoured in all the slices in which they appear.
Constraints: Participants are strongly encouraged to respect the following limits, whether 3-D conformal or IMRT approaches are used.
Small bowel: <30% to receive ≥ 40Gy, Dmax <46 Gy
Rectum: < 80% to receive ≥ 40Gy, Dmax <55 Gy
Bladder: < 50% to receive ≥ 45Gy, Dmax <60 Gy
Femoral heads: < 50% to receive ≥ 40Gy, Dmax <50 Gy.

No tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

Extended Field Radiation Therapy: 3D Conformal Portal and Treatment Volume: The boundaries are as follows:
AP/PA Fields: Cephalad Border:
A transverse line drawn within 2 cm of the T11-T12 interspace.
AP/PA Fields: Caudal Border:
The mid-portion of the obturator foramen or a minimum of 4 cm margin on the vaginal cuff, preferably defined by marker seed placement or by placement of a vaginal swab at the time of simulation.
Lateral Borders:
In the pelvis >1 cm beyond the lateral margin of the true pelvis at its widest points. Alternatively, use of a CT scan to outline the target vessels with a border of at least 1 cm is acceptable. Moving superiorly, the width of the field will taper to the lateral aspects of the spinal transverse processes at L4 and superior to L4. The approximate field width for the para-aortic portion of the field should be 8 cm, although some variation is expected.
Lateral Pelvic Fields:
The cephalad and caudal borders are same as above.
Anterior Border:
A horizontal line drawn anterior to the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodal regions or, in the absence or radiographic documentation, the line should pass at least 1.5 cm anterior to the L5 vertebral body. Individualized custom blocks can be used to achieve this goal. Moving superiorly, the anterior border of the para-aortic field should remain a minimum of 1.5-2 cm anterior to the anterior border of the vertebral body. Again, some variation is expected, particularly in patients who have positive PA nodes or in patients who kidneys are located more anteriorly than normal. The overall width of the PA field should be at least 5cm.

Posterior Border:
A cephalo-caudal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3cm. Moving superiorly, the posterior border of the PA field should extend back approximately 50% of the width of each vertebral body.
Suggested technique: Different techniques have been used to deliver extended field radiation therapy. The suggested technique for this study is to treat the pelvic and para-aortic fields in continuity, as opposed to splitting fields, or treating the para-aortic portion with AP-PA fields only. Treating in continuity, it is suggested that the AP-PA fields be weighted 70:30 in relation to the lateral fields, in terms of isocenter dose. This technique strikes an appropriate balance, in most cases, between small bowel dose and kidney dose. Other techniques or beam weightings are potentially permissible, if appropriate dose distributions to PTV and organs at risk (OAR's) are obtained

Extended Field Radiation Therapy: IMRT

Portal and Treatment Volume Definition:
Patient Immobilization:
Prior to simulation, it is recommended that radiopaque marker seeds are inserted into the vaginal apex to help to identify the area by CT scan. Patients are to be immobilized in the supine position in an immobilization device such as Vac-lok or alpha-cradle, or similar. Patients are to be treated in the immobilization device. CT scan thickness should be 3 mm or smaller through the region that contains the PTV, extending from at least L3-4 level to below the perineum.
Simulation:
CT simulation is required to define clinical target volume (CTV) and planning target volume (PTV). The CT scan should be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast are highly recommended for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation, as well as small bowel contouring, respectively.

The Clinical Target Volume (CTV) is defined as the vaginal apex with margins as given in the #d section. in addition to pelvic and para-aortic nodal regions lying within the field borders given in #d sections The nodal portion of the CTV should include the internal (hypogastric and obturator), external iliac lymph node, and para-aortic regions. The CTV should be delineated using the contrast-enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 6 mm axial margin around the vessels). Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 6 mm margin around the vessels). Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) may be added to the CTV for adequate coverage of presacral nodes, although this is optional and at the discretion of the treating radiation oncologist. In addition, the most anterolateral margin of the external iliac nodes that lie just proximal to the inguinal canal should be excluded from the CTV (nodal CTV should stop at the femoral head. Proximally, the CTV should end 7 mm from the T11-T12 interspace to account for the PTV. The PTV should provide a 7 mm-1 cm margin in all directions around the CTV. The definitions of volumes will be in accordance with the 1993 ICRU report #50. Prescribing, recording and reporting photon beam therapy and 1999 ICRU report #62.
Critical normal surrounding structures:
Bladder will be contoured in each slice in which it appears.
Rectum will be contoured in each slice in which it appears. As a general guideline, the radiation oncologist can consider the maximum caudal extent of the rectum to lie 1.5-2.0 cm from the bottom of the ischial tuberosities. Superiorly, judgment will be required to establish where the rectum ends and the sigmoid colon begins. The transition to the sigmoid colon is marked by increased curvature and tortuosity in its path. 4Bowel will be contoured as bowel bag will be contoured in each slice in which it appears, 2 cm above the PTV.

Femoral heads will be contoured in all the slices in which they appear.
Constraints: Participants are strongly encouraged to respect the following limits, whether 3-D conformal or IMRT approaches are used.
Bowel bag: <30% to receive ≥ 40Gy, Dmax <46 Gy
Rectum: < 60% to receive ≥ 40Gy, Dmax <55 Gy

Bladder: < 50% to receive ≥ 45Gy, Dmax <60 Gy
Femoral heads: < 50% to receive ≥ 40Gy, Dmax <50Gy.
Kidney volume (combined right and left): <40% to Receive>15 Gy
No more than 1% or 1 ml (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.
The volume irradiated with the whole pelvic fields will include the CTV and PTV as defined above. The whole pelvis will receive a total dose of 4500 cGy in 25 fractions at 180 cGy/fx. For patients treated with IMRT, the prescription dose is the isodose that encompasses at least 97% of the PTV. No more than 20% of any PTV should receive >110% of the prescribed dose. No more than 1% of the PTV should receive <93% of the prescribed dose. No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV will receive >110% of the dose prescribed to the PTV. However, with respect to this last constraint, it is recognized that there may be patients in which, due to obesity or other factors, this constraint may not be obtainable if other constraints, e.g. rectum, are met. In these cases it is recommended that the OAR constraints be favored to the extent possible that is consistent with good radiotherapy practice.

Documentation requirements
For 3-D conformal treatments, digital reconstructed radiographs (DRR) of the treatment fields with the three-dimensional reconstruction of the CTV are to be obtained
For 3-D conformal plans, localization or block-check images of virtually simulated fields are to be obtained in the simulator and/or treatment machine for all the treatment fields independently, whether cerrobend blocks or multi-leaf collimators are used.

For IMRT plans, Dose-Volume Histograms (DVHs) are to be obtained for each one of the target volumes defined above, as well as the critical surrounding structures, and need to be submitted for evaluation. For detailed description of radiation pelvic fields, please see Section 4.62.
Therapy Interruptions: If interruption of two weeks or less occurs, radiation should be completed to the prescribed total dose. Therapy interruptions of more than two weeks will be considered a major or minor deviation from the protocol, depending on clinical circumstances, and resumption of therapy will be at the discretion of the radiation oncologist. Follow-up must continue regardless of radiation treatment received.
Expected Toxicity: Toxicity will vary depending upon tolerance of individual patient's daily dose, total dose, overall treatment time, associated illness, etc.
The following toxicity criteria may be used:
Gastrointestinal: Nausea and vomiting is unusual, but may be seen after pelvic radiation. Anti-emetics may be used during treatment or may be given prophylactically the night prior to treatment. Intractable nausea or vomiting is rarely seen with pelvic radiation alone and is usually the result of another process, i.e., bowel obstruction. Increased bowel activity with diarrhea usually can be controlled with low- fiber, low-fat, bland diets and anti-diarrhea medication. Should G.I. toxicity become severe, hospitalization may be required, at which time the treatment is interrupted temporarily until the patient's condition improves.
Hematological: Hematological toxicity is seen infrequently, unless pelvic radiation is accompanied by chemotherapy. A CBC should be obtained weekly during radiotherapy. If the ANC falls below 1,000 /mcl or the platelet count below 50,000/mcl, the CBC should be obtained twice weekly. Radiotherapy should be stopped when ANC < 500 and/or platelets < 25,000.

Radiotherapy
Brachytherapy: If a vaginal brachytherapy boost is to be given based on the criteria given in the protocol. It should commence within 2 weeks of completion of the external beam RT. It should be delivered with a vaginal cylinder (HDR or LDR) or colpostats (LDR), and in the absence of gross residual disease following surgery the treating physician must choose one of the following:
A) HDR: 600 cGy x 2-3, 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. A minimum of 4 cm of vaginal length should be treated.
B) LDR 2000-3500 cGy prescribed at the vaginal surface in 1 insertion at a dose rate of 40-100 cGy/hr. A minimum of 4 cm of vaginal length should be treated.
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Physical Factors
If an intravaginal boost is to be used, it should be delivered with an intravaginal cylinder (HDR or LDR). Acceptable isotopes include cobalt or iridium for HDR, radium or cesium for LDR.

Expected Toxicity **(**Gastrointestinal: Nausea and vomiting may occur after extended field Gastrointestinal: Nausea and vomiting may occur after extended field (PAN) treatments, but can be effectively treated with an appropriate antiemetic in most cases. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is not commonly seen as a result of radiation alone. Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic radiation. It is recommended that instructions be given to patients for low-fiber, low-fat, bland diet. Most patients will require anti-diarrheal medications such as Diphenoxylate HCL with atropine sulfate (Lomotil) or Loperamide HCL to control diarrhea.
Hematological toxicity of a mild nature will be seen frequently with a decline in WBC and platelet count.

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6.0 DOSE MODIFICATIONS AND TOXICITY MANAGEMENT

No dose escalation is planned for this study. All dose modifications are relative to the actual starting dose of the original regimen. All dose modifications will be based on absolute neutrophil count (ANC) rather than total white blood cell (WBC).
6.1 Hematologic Toxicities
6.1.1 **Treatment delay for IV Paclitaxel**: Day 8 will be skipped if:
ANC < 500 cells/mcl or
Platelet < 50,000 / mcl
6.1.2 **Cycle delay**: Day 1 of each cycle will be delayed if:
ANC < 1000 cells/mcl
Platelet < 75,000 / mcl
If cycle is delayed for 2 weeks or more for reasons of toxicity, dose modification and/or growth factor support may be used and continued for 6 cycles of treatment.

6.1.3 **Hematopoietic Cytokines and Protective Agents:** Patients will not receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless: treatment delays have been encountered neutropenic complications (e.g. neutropenic fever) in accordance with clinical treatment guidelines physicians are allowed flexibility for treatment for severe neutropenia in the elderly (ANC < 500 in women > 70 years old).
Patients will not receive prophylactic thrombopoietic agents, iron supplements and/or transfusions as clinically indicated for anemia management erythropoiesis stimulating agents (Aranesp, Epogen, Procrit) are associated with a potential risk of shortening time to disease progression and are contraindicated in patients treated with curative intent. They are also associated with increased thrombotic events and should be administered only to avoid red blood cell transfusions as clinically indicated. Please consult updated package insert: http://www.fda.gov/Medwatch/safety/2007/safety07.htm
Amifostine or other renal and neuropathy protective reagents should be avoided
6.1.4 **Dose modifications**
6.1.4.1 Initial occurrence of dose-limiting neutropenia (DLT-ANC) requiring dose reduction will be managed according to Table A. DLT-ANC is defined as: febrile neutropenia: fever with or without clinically or microbiologically documented infection with ANC < 1000 and fever ≥ 38.5°C. prolonged grade 4 neutropenia persisting > 7 days delay of Day 1 of any cycle by > 7 days due to neutropenia ANC between 1000 and 1500 on day 1 of any cycle, or omission of day 8 or 15 IV paclitaxel due to neutropenia Only one dose modification per cycle is allowed.

6.1.4.2 Initial occurrence of dose limiting thrombocytopenia (DLT –PLT) requiring dose reduction will be managed according to Table ADLT-PLT is defined as:
Grade 4 thrombocytopenia (<25,000/mcl)
Bleeding associated with grade 3 thrombocytopenia (24,000 – 50,000/mcl)
Delay of treatment on day 1 of any cycle > 7 days due to thrombocytopenia or inability to give day 8 or 15 due to thrombocytopenia. Platelet count of 75,000 – 100,000/mcl on day 1 should have carboplatin dose reduction (Table A)

Table A: Modification for DLT – Hematologic Toxicity

DLT-ANC	**DLT-PLT**	**First Occurrence**	**Second Occurrence**	**Third Occurrence**	**Fourth Occurrence**
Yes	**No**	Reduce carboplatin by one AUC unit	Omit day 15 paclitaxel and add G-CSF* starting after day 8 paclitaxel	Reduce carboplatin by one AUC unit AND start G-CSF* after day 8 paclitaxel	Off - study
Yes	**Yes**	Reduce carboplatin by one AUC unit	Omit day 15 paclitaxel AND add G-CSF* starting after day 8 paclitaxel AND		Off-study

			reduce carboplatin by one AUC unit	
No	**Yes**	Reduce carboplatin by one AUC unit	Decrease carboplatin by one AUC	Off-study

* G-CSF can be given daily starting on day 9 (for up to 10 days) or Peg-filgrastim can be given once on day 9.

6.1.4.3 Dose modifications for delayed hematologic recovery

Delayed hematologic recovery > 7 days is a DLT and modification should occur on the next cycle according to Table A. Delay due to neutropenia is defined as ANC <1000 cells/mcl within 24 hours of scheduled Day 1 treatment

Delay due to thrombocytopenia is defined as platelet < 75,000/mcl within 24 hours prior to the scheduled Day 1 treatment .Delay > 21 days would be an indication for off-study. Patient may, at discretion of physician, continue with non-protocol directed platinum/taxane therapy (with dose reductions and growth factors)

Non-Hematologic Toxicity: Refer to Table B for dose level modifications for non-hematologic toxicity

Table B: Modification for Non-Hematologic Toxicity

Drug	**Regimen Starting Dose**	**Regimen -1 Level**	**Regimen -2 Level**
Paclitaxel IV weekly	135 mg/m2	100 mg/m2	80 mg/m2
Carboplatin IP	AUC 6	AUC 5	AUC 4
IP Paclitaxel Day 8	60 mg/m2	40 mg/m2	Omit day 8 IP Paclitaxel

6.2.1 **Neurologic:**

Persistent grade 2 or higher neurotoxicity require holding paclitaxel dose for maximum of three weeks until recovery to grade 1, and start next cycle at one level of dose reduction

If neuropathy fails to recover to grade 1 by three weeks, patient should be deemed off-study, and docetaxel may be considered per primary physician discretion as a substitute.

Ototoxicity and neurotoxicity are related to cumulative dose. Severe toxicity can be avoided by careful monitoring of symptoms. Patients should be queried about hearing loss and paresthesia prior to each course of carboplatin.

6.2.2 **Renal toxicity:**

Significant renal toxicity is not expected from carboplatin as a direct complication of chemotherapy. Target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, defined by serum creatinine > 1.5 times ULN (CTCAE grade 2

or more). Severe renal toxicity can be prevented by intravenous hydration and administration of mannitol.

6.2.3 **Hepatic toxicity:**
Significant hepatic toxicity is not expected as a direct complication of chemotherapy in this patient population. Development of ≥ grade 3 increase in SGOT (AST), SGPT (ALT), or alkaline phosphatase require one dose level reduction in paclitaxel dose after delay in subsequent treatment for maximum of three weeks until recovery to grade 1.
Development of abnormal bilirubin levels should prompt withholding treatment until resolution to normal for maximum of 3 weeks

6.2.4 **Gastrointestinal toxicity:**
Routine medical measures should be employed to manage nausea, vomiting. No dose adjustment is expected for these side effects
Paclitaxel can cause severe diarrhea. For grade 3 diarrhea, hold weekly paclitaxel and resume with a two level dose reduction after resolution to grade 1 or less, unless there is a clear alternative cause (i.e. c. difficile infection) If hospital admission is required for IV hydration, consider assessment for bowel complications or IP access device complications.

6.2.5 **Alopecia**
There will no dose modifications for alopecia

6.2.6 **Hypersensitivity / allergic reaction:**
Hypersensitivity reaction to paclitaxel or carboplatin is generally not considered a DLT. Treatment should only be discontinued after documentation of failure to tolerate agent after all attempts being made to: 1) immediately treat hypersensitivity 2) titrate drug at slower rate on the same day After recovery from immediate hypersensitivity and patient is table, steroid and H1 blocking agents may be re-dosed Remaining chemotherapy may be slowly infused with a dilute solution, or at a lower rate If recurrent hypersensitivities occur, the chemotherapy should be discontinued and patient should be off-study.

6.2.7 **Unanticipated Surgical Procedures**
Treatment delay is not required for minor procedures including: 1) removal or insertion of central venous catheter, nephrostomy tube or ureteral stent and 2) thoracentesis or paracentesis for symptom relief in absence of disease progression. All unanticipated surgeries performed for reasons other than disease progression, treatment should be held > 28 days post-operatively. All surgeries should be on the reporting form.

6.2.8 **IP Catheter Complications**

IP catheter may be replaced or revised
IP catheter and ports may be removed without laparotomy.

If IP catheter fails, and cannot be quickly revised, patients should be taken off-study and continue at primary physician's discretion with IV therapy
Pain related to IP therapy: (Table C)
Decrease IP fluid volume down to one liter is allowed
For persistent grade 3 abdominal pain, patients should not receive further IP therapy, and be taken off-study
Peritonitis due to intestinal perforation related to IP catheter: is situation is suspected, appropriate evaluation of catheter for infection and removal should be considered. Cultures of the catheter are helpful when infection is suspected

Table C: Abdominal Pain Score

Grade		**Pain**
0	None	No pain
1	Mild	Minimal interference with daily activity, lasting < 72 hours
2	Moderate	Narcotic analgesia; Moderate interference with daily activity, lasting > 72 hr
3	Severe	Narcotic analgesia; Confines pain to bed and cause severe interference with activity

6.2.9 **Cardiac Toxicity**
Symptomatic bradycardia is not an indication for removal from study or dose modification of paclitaxel. Any cardiac ischemia events experienced should prompt patients to be removed from study
6.2.10 **Radiation Toxicity**
Potential acute and sub-acute radiation toxicities are fatigue, diarrhea, fecal urgency, nausea, vomiting, proctitis, urinary frequency, urgency and dysuria, loss of pubic hair, hyperpigmentation and desquamation of skin in the irradiated field, and depression of blood counts. Long-term side effects may include chronic malabsorption, rectal ulcer, bleeding or stricture, dysuria, hematuria, bowel obstruction, dryness and shortening of the vagina, dyspareunia, vaginal vault necrosis and fistula formation between pelvic tissues.

7.0 **MEASUREMENT OF EFFECT**

7.1 **Antitumor Effect**
Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated prior to each cycle. In addition to a baseline scan, confirmatory scans will also be obtained following completion of treatment or last cycle completed.
Response will be evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. Progression free survival (PFS) is defined as date of entry to date of reappearance of disease. Site(s) and date of relapse will be recorded. Recurrent disease

will be defined as pelvic or distant. Pelvic sites will be specified as vaginal or other, and distant sites will be specified as to their anatomic location. Relapse should be confirmed by histological or cytological evaluation when possible.

7.2 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

7.3 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.4. **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. If there is no measurable disease at the beginning of treatment, the same method of assessment will apply only to the follow-up period. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. Non-measurable disease Patients with completely resected disease after primary surgery, or with non-measurable disease, will also be included for

evaluation of response. In these patients, no new growth of measurable disease detected by any of the following method will be considered an adequate method of measurement.
Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. Conventional CT and MRI These should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
PET/CT: At present, the low dose or attenuation correction of CT portion of a combined PET-CT is not always of optimal diagnostic quality for use with RECIST measurements. The PET portion of the CT introduces additional data which may bias an investigator if it is not routine or serially performed.
Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at later date, and they are operator dependent; it cannot be guaranteed that the same technique and measurement will be taken from one assessment to the next. If there is concern about radiation exposure at CT, MRI may be used instead.
Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. The Gynecologic Cancer Intergroup has developed CA-125 progression criteria that have been integrated with objective tumor assessment for use in first-line trials in ovarian cancer. [47] In women with high risk uterine carcinoma, CA-125 levels have been shown to correlate with advanced stage and prognosis1, [48, 49].
Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

7.5 **Response Criteria**

7.51 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions
Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. Or sustained non measurable disease, if there is no measurable disease at baseline.

7.53 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

7.54 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment. The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

	Non-Target Lesions	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	>4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	>4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once >4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

"symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

7.6 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

7.7 **Progression-Free Survival (PFS)**

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever happens first.

7.8 **Overall Survival (OS)**

OS is defined as the duration of time from start of treatment to time of death or date of last contact, whichever happens first.

8.0 DURATION OF STUDY

Patients may continue therapy until disease progression, death (from cancer or other), prohibitive toxicity, or until patient decides to withdraw from the study. The duration of study lasts until the completion of 6th cycle of IV/IP chemotherapy

8.1 Duration of Follow Up

Patients will be followed for every 3 months for the first two years, and every 6 months for three years and yearly thereafter, or until death, whichever occurs first. In total, patients will be followed for a maximum of 10 years. Testing such as CA-125 or CT scans may be performed at discretion of the primary physician once off-study. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

8.2 **Criteria for Removal from Study**

Patients may voluntarily withdraw from study at any time

Patients should be discontinued from study if there is clinical evidence of progression of disease, or prohibitive toxicity as indicated in section 6.0

Inability to comply with study requirements

9.0 **Adverse Event Reporting**

An adverse event refers to any adverse medical change from the patient's baseline (or pre-treatment) condition which occurs during the course of a clinical study, after starting treatment, whether considered treatment related or not.

Adverse events may be volunteered spontaneously by the patient, or be discovered as a result of general questioning by the investigator or by physical examination. Also to be reported is any patient requiring hospitalization while on protocol or any grade 4 hematologic or grade 3 or 4 non-hematologic toxicity. All adverse events occurring during this clinical study must be reported to the PI and accurately recorded in the adverse events form within 10 days of the toxic event.

Both chemotherapy and radiation treatment breaks should be noted and the reasons should be documented.

9.0 **Adverse Event Characteristics**
CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting (http://ctep.cancer.gov).

9.1.1 Attribution of the AE:
Definite – The AE is clearly related to the study treatment.
Probable – The AE is likely related to the study treatment.
Possible – The AE may be related to the study treatment.
Unlikely – The AE is doubtfully related to the study treatment.
Unrelated – The AE is clearly NOT related to the study treatment.
9.2 Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
9.3 Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported.

10.0 STUDY PARAMETERS

10.1 Pre Study Evaluation
This evaluation requires completion within 21 days of registration, unless otherwise described. Baseline requirements will consist of a thorough history and physical examination. An ECG < 6 months prior to registration and laboratory tests will be obtained. Tests include, CBC with differential, platelet count, serum chemistry, including electrolytes, creatinine, BUN, glucose, magnesium, calcium, albumin, phosphorous, liver function tests, CA-125, and urinalysis. Histological documentation of UPSC is required. Pre-study CA125, CT scan of chest, abdomen and pelvis, and CXR (not required if CT of the chest is available) will be obtained.
10.2 Tests during Treatment: Please refer to Appendix A (Study Schedule)
Weekly: CBC with differential and platelet count
Every 3 weeks (each cycle): CBC with differential and platelet count electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, CA125. Every 3 weeks (each cycle): Complete review of systems and complete physical examination, including pelvic examination, clinical evaluation for ototoxicity and neuropathy. Weight and performance status will be documented.
10.3 End of Study Evaluation
This evaluation includes a complete history and physical examination and documentation of weight and performance status. Laboratory tests include a complete blood count with differential and platelet count, electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, CA125 and urinalysis. CT scan of chest, abdomen and pelvis will be obtained at the completion of the entire IP/carboplatin protocol or earlier if indicated.
10.4 Follow-up
Patients will be evaluated every 3 months for the first 2 years and every 6 months for the next 3 years. Evaluation at each visit includes a complete history and physical examination and documentation of weight and performance status. Laboratory tests to be performed in this follow-up period is up to primary provider's discretion, but generally include a complete blood

count with differential and platelet count, electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, CA125, urinalysis. Surveillance imaging such as CT scan is performed up to provider's discretion, but generally performed annually or earlier if clinically indicated. After a total of 5 years, patients will be seen annually.

10.5 Quality of Life (QoL)

QOL will be assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-c30) version 3.0. To date, more than 2200 studies using QLQ-C30 have been registered. This 30-item summary score captures the dimension of physical well-being, functional well-being, and symptom scales. In addition, the ovarian cancer module (QLQ-OV28) questionnaire will supplement the core QLQ-c30 module, and is designed for patients with local or advanced disease who receive treatment by surgery with or without chemotherapy. It consists of 28 items assessing symptoms addressing peripheral neuropathy, chemotherapy side effects, body image and sexuality. Scoring for these questionnaires is formalized (Appendix 2) 10.5.1. Quality of Life assessment Intervals Three assessment points are recommended:

Prior to cycle 1

At completion of IV/IP chemotherapy (or at time of discontinuation from study)

At completion of the radiation therapy, if given.

At two years post diagnosis, if feasible.

Adverse Effects Profile: Neutropenia, thrombocytopenia, anemia, alopecia, injection sites reactions, radiation recall, rash, nausea, vomiting, mucositis, increased liver enzymes, hepatic failure and necrosis, sensory changes, peripheral neuropathy, arthralgia and myalgia, seizures, mood alterations, encephalopathy, motor and autonomic neuropathy, hypersensitivity (thought to be caused by Cremophor vehicle), atrial arrhythmia, sinus tachycardia and premature beats, syncope, hypotension, myocardial infarction, hypertension. Other: fatigue, headaches, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities.

Supplier: Commercially available.

Carboplatin

Other Names: CBDCA, Paraplatin ®, JM-8, NSC-241240

Classification: Second generation tetravalent organic platinum compound.

Mechanism of Action: Like cisplatin, carboplatin produces predominantly inter-strand DNA crosslinks rather than DNA-protein crosslinks. Cell-cycle nonspecific.

Storage and Stability: Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 500ucg/ml, solutions have the following stability: in normal saline, 8 hours at 25 C, 24 hours at 5 C; in 5% dextrose (when reconstituted in sterile water), 24 hours at 25 or 5 C.

Route of Administration: IP

NOTE: Avoid the use of aluminum, as carboplatin forms a precipitate.

Dose Specifics: The dose of carboplatin based on target AUC is calculated by the Calvert formula:

Dose (mg) = AUC x (GFR + 25).

Where AUC is 6.0 pre-radiation and 5.0 post-radiation and GFR is the calculated renal function according to the method of Cockcroft and Gault:
GFR (ml/min) = 0.85 x {(140-age)/Scr)} x {wt(kg)/72}.
Please refer to Appendix 3 for Carboplatin calculation form.
The normal range of serum creatinine is from 0.5 to 1.5 mg/dl. In patients of the same age with "normal creatinine", their carboplatin dosage may vary significantly if one has a value of 0.5 and the other has a value of 1.0. Patients of the same age with a creatinine of 0.5 would have a considerably higher carboplatin dose (two times) than a patient with the same age with a creatinine of 1.0. Therefore, we are using a creatinine of 0.8 mg/dl in the GFR calculation for all patients whose creatinine is at or below 0.8 mg/dl. While this may be arbitrary, it minimizes the potential significant toxicity associated with a very high carboplatin dosage, yet maintains dosages for all patients at therapeutic values."
Drug Interactions: Aminoglycosides may potentiate renal toxicity. Forms a precipitate when in contact with aluminum.
Adverse Effects Profile: Neutropenia, thrombocytopenia, anemia, rash, rare alopecia, hypersensitivity reactions, nausea, vomiting, increased liver enzymes, nephrotoxicity, elevations in serum creatinine and BUN, electrolyte losses (Mg, K, Na, Ca), peripheral neuropathy, rare ototoxicity, hypotension, flushing, chest pain, pruritus, bronchospasm, Other: pain, asthenia, flu-like syndrome.
Supplier: Commercially available.

8.1 Drug Information**:**

Paclitaxel
Other Names: Paclitaxel, NSC 673089
Classification: Anti-microtubule Agent
Mechanism of Action: Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.
Storage and Stability: Vials are stored at room temperature (approximately 25C F). Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/ml in normal saline or 5% dextrose are stable for up to 27 hours when stored at room temperature and normal room light. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2-micron filters showed no appreciable loss of potency.
Route of Administration: Intravenous
The concentrated solution must be diluted prior to use in normal saline, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 to 1.2 mg/ml. In-line filtration with a 0.22-micron filter should be used. Solutions exhibit a slight haze, common to all products containing nonionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC containing (nitroglycerin) infusion sets should be used. NOTE: Avoid the use of PVC bags and infusion sets, due to leaching of DEHP (Plasticizer). Solutions exhibiting excessive particulate formation should not be used.
Dose Specifics: Paclitaxel is given at a dose of 135 mg/m2, infused over one hour and given at a dose of 80 mg/m2 on Day 8 of treatment repeated every 3 weeks. In minimally pretreated patients, doses up to 200-250 mg/m2 have been used.

Drug Interactions: Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole may inhibit paclitaxel metabolism, based on in vitro data.

12.0 STATISTICAL CONSIDERATIONS

The primary objectives of this pilot Phase II study are to determine the tolerability and feasibility of the proposed regimen. In patients with advanced ovarian cancer who received the same types and doses of IV/IP chemotherapy in a similar clinical trial (GOG 172), discontinuation of IP therapy was most commonly due to: 1) catheter complications; 2) intolerance of platinum with nausea, renal dysfunction and electrolyte disturbances; 3) intolerance to the abdominal distention from IP infusion[50]. Neuropathy also occurred in some, but was generally not evident until the later cycles. Generally, when subjects are unable to tolerate IP chemotherapy, they receive the remainder of their cycles IV. Since advanced endometrial cancer patients have generally more bulky disease than ovarian cancer patients and are less likely to have an immediate response, it is expected that there will be subjects on this trial who will not be able to complete this therapy. The degree of tolerability will be estimated by the proportion of participants who complete 6 treatment cycles of IP-carboplatin. A total of **17** patients will be enrolled into the study. An early stopping rule for lack of tolerability will be implemented as follows, based on Simon's Minimax two-stage design. After the first 13 patients have been enrolled and evaluated, the trial will be terminated early if fewer than 5 patients tolerated the treatment. If 5 or more patients are observed to complete the regimen, the trial will continue until a total of 17 patients have been evaluated. At the end of the trial, the treatment will be considered tolerable and worthy of further study if 9 or more patients completed the regimen out of 17 patients. The target tolerability rate is assumed to be 60%. The design specified above has the following operating characteristics. The probability of accepting the treatment for further study if the tolerability rate is unacceptably low (< 40%) is at most 20%. In contrast, there is an 80% probability of accepting the treatment for further study if the tolerability rate is at least 60%. The expected sample size is 15.6 subjects. At the end of the study, the proportion of patients who tolerated the therapy will be estimated, along with corresponding 95% confidence intervals. Reasons for discontinuation of therapy will be categorized and summarized by computing frequencies. Response will be evaluated using an endpoint of one-year progression-free survival. The proportion of responders at one year will be estimated with the Kaplan-Meier method. Surrogate endpoint biomarkers including estrogen, progesterone, and Her2/neu receptor status will be correlated with progression-free survival using the Cox Proportional Hazards model, provided the availability of a sufficient number of events.

Based on our tumor board reporting, the accrual is expected to be at most 1 every other month, for a total accrual period of about twenty four months. Follow up is a minimum of one year after the last patient is accrued in order to assess response. Therefore, total study time is expected to be at least 40 months.

13.0 DATA SAFETY MONITORING PLAN

This study will be added to the CSSRC for internal study review. All adverse events will be forwarded to the committee and monitored on a monthly basis

14.0 RECORDS TO BE KEPT

Forms to be submitted:
ECOG Master On-Study Form Within one week of registration
Pathology Report Within one week of registration
ECOG CTC Flow Sheet Baseline within one week of registration.
On Treatment: Every month
Off Treatment: See Follow-up
ECOG Follow-Up Form Every month while on study
At completion of treatment
Every 3 months if < 2years from study entry
Adverse Reaction (ADR)
Within 10 days of reportable toxic event

15.0 PATIENT CONSENT AND PEER JUDGEMENT

All institutional, state, and national guidelines concerning informed consent and peer review will be observed.

16.0 MINORITIES AND WOMEN STATEMENT

This study will be open to patients undergoing treatment at Northwell Health.
Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the target population.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional, NCI and Federal regulations concerning the Informed Consent form will be fulfilled. Annual reports will be provided to the IRB.

18.0 ELIGIBILITY CHECKLIST

Histological/cytologically documented primary uterine serous carcinoma. Surgical staging to include total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washings, and lymph node sampling or surgical cytoreduction to include total abdominal hysterectomy, bilateral salpingo-oophorectomy, debulking of intraperitoneal tumor.
Residual disease after primary surgery ≤ 1 cm
Age > 18 years.
ECOG performance status of ≤ 2.
Written voluntary informed consent.
Patient has no impairment of renal, hepatic or hematologic function as defined in section 3.2
Patient has not received myelo-suppressive therapy in the past 3 weeks.

Patient does not have severe or uncontrolled concurrent medical disease (eg. uncontrolled diabetes, angina, myocardial infarction within 6 month, congestive heart failure, etc.)
Patients has no dementia or altered mental status that would prohibit the give and understanding of informed consent at the time of study entry.

Patient Name _____

Patient MR# _____

Treating Physician _____

Principal Investigator (Signature)_____

APPENDIX 1: STUDY SCHEDULE Parameter	**Pre-study** *(within 21 d)*	**D1 of Each cycle**	**D8of each cycle**	**Completion of Study**	**Follow-up Visit6**
Medical History & Physical Exam1	X	X	X	X7	
Informed Consent		X		X	
Weight, Height1	X	X	X	X	X7
Performance Status1	X	X	X	X7	
Vital Signs	X		X	X7	
CBC with differential, platelets1	X	X	X	X	X7
Serum Chemistry1,2	X	X	X	X7	
Urinalysis1	X		X	X7	
CA-1251	X	X	X	X7	
EKG3		X		X	
Serum Pregnancy Test4			X		
Radiologic Evaluation5	X		X	X7	
Adverse Event Evaluation1	X	X	X	X7	
QoL survey8		X		X	

1. May be performed within 7 days of start of new cycle

2. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
3. EKG within 6 months prior to registration is acceptable
4. Women of child bearing potential
5. CT scan including chest, abdomen and pelvis, with or without PO/IV contrast, or PET/CT
6. Recommend follow up visit every 3 months for two years, then every 6 months for three years, then yearly thereafter.
7. As clinically indicated.
8. QoL survey at four time points: beginning of study, after completion of chemotherapy, and completion of radiation (if given radiation as judged by primary physician), and at two years post diagnosis, if feasible

APPENDIX 2: See Attached

APPENDIX 3: Carboplatin Calculation Worksheet

CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).
2) Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.
3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to "non-IDMS" conversion) is also available, if needed for dose modifications (see below).

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
GOG-0262/ACRIN 6695
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:
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. 2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated

APPENDIX 4: FIGO Staging: Endometrial Cancer Stage

Ib	Tumor confined to the corpus uteri.
IAb	No or less than half myometrial invasion.
IBb	Invasion equal to or more than half of the myometrium.
IIb	Tumor invades cervical stroma but does not extend beyond the uterus.
IIIb	Local and/or regional spread of the tumor.
IIIAb	Tumor invades the serosa of the corpus uteri and/or adnexa.
IIIBb	Vaginal and/or parametrial involvement.
IIICb	Metastases to pelvic and/or para-aortic lymph nodes.
IIIC1b	Positive pelvic nodes.
IIIC2b	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes.
IVb	Tumor invades bladder and/or bowel mucosa, and/or distant metastases.
IVAb	Tumor invasion of bladder and/or bowel mucosa.
IVBb	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes.

aAdapted from FIGO Committee on Gynecologic Oncology.[1]
bEither G1, G2, or G3 (G = grade).
cEndocervical glandular involvement only should be considered as stage I and no longer as stage II.
dPositive cytology has to be reported separately without changing the stage.

APPENDIX 5: Abbreviation List

QoL
Quality of Life

EORTC	**European Organization for Research and Treatment of Cancer**
QLQ	**Quality of Life Questionnaire**
FIGO	**International Federation of Gynecology and Obstetrics**
IV / IP	**Intravenous / Intraperitoneal**
Fx	**Fraction**
IMRT	**Intensity Modulated Radiation Therapy**
USC	**Uterine Serous Carcinoma**
HDR	**High Dose Radiation**
Gy	**Gray**
GOG	**Gynecologic Oncology Group**
RT	**Radiation therapy**
AUC	**Area Under Curve**
PFS	**Progression Free Survival**
EBRT	**External Beam Radiation Therapy**
NCI	**National Cancer Institute**
ECOG	**Eastern Cooperative Oncology Group**
ANC	**Absolute Neutrophil Count**
GFR	**Glomerular Filtration Rate**
CT	**Computed Tomography**
PO	**Per Os (by mouth)**
Fr	**French**
AP	**Anterior Posterior**
WBC	**White Blood Cells**
G-CSF	**Granulocyte colony – stimulating factor**
PEG_filgrastim	**Pegylated - filgrastim**
GM-CSF	**Granulocyte macrophage colony stimulating factor**
DLT	**Dose Limiting Toxicity**
PLT	**Platelet**
AST	**Aspartine Aminotransferase**
ALT	**Alanine Aminotransferase**
RECIST	**Response Evaluation Criteria in Solid Tumors**
MRI	**Magnetic Resonance Imaging**
LD	**Longest Diameter**
PET	**Positron Emission Tomography**

CR	**Complete Response**
PR	**Partial Response**
PD	**Progression Disease**
SD	**Stable Disease**
BUN	
Mg	**Magnesium**
K	**Potassium**
Na	**Sodium**
Ca	**Calcium**

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