RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-05

A PHASE III STUDY OF ADJUVANT POSTOPERATIVE IRRADIATION WITH OR WITHOUT CISPLATIN/PACLITAXEL CHEMOTHERAPY FOLLOWING TAH/BSO FOR PATIENTS WITH ENDOMETRIAL CANCER

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SCHEMA (6/27/02)

S  R  ARM 1
Radiotherapy-50.4 Gy in 5.5 Weeks (1.8 Gy once a day, 5 x a week, 28 fractions)

T  Stage  A
1. IC-IIA

R  2. IIB  N
Optional: Vaginal brachytherapy boost

A  D  plus Cisplatin 50 mg/m² i.v. on days 1 and 28.
Optional: Vaginal brachytherapy boost

T  O  Followed by Cisplatin 50 mg/m² and Paclitaxel 160 mg/m² days 56, 84, 112, and 140 from start of RT

I  M

F  I

Y  Z

E

* See Section 6.0

Chemotherapy
Two courses cisplatin (50 mg/m²) given on days 1 and 28. Four courses of cisplatin (50 mg/m²) and paclitaxel (160 mg/m²) given at 4 week intervals following completion of radiotherapy. See Section 7.4 for details.

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
- No prior chemotherapy or radiation therapy
- Risk factors: patients must fit one of the following: uterine-confined Grade 2 or 3 with myometrial invasion >50% (Stages IC or IIA); or uterine-confined Grade 2 or 3 with stromal invasion of cervix (Stage IIB)
- No known extrauterine metastases, no known gross residual disease, no known positive peritoneal cytology or distant metastases
- Zubrod Performance Status 0-1
- ANC ≥ 1800/mm³, platelets ≥ 100,000/mcl
- Acceptable hepatic and renal function: creatinine ≤ 1.5 mg%, bilirubin ≤ 1.5 mg/dl and SGOT ≤ 2 x normal
- No medical contraindications to chemotherapy or radiation therapy
- Signed study-specific informed consent form

Required Sample Size: 436
1. Does the patient have histologically-proven endometrial cancer?

2. Does the patient have a grade I adenocarcinoma or ≥ 50% of the pathologic specimen containing papillary serous or clear cell cytology?

3. Did the patient have a hysterectomy (total abdominal, vaginal hysterectomy, or laparoscopic-assisted vaginal hysterectomy) and bilateral salpingo-oophorectomy?

4. Will the patient start XRT no more than 8 weeks after surgery?

5. Has the patient received prior chemotherapy or radiation therapy?

6. Does the patient have a history of other malignancies other than non melanomatous skin cancer?
   - (Y) If yes, has the patient been disease free for ≥ 5 years?

7. Does the patient have gross residual disease or suspected extra pelvic disease (other than positive pelvic washings)?

8. Does the patient have evidence of distant metastasis?

9. What is the patient’s Zubrod Performance Status?

10. Are the patient’s lab values within the limits specified in Section 3.1.5?

11. One of the following tumor characteristics must be present for eligibility, check one.
   - Grade 2 or 3 carcinoma with greater than 50% myometrial invasion (Stages IC and IIA)
   - Grade 2 or 3 carcinoma with stromal invasion of the cervix (Stage IIB)

12. Does the patient have a history of cardiac dysrhythmias?
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist (above) been completed? (Y)

3. Is the patient eligible for this study? (Y)

4. Date the study-specific Consent Form was signed? (must be prior to study entry)

5. Patient’s Name

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Social Security Number

11. Gender (Female)

12. Patient’s Country of Residence

13. Zip Code

14. Patient’s Insurance Status

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

16. Treatment Start Date

17. Treatment Assignment

18. Stage (IC-IIA vs. IIB)

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

1.1 Endometrial cancer is the most common gynecologic malignancy affecting American women. Over 6,000 women die each year of cancer of the uterine corpus. A recently completed GOG trial demonstrated an improved relapse-free survival rate at 2 years for patients receiving adjuvant pelvic radiation compared to those who did not (96% and 88%, respectively). The majority of these patients’ low-risk prognostic factors including low histologic grade and shallow depth of myometrial penetration. 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 extraterine disease.

Patients with high-risk features who have not received adjuvant irradiation have been reported to have a recurrence incidence ranging from 15-20%. Adjuvant pelvic radiation for patients with disease confined to the uterus results in local recurrences in 06.5%. 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. Distant metastasis have been documented in approximately 20% of patients with involvement of the cervix. At least 30% of patients with extraterine disease who receive adjuvant involved field irradiation recur at distant sites.

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. Secondly, preoperative assessment of grade and stage often underestimates the actual involvement appreciated at the time of pathologic assessment. 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. 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.

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. No statistically significant differences in survival rates could be demonstrated; however, the number of women accrued to this study was believed to be inadequate (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. Another nonrandomized trial reported 58% disease-free survival in 26 patients with adjuvant PAC plus pelvic irradiation.

Phase II chemotherapy trials in women with advanced or recurrent endometrial cancer have identified doxorubicin, cisplatin, and carboplatin as active agents with response rates of 30-35%. A trial by the GOG has suggested a similar level of activity for paclitaxel. 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. RTOG 97-08 has accrued patients with high-risk endometrial cancer to a phase II protocol combining cisplatin with radiation to the pelvic and followed by four cycles of cisplatin and paclitaxel. Treatment has been well tolerated, although many patients experienced grade 4 hematologic toxicities that were reversible and did not prevent the proposed delivery of the therapy.
Because the empiric addition of chemotherapy to adjuvant treatment of endometrial cancer has been increasing in the United States, we feel that a randomized protocol to test the efficacy of this regimen would be beneficial. Endometrial cancer is the most common female gynecologic cancer in the United States but few studies have been accomplished because the majority of the disease is early stage or low risk. A survey of the RTOG membership indicates approximately 167 patients per year who may potentially be accrued to this phase III randomized trial. The Gynecologic Oncology Group (GOG) has also agreed to participate in this trial.

2.0 OBJECTIVES
2.1 To test whether the addition of chemotherapy to radiation improves the relapse-free survival for endometrial cancer patients.
2.2 To determine patterns of recurrence associated with each treatment arm.
2.3 To determine the acute and late toxicity profiles associated with each treatment arm.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility (4/30/01)
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 extraterine metastases, no known gross residual disease no known positive peritoneal cytology, or distant metastases.
3.1.3 Patients must have uterine confined endometroid endometrial adenocarcinoma with one of the following:
   • Grade 2 or 3 carcinoma with greater than 50% myometrial invasion (Stage IC and IIA).
   • Grade 2 or 3 carcinoma with stromal invasion of the cervix (Stage IIB).
3.1.4 Patients must have a Zubrod performance score ≤ 1.
3.1.5 Patients with adequate bone marrow, renal and hepatic function:
   • ANC ≥ 1800/mm³; platelets ≥ 100,000/mcl; Creatinine ≤ 1.5 mg%; Bilirubin ≤ 1.5 times normal; hemoglobin ≥ 10 gm/dl; SGOT ≤ 3 times normal. Alkaline phosphatase and BUN should be recorded.
3.1.6 Patients must sign a study-specific informed consent form prior to randomization.
3.2 Ineligible Patients (6/27/02)
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 or extraterine disease or distant metastatic disease.
3.2.4 Patients with Grade I adenocarcinoma or who have ≥ 50% of the pathologic specimen containing 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, Performance Status (Appendix II) and body surface area (BSA).

4.1.2 Histologic proof of adenocarcinoma. All patients will have confirmation of diagnosis by hysterectomy.

4.1.3 All patients should undergo complete blood count, BUN, serum creatinine, bilirubin, SGOT and alkaline phosphatase; also serum calcium and magnesium. (6/27/02)

4.1.4 Chest radiograph (PA and lateral) or CT chest within 6 weeks prior to randomization.

4.1.5 Audiogram required when there is a history of hearing loss. (6/27/02)

5.0 REGISTRATION PROCEDURES (4/30/01)

5.1 RTOG Institutions

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 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

5.2 GOG Institutions

GOG patients will be registered through the GOG Statistical and Data Center by telephoning 1-800 523-2917 (between 9:00 AM and 5:00 PM EST/EDT Monday-Friday).

Following randomization with RTOG, the GOG Statistical and Data Center will contact the GOG member institution to confirm the registration and provide the treatment assignment, GOG patient number and the RTOG patient number.

6.0 RADIATION THERAPY (ARMS 1 & 2)

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

6.2 Patients will be treated with external irradiation.

6.2.1 External Radiation

The pelvis will be treated to a total dose of 50.4 Gy in 28 fractions over 5.5 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 (6/27/02)

Vaginal brachytherapy is optional. For low dose rate applications, 20 Gy to the vaginal surface in a single application will be given. For high dose rate application, 12 Gy to the vaginal surface in two applications will be given.

6.3 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)

6.3.2.2.1 Superior border A transverse line between L5 and S1.

6.3.2.2.2 Lateral border 1-1.5 cm lateral to the widest true pelvic diameter.

6.3.2.2.3 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.

6.3.2.2.4 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.

6.3.2.3 Pelvic Portal (lateral fields)

6.3.2.3.1 Superior border Identical to AP-PA fields.

6.3.2.3.2 Anterior border A line drawn through the symphysis pubis and at least 1 cm anterior to common iliac nodes at L5-S1.

6.3.2.3.3 Posterior border Care should be taken to include at least S2-S3.

6.3.2.3.4 Inferior border Identical to AP-PA fields

6.3.2.3.5 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 External Beam Treatment Techniques and Dose Specifications

6.3.3.1 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 the 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, 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 (optional treatment) (6/27/02)

6.4.1 If vaginal brachytherapy boost is given, it 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 two insertions prior to beginning chemotherapy on day 56. More than one insertion may be performed per week. At least three days should elapse between intracavitary treatments. External beam radiation and intracavitary treatment should not be given on the same day. Iridium or cesium sources are to be used for intracavitary application with vaginal applicators for the 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 .8 to 1.2 Gy per hour (see Appendix VII). 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. AP and/or lateral simulation films must be submitted to confirm placement of colpostats or cylinders.

6.4.2.2 For high dose rate applications: Two applications of 6 Gy each prescribed to the vaginal surface. This will give a total of 12 Gy. Dose will be prescribed at the vaginal surface (see Appendix VII). One set of AP and/or lateral simulation films must be submitted to confirm placement of the cylinder.

6.4.3 A report on the source specifications, strengths, spacings relative to the applicators, size of applicator, and dosimetry calculations for all points is MANDATORY. Dwell times and dwell positions for all HDR insertions are also required. For all films that are submitted, the points of dose calculations should be marked on the film (vaginal surface points) as well as bladder and rectal points if calculated. If cylinders are used and source specification and applicator size does not change, dose distributions may be made on only the first cylinder if desired. Dose to vaginal surface from ovoid (colpostat) should include contribution from both ovoids.
- Vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid or cylinder. See Appendix VI.
- If a cylinder is used, the dose at the apex of the cylinder should be calculated to be as close as possible (within +/- 25%) to the lateral vaginal surface dose. See Appendix VI.
- Dose points 0.5 cm posterior and anterior to the cylinder or colpostat should be calculated. See Appendix VI.

6.5 Dose to Critical, Sensitive Structures (6/27/02)

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 Variation from Protocol - Acceptable
- More than 2 weeks interruption of external beam RT
- External beam RT final doses vary ≤ 10%

6.7.2 Deviation from Protocol - Unacceptable
- No chemotherapy (if assigned to Arm 2)
- Doses of RT vary more than 10% for external RT
- Field of RT is other than pelvic contents (whole abdomen or paraaortic RT)
- Intracavitary RT final doses vary +/- 25% (6/27/02)

7.0 CHEMOTHERAPY (ARM 2)

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

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.

Otoxicity 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 pretreatment 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 Paclitaxel

7.2.1 Formulation
Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxymethylene 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 (6/27/02)
Paclitaxel, at the appropriate dose, will be diluted in 500 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. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags.

7.2.3 Storage
The intact vials should be stored between 225°C (36-77°F). Vials will bear an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

7.2.4 Administration of Paclitaxel
The solution will be given as a 3-hour continuous intravenous infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors such as the i.v. 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 i.v. 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) (See Section 7.4.6)

7.3.1 Dose Formulation (6/27/02)
G-CSF is available in preservative-free vials containing either 300 mcg of GCSF in 1 ml buffered sterile solution or 480mcg in 1.6 ml of solution. Each 1 ml contains 300 mcg of GCSF, 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. GCSF regulates the production of neutrophils with the bone marrow. Endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts and endothelial cells. r-met HuGCSF 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 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**

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

**7.3.4.2 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.

**7.3.4.3 Hematologic**: Leukocytosis occurs occasionally.

**7.3.4.4 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 leukocyte 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 on days 1 and 28 of daily external beam treatment. The subsequent four cycles of therapy (courses 3 through 6) will consist of cisplatin (50 mg/m²) and paclitaxel (160 mg/m²) given at 28-day intervals on days 56, 84, 112, and 140 from RT start.

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

**7.4.3 Method of Administration**

**7.4.3.1 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 ½ NS with 50 gm mannitol and administered intravenously over 2-4 hours. Cisplatin is to be given after daily external beam fraction.

**7.4.3.2 Courses 3 through 6 (Cisplatin + Paclitaxel) (6/27/02)**
Administering cisplatin with paclitaxel includes necessary hydration with at least a 3-hour administration of paclitaxel. Institutional protocols may vary as far as timing of the premedication and hydration. Details of pre- and post hydration are left to the discretion of the treating physician, but at least 1 liter NS prior to cisplatin should be given. Mannitol may also be mixed with cisplatin at the treating physician's discretion. An acceptable method of administration follows:
The patient is premedicated with Dexamethasone 20 mg PO 12 hours and 6 hours prior to the anticipated initiation of the paclitaxel infusion. (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 paclitaxel. Thirty minutes before the paclitaxel infusion is to begin, the patient is further premedicated with Diphenhydramine 50 mg intravenously and cimetidine 300 mg intravenously or Rantidine 50 mg intravenously. Paclitaxel at the appropriate dose and dilution will be given as a 3-hour continuous i.v. 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 paclitaxel infusion, 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 ½ NS with 50 gm mannitol and administered intravenously over 2-4 hours.

**7.4.4 Antiemetic Regimen (6/27/02)**
Suggested anti-emetic regimens include: Ondansetron (Zofran, Glaxo) which can 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. However, institutional anti-emetic guidelines are acceptable and may be substituted.

7.4.5 Dose Modification Schema
The dose levels for this paclitaxel/cisplatin regimen are as follows:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Level</th>
<th>0</th>
<th>-1</th>
<th>-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (mg/m²)</td>
<td>160</td>
<td>135</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Cisplatin (mg/m²)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

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 alopecia and 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>&lt; 500 for ≤ 7 days with no fever</td>
<td>or ≥ 25,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500 for &gt; 7 days</td>
<td>or &lt; 25,000</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>&lt; 500 for &lt; 7 days with fever</td>
<td>or &lt; 25,000</td>
<td>Decrease 1 level</td>
</tr>
</tbody>
</table>

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. See Section 7.3.4.2 for description of local injection site problems.

<table>
<thead>
<tr>
<th>Bone pain</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe pain: pain or analgesics severely interfering with activities of daily living</td>
<td>disabling</td>
<td></td>
</tr>
</tbody>
</table>

7.4.8.4 Modifications for Renal Toxicity
Persistent elevation of serum creatinine to > 1.8 mg% (which on work-up 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. King 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 *(Defined as Neurological Motor and Sensory in the New CTC Version 2.0)*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy-motor</td>
<td>Mild objective weakness interfering with function, but not interfering with activities of daily living</td>
<td>Objective weakness interfering with activities of daily living</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>Objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living</td>
<td>Sensory loss or paresthesia interfering with activities of daily living</td>
<td>Permanent sensory loss that interferes with function</td>
</tr>
</tbody>
</table>

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 paclitaxel 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 paclitaxel should be discussed with Dr. King.

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 *(6/27/02)*
Patients who experience severe hypersensitivity reactions to paclitaxel can be rechallenged, at the discretion of the Study Chairman, with paclitaxel. Premedication can be administered as follows:

- Dexamethasone 8 mg i.v. at 24, 18, 12, and 6 hours prior to paclitaxel; cimetidine 300 mg i.v. 30 minutes prior to paclitaxel; diphenhydramine 50 mg i.v. 30 minutes prior to paclitaxel.
- Alternative prophylaxis could include decadron (20 mg i.v.), diphenhydramine (50 mg i.v.), and cimetidine (300 mg i.v.) given 30 minutes prior to paclitaxel.
- Give paclitaxel in 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 paclitaxel will be administered according to the above procedure.
- Institutional hypersensitivity protocols for drug reactions are also acceptable.

7.5 Toxicity Reporting
7.5.1 The revised NCI Common Toxicity Criteria Version 2.0 *(3/98)* will be used to score acute drug therapy and radiation (*≤ 90 days*) toxicity. The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that 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. This study will be monitored by the Clinical Data Update System (CDUS) version 1.X. Cumulative CDUS data will be
submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. The following ADR’s attributed to commercial agent(s) should be:

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).

7.5.2 The ADR report should be documented on Form FDA 3500 and mailed to:

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

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY (4/30/01)

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 RTOG will reimburse pathologists from RTOG institutions $100. per case if proper materials are submitted (*reimbursement is handled through an invoice sent to RTOG Administration*).

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
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
Ldafurne@ihc.com

10.5 GOG Institutions:
Pathology materials (*P1, P2, S5*) will be submitted to the GOG Statistical and Data Center where they will be processed and forwarded to LDS Hospital.
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (4/30/01, 6/27/02)

<table>
<thead>
<tr>
<th>Test &amp; Observation</th>
<th>During Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to Study</td>
<td>Days 1-56 Weekly</td>
</tr>
<tr>
<td>History &amp; Physical Exam</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pelvic Exam</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance Status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Major Symptoms</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test &amp; Observation</th>
<th>During Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to Study</td>
<td>Days 1-56 Weekly</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height, Weight, BSA</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hgb</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WBC with Differential</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine, Bilirubin, SGOT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BUN, Alkaline phos</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum Magnesium and Calcium</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Appropriate Radiographya</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest X-rayb or CT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Audiogramd</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pap Smear</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

a. Appropriate radiography are imaging studies required to evaluate response when clinical examination measurements are not possible.
b. Within 6 weeks prior to registration.
c. At days 57, 112, 140, and at first follow-up.
d. For patients with a history of hearing loss.

11.2 Evaluation Criteria

11.2.1 All patients will undergo weekly examinations during irradiation. Examination will include general physical assessment, 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 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 Zubrod Performance Scale. Toxicities from protocol treatment will be graded according to the revised NCI Common Toxicity Criteria, Version 2.0.

11.2.5 Objective Response

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

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 either pelvic or distant metastasis. Distant sites should be coded as abdominal or other. Pelvic sites 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. Every attempt should be made to histologically document recurrent tumor.
- Every three months for one year,
- Every six months for three years,
- Annually thereafter.

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. 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 date of randomization 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 (4/30/01)
(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 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Operative Notes (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td></td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Intracavitary Dose Form (I9) (6/27/02)</td>
<td></td>
</tr>
<tr>
<td>Supplementary Calculations HDR/LDR (TL)</td>
<td>(6/27/02)</td>
</tr>
<tr>
<td>Intracavitary Films (T0) (6/27/02)</td>
<td></td>
</tr>
<tr>
<td>Initial Followup Form (FS)</td>
<td>At 3 months from treatment start</td>
</tr>
<tr>
<td>Chemotherapy Summary Form (TF) (Arm 2)</td>
<td>At two weeks after completion of</td>
</tr>
<tr>
<td></td>
<td>chemotherapy.</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>At 6, 9, and 12 months for the first year; q 6 months x 3 years, then annually. Also at progression/ relapse and at death.</td>
</tr>
<tr>
<td>Long Term Follow-up Form (FF)</td>
<td>Yearly after 5 years in place of the F1 form, as applicable. See FF Form for instructions.</td>
</tr>
</tbody>
</table>
12.2 **For GOG Institutions: (6/27/02)**
The above forms outlined in Section 12.1 will be submitted to the GOG Statistical and Data Center. The original and one copy will be required for the following RTOG forms: A5, I1, P1, S2, S5, FS, TF, F1, FF, D3. One copy of the radiation materials, T1, T6, and I9 will be submitted to the GOG Statistical and Data Center where they will be processed and forwarded to RTOG.

13.0 **STATISTICAL CONSIDERATIONS**

13.1 **Study Endpoints**

13.1.1 **Primary Endpoint**
Relapse-free survival (Failure: any relapse (local or distant) or death (regardless of cause)).

13.1.2 **Secondary Endpoints:**
- Patterns of recurrence
- Acute and Late Toxicity
- Local regional control
- Distant metastases
- Overall Survival

13.2 **Sample Size Determination**
The study is designed to evaluate the efficacy of postoperative pelvic irradiation with or without Cisplatin and paclitaxel with respect to relapse-free survival for endometrial cancer patients.

A trial conducted by GOG showed no statistically significant difference between patients who after receiving postoperative whole pelvic irradiation were randomized to 60mg/m$^2$ of doxorubicin every 3 weeks vs. those who were randomized to no further treatment after irradiation, although the study was believed to be underpowered with an accrual of 181. Two other non-randomized studies showed an increase in disease-free survival; one in high risk patients without extrauterine disease who received six cycles of cisplatin/doxorubicin/ cyclophosphamide and another in patients with adjuvant PAC + pelvic irradiation.

According to Kim and Tsiatis’ group sequential design approach to 3 treatment comparisons (2 interim and 1 final analyses) using a one-sided logrank test statistics, a maximum of 110 relapse/death events is required to detect the hypothesized 40% reduction in hazard rate by the addition of chemotherapy with a statistical power of 80% and significance level of 0.05.

The sample size required in this study is determined by the accrual rate, the lengths of accrual and follow-up periods, and the projected hazard rates for both arms. Based on a previous RTOG endometrial study (RTOG 97-08) and the participation of GOG in this study, we are expecting 8-9 patients per month. Uniformly accruing patients within 4 years (~ 9 patients/month) and with an additional 5 years of follow-up, 396 patients are needed to detect a 40% reduction in the annual relapse/death rate due to RT+chemo with a statistical power of 80%. Using previously reported relapse-free survival rates, we are assuming a 75% 5-year relapse-free survival rate for the control arm. Therefore, a 40% reduction in failure due to any relapse or death translates into a 5-year relapse-free survival improvement from 75% in the RT alone arm to 84% in the RT plus chemo arm. The relapse-free survival advantage will be tested using a one-sided logrank test statistics with a significance level of 0.05. An additional 10% is added to guard against ineligible or lack-of-data patients, therefore a total of 436 patients are required for this study.

13.3 **Randomization**
The treatment allocation scheme described by Zelen will be used. The stratifying variable is stage (IC-IIA vs. IIB).

13.4 **Analysis Plan**

13.4.1 **Statistical Methods**
Relapse-free survival and overall survival will be calculated by Kaplan-Meier method. Cumulative incidence methods will be used to estimate 5-year rates of local recurrence and distant metastases. The treatment effect by radiation therapy+chemo with respect to all the endpoints will be done using logrank test statistics. All eligible patients with follow-up will be included in the intent-to-treat analysis.
13.4.2 **Interim Reports**

Interim reports are prepared every six months until the closure of the study. In general, the interim reports will include:

- the patient accrual rate;
- protocol compliance and the quality of the submitted data;
- the frequencies and severity of the toxicity.

13.4.3 **Interim Analysis for Early Stopping**

Two such interim analyses shall be performed when we observe 36 (33%) and 73 (66%) of the 110 required relapse/death events. The first interim analysis is projected to take place when 75% of the total accrual is reached. The second interim analysis is projected to take place at the fifth year (1-year after the closure) during follow-up. For each of these interim analyses, toxicity, treatment delivery and efficacy statistics will be reported to the RTOG DMC. The boundaries for early stopping will be computed based on the observed number of relapse or death events according to the O'Brien-Fleming alpha spending function approach. This study has been designed to detect early rejection of both the null and the alternative hypothesis. If the difference is highly significant (rejecting the null; i.e., across the boundary or p-value less than the nominal level) or if the difference is highly significant ("rejecting" the alternative, i.e., across the boundary or p-value greater than the nominal level), the responsible statistician will recommend to DMC that the study be closed to new patient accrual (if open at the time) and be written up for publication.

13.4.4 **The Initial Analysis for Reporting Treatment Effects**

The analysis will be done after the end of the follow-up period, unless the study is stopped early according to 13.4.3. The report should be able to answer the questions about the primary endpoint, that is whether pelvic irradiation+chemo improves the relapse-free survival rate of high-risk endometrial cancer compared to pelvic irradiation alone.

13.5 **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, we have also considered the possible interaction between race and treatments. Based on the RTOG endometrial study (*RTOG 97-08*), we project that 81% of women in the study are white, 7% are black (not of Hispanic origin), 7% are Hispanic and 5% are Asian or Pacific Islander. The following table lists the projected accrual for each racial group. If this percentage remains the same in women who have experienced relapse or death at the time of analysis, the statistical power for detecting the hypothesized difference is 71% and 23% for white and non-white, respectively. With 24 projected relapse/death events in the non-white population, we are able to detect a 70% hazard reduction by radiation therapy for the subset of non-white with statistical power of 65%.

### Planned Gender and Minority Inclusion

<table>
<thead>
<tr>
<th></th>
<th>Asian</th>
<th>Black or African-American</th>
<th>Hispanic or Latino</th>
<th>White</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>21</td>
<td>31</td>
<td>31</td>
<td>353</td>
<td>0</td>
<td>436</td>
</tr>
</tbody>
</table>
REFERENCES


35. Greven, K: preliminary review of RTOG 97-08, personnel communication.


A PHASE III STUDY OF ADJUVANT POSTOPERATIVE IRRADIATION WITH OR WITHOUT CISPLATIN/PACLITAXEL CHEMOTHERAPY FOLLOWING TAH/BSO FOR PATIENTS WITH ENDOMETRIAL CANCER

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY

You have endometrial cancer, which, although removed surgically, has a high risk of returning. This cancer may return in your vagina or pelvis or at other parts in your body (abdomen, lung, liver, bone). This study includes the use of chemotherapy and radiation therapy. The purpose of this study is to determine if the combination of chemotherapy and radiation will prevent the recurrence of your tumor better than radiation given alone. This study will also see if one treatment method has less side effects than the other treatment method.

DESCRIPTION OF PROCEDURES (6/27/02)

The treatment you will be given will be one of two treatment methods. You will be assigned to one or the other treatment method by chance (at random). Although both treatments may be good, it is not known right now which of the two methods of treatment is better. The treatment you get will be assigned by a computerized selection process. Your doctor will call a statistical office where a computer will assign you to one of the two treatment methods. Your chance of receiving one of the two treatments is approximately equal. You will be assigned to one of the following:

Treatment 1: You will receive radiation therapy alone, once a day, five days a week (Monday-Friday), for five weeks. Within two weeks after you receive your radiation therapy, there is an option of receiving radioactive implants in the vaginal area. Your doctor will discuss this with you.

Treatment 2: You will receive radiation therapy plus chemotherapy. You will receive radiation therapy, once a day, five days a week (Monday-Friday), for five weeks. Chemotherapy called cisplatin will be given on the first day of irradiation and again four weeks later. The chemotherapy will be given in your vein (i.v.) after the daily radiation treatment and will be given as an outpatient. Before you receive the cisplatin, you will be hydrated (receive extra fluids by i.v.) for 2-4 hours. Towards the end of that time, you will be given medicine to prevent or reduce any nausea or vomiting you may experience from the cisplatin. The cisplatin itself will also be given by i.v. over 2-4 hours after the first i.v. is completed. If your blood counts drop because of the chemotherapy, you may receive a medicine called GCSF to reduce the incidence of fever caused by the lowered blood counts from the chemotherapy. Within two weeks after you receive your radiation therapy, there is an option of receiving radioactive implants in the vaginal area. Your doctor will discuss this with you. After completing all irradiation, you will be given more chemotherapy (cisplatin with paclitaxel [a second drug]) once a month for four months. The paclitaxel will be given by i.v. over three hours. The cisplatin will be given the same way it was given during radiation.
Also, at the time of your surgery, when your tumor was removed, tissue went to the hospital’s pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue may be sent to a central office for review and research investigation associated with this protocol.

**RISKS AND DISCOMFORTS**

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (*side effects*). The treatment used in this study 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 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 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; you 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 your blood. It is possible that you 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* commonly causes a lowering of blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You 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 your vein into the surrounding skin. Rarely paclitaxel can cause a severe allergic reaction resulting in the development of a rash, skin blisters, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If you are treated with a high dosage or for a prolonged period, you may experience numbness of the hands and feet. Paclitaxel can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that you 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.

Your physician will be checking you closely for these side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

**COSTS**

Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.
CONTACT PERSONS
(This section must be completed)

For information about your disease and research-related injury, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

ALTERNATIVES

Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; or (3) no treatment except medications to make you feel better.

These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the treatment you will be given in this research study will help your condition more than the standard treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

CONFIDENTIALITY

Records of your progress while on the study will be kept in a confidential form at this institution and 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 this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.
I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or legal Representative)                   Date

TISSUE AND BLOOD TESTING *(RTOG 99-05)*

I agree to the use of my tissues/other samples for additional research studies.

☐ Yes    ☐ No

Patient Signature (or Legal Representative)                   Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0  Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1  Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3  Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4  Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
APPENDIX III  
STAGING FOR ENDOMETRIAL CANCER  
(AJCC, 5th Edition)

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>TNM FIGO Category</th>
<th>Stage</th>
</tr>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to corpus uteri</td>
</tr>
<tr>
<td>T1a</td>
<td>IA Tumor limited to endometrium</td>
</tr>
<tr>
<td>T1b</td>
<td>IB Tumor invades up to or less than one-half of the myometrium</td>
</tr>
<tr>
<td>T1c</td>
<td>IC Tumor invades more than one-half of the myometrium</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades cervix but does not extend beyond uterus</td>
</tr>
<tr>
<td>T2a</td>
<td>IIA Endocervical glandular involvement only</td>
</tr>
<tr>
<td>T2b</td>
<td>IIB Cervical stromal invasion</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>
</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>
</tr>
<tr>
<td>T3b</td>
<td>IIIB Vaginal involvement (direct extension or metastasis)</td>
</tr>
<tr>
<td>N1</td>
<td>IIIC Metastasis to the pelvic and/or para-ortic lymph nodes</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>
</tr>
<tr>
<td>M1</td>
<td>IVB Distant metastasis. (Excluding metastasis to vagina, pelvic serosa or adnexa. Including metastasis to intra-abdominal lymph nodes other than para-ortic, and/or inguinal lymph nodes).</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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</table>

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed.</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
## APPENDIX III (cont’d)

STAGING FOR ENDOMETRIAL CANCER

(AJCC, 5th Edition)

### STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Classification</th>
<th>N Classification</th>
<th>M Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IC</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>IIIC</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>Any N</td>
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</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 supersede 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.

All deaths within 30 days of termination of the agent. As above

26
All life threatening (grade 4) events which may be due to agent.

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.

All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.

All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

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

Definition of Bladder and Rectal Points

Vaginal Colpostats

Bladder reference point (Balloon 7 cm³)

Active intravaginal sources

Posterior vaginal wall

Rectal reference point

0.5 cm
APPENDIX VI (cont'd)

Definition of Bladder and Rectal Points

Vaginal Cylinder

Active intravaginal sources

Bladder reference point (Balloon 7 cm³)

Vaginal surface dose

0.5 cm

Rectal reference point
APPENDIX VII

Points of Calculation