RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-08

A PHASE II STUDY OF ADJUVANT POSTOPERATIVE IRRADIATION
COMBINED WITH CISPLATIN/TAXOL CHEMOTHERAPY FOLLOWING TAH/BSO
FOR PATIENTS WITH HIGH-RISK ENDOMETRIAL CANCER

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**Surgery** (prior to study entry)
Total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without additional staging.

**Chemotherapy**
Two courses cisplatin (50mg/m²) given on days 1 and 28. Four courses of cisplatin (50mg/m²) and Taxol(175mg/m²) given at 4 week intervals following completion of radiotherapy.

**External Radiotherapy**
Pelvic radiation to 45 Gy, 1.8 Gy per day, five days per week (25 fractions). Within two weeks after completion of external beam, brachytherapy boost to the vagina will be delivered.

**Intracavitary RT**
Intracavitary insertions will be given with either a single low dose rate (LDR) application of 20 Gy to the vaginal surface or three high dose rate (HDR) applications to deliver an additional 18 Gy to the vaginal surface. If HDR brachytherapy is used, the three insertions should be completed before day 56. More than one insertion may be given per week.

**Eligibility** (see Section 3.0 for details)
- Patients must have had a hysterectomy (total abdominal, vaginal hysterectomy, or laparoscopic-assisted vaginal hysterectomy) and bilateral salpingo-oophorectomy no more than 8 weeks prior to start of radiation therapy. Additional surgical staging procedures are permissible but not required.
- No prior chemotherapy or radiation therapy.
- Risk factors: patients must fit one of the following:
  - Grade 2 or 3 with myometrial invasion >50%
  - Grade 2 or 3 with stromal invasion of cervix
  - Known extrauterine disease (excluding second primary) confined to the pelvis. Positive peritoneal cytology is acceptable.
- No known metastases above the iliac bifurcation, no known gross residual disease, or distant metastases.
- KPS ≥ 70; Age ≥ 18.
- WBC ≥ 4000/mm³, granulocytes ≥ 1500/mcl, platelets ≥ 100,000/mcl.
- Acceptable hepatic and renal function: creatinine ≤ 1.4 mg%, bilirubin and SGOT ≤ 2 x normal.
- No medical contraindications to chemotherapy, or radiation therapy.
- Study-specific signed informed consent.

**Required Sample Size:** 40 9/8/98
<table>
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<th>Case #</th>
<th>ELIGIBILITY CHECK (9/8/98)</th>
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1. Does the patient have histologically proven endometrial cancer? (Y/N)  
2. Does the patient have a grade I adenocarcinoma, papillary serous or clear cell cytology? (Y/N)  
3. Did the patient have a hysterectomy (total abdominal, vaginal hysterectomy, or laparoscopic-assisted vaginal hysterectomy) and bilateral salpingo-oophorectomy? (Y/N)  
4. Will the patient start XRT no more than 8 weeks after surgery? (Y/N)  
5. Has the patient received prior chemotherapy or radiation therapy? (Y/N)  
6. Does the patient have a history of other malignancies other than non melanomatous skin cancer? (Y/N)  
   - If yes, has the patient been disease free for ≥ 5 years? (Y/N)  
7. Does the patient have gross residual disease or suspected extra pelvic disease (other than positive pelvic washings)? (Y/N)  
8. Does the patient have evidence of distant metastasis? (Y/N)  
9. What is the patient's age? (≥18)  
10. What is the patient's Karnofsky Performance Status? (≥ 70)  
11. What is patient's WBC count? (x 1000) (≥ 1500)  
12. What is the patient's granulocyte count? (≥ 100)  
13. What is the patient's platelet count? (x 1000) (≤ 1.4)  
14. What is the patient's creatinine? (Y)  
15. Are the bilirubin and SGOT ≤ two times normal? (Y)  
16. One of the following tumor characteristics must be present for eligibility, check one.  
   - Grade 2 or 3 carcinoma with greater than 50% myometrial invasion  
   - Grade 2 or 3 carcinoma with stromal invasion of the cervix  
   - Known extrauterine disease (excluding second primary) confined to the pelvis. Positive peritoneal cytology is acceptable.
N 17. Does the patient have a history of cardiac dysrythmias?
Y 18. Did the patient sign a study-specific informed consent form?

The following questions will be asked at Registration:

Y 1. Was the Eligibility Checklist (above) completed?
Y 2. Is the patient eligible for this study?

__________________________
Patient's Name

__________________________
Verifying Physician

__________________________
Patient ID #

__________________________
Referring Institution # (if different)

__________________________
Medical Oncologist

__________________________
Birthdate

__________________________
Race

__________________________
Social Security Number

__________________________
Zip Code (9 digit if available)

__________________________
Method of Payment

__________________________
Will any component of the patient’s care be at a VA or military facility?

__________________________
Treatment Start Date

__________________________
Treatment Assignment

Completed by ____________________________ Date ____________________________
INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy affecting American women. Over 6,000 women die each year of cancer of the uterine corpus.1 Women who experience the greatest risk of disease recurrence and death include those with high grade histology, deep myometrial penetration, cervical stromal involvement, and/or extrauterine disease.2

Patients with high-risk features who have not received adjuvant irradiation have been reported to have a recurrence incidence ranging from 15-20%.3-5 Adjuvant pelvic radiation for patients with disease confined to the uterus results in local recurrences in 0-6.5%.3,7 However, distant metastases remain a problem. Greven et al. and Mayr et al. reported that 25% and 26% of patients respectively, with grade 3 histology confined to the uterus recurred with distant metastasis.8,9 Distant metastasis have been documented in approximately 20% of patients with involvement of the cervix.10-12 At least 30% of patients with extrauterine disease who receive adjuvant involved field irradiation recur at distant sites.13-15

Although surgical staging has been adopted by FIGO for women with endometrial cancer, it is not clear that the standard of care in the community, or even in academic tertiary referral centers, includes a universally accepted systematic approach to staging. Further recommendations regarding adjuvant therapy are then tailored to reflect the risk factors related to nodal positivity: depth of myometrial penetration, histologic grade and cervical involvement. Reasons that lymph node evaluations may not be done include the fact that at least three studies have shown a significantly increased risk of severe late complications when pelvic irradiation follows lymphadenectomy.16-18 Secondly, preoperative assessment of grade and stage often underestimates the actual involvement appreciated at the time of pathologic assessment.19,20 Thirdly, a proportion of patients with this disease (perhaps 20-30%) are poor candidates for extensive surgical procedures because of body habitus or concurrent medical conditions.21 Finally, Morrow et al. in a large surgical staging protocol for patients with clinical stage I endometrial cancer, documented that only 2% of patients (18/895) had isolated pelvic node involvement.2

Because "complete" surgical staging is not always performed, such patients are not eligible for most national cooperative group protocols. A protocol directed at these patients has not been previously proposed. Typically these patients are treated in a variety of ways based on institutional policies founded upon individual biases or historical experiences. For this reason, it is proposed to treat patients with a demonstrated high rate of distant metastasis with both local irradiation and systemic chemotherapy.

There is limited published experience using adjuvant cytotoxic agents for endometrial cancer. The Gynecologic Oncology Group (GOG) has conducted an adjuvant trial for high-risk patients who received postoperative whole pelvic irradiation and were then randomized to receive 60 mg/m² of doxorubicin every 3 weeks or no further therapy.22 No statistically significant differences in survival rates could be demonstrated. However, the number of women accrued to this study was believed to be adequate (n=181). A nonrandomized study from M.D. Anderson Cancer Center documented an excellent disease-free survival rate in high-risk patients without extrauterine disease who received six cycles of cisplatin/doxorubicin/cyclophosphamide.23 Another nonrandomized trial reported 58% disease-free survival in 26 patients with adjuvant PAC + pelvic irradiation.24

Phase II chemotherapy trials in women with advanced or recurrent endometrial cancer have identified doxorubicin,25,26 cisplatin,27-29 and carboplatin30-32 as active agents with response rates of 30-35%. A recent trial by the GOG has suggested a similar level of activity for paclitaxel.33 In the preliminary report, objective responses were reported in 10 of 28 (36%) evaluable patients treated at a dose of 250 mg/m². Experience combining cisplatin (in a variety of dose schedules) with external beam irradiation is extensive. Similar clinical experience suggests poor tolerance for combined therapy that includes simultaneous radiotherapy and doxorubicin. At present, toxicity data for the combination of irradiation and paclitaxel is limited and preliminary. For these reasons, this protocol proposes to use a sequential approach to combined modality therapy: initial treatment with cisplatin and external beam irradiation will be followed by 4 cycles of cisplatin/paclitaxel chemotherapy. This sequential approach addresses the dual risks of local and distant failure in the high-risk group of patients selected. The 50 mg/m² dose for cisplatin was selected because of known activity at this dose level and concern for inducing significant neutropenia and neurotoxicity if larger doses were employed. The 175 mg/m² dose for paclitaxel was selected on the basis of experience in women with ovarian cancer who tolerated cisplatin/paclitaxel combinations at these dose...
levels with acceptable morbidity. Paclitaxel dose reductions are planned in patients with severe neutropenia not responsive to G-CSF support or those with significant neurotoxicity.

In summary, this study attempts to address a common clinical dilemma: how to manage incompletely staged patients with known high-risk disease and a substantial historical incidence of distant failure despite the widespread use of adjuvant pelvic irradiation. If this trial proves feasible with acceptable toxicity, further exploration in a phase III setting will be planned.

2.0 OBJECTIVES
2.1 To establish the safety and toxicity of this combination of chemotherapy and irradiation when given following surgery for endometrial carcinoma.
2.2 To determine patterns of recurrence and survival in this patient group.
2.3 To determine the feasibility of this treatment approach.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility
3.1.1 Patients must have undergone hysterectomy (total abdominal, vaginal hysterectomy or laparoscopic-assisted vaginal hysterectomy) and bilateral salpingo-oophorectomy with or without additional surgical staging procedures for endometrial cancer no more than 8 weeks prior to start of RT.
3.1.2 Patients must have no known metastatic disease outside of the pelvis.
3.1.3 Patients must have typical endometrial adenocarcinoma with one of the following:
   • Grade 2 or 3 carcinoma with greater than 50% myometrial invasion.
   • Grade 2 or 3 carcinoma with stromal invasion of the cervix
   • Extrapelvic disease (excluding second primary) confined to the pelvis. Positive peritoneal cytology is acceptable.
3.1.4 Patients must have a Karnofsky performance score ≥ 70.
3.1.5 Age ≥ 18 years.
3.1.6 Patients with adequate bone marrow, renal and hepatic function:
   WBC ≥ 4,000/mcl;
   Granulocytes ≥ 1500/mcl;
   Platelets ≥ 100,000/mcl;
   Creatinine ≤ 1.4 mg/%;
   Bilirubin, SGOT ≤ two times normal.
3.1.7 Patients must sign a study-specific informed consent form.
3.2 Ineligible Patients
3.2.1 Patients who have received prior radiation therapy or chemotherapy.
3.2.2 Patients who have a history of other malignancy, with the exception of non-melanomatous skin cancer, unless disease free for ≥ 5 years.
3.2.3 Patients who have gross residual disease, suspected extrapelvic disease (other than peritoneal washings), or distant metastatic disease.
3.2.4 Patients with Grade I adenocarcinoma, any papillary serous, or clear cell histology.
3.2.5 Patients with cardiac dysrhythmias.

4.0 PRETREATMENT EVALUATION
4.1 Required Evaluations
4.1.1 Complete history and physical examination including height, weight, Karnofsky Performance Status (Appendix II) and body surface area (BSA).
4.1.2 Histologic proof of adenocarcinoma. All patients will have confirmation of diagnosis by total abdominal hysterectomy.
4.1.3 All patients should undergo complete blood count, BUN, serum creatinine, bilirubin, SGOT and alkaline phosphatase.
4.1.4 Chest radiograph (PA and lateral) within 6 weeks prior to registration.
4.1.5 CT abdomen and pelvis; imaging studies to evaluate response when clinical exam measurements are not possible.
4.1.6 Audiogram.
REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. Patients may also be registered via computer modem 24 hours a day, 7 days a week. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Demographic Data
- Treatment Start Date

RADIATION THERAPY

6.1 Radiation therapy is to begin within 8 weeks following surgery.

6.2 Patients will be treated with a combination of external and intracavitary irradiation.

6.2.1 Pelvic Radiation: The pelvis will be treated to a total dose of 45 Gy in 5 weeks. Patients will be treated once-a-day, 5 days per week with a daily fraction size of 1.8 Gy. Four-field technique (AP-PA opposed and lateral opposed fields) must be used if treatment is delivered with a beam energy of < 15MV.

6.2.2 Intracavitary Applications: Cesium may be used with standard intracavitary systems. For low dose rate applications, 20 Gy to the vaginal surface in a single application will be given. For high dose rate application, 18 Gy in three applications will be given.

External Radiotherapy

6.3.1 Physical Factors: A megavoltage beam of 4 MV or greater, with a minimum source-axis distance of 100 cm.

6.3.2 Radiation Therapy Fields:

6.3.2.1 Simulation: All fields treated require simulation and portal verification on the treatment unit. Patients should drink barium 1 hour prior to simulation to opacify the small bowel. Copies of these films are to be submitted to RTOG Headquarters.

6.3.2.2 Pelvic Portal (AP-PA)
- Superior border: A transverse line between L5 and S1.
- Lateral border: 1-1.5 cm lateral to the widest true pelvic diameter.
- Inferior border: A transverse line below the obturator foramen and at least 4 cm beyond the vaginal cuff. A radio-opaque marker in the vagina to mark the vaginal cuff will help to facilitate proper placement of the lower border.
- Custom blocking: to shield small bowel and femoral heads should maintain a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina.

6.3.3 Pelvic Portal (lateral fields)

Superior border: Identical to AP-PA fields.
Anterior border: A line drawn through the symphysis pubis and at least 1 cm anterior to common iliac nodes at L5-S1.
Posterior border: Care should be taken to include at least S1-S3.
Inferior border: Identical to AP-PA fields
- Custom blocking: should be used to shield anterior small bowel if possible, maintaining a margin of at least 1 cm from common and external iliac nodes. Blocking MAY split the L5/S1 vertebral body to shield posterior soft tissue and split the sacrum to provide adequate margin for pre-sacral nodes. Posterior rectum may be blocked.

6.3.3.1 External Beam Treatment Techniques and Dose Specifications:

When patients are treated with a 4-field technique the contribution to AP-PA and lateral ports should be calculated by optimizing the dose distribution by obtaining isodose curves of the pelvis.
All fields should be treated daily throughout the treatment course. AP and PA fields alone may be used if the external beam energy is $\geq 15$ MV.

6.3.3.2 The specification of target dose is in terms of a dose to a point at or near the center of the target volume. For the following portal arrangements, the target dose will be specified as follows:
- For 2 opposed coaxial equally weighted beams: On the central ray at mid separation of beams.
- For a 4-field arrangement of beams: At the isocenter of the beams.

The maximum dose in the target volume should not exceed the central dose by more than 5%.

6.3.4 Radiation Treatment Interruption

6.3.4.1 If interruption of two weeks or less occurs, radiation should be completed to the prescribed total dose.

6.3.4.2 When therapy interruptions of more than two weeks occur, this will be considered a major deviation from the protocol and resumption of therapy will be at the discretion of the Radiation Oncologist.

Follow-up must continue regardless of radiation treatment received.

6.4 Intracavitary Radiotherapy Technique and Dose Specifications (Appendix VI)

6.4.1 (9/8/98) The vaginal brachytherapy boost should follow the external beam irradiation and be started within two weeks of completion of the pelvic irradiation. If high dose rate applications are to be used, the insertions should be given in such a way to allow completion of the three insertions prior to beginning chemotherapy on day 56. More than one insertion may be performed per week. Iridium OR cesium sources are to be used for intracavitary application(s) with vaginl applicators for after-loading applicator system.

6.4.2 It is preferable to treat the vaginal cuff only (treatment of the entire length of the vagina is discouraged and may increase morbidity). Not more than 2/3 of the vagina should be included in the treatment volume. Colpostats/ovoids or cylinders may be used.

6.4.2.1 For low dose rate applications: A dose of 20 Gy prescribed to the vaginal surface at a dose rate of 0.8-1.2 Gy per hour. Colpostats or cylinders may be used. The largest possible cylinder diameter should be selected. Colpostats should be secured with maximal packing in order to minimize dose to the adjacent bladder and rectum.

6.4.2.2 For high dose rate applications: Three applications of 6 Gy each prescribed to the vaginal surface. This will give a total of 18 Gy. Dose will be prescribed at the vaginal surface.

6.4.3 A report on the dose to rectum and bladder and vaginal surface is mandatory.
- Bladder dose may be calculated at a reference point which is obtained as follows: A Foley catheter is used. The balloon must be filled with 7cm$^3$ of radio-opaque fluid. On the lateral radiograph, the reference point is obtained on an anterior-posterior line drawn through the center of the balloon. The reference point is taken on this line at the posterior surface of the balloon (see Appendix VI). On the frontal radiograph, the reference point is taken at the center of the balloon.
- Rectal dose may be calculated by either introducing contrast material in the rectum and marking a point on the rectal wall adjacent to the applicator system or determining the point 0.5 cm posterior to the vaginal ovoids or vaginal packing in the lateral projection.
- Vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid or cylinder.

6.5 Dose to Critical, Sensitive Structures

Critical sensitive structures are to be considered in the treatment planning. The following maximal doses for the entire radiotherapy regimen are suggested.

6.5.1 Small bowel: 55 Gy
6.5.2 Bladder: 70 Gy
6.5.3 Rectum: 65 Gy
6.5.4 Vaginal surface: 100 Gy

6.6 Expected Radiation Toxicities

6.6.1 Side effects expected from radiotherapy include tiredness near the end of treatment, diarrhea, nausea and vomiting, rectal irritation, urinary frequency and dysuria, loss of pubic hair, reddening and irritation of the skin in the irradiated field, and depression of blood counts. Long-term side effects, although uncommon, may include chronic malabsorption, rectal ulcer, bleeding or stricture, dysuria, hematuria, bowel obstruction, shortening of the vagina, dyspareunia, vaginal vault necrosis and fistula formation between pelvic tissues.

6.6.2 RT toxicities and time of onset will be recorded on data collection forms.

6.6.3 Treatment breaks should be noted. The reason should be documented.
6.7 Protocol Compliance

6.7.1 Per Protocol

6.7.2 Variation from Protocol - Acceptable
- More than 2 weeks interruption of external beam RT
- External beam RT–final doses vary +/-10%
- Intracavitary RT–final doses vary +/-25%

6.7.3 Deviation from Protocol - Unacceptable
- No chemotherapy
- Doses of RT vary more than 10% for external RT and 25% for intracavitary RT
- Field of RT is other than pelvic contents (whole abdomen or paraaortic RT).

7.0 CHEMOTHERAPY DRUG INFORMATION

7.1 Cisplatin (Platinol)

7.1.1 Formulation: Cisplatin is available as a dry powder supplied in 10 mg and 50 mg vials and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride.

7.1.2 Preparation: The 10 mg and 50 mg vials should be reconstituted with 10 ml or 50 ml sterile water for injection, USP respectively. Each ml of the resulting solution will contain 1 mg of Platinol. Reconstitution as recommended results in a clear colorless solution.

NOTE: Aluminum reacts with Platinol causing precipitation 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 Platinol.

7.1.3 Storage: Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature. The aqueous solution should be stored at room temperature and protected from light. The reconstituted solution is stable for 20 hours at room temperature.

NOTE: Once reconstituted, the solution should be kept at room temperature. If the reconstituted solution is refrigerated, a precipitate will form.

7.1.4 Adverse Effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions. Infrequent: Cardiac abnormalities, anorexia, elevated SGOT; rash and alopecia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

Severe renal toxicity can be largely avoided by intravenous hydration or administration of mannitol. Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if BUN > 30 mg/dl or creatinine > 1.8 mg/dl develop. Mild or severe electrolyte abnormalities may occur (5%) as acute or chronic complications, especially hypokalemia or hypomagnesemia. Monitoring of electrolytes and electrolyte replacement will usually correct these abnormalities. Rarely, severe hypomagnesemia and hypocalcemia may require replacement therapy and discontinuation of treatment with cisplatin.

Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment. Patch or skin tests are recommended for patients with suspected allergy to cisplatin. An emergency set for the treatment of allergic reactions should be available in the treatment area.

Local necrosis and thrombophlebitis can be avoided by careful administration.

Neurotoxicity is related to cumulative dose and severe toxicity can be largely avoided by careful monitoring for evidence of paresthesias and timely discontinuation of treatment. Ataxia has been described.

Ototoxicity may occur.

NOTE: Eighth (VIII) nerve toxicity resulting in hearing loss and (less commonly) vestibular symptoms, is a well-documented complication of cisplatin treatment and is usually related to total cumulative dose. It is advised that patients placed on cisplatin, whether as a single agent therapy or combination, be questioned concerning hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow-up audiometry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each course of cisplatin.

7.1.5 Supplier: Commercially available

7.2 Taxol (NSC #125973)
7.2.1 *Formulation:* Taxol 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. A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxymethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use.

7.2.2 *Solution Preparation:* Taxol, at the appropriate dose, will be diluted in 1000 ml of 5% Dextrose injection or 0.9% Sodium Chloride injection. The solutions when prepared at a concentration of 0.3 to 1.2 mg/ml are stable for 27 hours. Taxol must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags. (1/8/99)

7.2.3 *Storage:* The intact vials should be stored under refrigeration (2-25°C/36-77°F). Shelf-Life Surveillance of the vials is ongoing. All solutions of Taxol 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 Taxol (0.3-1.2 mg/ml) are physically and chemically stable for 24 hours.

7.2.4 *Administration of Taxol:* The solution will be given as a 24-hour continuous intravenous infusion. Taxol will be administered via an infusion control device (pump) using non-PVC tubing and connectors such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral Nitroglycerin. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV, Millipore Products) into the IV fluid pathway distal to the infusion pump.

7.2.5 *Adverse Effects:

7.2.5.1 Hematologic: Myelosuppression
7.2.5.2 Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis
7.2.5.3 Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI). These reactions are rare and do not require monitoring in patients without any cardiac risk factors.
7.2.5.4 Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings
7.2.5.5 Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
7.2.5.6 Other: Alopecia, fatigue, arthralgia, myalgia

7.2.6 *Supplier:* Commercially available.

7.3 Filgrastim (*r*-metHuG-CSF, Neupogen)

7.3.1 *Dose Formulation:* G-CSF is available in preservative-free vials containing either 600 mcg of G-CSF in 2 ml buffered sterile solution or 480 mcg in 1.6 ml of solution. Each 1 ml contains 300 mcg of G-CSF, a preservative-free solution containing 0.59 mcg acetate, 50 mg sorbitol, 0.004% Tween 80, 0.035 mg sodium, and 1 ml water for injection, USP pH 4.0.

G-CSF will be administered subcutaneously. Injection sites should be rotated. If the volume to be injected is > 1.5 ml, the dose should be divided in half and both doses should be given at the same time in two sites. Patients may be instructed in self-administration. Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

7.3.2 *Mechanism of Action:* Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. G-CSF regulates the production of neutrophils with the bone marrow. Endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts and endothelial cells. r-met HuG-CSF is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by Escherichia Coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Phase III clinical trials have demonstrated that G-CSF significantly reduces the incidence of febrile neutropenic episodes. With discontinuation of therapy, neutrophil counts returned to baseline, in most cases within 4 days.

7.3.3 *Storage:* Unopened vials should be stored in a refrigerator at 2-8°C (36-46°F). Avoid shaking. If accidentally frozen for a short while (< 24 hours), it may still be used. Prior to injection, G-CSF may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded. G-CSF is stable for at least 1 year when stored at 2-8°C.

7.3.4 *Side Effects:

*Musculoskeletal:* Mild to moderate medullary bone pain in 20% to 25% of patients.

*Dermatologic and Hypersensitivity:* Redness, swelling, itching, and pain may occur at the injection site. Transient, generalized rash has been reported occasionally. Anaphylactoid and allergic reactions have been reported rarely.
Hematologic: Leukocytosis occurs occasionally.

Other: Less frequently reported side effects include transient supraventricular arrhythmia, splenomegaly, and vasculitis. Transient increases in serum concentrations of uric acid, LDH, alkaline phosphatase and leucocyte alkaline phosphatase have been reported after cytotoxic chemotherapy. G-CSF should not be used in patients with known hypersensitivity to e-coli-derived drug preparation.

7.3.5 Drug Availability: G-CSF is commercially available.

7.4 Treatment Plan

7.4.1 Overall, six cycles of chemotherapy will be given. The first two cycles will consist of cisplatin (50 mg/m²) alone given after external beam irradiation on days 1 and 28. The subsequent 4 cycles of therapy (courses 3 through 6) will consist of cisplatin (50 mg/m²) and paclitaxel (175 mg/m²) given at 28-day intervals on days 56, 84, 112, and 140.

7.4.2 Patients will be treated on an outpatient basis whenever possible.

7.4.3 Method of Administration:

Courses 1 and 2 (Cisplatin)

Intravenous hydration consisting of 1 liter NS with 20 mEq KCl and 2 gm MgSO₄ will be given over 2-4 hours. Near the completion of the hydration, an antiemetic regimen is administered (see Section 7.4.4). Immediately following completion of the intravenous hydration, cisplatin at the appropriate dose will be mixed in 1 liter 1/2 NS with 50 gm mannitol and administered intravenously over 2-4 hours. Cisplatin is to be given after daily external beam fraction.

Courses 3 through 6 (Cisplatin + Taxol)

The patient is premedicated with Dexamethasone 20 mg PO 12 hours and 6 hours prior to the anticipated initiation of the Taxolinfusion. (Note: Intravenous Dexamethasone should be substituted for oral Dexamethasone in patients who are vomiting). Additional doses are not necessary if there is no greater than a 4-hour delay in starting taxol. Thirty minutes before the Taxol infusion is to begin, the patient is further premedicated with Diphenhydramine 50 mg intravenously and cimetidine 300 mg intravenously. Taxolat the appropriate dose and dilution will be given as a 24-hour continuous IV infusion placed only in glass or polyolefin containers and polyethylene-lined nitroglycerin tubing. Polyvinylchloride (PVC) infusion sets are not to be used. Immediately following the completion of the Taxolinfusion, intravenous hydration consisting of 1 liter NS with 20 mEq KCl and 2 gm MgSO₄ will be administered over 2-4 hours. Near completion of the hydration, an antiemetic regimen as outlined in Section 7.4.4 is administered. Immediately following completion of the intravenous hydration, cisplatin at the appropriate dose will be mixed in 1 liter 1/2 NS with 50 gm mannitol and administered intravenously over 2-4 hours.

7.4.4 Antiemetic Regimen

Ondansetron (Zofran, Glaxo) will be administered 15 minutes prior to administration of cisplatin at a dose of 0.15 mg/kg and repeated every 3-4 hours for an additional 2 doses. As an alternative, Granisetron (Kytril, Smith Kline) 2 mg may be given orally or Ondansetron (Zofran, Glaxo) 32 mg may be given intravenously prior to beginning Cisplatin infusion. Other antiemetics (e.g., Dexamethasone, Diphenhydramine, or Reglan) may be used during Taxoladministration, if necessary.

7.4.5 Dose Modification Schema

The dose levels for this taxol/cisplatin regimen are as follows:

<table>
<thead>
<tr>
<th>Agent</th>
<th>(dose)</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxol</td>
<td>(mg/m²)</td>
<td>135</td>
<td>150</td>
<td>175</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>(mg/m²)</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

No dose escalation is planned

7.4.6 G-CSF Administration

Patients failing to achieve an AGC equal to or greater than 1500/mcl by day 22 may start G-CSF therapy at a dose of 5 mcg/kg/d subcutaneously until the neutrophil count reaches or exceeds this level on at least 2 successive days. The next cycle, however, will be delayed until patients have been off G-CSF for at least 24 hours. After appropriate instruction from the nursing staff, patients may self-administer subsequent G-CSF doses. If the volume of the calculated daily dose is > 1.5 cc, the dose should be divided and given at separate sites.

7.4.7 Laboratory Monitoring
7.4.7.1 CBC with differential and platelet count will be obtained weekly during therapy. Laboratory studies prior to each course of chemotherapy will include: CBC with differential and platelet count, serum electrolytes, serum magnesium, creatinine, BUN, SGOT, total bilirubin.

7.4.8 Dose Modifications

7.4.8.1 No subsequent treatment course is to begin until all toxicities (except anemia) ≥ grade 2 have abated. Most patients requiring delay are those experiencing incomplete recovery of hematologic toxicities. No subsequent treatment course is to begin until the granulocyte count is greater than or equal to 1500/mcl and the platelet count ≥ 100,000/mcl.

7.4.8.2 Modifications for Hematologic Toxicity

<table>
<thead>
<tr>
<th>Granulocyte Nadir</th>
<th>Platelet Nadir</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000</td>
<td>&gt;100,000</td>
<td>No change</td>
</tr>
<tr>
<td>500-1,000</td>
<td>50,000-100,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500 for ≤ 7 days with no fever</td>
<td>50,000-100,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500 for ≤ 7 days with fever</td>
<td>50,000-100,000</td>
<td>No change(*)</td>
</tr>
<tr>
<td>&lt; 500 for &gt; 7 days &lt; 50,000</td>
<td>Decrease 1 level</td>
<td></td>
</tr>
</tbody>
</table>

*Increase the dose of G-CSF by 5 mcg/kg/d (i.e. from 5 mcg/kg/d to 10 mcg/kg/d).

7.4.8.3 Modifications for G-CSF Toxicity
For ≥ Grade 3 toxicity (Section 7.3.4), other than symptomatically controlled bone pain referable to the G-CSF, the drug will be withheld until toxicity has decreased to Grade 2. For subsequent cycles, G-CSF dose will be reduced by 50%. If Grade 3 or 4 toxicity recurs, G-CSF will be discontinued. If a patient has recurrent local problems at the injection sites, the G-CSF may be divided to be given BID.

7.4.8.4 Modifications for Renal Toxicity
Persistent elevation of serum creatinine to > 1.8 mg% (which on workup is not shown to be secondary to pre-renal causes or due to obstructive uropathy) requires withholding treatment until creatinine is within a normal range. If this creatinine elevation persists beyond 6 weeks after a previous dose, then Dr. Burke should be called. If cisplatin is considered to have contributed to this degree of irreversible renal toxicity, it will be omitted from all subsequent treatments.

7.4.8.5 Modifications for Peripheral Neurotoxicity (see page 24, sensory)
Grade 2 peripheral neuropathy will require that the Taxol dose be decreased one level. Grade 3 peripheral neuropathy will require that the Taxol dose be decreased to one level below that of the former cycle.
Grade 4 peripheral neuropathy requires that the patient be removed from the study.

7.4.8.6 Modifications for Ototoxicity
Symptomatic hearing loss will require discontinuation of cisplatin.

7.4.8.7 Modifications for Cardiac Toxicity
Cardiovascular toxicity of any nature will be evaluated by a cardiologist. Asymptomatic bradycardia is not an indication for discontinuation of therapy or for routine monitoring. If any other arrhythmia is documented, monitoring may be required. A Taxol infusion may be discontinued for a cardiac arrhythmia that shows evidence of AV nodal block (e.g. Mobitz type 1 or 2 or total heart block). Any arrhythmia that is felt to necessitate discontinuation of Taxoldose should be discussed with Dr. Burke.

7.4.8.8 Modifications for Gastrointestinal Toxicity
No adjustments are allowed for gastrointestinal toxicity. If volume contraction becomes a problem, the attending physician is encouraged to admit the patient for more vigorous pre- and post-treatment hydration.

7.4.8.9 Management of Hypersensitivity Reactions
Patients who experience severe hypersensitivity reactions to Taxolcan be rechallenged, at the discretion of the Study Chairman, with taxol. Premedication will be administered as follows: Dexamethasone 8 mg IV at 24, 18, 12, and 6 hours prior to TaxolCimetidine 300 mg IV 30 minutes prior to TaxolDiphenhydramine 50 mg IV 30 minutes prior to taxol.
Give Taxolin the usual volume but at one quarter of the planned rate over the first 6 hours. Patients will be under close observation for this period. Thereafter, if no reaction has been observed, the rate may be increased to the normal infusion rate. Should severe reaction still develop, the patient will go off study. In patients with no or minimal reactions, subsequent courses of Taxol will be administered according to the above procedure.

7.5 RTOG Adverse Reaction Reporting

7.5.1 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

7.5.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.5.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.5.1.3 Any death on study if clearly related to the commercial agent(s).
7.5.1.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.5.2 The ADR report should be documented on Form FDA 3500 (Appendix V) and mailed to the address on the form, to RTOG Headquarters and:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
(301) 230-2330 (available 24 hours)
FAX (301) 230-0159

7.5.3 Any death, regardless of cause, while patient is receiving treatment or occurring within 30 days of treatment should be reported to RTOG Headquarters by telephone.

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY

10.1 The pathology report must document depth of myometrial penetration, thickness of myometrium, cervical stroma involvement, assessment of adnexa and serosa as well as histologic grade of adenocarcinoma. The presence or absence of capillary space invasion should be documented. Submit:

10.1.1 One paraffin block of tumor or 15 unstained slides (maximum thickness of 5 microns each). Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.
10.1.2 Pathology report documenting that submitted block or slides contain tumor.
10.1.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials.

10.2 To encourage compliance, your Pathology Department can be reimbursed for obtaining blocks or cutting slides.
10.3 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).
10.4 Materials will be sent to:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters
### Evaluation Criteria

#### 11.2.1 All patients will undergo weekly examinations during irradiation. Examination will include general physical assessment, Karnofsky Performance Status, bowel/bladder complaints and assessment of skin in the treated area.

#### 11.2.2 Complete blood count with differential and platelet count will be performed weekly.

#### 11.2.3 At the time of each isotope insertion and one month following the completion of radiation therapy, additional physical examinations will be performed to document the presence of disease. Suspected recurrent disease must be documented by biopsy.

#### 11.2.4 Subjective Assessment

Performance status will be defined according to the Karnofsky Performance Scale. Major symptoms will be graded according to severity on the RTOG scoring system.

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Life Threatening

#### 11.2.5 Objective Response

Survival will be defined as observed length of life from entry into this study to death or, for living patients, date of last contact.

---

<table>
<thead>
<tr>
<th>Test &amp; Observation</th>
<th>Prior to Study</th>
<th>Days 1-56 Weekly</th>
<th>Days 57-140 q Course</th>
<th>q 4 mo. x 2 Yrs, q 6 mo x 3 yrs.</th>
<th>Yearly</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; Physical Exam</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pelvic Exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance Status (KPS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Major Symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Test &amp; Observation</th>
<th>Prior to Study</th>
<th>Days 1-56 Weekly</th>
<th>Days 57-140 q Course</th>
<th>q 4 mo. x 2 Yrs, q 6 mo x 3 yrs.</th>
<th>Yearly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Effects</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height, Weight, BSA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hgb or Hct</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine, Bilirubin, BUN</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SGOT, Alkaline phos</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Appropriate Radiography</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/Abdomen &amp; Pelvis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Audiogram</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pap Smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

---

- Appropriate radiography = imaging studies required to evaluate response when clinical examination measurements are not possible.
- Within 6 weeks prior to registration.
- At days 57, 112, 140, and at first followup.
11.2.5.2 Progression-free interval will be defined as date from entry into this study to date of reappearance of disease or to date of last contact.

11.2.5.3 Site of relapse - when a relapse of disease occurs, the site and the date of relapse will be recorded. Relapses will be classified as pelvic distant metastasis. Distant should be coded as abdominal or other. Pelvic should be coded as vaginal or other. Relapse should be confirmed by histologic or cytologic biopsy of the recurrent lesion.

11.3 Evaluation of Response and Toxicity

Patients will be followed for disease status and for the appearance of chronic toxicity with history & physical examination that includes a pelvic exam. Pap Smears and chest x-rays should be obtained yearly.

First and second years post therapy - every four months
Third to fifth year post therapy - every six months
Fifth year - annually thereafter.
Every attempt should be made to histologically document recurrent tumor.

11.4 Toxicity Evaluation

Myelosuppressive toxicity shall be reported as the lowest observed WBC and platelet count. Anemia and red blood cell transfusions will be noted.

Other toxicities will be described according to Appendix IV.

Every effort will be made to obtain an autopsy on patients who die during or immediately after the study.

11.5 Criteria for Response

11.5.1 Progression-free interval: time from onset of treatment until documentation of recurrence.

11.5.2 Recurrent disease: Appearance of any measured lesion, positive vaginal cytology, or the appearance of new metastatic lesions.

11.6 Criteria for Discontinuing Study Treatment

11.6.1 Appearance of disease as defined in Section 11.5.2 after two weeks of therapy.

11.6.2 The development of unacceptable toxicity.

11.6.3 Patient request.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
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</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Surgery Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within 1 wk of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form)</td>
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</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
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<tr>
<td>Daily Treatment Record (T5)</td>
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<tr>
<td>Isodose Distribution (T6)</td>
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<tr>
<td>Intracavitary Dose Form (I9)</td>
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</tr>
<tr>
<td>Supplementary Calculations (HDR/LDR) (TL)</td>
<td></td>
</tr>
<tr>
<td>Intracavitary Films (T0)</td>
<td></td>
</tr>
</tbody>
</table>
Chemotherapy Flowsheets (M1) Two weeks from start of treatment, (*to include pre-tx labs and first dose of chemo*), then at 10, 16, and 24 weeks.

Follow-up Form (F1) Every 4 months from treatment start for 2 years, q 6 months x 3 years, then annually. Also at progression/relapse and at death.

Autopsy Report (D3) As applicable

13.0 Statistical Considerations

13.1 Study Endpoints

13.1.1 Primary Endpoint
Treatment completion per protocol or with acceptable variation (*study chair review of radiation therapy and chemotherapy is required*).

13.1.2 Secondary Endpoints
- Toxicity from external RT, brachytherapy, and chemotherapy (*cisplatin and taxol*)
- Local regional control (*pelvic control*)
- Distant control
- Disease free survival
- Overall survival

13.2 Sample size
The safety and feasibility of the treatment approach is the main interest of this phase II trial. The early GOG study of postoperative adjuvant chemotherapy and RT for high risk endometrial carcinoma\(^{22}\) showed an unacceptably high rate (32%) of protocol violations in the adjuvant chemo arm. This protocol treatment approach attempts to achieve a 90% treatment completion per protocol or with acceptable variation. Thus, this study is designed to detect a 90% against a 70% completion with at least acceptable compliance. Using an optimal two-stage design proposed by Simon,\(^{36}\) a maximum of 36 patients are required to test the hypothesis with a one-sided significance level of 0.05 and a statistical power of 90%. Considering 10% unevaluable cases, the maximum sample size of the study is 40.

13.3 Accrual and Duration
GOG accrued 224 patients in their study in over eight years with an average monthly accrual of 2.15 cases. It is expected that RTOG will enter cases at the same rate as GOG. Thus, the accrual should be completed in about two years. If the accrual follows below one case per month, the feasibility of continuing this study will be discussed at the RTOG Research Strategy Committee.

13.4 Follow Up if the Treatment is Well Tolerated
For the efficacy of the treatment, additional follow-ups after the closure of the accrual are needed. With the additional one year of follow-up, we may have a better estimates of 2-year survival rate.

13.5 Analysis Plan

13.5.1 Interim Reports
Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about:
- patient accrual rate with projected completion date,
- pretreatment characteristics of patients accrued,
- compliance rate of treatment per protocol,
- the frequencies and severity of toxicity due to chemotherapy, external radiation therapy and brachytherapy.

13.5.2 Interim Analysis for Early Stopping
The interim analysis will be performed when 15 evaluable patients have been entered and have finished their protocol treatment. If only 11 or less of these 15 patients complete the treatment per protocol or with acceptable variations, the study statistician will recommend to the RTOG Research Strategy Committee that study registration will be discontinued.

13.5.3 Analysis of the Initial Treatment Delivery
The initial treatment analysis will be performed upon the completion of the treatment of the final patient entered. The number of patients entered in the study will be tabulated by the factors of completion of treatment and protocol compliance. The primary endpoint of treatment completion per protocol or with acceptable variation will be tested using binomial distribution. If the number of patients who complete the treatment per protocol or with acceptable variations is more than 29 out of 36 evaluable patients we reject the null hypothesis of a 70% completion rate and conclude that the treatment is well tolerated. Furthermore, the frequencies and severity of combined toxicity from all regimens will be reported as well as the toxicity from each of the regimens.

13.5.4 Analysis of the Treatment Efficacy
If the treatment is shown to be well tolerated, the efficacy analysis of the treatment will be delayed to one year after the initial treatment delivery analysis. With additional one year follow-up, the 2-year probability of local-regional failure, distant failure and disease failure will be reported using the cumulative incidence approach. A 2-year overall survival will also be computed using Kaplan-Meier method.

13.6 Inclusion of Minorities
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the possible difference in any of the above endpoints among the racial groups will be investigated. Summary statistics such as percentage of minorities entered, estimates of the endpoints by the racial groups will be reported.
REFERENCES


APPENDIX I

RTOG 97-08

A Phase II Study of Adjuvant Postoperative Irradiation
Combined with Cisplatin/TaxolChemotherapy Following TAH/BSO
for Patients with High-Risk Endometrial Cancer

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity
to decide whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is an
effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have endometrial cancer which, although removed surgically, has a high risk of recurring.
This cancer may return (1) in my vagina or pelvis or (2) at other parts in my body (abdomen, lung, liver, bone). This study
includes the use of chemotherapy and radiation therapy (RT). This study will determine whether the combination of
chemotherapy and RT for patients with tumors such as mine may be beneficial. This study will also document what the side
effects are for combined treatment with chemotherapy and RT.

DESCRIPTION OF PROCEDURES

The treatment offered to me includes RT and chemotherapy. The RT will involve daily outpatient external radiation
treatments once a day, five days a week (Monday-Friday) for 5 weeks.

Chemotherapy called cisplatin will be given on the first day of irradiation and again 4 weeks later. The chemotherapy will
be given in my vein after the radiation treatment and will be given as an outpatient. If my blood counts drop because of the
chemotherapy, I may receive a medicine called G-CSF to reduce the incidence of fever caused by the lowered blood counts
from the other chemotherapy.

Following external irradiation, I will have a radiation treatment that will be given by placing a radioactive source into my
vagina. This will be given as an outpatient on three separate visits in some hospitals. Other hospitals may require me to be
admitted for two days for one vaginal insertion.

After completing all irradiation, I will be given more chemotherapy (cisplatin with Taxol[a second drug]) once a month for
four months.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side
effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Radiation Therapy: Possible side effects include tiredness, diarrhea, nausea, and vomiting, rectal irritation, urinary
frequency, difficulty in urination, loss of public hair, reddening and irritation of the skin in the irradiated field, and
depression of blood counts. Long-term side effects, although uncommon, may include malnutrition, rectal ulcer, bleeding
or narrowing of the rectum, difficulty in urination, bloody urine, bowel obstruction, shortening of the vagina, vaginal vault
necrosis (ulceration), and fistula formation (openings) between pelvic tissues.

Cisplatin (Platinol) may cause nausea, vomiting, weakness, hearing loss, ringing of the ears, and numbness of the fingers
and toes. It can also cause damage to the kidneys; I will be given extra amounts of fluids and other medications to lessen
the risk of kidney injury. It can lower the blood counts and the levels of calcium and magnesium in my blood. It is possible
that I may become anemic and require transfusion. Other less common side effects include allergic reactions such as sweating, difficulty breathing, and rapid heart beat. Rarely the drug causes restlessness, facial swelling, loss of coordination, involuntary movement, liver damage, loss of taste, spasm, muscle cramps, or acute leukemia.

*Paclitaxel (Taxol)* commonly causes a lowering of blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need treatment with antibiotics, require hospitalization, and need transfusions if these problems are severe. Other possible side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, visual loss, and fatigue. There is the possibility of skin irritation should paclitaxel leak from my vein into the surrounding skin. Rarely paclitaxel can cause a severe allergic reaction resulting in the development of a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If I am treated with a high dosage or for a prolonged period, I may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that I would notice. In addition, paclitaxel may increase the risks of radiation as listed above.

*G-CSF* is given by injection in the skin and there is some discomfort associated with this. It also may cause mild to moderate muscle/bone aching which is usually relieved with mild medication such as acetaminophen.

*Blood Drawing* may cause discomfort, bruising, and/or bleeding at the site of needle insertion. Occasionally, some people feel faint or dizzy.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

**CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. ______ the inve: ____________________________. In addition, I may contact ____________________________ at ____________________________ for information regarding patients' rights in research studies.

**BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

**ALTERNATIVES**

Alternatives which could be considered in my case include radiation therapy performed off-study either alone or with chemotherapy or treatments to make me feel better. An additional alternative is no further therapy. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been
told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain procedures related to this protocol. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

**VOLUNTARY PARTICIPATION**

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

**CONFIDENTIALITY**

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_________________________ ________________
Patient Signature (or Legal Representative) Date
# APPENDIX II

## KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX III

STAGING FOR ENDO METRIAL CANCER

(AJCC, 1997)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>TNM FIGO Category</th>
<th>FIGO Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to corpus uteri</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>IA Tumor limited to endometrium</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>IB Tumor invades up to or less than one-half of the myometrium</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>IC Tumor invades to more than one-half of the myometrium</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades cervix but does not extend beyond uterus</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>IIA Endocervical glandular involvement only</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>IIB Cervical stromal invasion</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Local and/or regional spread as specified in T3a, b and/or N1 and FIGO IIIA, B and C below.</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA Tumor invades serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings.</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB Vaginal involvement (direct extension or metastasis)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>IIIC Metastasis to the pelvic and/or para-ortic lymph nodes</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>IVA Tumor invades bladder mucosa and/or bowel mucosa (Bullous edema is not sufficient evidence to classify a tumor as T4).</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>IVB Distant metastasis. (Excluding metastasis to vagina, pelvic serosa or adnexae. Including metastasis to intra-abdominal lymph nodes other than para-ortic, and/or inguinal lymph nodes).</td>
<td></td>
</tr>
</tbody>
</table>

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Distant metastasis cannot be assessed.
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>IA</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment **regardless of cause** requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters’ Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters’ Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. **Report by phone within 24 hours to IDB and RTOG Headquarters.

**A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent. As above

- All life threatening (grade 4) events which may be due to agent. As above

- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. *Phase II, III Studies Utilizing Investigational Agents*

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent. Report by phone to RTOG Headquarters and the Study Chairman within 24 hours. **A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
APPENDIX VI

Definition of Bladder and Rectal Points
APPENDIX VI (cont’d)

Definition of Bladder and Rectal Points