

RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-13

**A PHASE II STUDY OF EXTENDED FIELD RADIATION FOLLOWING
THERAPEUTIC PARA-AORTIC NODE DISSECTION FOR PATIENTS
WITH CARCINOMA OF THE UTERINE CERVIX WITH PARA-AORTIC NODAL
METASTASES**

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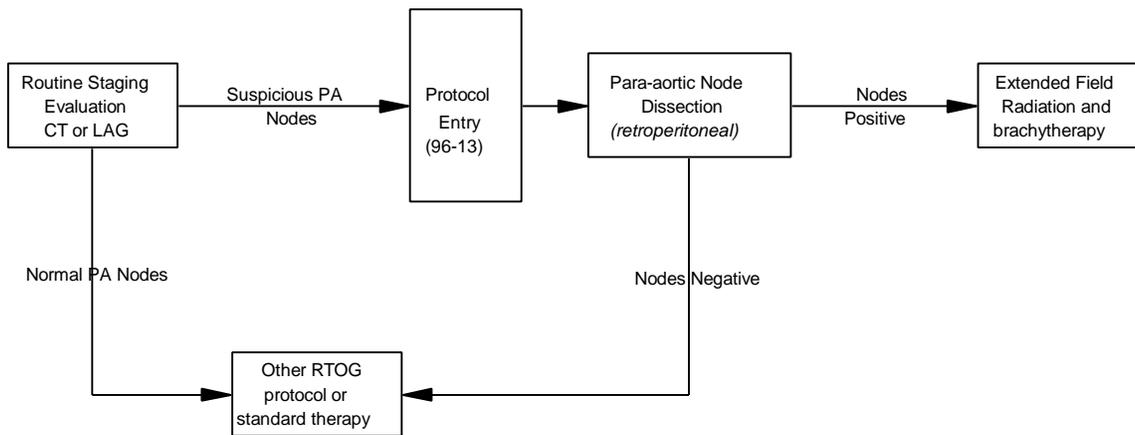
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SCHEMA



Surgery

Retroperitoneal lymph node dissection from the level of the renal vessels down to the bifurcation of the common iliac arteries with maximal attempt to remove all visible nodal tissue so that no gross residual nodal tumor remains.

External Radiotherapy

Pelvic and para-aortic radiation to 45 Gy in 5 to 5 1/2 weeks, 1.8 Gy per day, five days per week. Following this, pelvic boosts may be delivered as indicated. See Sections 6.2. 1-2.

Intracavitary RT

1-2 intracavitary insertions (*intra-uterine tandem and vaginal sources*) to deliver intracavitary dose necessary to complete 85 Gy to Point A adding whole pelvis external and intracavitary RT doses. See Section 6.2.3.

Eligibility (see Section 3.0 for details)

- Biopsy-proven squamous carcinoma of the cervix with biopsy proven para-aortic lymph nodes or radiographic evidence of para-aortic lymph node involvement
- No prior chemotherapy, radiation therapy or definitive surgery
- Stage Ib, IIa, IIb, IIIa, or IIIb (*FIGO*) lesions
- No intraperitoneal disease, demonstrable nodal metastases above the renal vessels or any other distant metastases
- KPS \geq 70
- Age \geq 18
- Hemoglobin \geq 10 gm, WBC \geq 4000/mm³
- No medical contraindications to surgical procedure
- Study-specific informed consent

Required Sample Size: 53

Institution # _____

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ELIGIBILITY CHECK

Case # _____

- _____(Y) 1. Does the patient have biopsy proven squamous carcinoma of the cervix?
- _____(Y) 2. Was there biopsy or radiographic evidence of para-aortic lymph node involvement?
- _____(N) 3. Any evidence of mets outside the pelvis other than para-aortic?
- _____(N) 4. Any intraperitoneal diseases?
- _____(N) 5. Any disease above the level of the renal vessels?
- _____(≥ 70) 6. What is the KPS?
- _____(≥ 18) 7. What is the patient's age?
- _____(Ib-IIIb) 8. What is the patient's FIGO stage?
- _____(Y) 9. Has the patient signed a study specific informed consent?
- _____(N) 10. Any prior RT, chemo, hysterectomy or transperineal node dissection?
- _____(N) 11. Any prior malignancy other than non-melanomatous skin cancer?
- _____(N) 12. Is the patient pregnant?
- _____(Y) 13. Will patient undergo an extraperitoneal lymph node dissection?

_____ Patient's Name
_____ Verifying Physician
_____ Patient ID #
_____ Referring Institution # if different
_____ Birthdate
_____ Race
_____ Social Security Number
_____ Zip Code (9 digit if available)
_____ Method of Payment
_____ Date of Surgery
_____ Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

It is estimated that there will be 15,700 new cases of invasive cervical cancer in 1996.¹ While the mortality rate from this cancer has been decreasing over the past 20 years, this is primarily due to earlier diagnosis and improved screening programs. Over this time period, however, few advances have been made in the therapy of cervical cancer. For early stage disease, either radical surgery or pelvic radiation can result in 5-year survival of 85 - 95%. Nevertheless, nearly 7,000 women die annually in the United States from invasive carcinoma of the cervix, and a great majority of these present initially with advanced lesions. The 5-year survival rates of FIGO stages IIb through IVb range from approximately 60 to 10% respectively.

A group of patients with a particularly poor prognosis has been those women with metastatic disease in the para-aortic region. It has been noted that patients with bulky para-aortic disease are usually not curable. In some situations this may be due to the fact that additional metastatic deposits are beyond the potential radiation field. Other patients may have disease encompassed by the radiation field. However, with standard fractionation the maximum tolerated para-aortic dose is in the range of 45 Gy, below that which is required to sterilize gross tumor (*small boost fields can clearly be given at least 55-60 Gy*). It has been observed that patients with microscopic tumor in the para-aortic nodes can have a 5-year survival as high as 50%.²⁻⁷

It is unknown if patients with grossly positive para-aortic nodes who are surgically reduced to microscopic disease prior to radiotherapy have an improved survival when compared to women who undergo radiation alone. It is also unknown what percentage of women with grossly positive para-aortic nodes can be rendered clinically disease-free by surgery and what toxicity is associated with such an approach. If surgical reduction of involved para-aortic nodes prior to radiotherapy confers a survival advantage, this would have significant implications for the treatment of women with involved pelvic nodes.

2.0 OBJECTIVES

- 2.1 To determine the feasibility and tolerance of surgical debulking for patients with clinically involved para-aortic nodes from metastatic squamous carcinoma of the cervix prior to administration of extended field radiation therapy delivered with curative intent.
- 2.2 To determine the acute toxicity of surgery and radiotherapy.
- 2.3 To determine local control and survival in this patient group.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

- 3.1.1 Patients must have biopsy proven squamous carcinoma of the uterine cervix and either biopsy proven or radiographic evidence of metastatic disease in the para-aortic nodes.
- 3.1.2 Patients must have no evidence of metastatic disease outside of the pelvis other than the para-aortic metastases, no intraperitoneal diseases, and no disease above the level of the renal vessels.
- 3.1.3 Patients must have a Karnofsky performance score ≥ 70 .
- 3.1.4 Age ≥ 18 years
- 3.1.5 Patients may have FIGO stages Ib, IIa, IIb, IIIa, or IIIb.
- 3.1.6 Patients must sign a study-specific informed consent

3.2 Ineligible Patients

- 3.2.1 Stage IV lesions are not eligible.
- 3.2.2 Patients who have received prior radiation therapy, chemotherapy or hysterectomy
- 3.2.3 Patients with medical indications that would contraindicate the surgery required by this study.
- 3.2.4 Patients who have a history of other malignancy with the exception of non-melanomatous skin cancer.
- 3.2.5 Pregnant women are ineligible and those of child-bearing potential should practice contraception.
- 3.2.6 Patients who have undergone a transperitoneal lymph node dissection.
- 3.2.7 Patients with adenocarcinoma, adenosquamous, small cell or other histologic variants are not eligible.

4.0 PRETREATMENT EVALUATION

4.1 Required Evaluations

- 4.1.1 Complete history and physical examination including height, weight, and Karnofsky Performance Status (*Appendix II*). Documentation of the nature and size (*including measurements in three*

dimensions and diagram) of the primary tumor is required. Initial examination should be performed by a gynecologist and radiation oncologist.

- 4.1.2 Histologic proof of squamous carcinoma. All patients will have confirmation of diagnosis by cervical biopsy.
- 4.1.3 All patients should undergo complete blood count, urinalysis, BUN, serum creatinine, bilirubin, transaminase and alkaline phosphatase within four weeks prior to registration.
- 4.1.4 Chest radiograph (*PA and lateral*) within 6 weeks of planned surgery.
- 4.1.5 Intravenous pyelography. If CT has been performed within 6 weeks of planned surgery the IVP may be omitted.
- 4.1.6 CT scan of the abdomen and pelvis or bipedal lymphangiogram. These tests may not show evidence of disease above the level of the renal vessels.
- 4.1.7 If patients have radiographic evidence of para-aortic metastases, they may be biopsied prior to any surgery. If a biopsy is performed, the results must be recorded. Biopsy of the para-aortic region is not required prior to surgery but is strongly recommended to decrease the incidence of unnecessary surgery. **Patients may not be entered on study after surgery since the feasibility of the surgical procedure is a major objective.**

4.2 Optional Tests

- 4.2.1 Other tests to complete standard FIGO staging or to evaluate for metastatic disease should be performed as needed. Biopsy of the scalene node should be performed at the discretion of the surgeon. If this procedure is performed, the results should be noted.

5.0 REGISTRATION PROCEDURES

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

6.0 RADIATION THERAPY

- 6.1 Radiation therapy should begin 10-14 days following surgery. If necessary due to surgical complications, radiotherapy may start as late as 21 days following the surgical procedure.
- 6.2 Patients will be treated with a combination of external and intracavitary irradiation. Every effort should be made to use intracavitary or, if necessary, interstitial therapy. When brachytherapy is not performed, a detailed explanation should be provided to RTOG Headquarters data management and dosimetry.
- 6.2.1 Pelvic Radiation - The pelvis will be treated to a total dose of 45 Gy in 5 weeks. Four-field technique (*AP-PA opposed and lateral opposed fields*) must be used if treatment is delivered with a beam energy of < 15 MV. A midline block may be added after 20 Gy to the pelvis using AP-PA fields. Patients will be treated once-a-day, 5 days per week with a daily fraction size of 1.8 Gy. A maximum whole pelvis dose of 45 Gy should be delivered unless the patient has massive disease precluding optimal intracavitary treatment, in which case an additional 5-10 Gy may be delivered. Involved lateral parametrium and/or involved pelvic nodes should be boosted with fields tailored to encompass known areas of disease to achieve a total dose (*including contribution of intracavitary treatment*) of 60 Gy \pm 5%. This may be delivered between the two intracavitary treatments, using the predicted intracavitary contribution based upon dosimetry from the first application.
- 6.2.2 Para-aortic Radiation - The para-aortic region is to receive 45 Gy in 5 to 5 1/2 weeks. Daily fractions of 1.8 Gy/day should be used unless acute toxicity is excessive, when the daily fraction size may be reduced to no less than 1.65 Gy/day. The para-aortic nodes may be treated in continuity with the pelvic field preferably using a four-field technique as described above and custom blocking. If four fields are used, CT-based treatment planning should be used to document the dose to kidneys and, if necessary, AP-PA and lateral fields should be weighted to avoid delivering >18 Gy to more than 1/3 of the renal

parenchyma. Treatment may be delivered with AP-PA fields alone if ≥ 15 MV photons are used. Known gross residual para-aortic disease or extracapsular extension should be boosted to 55.8 Gy if possible. Boosts may be delivered with oblique or lateral fields to avoid exceeding spinal cord or renal tolerance. Lateral boosts are preferred if the initial treatment was delivered AP-PA.

6.2.3 Intracavitary Applications - Radium or cesium may be used with standard intracavitary systems, **preferably in two intracavitary applications. An effort should be made to deliver a minimum cumulative external and intracavitary dose to Point A of 85 Gy.** Occasionally, normal tissue tolerance limits may demand a lower dose when vaginal and uterine anatomy does not permit optimal brachytherapy. The first intracavitary application should be given within 1 week of the completion of external irradiation. If tumor and normal tissue anatomy permit acceptable intracavitary geometry, intracavitary treatment may be performed during external beam therapy. The interval between the two applications will be 2-3 weeks. It is recommended that the total course of treatment be completed in less than 56 days. Interstitial brachytherapy may be used to treat distal vaginal disease that cannot be adequately covered with intracavitary treatment. See Section 6.4.

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 will be used.

6.3.2 Radiation Therapy Fields (Appendix VI)

6.3.2.1 Simulation. All fields treated require simulation and portal verification on the treatment unit. Copies of these are to be submitted to RTOG Headquarters.

6.3.2.2 Pelvic Portal (AP-PA)

Superior border. A transverse line between L4 and L5 (*may be treated in continuity with para-aortic fields*).

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

Inferior border. A transverse line through the mid pubis or 4 cm beyond the most distal vaginal disease, to include the introitus if necessary. Radio-opaque markers at 6 and 12 o'clock in the cervix and to mark distal vaginal disease will help to facilitate proper placement of the lower border.

Custom blocking to shield small bowel and femoral heads should maintain a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina.

6.3.2.3 Pelvic Portal (lateral fields)

Superior border. Identical to AP-PA fields.

Anterior border. A line drawn through the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4-5.

Posterior border. Care should be taken to include at least S1-S3 and all gross cervical, uterosacral, and paracervical disease. CT or MRI-based planning is encouraged to avoid shielding gross tumor.

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 should split the L4-5 vertebral body to shield posterior soft tissue and split the sacrum to provide adequate margin for pre-sacral nodes. Posterior rectum may be blocked if the patient does not have utero-sacral involvement with tumor.

6.3.2.4 Para-aortic Portal

Superior border. A transverse line drawn through the T11-12 interspace (*may be treated in continuity with pelvic fields*).

Anterior, posterior and inferior borders. Identical to borders of pelvic portal, maintaining a minimum 1 cm margin from para-aortic nodes. The width of the para-aortic "chimney" on lateral fields should be at least 5 cm at isocenter.

6.3.2.5 Reduced fields for parametrial and nodal boosts

Parametrial boosts. AP-PA fields with inferior and lateral borders identical to pelvic fields. Superior margin 9-12 cm above inferior border, tailored to the position of the cervix and uterus from radio-opaque markers and intracavitary films. Central blocking should measure at least 4.5 cm at midplane and should be tailored to the position of the intracavitary system. Nodal boosts should be at least 4x4 cm and maintain a margin of 1-1.5 cm from involved nodes.

Para-aortic boosts. Boosts should be at least 4x4 cm and maintain a margin of 1-1.5 cm from involved nodes. Oblique or lateral fields may be used to avoid spinal cord, small bowel, or kidneys.

6.3.3 Treatment Technique and Dose Specifications

6.3.3.1 When initial fields are treated with a 4-field technique using < 15 MV photons, AP-PA fields should be weighted somewhat more heavily than lateral fields to avoid delivering an excessive dose to

lateral tissues. This may be accomplished by equalizing the given dose from the four fields. In some cases, greater weighting may be placed on the AP-PA fields to avoid delivering an unacceptable dose to the kidneys. Opposing fields must be treated daily throughout the treatment course. When machine energies of less than 15 MV are used it is recommended that all four fields be treated daily. AP and PA fields alone may be used if the external beam energy is ≥ 15 MV.

6.3.3.2 The specification of target dose is in terms of a dose to a point at or near the center of the target volume. For the following portal arrangements, the target dose will be specified as follows:

For 2 opposed coaxial equally weighted beams: On the central ray at mid separation of beams.

For a 4-field arrangement of beams: At the isocenter of the beams.

The maximum and minimum doses in the target volume should be within $\pm 5\%$ of the dose at the isocenter.

6.3.3.3 Isodose distributions are required at the mid pelvis, and at the mid para-aortics (*L2-3*) whether both regions are treated as a single site or as two separate sites. Copies of isodose distributions for the two separate plans must be submitted to RTOG Headquarters.

6.4 Intracavitary Radiotherapy Dosimetry

6.4.1 Radium sources or equivalent cesium sources are to be used for intracavitary application(s) with intra-uterine tandems and vaginal applicators such as the Fletcher-Suit-Delclos afterloading applicator system.

6.4.2 A report on the dose to Points A, B, rectum and bladder, and vaginal surface, is mandatory. Point A is found by measuring 2 cm along the intrauterine tandem from the cervical os or phlange of the central tandem and 2 cm laterally in the plane of the intra-cavitary system. Point B is 5 cm lateral from a point 2 cm vertically above the cervical os or phlange of the central tandem. Bladder dose may be calculated at a point in the center of a contrast-filled (7 cc) balloon of a Foley catheter closest to the system on the lateral view. Rectal dose may be calculated by introducing contrast material in the rectum and marking a point adjacent to the applicator system or at 0.5 cm posterior to the vaginal ovoids or vaginal packing in the lateral projection. The vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid.

6.5 Compliance Criteria

Normal Tissue	Specified	Per Protocol	Acceptable Variation	Unacceptable Deviation
Spinal Cord	Maximum Dose	≤ 45.5 Gy	45.6 - 48 Gy	> 48 Gy
Bladder	ICRU point	≤ 75 Gy	≤ 81 Gy	> 81 Gy
Rectum	ICRU point	≤ 70 Gy	≤ 76 Gy	> 76 Gy
Vaginal Surface	Lateral surface of ovoid or cylinder	≤ 135 Gy	≤ 140 Gy	> 140 Gy
Kidney	At least 2/3 of renal parenchyma	≤ 15 Gy	≤ 18 Gy	> 18 Gy

For Tumor Doses and Times	Per Protocol	Acceptable Variation	Unacceptable Deviation
Total elapsed days, 45 Gy to pelvic and PA nodes.	≤ 37 days	≤ 42 days	> 42 days
Total elapsed days to pelvic and PA nodes (<i>including boosts</i>)	≤ 44 days	≤ 49 days	> 49 days
Total elapsed days primary (<i>point A</i>)	≤ 60 days	≤ 67 days	> 67 Gy
Total dose, point A	≥ 83 Gy	≥ 79 Gy	< 79 Gy

6.6 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, ureteral obstruction, shortening of the vagina, dyspareunia, vaginal vault necrosis and fistula formation between pelvic tissues.

- 6.6.2 RT toxicities and the time of their onsets in relation to RT administration will be recorded on the data collection forms.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

- 8.1 All patients will undergo an extraperitoneal lymph node dissection of the para-aortic area.
- 8.1.1 The skin incision may be of the surgeon's choosing including midline vertical, transverse and lateral vertical
- 8.1.2 The peritoneum is exposed and may be opened before or after retroperitoneal exploration if biopsies or washings are indicated.
- 8.1.3 The retroperitoneum is exposed by rolling the peritoneum medially until the psoas muscle and iliac vessels are visualized.
- 8.1.4 The aorta, vena cava and iliac vessels on the side of the entry are exposed
- 8.1.5 Aortic dissection then proceeds:
- The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, the inferior mesenteric artery (*IMA*), the ureters and duodenum should be identified
 - The nodal tissue over the distal vena cava from the level of the IMA to the mid right common iliac artery is removed.
 - The nodal tissue between the aorta and the left ureter from the inferior mesenteric artery to the left mid common iliac artery is removed.
 - Ligation of the proximal and distal nodal tissue is recommended.
 - Dissection cephalad to the IMA is restricted to cases in which palpable adenopathy or radiographically suspicious nodes are above that area. No dissection should attempt to go above the level of the renal arteries. When there is radiographic evidence of disease or palpable disease above the level of the IMA but still below the renal vessels, it is required that an attempt be made to continue the dissection to the upper limit of the renal vessels unless contraindicated for surgical or medical reasons.
- 8.1.6 Pelvic node sampling may be accomplished if indicated.
- 8.1.7 Unresectable nodes should be outlined with clips.

8.2 Documentation of Surgical Procedure

- 8.2.1 Diagrams that outline the presence of suspicious or abnormal nodes should be completed to represent the anatomy prior to surgery and after surgery. The presence of unresectable nodes should be delineated. A standard typed operative note must be submitted also.
- 8.2.2 The length of the surgical procedure ("*skin to skin*"), estimated blood loss, description of the nodal areas, description of residual disease and documentation of any intra or post-operative complications must be entered on the Surgery Form and submitted to RTOG.

8.3 Surgical Results

Patients who are found NOT to have para-aortic metastases after thorough surgical dissection (*false positive radiographic findings*) are terminated from this study. They may be eligible for other studies or treated off protocol.

8.4 Surgical Toxicities

- 8.4.1 Acute effects may include blood loss requiring transfusion, pelvic infection, wound infection, lymphocyst formation and a variety of anesthetic complications. Any of these effects could result in a delay in radiotherapy.
- 8.4.2 Long term effects of surgery may included lymphedema, lymphocyst and the possibility of additional gastrointestinal toxicity following radiation therapy when compared to patients who had not had a surgical procedure.

9.0 OTHER THERAPY

Not applicable to this study

10.0 PATHOLOGY

A central pathology review is not planned for this study.

11.0 PATIENT ASSESSMENTS

11.1 Evaluation During Treatment

- 11.1.1** All patients will undergo weekly clinical examinations that preferably will be performed by at least two examiners independently, including a gynecologist and radiation therapist. Examination will include pelvic assessment and measurement. Studies such as CT and MRI evaluation will be performed as indicated by the patient's tumor status.
- 11.1.2** Complete blood count with differential and platelet count will be performed weekly
- 11.1.3** At the time of each isotope insertion and one month following the completion of radiation therapy, additional physical examinations will be performed to document the presence of disease. Suspected persistent or recurrent disease must be documented by cervical and/or para cervical biopsies.

11.2 Evaluation of Response and Toxicity

- 11.2.1** Patients will be followed for disease status and for the appearance of toxicity with history, physical examination, and indicated laboratory and radiologic tests according to the following schedules:
First year - every three months
Second year - every four months
Third through fifth years - every six months, annually thereafter.
Every attempt should be made to histologically document recurrent tumor.
- 11.2.2** Toxicity Evaluation
- Myelosuppressive toxicity shall be reported as the lowest observed WBC and platelet count. Anemia and red blood cell transfusions will be noted.
 - Other toxicities will be scored according to Appendix IV.
 - Every effort will be made to obtain an autopsy on patients who die during or immediately after the study.

11.3 Criteria for Response

- 11.3.1** Complete clinical remission: Disappearance of all clinical evidence of active tumor for a minimum of four weeks documented by negative cervical biopsies. The patient must be free of all symptoms.
- 11.3.2** Partial remission: Fifty percent or greater decrease in the product of the diameters of the measured cervical lesion. No simultaneous increase in the size of any lesion or the appearance of new metastatic lesions may occur.
- 11.3.3** No change (stable disease): No change in the tumor size ($< 50\%$ decrease, or $< 25\%$ increase).
- 11.3.4** Progressive disease: Increase $\geq 25\%$ in the size of any measured lesion or the appearance of new metastatic lesions.

11.4 Criteria for Discontinuing Study Treatment

- 11.4.1** Increasing disease as defined in Section 11.3.4 after two weeks of therapy.
- 11.4.2** The development of unacceptable toxicity.
- 11.4.3** Patient request.

12.0 DATA COLLECTION

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

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 1 week of treatment start
Initial Evaluation Form (I1)	Within 2 wks of treatment start
Diagnostic Pathology Report (P1)	
Surgery Form (S1)	
Operative Notes (S2)	
Surgical Pathology Report (S5)	
<u>Preliminary Dosimetry Information:</u>	Within 1 wk of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	

13.4.2 *Analysis for Reporting the Initial Treatment Results*

- a. tabulation of all cases entered, and any excluded from the analyses with reasons for exclusion;
- b. institutional accrual;
- c. distribution of the important prognostic baseline variables
- d. observed results with respect to the endpoints described in Section 13.1. Further subgroup analysis would not be undertaken because of the small sizes involved in each subgroup.

13.5 **Inclusion of Minorities**

In conformance with National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered the possible interaction between race and treatments. The study is designed to evaluate the treatment tolerance with the assumption of the same tolerance rate across the races. However, a statistical analysis will be performed to examine the possible difference among races. In a prior study RTOG 9210 with similar eligibility criteria, 63% (19/30) of patients were white and 37% were non-white. For the planning purpose, we assume that 70% of patients entered into this protocol are white. With the proposed sample size, if 70% of the patients accrued are white, we have a 95% one-sided confidence interval with a lower bound of 68% around the hypothesized 80% tolerance for white, and a lower bound of treatment tolerance of 63% for non-white.

The interim analysis will include a tabulation of all cases by racial categories. The analysis for reporting the initial treatment results will include 95% confidence intervals of treatment tolerance and local-regional control and survival statistics within racial categories, i.e., white and non-white.

REFERENCES

1. Parker S.I., Tong T., Bolden S. Wingo P.A., Cancer Statistics, 1996. *CA- A Cancer Journal for Clinicians* 46:5-28, 1996
2. Hughes, R.R., Brewington, K.C., Hanjani, P., et al. Extended field irradiation for cervical cancer based on surgical staging. *Gynecol Oncol* 9:153, 1980
3. Tewfik H., Buchsbaum, H., Lifshitz, L., Tewfik, F. Para-aortic lymph node irradiated in carcinoma of the cervix after exploratory laparotomy. ASCO Abstracts, C-132, 1980
4. Ballon, S, Berman, M., Lagasse, L., et al. Survival after extraperitoneal pelvic and para-aortic lymphadenectomy and radiation therapy in cervical carcinoma. *Obstet Gynecol* 57:90, 1981
5. Welander, C., Pierce, V, Nori, D. et al. Pretreatment laparotomy in carcinoma of the cervix. *Gynecol Oncol*, 12:336, 1981
6. Potish, R., Twiggs, L. Okagaki, T., et al. Therapeutic implications of the natural history of advanced cervical cancer as defined by pretreatment surgical staging. *Cancer* 56:956, 1985
7. LaPolla, J., Schlaerth, J, Gaddis, O., Morrow C. The influence of surgical staging on the evaluation and treatment of patients with cervical carcinoma. *Gynecol Oncol* 24:194, 1986

APPENDIX I

RTOG 96-13

A PHASE II STUDY OF EXTENDED FIELD RADIATION FOLLOWING THERAPEUTIC PARA-AORTIC NODE DISSECTION FOR PATIENTS WITH CARCINOMA OF THE UTERINE CERVIX WITH PARA-AORTIC NODAL METASTASES

Sample Patient Consent Form

RESEARCH STUDY

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

PURPOSE OF THE STUDY

This is a clinical research trial designed to evaluate the effectiveness and toxicity of the surgical removal of para-aortic lymph nodes combined with extended field radiation for women who have advanced cervical cancer.

DESCRIPTION OF PROCEDURES

If I am eligible for this study, I will undergo careful evaluation. This will include physical examination, blood tests, urinalysis, kidney scan, and special x-ray tests, such as CT scan or lymphangiogram (*scan of lymph glands[nodes]*), to evaluate the amount of tumor present. I may have a biopsy of the lymph nodes which are suspicious for cancer in the para-aortic area (*abdominal*) using a fine needle. I will have exploratory surgery when the presence of cancer is strongly suspected or confirmed in the lymph nodes. The surgeon will attempt to remove as many as possible of these involved lymph nodes and nearby normal lymph nodes in the para-aortic and upper pelvic areas.

Once I recover from surgery, I will receive radiation to both the pelvis and para-aortic area. This will start as an external radiation treatment lasting a few minutes a day, five days a week, for a period of 4 to 5 weeks. Depending upon the response of the tumor, additional external radiation treatments or 1-2 radioactive insertions into the tumor 1-3 weeks apart may be performed. The insertions will require 2-3 day hospital stay.

This clinical trial is being conducted at several institutions in the United States and is coordinated by the Radiation Therapy Oncology Group (*RTOG*). It is expected that a maximum of 53 patients will be entered in this study. Patients will be closely followed after treatment is finished.

RISKS AND DISCOMFORTS

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

Radiation Therapy

Side effects expected from radiotherapy include tiredness near the end of treatment, diarrhea, nausea and vomiting, rectal irritation, urinary frequency and difficulty, loss of pubic hair, reddening and irritation of the skin in the treatment field, and low blood counts causing easy bruising. Long-term side effects, although uncommon, may include chronic malabsorption, rectal ulcer, bleeding or narrowing of the rectum, difficulty urinating, bloody urine, bowel obstruction, ureteral (*tube connecting kidneys to the bladder*) obstruction, shortening and narrowing of the vagina, pain with sexual intercourse, and fistula formation (*opening*) between pelvic tissues. Radiation to the pelvis causes sterility and I will not be able to become pregnant.

Surgery

Side effects may include blood loss requiring transfusion, pelvic infection, wound infection, lymphocyst formation and a variety of anesthetic complications. Any of these effects could result in a delay in radiotherapy. Long term effects of surgery may include lymphedema (*swelling of my extremities*), lymphocyst (*cysts in my glands*) and the possibility of additional gastrointestinal toxicity following radiation therapy when compared to patients who had not had a surgical procedure.

Other Risks

This study may be harmful to an unborn child. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. The results will be made available to the study participant prior to the initiation of this study.

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

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

CONTACT PERSONS

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

BENEFITS

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

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

ALTERNATIVES

Alternatives which could be considered in my case include surgery performed off-study with or without radiation therapy either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

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

VOLUNTARY PARTICIPATION

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

CONFIDENTIALITY

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

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

Patient Signature (*or Legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III

ANATOMICAL STAGING FOR CERVIX CANCER (AJCC, 3RD EDITION)

TNM CATEGORIES

Primary Tumor (T)

TNM	FIGO	DEFINITION
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma <i>in situ</i>
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	Ia	Preclinical invasive carcinoma, diagnosed by microscopy only
T1a1	Ia1	Minimal microscopic stromal invasion
T1a2	Ia2	Tumor with invasive component 5 mm or less in depth taken from the base of the epithelium and 7 mm or less in horizontal spread
T1b	Ib	Tumor larger than T1a2
T2	II	Cervical carcinoma invades beyond uterus but not to the pelvic wall or to the lower third vagina
T2a	IIa	Without parametrial invasion
T2b	IIb	With parametrial invasion
T3	III	Cervical carcinoma extends to the pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIa	Tumor involves lower third of the vagina, no extension to pelvic wall
T3b	IIIb	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4* IVa		Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis
M1	IVb	Distant Metastasis

* **Note: Presence of bullous edema is not sufficient evidence to classify tumor T4**

REGIONAL LYMPH NODES (N)

Regional lymph nodes include paracervical, parametrial, hypogastric (obturator), common, internal and external iliac, presacral and sacral.

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

NI Regional Lymph node metastasis

DISTANT METASTASIS (M)

MX Presence of distant metastasis cannot be assessed

M0 No distant metastasis

M1 IVb Distant metastasis

STAGE GROUPING

Stage 0 Tis N0 M0

Stage IA T1a N0 M0

Stage IB T1b N0 M0

Stage IIA T2a N0 M0

Stage IIB T2b N0 M0

Stage IIIA T3a N0 M0

Stage IIIB T1 N1 M0

T2 N1 M0

T3a NI M0

T3b Any N M0

Stage IVA T4 Any N M0

Stage IVB Any T Any N M1

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (*grade 4*) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *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 (\geq *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. **A written report to follow within 10 working days.
 - All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.
**A written report may be required.
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within working days with a copy to IDB.
(*Grade 4 myelosuppression not reported to IDB*)
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report **in writing** to RTOG Headquarters and IDB within 10 working days.

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

APPENDIX VI

RADIATION THERAPY FIELDS

