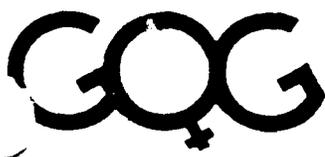


94-018



**GYNECOLOGIC ONCOLOGY GROUP
ADMINISTRATIVE OFFICE**

1234 MARKET STREET • SUITE 1945 • PHILADELPHIA, PA 19107 • 215-854-0770 FAX 215-854-0716

Robert C. Park, M.D.
Chairman

John R. Kellner
Administrative Director

TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS
FROM: *BADaly* BARBARA AD DALY NAV1.954721.002
OFFICE MANAGER
DATE: FEBRUARY 8, 1991
RE: ACTIVATION OF PROTOCOL GOG #109/SWOG #8797

EFFECTIVE FEBRUARY 1, 1991, Protocol #109/SWOG #8797, "A Randomized Comparison of 5-FU Infusion & Bolus Cisplatin as an Adjunct to Radiation Therapy, Versus Radiation Therapy alone in Selected Patients with Stages I-A2, I-B and II-A Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection", was re-opened for patient entry.

Attached are replacement pages and a new Fast Fact Sheet.

The following changes have been made by SWOG and the revised pages are enclosed:

Replacement pages are for Eligibility Checklist, the Face Sheet (pages 1 & 2), the Schema (page 3), and pages 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 19, 20, 21, 22, 23, 24, 25, 26, 48, and the Study Specific Solid Tumor Flow Sheet. (Please note GOG will use GOG Fast Fact Sheet.)

Please replace these pages in all copies of the protocol at your institution and destroy the earlier ones. A copy of this memo should be placed at the back of the protocol to reflect what changes were made on this date.

You are reminded that a signed, original HHS-596 Form indicating your Investigational Review Board's approval of this protocol must be on file in the GOG Administrative Office before patient entries onto the study will be accepted. In addition, a copy of the informed consent being used at your institution (if it differs from the suggested form appended to the protocol) or a letter from the Principal Investigator stating that the suggested form is being used, must accompany the HHS-596 Form.

BAD/mch
Attachment

cc: Rolland J. Barrett, M.D.
Richard Stock, M.D.
Frederick Stehman, M.D.
Gillian Thomas, M.D.
Dana Sparks (SWOG)

Robert C. Park, M.D.
John Blessing, Ph.D.
J. Tate Thigpen, M.D.
William Hoskins, M.D.
File

ENCLOSURE (25)

SCHEMA

Primary Stage I-A2, I-B or II-A Carcinoma of the Cervix

- Squamous
- Adenocarcinoma
- Adenosquamous

↓
Radical Hysterectomy Plus Bilateral
Pelvic Lymphadenectomy and Para-
aortic Lymphadenectomy

↓
Histologically Confirmed

Positive Pelvic Lymph Nodes
Positive Parametrial Involvement or
Positive Surgical Margin

↓
Randomize

← Arm I

5-FU Infusion
Cisplatin
Radiation Therapy

→ Arm II

Radiation Therapy

1.0 OBJECTIVES

- 1.1 To determine whether the combination of 5-fluorouracil (5-FU) and cisplatin used as an adjunct to radiation therapy will improve survival rate or progression-free survival and decrease extra pelvic failure compared to radiation therapy alone in patients with positive pelvic lymph nodes, positive parametrial involvement or positive surgical margins following radical hysterectomy and lymph node dissection for Stages I-A2, I-B and II-A carcinoma of the cervix.
- 1.2 To determine the increase in toxicities due to 5-FU and cisplatin as an adjunct to radiation therapy versus radiation therapy alone.

2.0 BACKGROUND

The relative frequency of Stage I invasive carcinoma of the cervix continues to increase, and is presently estimated to occur in 70% of all cases.(1) Stage I disease is adequately treated in many cases by radical hysterectomy with pelvic and para-aortic lymph node dissection. Survival following radical hysterectomy and node dissection for early carcinoma of the cervix has been found to be dependent upon multiple prognostic factors including the presence or absence of tumor extension or metastasis to the regional lymph nodes, parametrium or surgical margins. Involvement of regional lymph node metastatic disease has been reported to occur in approximately 12-23% of all cases.(2-6) Tumor involvement of the parametrial tissue has been found in 7-17% of cases studied, (6-8) with the incidence of positive surgical margins reported as approximately 5%.(4) A significant decrease in five-year survival rate has been found when these prognostic factors are positive on postoperative histologic review. Survival rate decreases from 96% to 60% when there is regional lymph node involvement with tumor.(7, 9, 10) Parametrial involvement with tumor spread as well as surgical margins involved with microscopic tumor have each independently been reported to decrease the five-year survival rate to approximately 70% as compared to 90% five-year survival when such factors are absent on pathology review.(4,6,7) In most centers, the standard treatment approach to the presence of these poor prognostic factors found on histologic review of radical hysterectomy specimens continues to be postoperative whole pelvic external beam radiation therapy. (3, 11)

Although prospective studies have demonstrated that external beam radiation therapy can eradicate microscopic tumor implants in regional pelvic lymph nodes, (12) retrospective studies reported to date have failed to demonstrate a survival advantage when radiation therapy is used postoperatively for positive lymph node involvement. (7, 9, 13-15) Although there is less retrospective information available to examine the role of postoperative external radiation therapy for parametrial or surgical margin involvement with a tumor, there is again little evidence to support its usefulness in improving long-term survival.(6) Possible explanations for the lack of effectiveness found in using postoperative radiation therapy to eradicate microscopic disease include pelvic fibrosis and decreased vascularity following pelvic surgery, the presence of occult metastatic disease outside of the pelvis at the initiation of treatment, and the possibility of significantly different tumor biology and immune status in patients with these poor prognostic factors. Retrospective studies examining postoperative radiation therapy in early stage carcinoma of the cervix also suggest that the decrease in pelvic recurrence achieved may be at the expense of an increase in extra pelvic or distant recurrence of disease.(3, 9, 16, 17)

An alternative approach for patients with positive lymph nodes, positive parametrial involvement or positive surgical margins after radical hysterectomy would involve the addition of cytotoxic chemotherapy to postoperative radiation therapy in an attempt to improve control of extra pelvic recurrence, to possibly improve local control of disease, and to improve overall survival.

Ashraf and Bojo have recently reported a series of patients with positive nodes at radical hysterectomy who were treated with cisplatin, 70 mg/M², every four weeks. Patients with only positive pelvic nodes received 3-6 cycles of treatment, while patients with positive high common iliac nodes received nine cycles of therapy. With a minimum of two years of follow-up, 20 of 22

patients are NED. This includes 13 of 14 patients with positive pelvic nodes only, and eight of nine with high common iliac or para-aortic node involvement. None of these patients received adjuvant irradiation.(18)

Recent experience in treating squamous cell carcinomas of the head and neck with combination chemotherapy followed by surgery or irradiation has demonstrated effectiveness in the treatment of advanced disease. Kish, et al. achieved a response rate of 88.5% in 26 patients with advanced squamous cell carcinoma of the head and neck utilizing a combination of bolus cisplatin combined with a 96 hour infusion of 5-FU.(19) Decker, et al., utilizing a similar regimen found a 93% response rate after three cycles of combination chemotherapy in patients with Stages III and IV squamous cell carcinoma of the head and neck.(20) Seven patients received radiation therapy after the completion of combination chemotherapy and surgical exploration without evidence of unusual toxicity. Only three of 35 patients studied were unable to complete the cisplatin and 5-FU regimen and in no case was discontinuation related to the chemotherapy. The use of continuous infusion of 5-FU over a 96-hour period appears preferable to bolus infusion due to significant differences in terms of both response rate and toxicity encountered.(21) Animal data utilizing the mouse L1210 leukemia model also support the existence of a synergistic relationship between cisplatin, 5-FU and radiation that is not demonstrated when the cytotoxic agents are used individually.(22) This same study also demonstrates increased effectiveness when cisplatin is administered prior to radiation therapy.

A recent clinical trial of 5-FU combined with cisplatin in advanced carcinoma of the cervix employed a similar regimen of bolus cisplatin and continuous infusion of 5-FU. In six patients with recurrent tumor following radiation therapy and one additional patient with Stage IV disease at the time of presentation, a 57% objective response rate was attained with this regimen. Myelosuppression was generally mild and toxicity was found to be manageable.(23) The Puget Sound Oncology Consortium has utilized cisplatin and 5-FU infusion in combination with methotrexate and leucovorin rescue with minimal morbidity and a high degree of activity in squamous cell carcinomas of the head and neck and have recently reported pilot study data for patients with advanced primary or recurrent squamous cell carcinoma of the cervix treated with the same regimen.(24) Of the 16 patients evaluable for response, 50% achieved a complete remission after 3-4 cycles of chemotherapy and 19% achieved a partial response. In patients who received chemotherapy as their initial treatments, consolidation radiotherapy was administered and resulted in no greater toxicity than expected with radiotherapy alone. Other cytotoxic drug combination utilized prior to and concurrently with radiation therapy following surgery for early stage carcinoma of the cervix have achieved early encouraging results in small groups of patients.(25,26) The data from GOG 85 (SWOG-8585), based on 151 patients, has been reviewed for toxicity. One arm of this protocol used 5-FU and cis-platinum in similar doses combined with radiation therapy to the pelvis delivered at 170 cGy fractions to a total dose of at least 5,100 cGy. These patients were surgically staged. The toxicity was quite acceptable. Only eight patients in the entire group had GI or GU toxicity, Grade III or better. The goal of the present study is to determine whether the combination of bolus cisplatin and continuous infusion of 5-FU can improve progression-free interval and survival in patients receiving postoperative radiation therapy for specific poor prognostic factors found on histologic review after radical hysterectomy and node dissection.

3.0 DRUG INFORMATION

3.1 Cis-Platinum (CDDP)(NSC-119875)

- a. **Pharmacology and Pharmacokinetics:** The dominant mode of action of cis-platinum appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Plasma levels of cis-platinum decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 45% of the radioactivity excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate

that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

- b. Human Toxicity: Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are loss of taste, allergic reactions, and loss of muscle or nerve function.

- c. Pharmaceutical Data: Formulation: Cis-platinum (Platinol*) is available as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of sterile water for Injection USP, respectively.

Storage & Stability: The intact vials should be stored under refrigeration. However, once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5-1/2NS (ppt. occurs in D5W). Cis-platinum has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Administration: Cis-platinum should be given immediately after preparation as a slow intravenous infusion.

- d. Supplier: Cis-platinum is commercially available, and should therefore be purchased by the third party. This drug will not be supplied by the NCI.

3.2 5-Fluorouracil (5-FU)(NSC-19893)

- a. Chemistry: Synthesis of 5-fluorouracil was first described by Heidelberger in 1957.

- b. Biochemistry: 5-FU is considered to act primarily as an inhibitor of thymidylate synthetase.

- c. Animal Toxicology: A wide variety of transplantable tumors in rodent species respond to 5-FU.

- d. Human Toxicology: Side effects include anorexia, nausea, vomiting, mucositis, alopecia, myelosuppression, maculopapular eruptions, fingernail changes, hyperpigmentation, photosensitization, ataxia, dizziness, slurred speech, uncontrolled eye movements, myocardial ischemia and angina.

- e. Pharmaceutical Data: Formulation: 5-FU is a colorless to faint yellow solution supplied in 500 mg ampules containing 50 mg/cc.

Storage & Stability: Store at room temperature and protect from light.

Administration: Continuous intravenous infusion.

- f. Supplier: 5-FU is commercially available and should be purchased by a third party. This drug will no longer be supplied by the NCI.

4.0 STAGING CRITERIA

4.1 All eligible patients are staged in accordance with the FIGO classification system (Section 20.2). Only those patients with FIGO stages I-A2, I-B and II-A will be eligible.

a. Preoperative Clinical Staging

Patients will have a chest x-ray prior to therapy. Pelvic examination should be performed under general anesthesia at the time of surgery, to determine the clinical stage.

b. Surgical Staging

Determination of nodal involvement will be made at the time of surgery. Surgical guidelines require pelvic lymphadenectomy plus sampling of the para-aortic lymph nodes. Only those patients with positive pelvic nodes or positive surgical margins or positive parametrial involvement will be eligible. Patients with positive para-aortic lymph nodes are excluded.

1. Pelvic lymphadenectomy will include the removal of all nodal tissue and the skeletonization of all vessels from the mid portion of the common iliac artery to the circumflex iliac vein; laterally, from the mid portion of the psoas muscle to ureter medially including the hypogastric artery and vein and from the obturator fossa anterior to the obturator nerve. Metal clips should be used to mark node removal sites. Dissection should be carried up to include the high common iliac and para-aortic lymph nodes.
2. Radical hysterectomy requires the removal of the uterus and contiguous parametrial tissue to its most lateral extent along with para-vaginal tissue and the upper one quarter of the vagina along with the proximal utero-sacral ligaments. The uterine artery should be transected at its origin lateral to the ureter. The ureter must be unroofed from its entry into the broad-ligament to its-intramural portion in the bladder and dissected laterally from its attachment to the cardinal ligament.

5.0 ELIGIBILITY CRITERIA

- 5.1 Patients must have primary, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix, clinical Stages I-A2, I-B or II-A.
- 5.2 Patients must have had a radical hysterectomy with total pelvic lymphadenectomy and para-aortic sampling.
- 5.3 Patients must have, at surgical evaluation, either histologically confirmed positive pelvic lymph nodes, positive parametrial involvement, or positive surgical margins.
- 5.4 Patients must have confirmed negative para-aortic lymph nodes. Exception: Patients whose para-aortic nodes have not been separately sampled are eligible only if they have negative common iliac nodes. (Patients with positive common iliac nodes are eligible only if para-aortic nodes are negative.) (Patients with unresectable nodal disease are ineligible.)
- 5.5 Patients must not have received prior systemic chemotherapy or prior pelvic irradiation. Patients must have had no prior immunotherapy (including biologics) or hormonal therapy as cancer treatment.

- 5.6 No more than ~~six~~ weeks may have elapsed between surgery and registration.
- 5.7 Radiotherapy must be planned to begin within 5 working days of registration and chemotherapy must be planned to begin simultaneously with radiotherapy.
- 5.8 Patients must have a performance status of 0-2, (see Section 10.4).
- 5.9 Required ~~values~~: Evidence of adequate bone marrow, renal, hepatic function must be demonstrated. WBC must be $\geq 3,000/\mu\text{l}$, platelets $\geq 100,000/\mu\text{l}$, creatinine and bilirubin within institutional normal limits.
- 5.10 No prior ~~malignancy~~ is allowed except for adequately treated basal cell (or squamous cell) skin cancer, ~~in situ~~ cervical cancer, or other cancer for which the patient has been disease-free for five years.
- 5.11 The following ~~patients~~ are not eligible for this study:
- a. ~~Patients~~ currently experiencing sepsis or other infection \geq Grade III.
 - b. ~~Patients~~ with a history of severe pelvic inflammatory disease defined as follows:
 1. requiring surgical drainage
 2. requiring hysterectomy/salpingo oophorectomy
 3. inducing sterility
 4. producing other symptomatic sequelae
 - c. ~~Patients~~ with "horseshoe kidney" (which may have been detected by CT scan, ~~abdominal~~ sonography, IVP or at surgery).
- 5.12 To be ~~completed~~ within 14 days prior to registration:
- Bloodwork ~~or~~ other body fluid analyses (urinalysis, creatinine clearance) required for ~~determination~~ of eligibility.
- In ~~calculating~~ days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday two weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines.
- 5.13 To be completed within 42 days prior to registration:
- Exams used for screening (e.g., audiogram, PFT) other than blood or body analyses; x-rays, scans, or ultrasound of non-measurable disease or uninvolved organs.
- 5.14 Southwest Oncology Group patients must be treated at a Southwest Oncology Group-approved radiotherapy facility. The planned start date of radiation therapy, the radiotherapist's name, and the treating radiotherapy facility must be given at the time of registration.
- 5.15 Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- 5.16 At the time of registration, the date of institutional review board approval must be provided to the Statistical Center.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 Stratification factors:

Stage: IA2 vs IB vs IIA
Risk: involved nodes: yes vs. no
Group: GOG vs SWOG vs. RTOG

6.2 Descriptive factors:

positive high common iliac nodes: yes vs. no
other positive pelvic nodes: yes vs. no
positive parametrial involvement: yes vs. no
positive surgical margin: yes vs. no

6.3 A dynamic allocation scheme will be used to randomize patients to the two treatment arms. Patients will be balanced within group (SWOG vs. GOG vs. RTOG) by stage and risk category.

7.0 TREATMENT PLAN

7.1 Randomization: Eligible patients will be randomly assigned to receive either 5-FU and cisplatin plus pelvic irradiation (Arm-I), or pelvic irradiation alone (Arm-II). (Patients with positive high common iliac lymph nodes will receive extended field para-aortic irradiation.) See Section 13.0 for registration procedure.

7.2 Arm I

AGENT	DOSE	ROUTE	DAYS	RERX INTERVAL	NOTES
5-FU	1,000 mg/M ² /d	CI	1-4	Q 3 wks x 4	96 hr continuous infusion; total dose 4,000 mg/M ² . Repeat Day 22, 43, 64
Cisplatin	70 mg/M ²	IV	1	Q 3 wks x 4	Dissolve in 1L NS & give over 2 hrs with 40 gms mannitol and 3 gms MgSO ₄ *
Whole Pelvis XRT	170 cGy/day		1-5	Q wk x 6	4,930 cGy total dose in 29 fractions

* NOTE: Prehydration with 1L of 1/4 NS or 1/2 NS should be infused intravenously one hour before cisplatin. Increased oral intake should be encouraged starting the day before treatment. Additional fluid may be given as needed for symptomatic support. Immediately after completion of the cisplatin infusion, an additional 1L of 1/4 NS or 1/2 NS should be infused over four hours. This is the minimum fluid administration recommendation and more fluid may be given at the discretion of the treating physician.

a. Patients with positive high common iliac nodes also receive:

Para-aortic XRT	150 cGy/day		1-5	Q wk x 6	4,500 cGy total
-----------------	-------------	--	-----	----------	-----------------

b. XRT will begin within six weeks after surgery; simultaneous with the start of first chemotherapy cycle.

7.3 Arm II

AGENT	DOSE	DAYS	RERX INTERVAL	NOTES
Whole Pelvis XRT	170 cGy/day	1-5	Q wk x 6	4930 cGy total dose in 29 fractions

a. Patients with positive high common iliac nodes also receive:

AGENT	DOSE	DAYS	RERX INTERVAL	NOTES
Para-aortic XRT	150 cGy/day	1-5	Q wk x 6	4,500 cGy total dose in 30 fractions

b. XRT will begin within six weeks after surgery.

7.4 Radiotherapy (Arms I and II):

Radiation therapy must be started within six weeks after surgery (Arms I and II), and simultaneous with the start of first chemotherapy (Arm-I). See Section 8.2 for dose modifications for radiation therapy toxicities.

a. External Whole Pelvis Irradiation

Patients will receive 4930 cGy with a homogeneity of no more than +/-5% to the pelvis in 29 fractions of 170 cGy daily, 5 times per week. All fields should be treated each day.

b. External Para-aortic Irradiation

Concurrent with whole pelvis irradiation, patients with positive high common iliac nodes will receive 4,500 cGy delivered in 30 fractions of 150 cGy, five times per week. All fields should be treated each day. It is strongly recommended that the treating surgeon submit a diagram showing the location of the nodes that he designated as high common iliac.

c. Dose Distribution

1. A 4 field box technique is mandatory for inclusion in this protocol. In an effort to reduce toxicity, it is highly recommended that each patient swallow a dilute solution of an appropriate contrast material approximately 30 minutes before simulation so that the small bowel can be identified on the simulator films. The use of individualized custom blocking is highly recommended. Dose to the tumor volume should not vary by more than +/- 5% from the prescribed dosage. The prescription point is to be at isocenter. The use of tissue wedges and/or compensating filters may be necessary to accomplish this goal. Isodose distributions and/or dosimetry calculations should be submitted as per instructions in Section 12.3d and e.

2. Whole Pelvic Radiation will be delivered to all suspected disease with a minimum 1 cm margin. At a minimum the field should include the upper 1/2 of the vagina, the paracervical, parametrial and the uterus sacral tissue as well as the external iliac hypogastric and obturator nodes. The boundaries are as follows.

AP/PA Fields:

Cephalad Border:

A transverse line drawn through the L4, L5 inter space.

Caudal Border:

The mid-portion of the obturator foramen or the lowest extension of suspected disease with a minimum of 1 cm margin

Lateral Borders:

1 cm beyond the lateral margin of the true pelvis at its widest points.

Lateral Pelvic Fields:

The cephalad and caudal borders are as above.

Anterior Border:

A horizontal line drawn through the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodes or in the absence of radiographic documentation, the line should pass at least 1.5 cm anterior to the lumbar vertebral bodies. Individualized custom blocks can be used to achieve this goal.

Posterior Border:

A horizontal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm. Surgical clips that are known to mark sites of lymph node removal should always be included.

3. Paraortic Fields

A four field arrangement for para-aortic irradiation is mandatory. An appropriate gap calculation should be made.

AP/PA Fields:

Cephalad Border:

A transverse line drawn at the L1 and L2 inter space.

Caudal Border: See above.

AP/PA Lateral Borders:

If radiographic evidence is available, the field should include all lymph nodes with at least a 1 cm margin. In the absence of such evidence, the minimum width will be 5 cm and it is suggested that the borders pass through the tips of the lumbar transverse processes.

Periportal Lateral Fields:

It is necessary to document the location of the kidneys via a CT scan or IVP. Under no circumstances should more than 1/3 of each kidney be included in the treatment volume.

The cephalad and caudal borders are as above.

Anterior:

The anterior border should encompass all known lymph nodes with a margin of 1 cm. In the absence of radiographic documentation, it is recommended that this border be at least 2 cm anterior to the vertebral bodies.

Posterior:

The posterior border will be defined by an individualized custom block in conjunction with the primary collimators. The ultimate result is that the spinal cord should be shielded throughout its entire length with a margin of at least 0.5 cm.

e. Radiation Sources

Radiation sources employed in this study will be x-ray generators which produce x-ray beams with a photon energy of 4 MeV or more. Radiation output of the unit must be adequate to permit employment of a TSD or SSD of 80 cm or more.

f. Simulation

All fields require simulation and copies of the port films are to be submitted within 48 hours of the start of treatment to the Quality Assurance Center, (see Section 12.3).

Simulator localization films and verification films taken on the treatment machine will be necessary in all cases. Polaroid pictures of the patient in the treatment position for each field are recommended.

Isodose distribution through the Para-aortic of the pelvic and para-aortic portals will be obtained and submitted for review.

7.5 Criteria for Removal from Protocol Treatment:

- a. Progression of disease (as defined in Section 10.3c).
- b. Unacceptable toxicity (see Section 8.0).
- c. The patient may withdraw from the study at any time for any reason.

7.6 All reasons for discontinuation of treatment must be documented in the Flow Sheets Notice.

7.7 All patients will be followed until death.