MEMORANDUM

TO: RTOG Principal Investigators and CRAs
FROM: Elaine Pakula
   Director, Protocol Development
DATE: March 30, 2000
SUBJECT: Protocol Update

Activated

RTOG 99-11, "Phase II Study of Paclitaxel and Cisplatin in Combination with Split Course Concomitant Hyperfractionated Re-Irradiation in Patients with Recurrent Squamous Cell Cancer of the Head and Neck"

Closing to Patient Accrual

RTOG 97-16 (C9781) Esophagus Poor Accrual

Terminated for Data Collection

RTOG 97-07 Cervix

CTC Booklet Reprinted

A second printing of the CTC booklet is now available. Call 1-800-4CANCER, follow the menu for publications and ask for CTC v 2.0. Up to 20 copies can be requested free of charge. For orders over 20, a nominal fee is charged. Because of the interactive application available on the web (http://ctep.info.nih.gov/CTC3/default.htm), the CTC Index will not be reprinted.

Supported by the Division of Cancer Treatment and Diagnosis, National Cancer Institute
Protocol Update
March 30, 2000
page 2

New Version of the A5 (Demographic Form)

A new version of the A5 (Demographic Form) has been approved and will appear in newly activated studies. The new edition may not be substituted in studies already using the "old" version. Please check the study-specific forms packets for the correct version.

The "new" version includes additional information, therefore requires two pages. Instructions for completion are provided. The Demographic Form is designed for completion by the patient or by a family member and not by institutional personnel. If the patient/family refuses to complete any items on the form, submit the form with this refusal indicated in Question 1 (see code 4 = Not applicable, no items completed).

cc: Study Chairs
CALGB (9781)
MEMORANDUM

TO: RTOG Principal Investigators and CRAs
FROM: Elaine Pakulis
Director, Protocol Development
DATE: December 3, 1998
SUBJECT: Protocol Update

Closing (effective 12/9/98)

RTOG 96-04 LENT Met Accrual

Closing (effective immediately)

RTOG 97-07 Cervix

The RTOG Data Monitoring Committee recommended the early publication of the phase III cervix study, RTOG 90-01, at the July meeting because of the highly significant survival advantage with concurrent chemotherapy. In addition, there are four other trials which confirm this observation. In the light of this, the Gynecology committee and the Group chair decided that this protocol, which does not include chemotherapy, should be closed to new patient entries.

FAX Numbers

Using the following numbers will speed delivery of your faxes:

Administration, Data Management, Membership, Statistics 215-928-0153
Dosimetry 215-923-1737
IRB, Patient Registrations (Intergroup), Audit Info, Protocol Development, Protocol/Data Form Requests, Regulatory 215-574-0300

cc: Study Chairmen

Supported by the Division of Cancer Treatment and Diagnosis, National Cancer Institute
SUMMARY OF CHANGES

RTOG 97-07, Cervix

September 8, 1998

The following changes are in effect:

**Schema** - Delete “50-55 Gy to” (error)

**Eligibility Checklist** - Added

"Will the patient get any care at a VA or military facility?"

Replacement pages are attached.
RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-07

PHASE I/II STUDY OF CONCOMITANT PARAMETRIAL BOOST RADIATION THERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

Study Chairmen
Radiation Oncology
K.S. Clifford Chao, M.D.
Radiation Oncology Center
Washington University Med Ctr
4939 Children's Place
St. Louis, MO 63110
(314) 362-8502
FAX# (314) 362-8521

Co-chairs
Perry W. Grigsby, M.D., M.B.A.
(314) 362-8502
FAX# (314) 362-8521
Randy Stevens, M.D.
(212) 263-5055
FAX# (212) 263-6274

Activation Date: October 1, 1997
Current Edition: September 8, 1998
Includes Revision 1

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RADIATION THERAPY ONCOLOGY GROUP
RTOG 97-07

PHASE I/II STUDY OF CONCOMITANT PARAMETRIAL BOOST
RADIATION THERAPY FOR LOCALLY ADVANCED
CERVICAL CANCER

SCHEMA

R  Whole pelvis 45.00Gy
    (AM)  1.8 Gy/per fraction x 25
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Concomitant

I  parametrial boost
    (PM)  9.6 Gy (1.2 Gy per fraction x 8)

S

T  ICI: Intracavitary implant: Point A dose of 40.00 to 45.00 Gy
    in two insertions following complete external beam radiotherapy.

E

R

Eligibility: (See Section 3.0 for details)

- Patients with FIGO Stage IIIB biopsy proven squamous cell carcinoma of the cervix
- No prior chemotherapy, radiation therapy or definitive surgery.
- Patients are required to have a Karnofsky performance score ≥ 70; Age ≥ 18.
- Adequate bone marrow function: hemoglobin ≥ 10 mg/ml, WBC ≥ 4000/mm³, platelets ≥ 100,000/mm³.
- Known HIV(+) patients are ineligible.
- Biopsy proven or radiographic evidence of para-aortic nodal disease is not eligible.
- Signed study-specific informed consent.

Required Sample Size: 46

9/8/98
Institution #

RTOG 97-07

ELIGIBILITY CHECK (9/8/98)

Case #

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Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

1.1 While the mortality rate for cervical cancer has been decreasing over the last 20 years, this is predominantly due to improved screening programs and early diagnosis. For early stage disease, either radical surgery or irradiation can result in 5-year survival of 85% to 90%. Nevertheless, nearly 8,000 women die annually in the United States from invasive carcinoma of the cervix. A great majority of those present initially with large advanced lesions. The 5-year survival for FIGO Stage IIB through IVB ranges from approximately 60% to 10%, respectively.

1.2 Although distant metastases may be a major component of failure, they still remain prognostic significant factors for those patients with locally advanced cervical cancer, the data from the Mallinckrodt Institute of Radiology (MIR) have shown that patients with tumor control in the pelvis had significantly lower incidence of distant metastases than patients who initially failed in the pelvis. The analysis by Jacobs et al. has shown that the tumors that do not regress promptly are likely to recur with distant metastases. Therefore, it shall be considered that some of this distant recurrence may have originated after treatment from persistent pelvic disease rather than from microscopic metastasis present in an undetectable state at the time of the treatment. It is reasonable to assume that the overall and disease-free survival will be improved if a better local control can be achieved. Jampolis and associates, analyzing postirradiation recurrences in 916 patients with squamous cell carcinoma of the intact uterus, pointed out that central recurrences were extremely rare in Stage IB and IIA (2%) and that in most instances they could be attributed to improper placement of the vaginal colpostats, which could produce low doses of irradiation in the cervix. Parametrial recurrences in Stage I, IIA, and IIB carcinoma were correlated with lateral deviation of the radium system without compensation from the external irradiation in about 75% of the patients. The overwhelming cause of failure in patients with Stage IIIIB disease was parametrial infiltration that could not be controlled with conventional regimen.

1.3 At MD Anderson Cancer Center, 36% of Stage III lesions recurred in the pelvis. RTOG 79-20 study also showed a similar trend. At MIR, the total pelvic failure rate was 23% for Stage IIB and 41% for Stage IIIIB patients. The total pelvic failure rate for Stage IIB patients was greater in those whose disease extended into the lateral parametrium. Among those failed in pelvis, lateral parametrial component is twice often than central component (MIR unpublished data), Table 1.

<table>
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<th>Table 1: Patterns of Pelvic Recurrence</th>
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<tr>
<td>No. recurrence</td>
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<tr>
<td>Distribution of rec.</td>
</tr>
<tr>
<td>Central component</td>
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<tr>
<td>Lat. parametrial</td>
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The combination of conventional low dose rate intracavitary brachytherapy and external beam radiation give the central portion of cervical cancer a dose of greater than 85-100 Gy. This implies that if tumors still recur within such high dose region, these tumors are most likely radioreistant. Increased dose or changed fractionation schedules might not be as helpful as incorporating additional cytotoxic or radiosensitizing modifiers (i.e. chemotherapy) in this group of patients. On the other hand, recurrence in the lateral parametria may be contributed by insufficient doses which delivered over a protracted period of time.

1.4 In an attempt to improve tumor control, a variety of innovative modalities have been investigated. These include fast neutron therapy, intra-arterial chemotherapy prior to irradiation, use of radiosensitizers, and chemo-radiotherapy. Several of these treatment
modalities either increase local control with an increase in the complication rate or not efficacious. Altered fractionation is another approach to improve radiation effect. Recently, a number of strategies have also been used to modify fractionation scheme:

1.4.1 **Accelerated fractionation**: A shortening of the overall duration by giving two or three fractions per day but using similar total dose per fraction as conventional fractionation.

1.4.2 **Hyperfractionation**: An increase in the number of fractions giving two or three fractions per day, with smaller doses per fraction than conventional treatment, higher total dose, but same overall time as conventional.

1.4.3 **Accelerated hyperfractionation**: Greater fraction number, smaller fraction size and a shorter overall treatment duration than conventional.

1.4.4 **Concomitant boost**: A variation of accelerated hyperfractionation, giving a second daily dose of radiation to a reduced field or boost during the course of the conventional fractionated radiotherapy.

1.5 The biological basis and the rationale for altered fractionation schemes have been reviewed by Withers, Thames and their colleagues. The object of accelerated fractionation is to reduce the opportunity for tumor cell regeneration during the treatment by shortening the overall treatment duration. With accelerated hyper-fractionation, an increased therapeutic gain can be achieved by combining both the decrease in dose per fraction and shortening of overall treatment duration. However, the main limitation of both treatment schemes is increased toxicity and may not be justified for the cervical cancer when cure but not palliation is attempted. The objects of hyperfractionation are to increase the therapeutic difference between tumor response and normal tissue injury through an increase opportunity for tumor cell redistribution and re-oxygenation, greater sparing of the late reaction normal tissue and possible lower oxygen enhancement ratio at low doses. However, overall treatment time remains lengthy. In RTOG 88-05 for cervical cancer, in which patients were treated with a twice-daily hyperfractionation schedule, no difference in the investigated endpoints was noticed. The toxicity was quite acceptable.

1.6 The analysis by Withers and his colleagues has shown that squamous cell carcinoma of the head and neck has rapid tumor growth during extensions of the treatment from about 5 weeks to 8 weeks which is normally the treatment duration for cervical cancer. This suggests that, on average, clonogenic re-population in squamous cell carcinoma accelerates only after a lag period on the order of 4+1 weeks after initiation of the radiotherapy and that dose increments of about 0.6 Gy per day is required to compensate for this re-population. Such a dose increment is consistent with a 4-day clonogenic doubling time, compared with a median of about 60 days in published reports of unperturbed tumor doubling time. A phase I/II study for head and neck cancer at M.D. Anderson Cancer Center comparing different concomitant boost treatment schemes, has shown that if the boost is given during the last 2 weeks of the large field treatment, better primary tumor control was achieved. The overall two-year actuarial primary and nodal control rate for advanced stage head and neck cancer were 74% and 76%, respectively. The acute mucosa reaction was as expected, more severe than those observed with conventional fractionation. The late complications, however, have been few.

1.7 Although, there was no such analysis done for cervical cancer, it is not unreasonable to assume that squamous cell carcinoma of the uterine cervix might behave similarly. In addition, shortening over all treatment time of one or two weeks for tumor in parametria by concomitant boost may result in the improvement of local control. Patterns-of-care study has shown the trend of 10% decrease in pelvic recurrence rate if treatment shortened from 8 weeks to 6 weeks. Therefore, we propose a phase I/II study to examine the tolerance and efficacy of concomitant boost regimen for locally advanced cervical cancer. Since pelvic failure is predominantly in parametria which is usually beyond the reach of high dose brachytherapy coverage, the concomitant boost will be aimed at this region.

1.8 The possible benefits of this proposed schema are:
1.8.1  **To reduce overall treatment time.** Assuming 1% improvement in local control per day shortened, an approximate 10% improvement in the local control in parametria will be achievable.

1.8.2  **To overcome accelerated proliferation.** Tumors in the parametria or pelvic lymph nodes already receive a lower total dose than the central tumor due to a less contribution from the implant treatment (*also at very low dose rate, 10-20 cGy per hour to point B and P*). Giving a concomitant boost in the last 2 weeks of whole pelvic irradiation will shorten overall treatment duration for tumor in this region and also possess biological advantages. For example, in MD Anderson's head and neck experience, 4-year actuarial local control rate was significantly better when the concomitant boost was given in the last 2 weeks compared with the same amount of boost dose given in the early phase of radiation course (71% vs. 41%, \( P=0.043 \)). The overall treatment times were identical in both regimens. This implies that the improvement in local control was resulted from the appropriate implementation of concomitant boost schema to overcome the accelerated proliferation of clonogenic tumor cells. It is not only simply shortening the overall treatment time. If we conservatively extrapolate the result from the head and neck cancer experience, this biological advantage might add another 15-20% chance of improvement in local control.

1.9  Since the small bowel may not be completely excluded in the boost field, the protocol mandates a small bowel series during the simulation for boost field. All possible attention needs to be paid to reduce the amount of small bowel in the boost field. Further, a study from University of Arkansas\(^1\) revealed that giving concomitant boost irradiation to small bowel will not significantly increase bowel complication if the boost dose is given in the latter half of radiation course. Therefore, the treatment schema was designed to give concomitant boost in the last 2 weeks of treatment.

2.0  **OBJECTIVES**

2.1  To determine the tumor response and the local control rate of concomitant (*field-within-field*) parametrial boost radiation regimen in patients with locally advanced cervical cancer.

2.2  To determine the frequency and severity of adverse effect of such treatment.

3.0  **PATIENT SELECTION**

3.1  **Conditions for Eligibility Criteria**

3.1.1  Patients with FIGO Stage IIIB biopsy proven cervical cancer who had no prior abdominal or pelvic radiation therapy.

3.1.2  Patients with squamous cell carcinoma are eligible.

3.1.3  Patients are required to have a Karnofsky performance score of 70% or better.

3.1.4  Adequate bone marrow function: hemoglobin \( \geq 10 \text{ mg/ml, WBC } \geq 4000/\text{mm}^3, \text{ platelets } \geq 100,000/\text{mm}^3 \).

3.1.5  Signed study-specific informed consent.

3.2  **Conditions for Patient Ineligibility**

3.2.1  Simultaneous or prior malignancies (*other than cutaneous basal cell carcinoma*) within 5 years.

3.2.2  Karnofsky performance \( \leq 60\% \), or Stage IVB.

3.2.3  Patients with the following histology are excluded: adenocarcinoma, adenosquamous, small cell, carcinoid, glassy cell, clear cell, adenoid cystic.

3.2.4  Life expectancy less than 6 months.

3.2.5  Prior surgery for the treatment of current cervical cancer other than exploratory laparotomy or biopsy.

3.2.6  Previous systemic chemotherapy.

3.2.7  Prior pelvic radiotherapy other than transvaginal radiation to control bleeding.

3.2.8  Patients who are known to be HIV (+).

3.2.9  Patients who have either biopsy proven or radiographic evidence of metastatic disease in the para-aortic nodes are not eligible.

3.2.10  Treatment plans including interstitial implant.
4.0 PRETREATMENT EVALUATIONS

4.1 Required Evaluations
4.1.1 History and physical examination including height, weight, body surface area and Karnofsky Performance Status. Documentation of the nature and size (including measurements in at least 2 dimensions and diagram) of the primary tumor is required. Initial examination should be performed by a gynecological and radiation oncologist.
4.1.2 Histologic proof of squamous cell carcinoma. All patients will have the confirmation of diagnosis by cervical biopsy.
4.1.3 All patients will undergo complete blood count with differential and platelets; BUN, serum creatinine, bilirubin, transaminase and alkaline phosphatase.
4.1.4 Chest x-ray (PA and lateral).
4.1.5 CT or MRI scan of abdomen/pelvis.
4.1.6 Bipedal lymphangiogram or retroperitoneal lymph node sampling if para-aortic lymph node metastasis is suspected.
4.1.6 Pregnancy test for pre-menopausal women as applicable.

4.2 Optional Tests
4.2.1 Barium enema
4.2.2 Metastatic evaluation (nuclear medicine studies) as indicated.
4.2.3 SGOT
4.2.4 Electrolytes

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. Patients may also be registered via computer modem 24 hours a day, 7 days a week. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Eligibility Criteria Information
- Demographic Data

6.0 RADIATION THERAPY
6.1 Treatment Summary
6.1.1 The pelvis will be treated to a total dose of 45 Gy, 1.8 Gy per fraction, 5 fractions per week for five weeks. Additional 5 Gy may be given to the pelvic lymphatics with midline shield using 5-6 cm wide rectangular or customized blocks. AP-PA or four-field technique (AP-PA and right/left lateral opposed fields) is recommended.
6.1.2 The involved lateral parametrium and/or involved pelvic nodes will be boosted with 9.6 Gy given 1.2 Gy per fraction per day x 8 fractions during weeks 4-5 concomitantly with midline shield, as shown in the example schema. Dose to Point P (6 cm lateral to the midline of pelvis) from external beam only will be 54.6 Gy
6.1.3 Concomitant boost to parametria will be given at least 6 hours after the large field (whole pelvic) treatment.
6.1.4 Point A dose of 40.00 to 45.00 Gy will be given in two applications. An attempt must be made to deliver minimal dose to Point A of 85 Gy with the combination of external beam and implant. The first intracavitary application will be given within one week after completion of external beam therapy. The second application will be inserted a week after the first. Cesium or Iridium-192 may be utilized with standard intracavitary applicator systems.
6.1.5 Interstitial implant: Interstitial implant is not allowed in the study.

6.2 External Beam Radiation
6.2.1 Physical Factors:
Megavoltage beam will be utilized with photon energies greater than 6 MV and a minimum source-axis distance of 100 cm.
6.2.2 Radiation Therapy Fields

6.2.2.1 Pelvic Portal (AP-PA)

Superior border: A horizontal line between L4 and L5 including the common iliac lymph nodes.

Lateral border: Intertrochanteric line or 1.5-2.0 cm lateral to widest true pelvic diameter.

Inferior border: A horizontal line through the lower border of obturator foramen or 4 cm below distal vaginal disease, down to the introitus if necessary.

6.2.2.2 Lateral Pelvic Fields

Superior and inferior margins: Identical to AP-PA fields.

Anterior: A line drawn anterior to the pubic symphysis.

Posterior: A line through S3 to include the cervical disease with a margin of 3-4 cm. Custom blocking to split sacrum to provide adequate margin for presacral nodes. Posterior rectum may be shielded if the tumor dose not involve utero-sacral space.

6.2.2.3 Parametrial boost: The field size for parametrial boost is 8 cm wide and 12 cm long for unilateral and 16 cm wide and 12 cm long for bilateral parametrial boost centered at the cervical mass based on the physical findings, radio-opaque markers, or CT imaging. Midline block (5-6 cm wide rectangular block or customized block) will be used during parametrial boost to reduce the dose to rectum and bladder. All the unremoved metastatic lymph nodes are to be included in boost field with 1 cm margin. A barium swallow (small bowel series) needs to be performed at the time of simulation for parametrial boost. All possible effort should be made to exclude small bowels in boost fields without shielding tumor in parametria.

6.3 Technique and Dose Specifications.

6.3.1 Initial pelvic fields to be irradiated through AP-PA or 4-field technique with photon energies of at least 6 MV. Parametrial boost will be given through opposing AP-PA fields only. Both fields must be treated daily.

6.3.2 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 followed:

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

For an arrangement of 2 or more intersection beams: At the intersection of central rays of the beams.

6.4 Intracavitary Radiotherapy Dosimetry

6.4.1 Cesium or Iridium sources are to be used for intracavitary application(s), with intrauterine tandem 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, is mandatory. Point A is found by measuring 2 cm along the intrauterine tandem from vaginal vault (top of the ovoids or vaginal cylinder should ovoids can not be placed) and then going out 2 cm on either side perpendicular to the central tandem. Point B, however, is 5 cm lateral from a point 2 cm vertically above vaginal vault along the bony axis of patient. Dose to lateral pelvic wall will be calculated at 6 cm from the midline, 2 cm above the vaginal vault. Bladder dose may be calculated at a point in the center of a contrast-filled balloon of a Foley catheter. Rectal dose may be calculated by introducing contrast material in the rectum and selecting a point adjacent to the applicator system or at 0.5 cm posterior to the vaginal ovoids in the lateral projection (depending on packing).

6.4.3 Doses to Critical, Sensitive Structures

Critical sensitive structures are to be considered in treatment planning. The following maximal doses for the entire radiotherapy regimen are suggested, unless higher doses are required to treat adjacent tumor or lymph nodes.

6.4.4 Small bowel (limited volume ≤ 6x6 cm²): 60 Gy

6.4.5 Bladder (ICRU #38 point dose): 80 Gy

6.4.6 Rectum (ICRU #38 point dose): 75 Gy

6.4.7 Vaginal surface: 140 Gy (45 Gy external beam plus surface dose contribution from single colpostat)
6.5 **Expected Toxicity**

6.5.1 Side effects expected from radiotherapy include fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, and reddening around irradiated area. These should disappear once treatment is completed. In addition, blood counts may be temporarily suppressed. Long-term side effects, although uncommon, may include rectal ulcer, bowel obstruction, ureteral obstruction, chronic cystitis, and fistula formation between pelvic tissues.

6.5.2 RT toxicity and the time of onset in relation to RT administration will be recorded on the data forms. Toxicity values should be recorded over the date on which the treatment was given. Late RT toxicity, however, should be recorded over the date on which they actually occur. See RTOG Toxicity Reporting Guidelines for detail.

6.5.3 **Toxicity**

If absolute granulocyte count falls < 1000/ml and/or platelets < 75,000/ml, radiotherapy should be withheld and the study chairperson contacted.

6.6 **Treatment Compliance**

6.6.1 No alteration in dose per fraction or fractionation schedule is permitted.

6.6.2 Administration of a cumulative dose of external beam radiation in the initial whole pelvic treatment, and "boost" treatment which varies from the protocol specified dose by ±10% will be scored a protocol variation/acceptable for purposes of radiation therapy quality assurance and assignment of protocol compliance score.

6.6.3 Administration of intracavitatory dose which varies from protocol by ±10% will be scored a protocol variation/acceptable for purposes of radiation therapy quality assurance and assignment of protocol compliance score.

6.6.4 Any of the following will result in mandatory assignment of the case to the category protocol deviation/unacceptable for purposes of radiation therapy quality assurance and assignment of protocol compliance score:

- Failure to treat with either of the approved initial technique options in outlined in Sections 6.2 and 6.3.
- Use of interstitial implant
- Administration of chemotherapy

7.0 **DRUG THERAPY**

Not applicable to this study.

8.0 **SURGERY**

Not applicable to this study.

9.0 **OTHER THERAPY**

Not applicable to this study.

10.0 **PATHOLOGY**

A central review is not planned for this study.
## 11.0 STUDY PARAMETERS

### 11.1 Patient Assessments

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<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, BUN</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SGOT, electrolytes</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Alkaline Phosphatase Transamisase</td>
<td></td>
<td></td>
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<tr>
<td>Chest X-ray&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan, barium enema</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI or CT scan of Abdomen/Pelvis&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipedal lymph/retro. node sampling</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>As applicable</td>
</tr>
</tbody>
</table>

- To be repeated 3 months after finishing treatment as clinically indicated.
- Note: The above guidelines for follow-up studies, while required for proper medical care and follow-up of the patient, recognize that circumstances may necessitate minor deviations from time to time, which are permissible within the judgment of the responsible physician or his designated representative.
- b. If paraaortic lymph node metastasis is suspected.
- c. Optional

### 11.2 Evaluation Criteria

11.2.1 Assessment of the side effect and toxicity is the major goal of the current study. Careful documentation is mandatory.

11.2.2 Type and duration of tumor response as well as survival will be observed.

11.2.3 Survival will be defined as observed length of life from entry onto protocol to death or, for living patients, the date of last contact (regardless of whether or not this contact is on a subsequent protocol).

11.2.4 **Measurable Disease**

When possible, measurement of lesion size in two perpendicular diameters should be made in order to obtain some estimate of change in tumor size. Reporting these changes in an individual case should be in terms of the best response achieved by that case.

11.2.5 **Complete response** is a disappearance of all gross evidence of disease for at least one month.

11.2.6 **Partial response** is a 50% or greater reduction in product obtained from measurement of each lesion for at least one month.

11.2.7 **Progressive disease** is a 50% or greater increase in the product from any lesion documented in two separate examinations at least two weeks apart or the appearance of any new lesion within three months of entry onto study.

11.2.8 **Stable disease** is disease not meeting any of the above criteria.

11.2.9 **Subjective Response**

Performance status will be recorded on the patient's record according to the Performance Scale in Appendix II.

11.2.10 Patients will be followed until expiration.
12.0 DATA COLLECTION
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 1 week of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within 1 wk of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (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>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</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>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Intracavitary Dose Form (I9)</td>
<td>For Implant #1</td>
</tr>
<tr>
<td>Intracavitary Films (T0)</td>
<td></td>
</tr>
<tr>
<td>Intracavitary Dose Form (I9)</td>
<td>For Implant #2</td>
</tr>
<tr>
<td>Intracavitary Films (T0)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from treatment start for 1 year; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/ relapse and at death</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoints
- Complete Response
- Treatment Toxicity

13.1.2 Secondary Endpoints
- Local Control Rate
- Survival Time

13.2 Sample Size

The main question to be answered is the complete response rate. Prior RTOG 80-05 showed a 70% complete response rate for patients with FIGO stage IIIB or IVA carcinoma of the cervix treated with RT followed by intracavitary or external boost. This study expects to achieve the similar complete response rate and is designed to be 95% confident that our estimate of the true response rate is within ± 14% of the hypothesized 70%. Therefore, 41 eligible patients are needed. Including an extra 10% for possibly un evaluable patients, the total sample size needed for this study is 46 patients.

To investigate the possible benefit of the treatment regimen, the local regional control at two years from registration will be estimated and compared with prior standard regimens. With 41 evaluable patients, we will be able to detect an improvement of local regional control rate from 50% to 70% with 74% power (two-sided chi-squared test with the significance level of 0.05).
13.3 Early Stopping Rules for Severe Toxicity
A severe toxicity is defined as a grade 4 or 5 toxicity due to radiation therapy. The following rules have been developed to test the null hypothesis that the percentage of severe toxicities is 5% with a significance level of 0.05. We will reject the null hypothesis if we observe more than:

- 2 severe toxicities in the first 10 eligible patients
- 3 severe toxicities in the first 23 eligible patients
- 4 severe toxicities in the first 36 eligible patients
- 5 severe toxicities in the first 41 eligible patients

If the specified number (or fewer) of severe toxicities is observed after the indicated number of eligible patients have been accrued, the trial will continue as planned. If more than the specified number of severe toxicities are observed at any of those times, then the null hypothesis of 5% severe toxicities will be rejected and we will conclude that the true proportion of severe toxicities is > 5%. Recommendations will then be made to the RTOG Research Strategy Committee by the study chair, disease site chair and the statistician as to what appropriate actions should be taken.

Note that the boundary above is set in such a way that the probability that the observed number of severe toxicity exceeds the boundary is 0.05 if the true toxicity rate is 5%. If the true toxicity rate is 10% or 20%, then the probability is 0.34 or 0.90 respectively.

13.4 Accrual and Duration
RTOG 90-01 accrued an average of 5 patients per month. Because this study is restricted to patients with stage IIIB biopsy proven cervical cancer, we are expecting approximately 2 patients per month. The trial should be completed in 2 years. Additional followups after the closure of accrual are needed. With the additional one year of followup, we may have a better estimate of 2-year rates for the local regional control and distant metastasis.

13.5 Analysis Plan
13.5.1 Interim Reports
Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about

- patient accrual rate with projected completion date
- pretreatment characteristics of patients accrued
- the frequencies and severity of toxicity due to radiation therapy.

13.5.2 Final Analysis
The final analysis will be performed about one year after study closure. At this time a complete response rate and acute and late toxicities will be reported. An estimate of the local regional control and distant metastasis rates will also be reported at this time.

13.6 Inclusion of Minorities
In accordance with the 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. This study is designed to evaluate the complete response rate under the assumption that the rate is the same across the races. However, a statistical analysis will be performed to examine the possible difference among races. In a prior study, RTOG 90-01, with similar eligibility criteria, 46% (162/352) of the patients were white and 54% (190/352) were non-white. For the planning purpose, we assume that 50% of patients entered into this protocol will be white. With the proposed sample size, if 50% of the patients accrued are white, a 95% one-sided confidence interval around the hypothesized 70% complete response rate has a lower bound of 50% for both white and 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 complete response and local-regional control and survival statistics within racial categories, i.e., white and non-white.
REFERENCES


APPENDIX I

RTOG 97-07

PHASE I/II STUDY OF CONCOMITANT PARAMETRIAL BOOST RADIATION THERAPY FORLOCALLY ADVANCED CERVICAL CANCER

Sample Patient Consent Form

RESEARCH STUDY

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

PURPOSE OF THE STUDY

I have been told that I have cervical cancer which is usually treated with surgery and once a day radiation treatment. The purpose of this research is to study whether using concentrated radiation to the tumor next to the cervix will improve the chance of cure. This research will also evaluate the frequency of side-effects for advanced cervical cancer. The radiation schedule involves radiation treatment once daily in the beginning of the treatment course and twice daily in the last two weeks of the radiation course.

DESCRIPTION OF PROCEDURES

Before starting treatment I will have a thorough work-up to include: physical exam including measurement of my tumor, blood work (approximately 2 teaspoons), urine collection, and a chest x-ray. A Computed Tomography (CT) scan is a special x-ray which evaluates the deep structures of the body. Magnetic Resonance Imaging (MRI) scan is a special procedure using a strong magnet which allows the organs being studied to be seen. A CT or MRI scan of my abdomen and pelvis will be done. Whether or not I will have an injection of contrast dye to highlight my organs for CT or MRI scan will depend on my physician.

Radiation treatments will be given five days per week Monday - Friday for 5 weeks on an outpatient basis. The external radiation involves once daily treatment for 5 weeks with twice daily treatments in the fourth and fifth weeks of the radiation course. Each treatment takes less than one hour. On the days I get two treatments, they will be timed at least 6 hours apart.

After my external radiation treatments are finished, I will have two radioactive implant treatments. I will be hospitalized for 3 days during each treatment. Hospitalization is necessary for the radioactive implant treatment. I will have the first implant treatment the week after the end of external radiation. The second implant will be done about a week after that.

During treatment I will have weekly physical exams and blood tests (approximately 2 teaspoons of blood will be drawn). A chest x-ray may be done as indicated by my physician about 3 months after I finish treatment. Follow-up visits will begin one month after protocol treatment ends. Then I will be seen every 3 months for the first year, then every 4 months for the next year, then every 6 months for 3 years, then once a year.

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

The side effects possible from radiotherapy include tiredness near the end of treatment, diarrhea, nausea, and vomiting, rectal irritation, frequent urination, loss of pubic hair, reddening and irritation of the skin in the area of irradiation. These should disappear once treatment is completed. In addition, blood counts may be temporarily lowered. Long-term side-effects, although uncommon, may include digestive problems, rectal ulcers, narrowing of the rectum, painful urination, blockage of the intestine or urinary tract, shortening of the vagina, pain with intercourse, and formation of a fistula (a hole between two organs) from the vagina to the bladder or rectum. When radiation boost (concentrated dose of radiation) is also given to the parametrial area (tumor next to the cervix), due to tumor involving that area, the risks of these complications may be increased. Radiation to the pelvis will cause sterility and I will not be able to become pregnant.

Blood Drawing: I may experience discomfort, bruising, and/or bleeding at the site of needle insertion. Occasionally some people experience dizziness or feel faint.

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

CONTACT PERSON

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 of injuries, I can notify Dr. _________, the investigator in charge at _________. 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 use of the treatment program. I understand that the information which is obtained from this study may be useful 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 than would be obtained with non-research treatment, but 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

Alternative treatments which could be considered in my case include radiation therapy combined with chemotherapy or standard once-a-day treatment. Another alternative would be no further treatment, 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 treatment available. I have been told that I should feel free to discuss my disease and my prognosis with my doctors. The physicians 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 which would not otherwise be necessary. 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 slides, may be sent to a central office for review.

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 (p.1)

### STAGING FOR CERVIX CANCER

*(AJCC, 1997)*

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>-</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>-</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>0</td>
<td>Carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>Cervical carcinoma confined to uterus <em>(extension to corpus should be disregarded)</em></td>
</tr>
<tr>
<td>T1a</td>
<td>IA</td>
<td>Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions—even with superficial invasion—are T1b/IB. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.</td>
</tr>
<tr>
<td>T1a1</td>
<td>IA1</td>
<td>Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread.</td>
</tr>
<tr>
<td>T1a2</td>
<td>IA2</td>
<td>Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less.</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2.</td>
</tr>
<tr>
<td>T1b1</td>
<td>IB1</td>
<td>Clinically visible lesion 4.0 cm or less in greatest dimension.</td>
</tr>
<tr>
<td>T1b2</td>
<td>IB2</td>
<td>Clinically visible lesion more than 4.0 cm in greatest dimension.</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina</td>
</tr>
<tr>
<td>T2a</td>
<td>IIA</td>
<td>Tumor without parametrial invasion</td>
</tr>
<tr>
<td>T2b</td>
<td>IIB</td>
<td>Tumor with parametrial invasion</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Tumor involves lower third of the vagina, no extension to pelvic wall</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney</td>
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</table>


APPENDIX III (p.2)

STAGING FOR CERVIX CANCER
(AJCC, 1997)

T4 IVA
Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (Bullous edema is not sufficient evidence to classify tumor as T4)

M1 IVB
Distant Metastasis

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

STAGE GROUPING

Stage 0 Tis N0 M0
Stage IA1 T1a1 N0 M0
Stage IA2 T1a2 N0 M0
Stage IB1 T1b1 N0 M0
Stage IB2 T1b2 N0 M0
Stage IIA T2a N0 M0
Stage IIB T2b N0 M0
Stage IIIA T3a N0 M0
Stage IIIB T1 N1 M0
Stage IIIB T2 N1 M0
Stage IIIB T3a N1 M0
Stage IIIB T3b Any N M0
Stage IVA T4 Any N M0
Stage IVB Any T Any N M1
### RTOG Acute Radiation Morbidity Scoring Criteria

#### APPENDIX IV

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td>No change over baseline</td>
<td>Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating</td>
<td>Tender or bright erythema, patchy moist desquamation / moderate edema</td>
<td>Confluent, moist desquamation other than skin folds, pitting edema</td>
<td>Ulceration, hemorrhage, necrosis</td>
</tr>
<tr>
<td><strong>MUCOUS MEMBRANE</strong></td>
<td>No change over baseline</td>
<td>Injection / may experience mild pain not requiring analgesic</td>
<td>Patchy mucositis which may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia</td>
<td>Confluent fibrinous mucositis / may include severe pain requiring narcotic</td>
<td>Ulceration, hemorrhage or necrosis</td>
</tr>
<tr>
<td><strong>EYE</strong></td>
<td>No change</td>
<td>Mild conjunctivitis with or without scleral injection / increased tearing</td>
<td>Moderate conjunctivitis with or without keratitis requiring steroids &amp;/or antibiotics / dry eye requiring artificial tears / iritis with photophobia</td>
<td>Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis</td>
<td>Loss of vision (unilateral or bilateral)</td>
</tr>
<tr>
<td><strong>EAR</strong></td>
<td>No change over baseline</td>
<td>Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audigram unchanged from baseline</td>
<td>Moderate external otitis requiring topical medication / serous otitis modus / hypoacusis on testing only</td>
<td>Severe external otitis with discharge or moist desquamation / symptomatic hypoacusia / tinnitus, not drug related</td>
<td>Deafness</td>
</tr>
<tr>
<td><strong>SALIVARY GLAND</strong></td>
<td>No change over baseline</td>
<td>Mild mouth dryness / slightly thickened saliva / may have slightly altered taste such as metallic taste / these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals</td>
<td>Moderate to complete dryness / thick, sticky saliva / markedly altered taste</td>
<td>------------</td>
<td>Acute salivary gland necrosis</td>
</tr>
<tr>
<td><strong>PHARYNX &amp; ESOPHAGUS</strong></td>
<td>No change over baseline</td>
<td>Mild dysphagia orodynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet</td>
<td>Moderate dysphagia orodynophagia / may require narcotic analgesics / may require purée or liquid diet</td>
<td>Severe dysphagia orodynophagia with dehydration or weight loss &gt;15% from pre-treatment baseline requiring N-G feeding tube, I.V. fluids or hyperalimentation</td>
<td>Complete obstruction, ulceration, perforation, fistula</td>
</tr>
<tr>
<td><strong>LARYNX</strong></td>
<td>No change over baseline</td>
<td>Mild or intermittent hoarseness / cough not requiring antitussive / erythema of mucosa</td>
<td>Persistent hoarseness but able to vocalize / referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/cough requiring antitussive</td>
<td>Whispered speech, throat pain or referred ear pain requiring narcotic/ con fluent fibrinous exudate, marked arytenoid edema.</td>
<td>Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary</td>
</tr>
<tr>
<td><strong>UPPER G.I.</strong></td>
<td>No change</td>
<td>Anorexia with &lt;=5% weight loss from pretreatment baseline / nausea not requiring antiemetics / abdominal discomfort not requiring parasympatholytic drugs or analgesics</td>
<td>Anorexia with &lt;=15% weight loss from pretreatment baseline / nausea /or vomiting requiring tube or parenteral support / abdominal pain, severe despite medication / hematemesis or melena / abdominal distention (flat plate radiograph demonstrates distended bowel loops)</td>
<td>Anorexia with &gt;15% wt loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea /or vomiting requiring tube or parenteral support / abdominal pain, severe despite medication / hematemesis or melena / abdominal distention (flat plate radiograph demonstrates distended bowel loops)</td>
<td>Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion / abdominal pain requiring tube decompression or bowel diversion.</td>
</tr>
</tbody>
</table>
# RTOG Acute Radiation Morbidity Scoring Criteria

## APPENDIX IV

<table>
<thead>
<tr>
<th>LOWER G.I. INCLUDING PELVIS</th>
<th>[0]</th>
<th>[1]</th>
<th>[2]</th>
<th>[3]</th>
<th>[4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Increased frequency or change in quality of bowel habits or rectal discomfort or change in analgesics</td>
<td>Diarrhea requiring parasympathetic drugs (e.g., Lomotil), mucus discharge not necessitating sanitary pads or rectal or abdominal pain requiring analgesics</td>
<td>Diarrhea requiring parenteral support, severe mucous or blood discharge necessitating sanitary pads, abdominal distention (flat plate radiograph demonstrates distended bowel loops)</td>
<td>Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or bowel diversion</td>
<td></td>
</tr>
</tbody>
</table>

| LUNG                       | No change | Mild symptoms of dry cough or dyspnea on exertion | Persistent cough requiring narcotic, antitussive agents, or dyspnea at rest or clinical or radiologic evidence of acute pneumonitis, intermittent oxygen or steroids may be required | Severe respiratory insufficiency, continuous oxygen or assisted ventilation |

| GENITOURINARY              | No change | Frequency of urination or nocturia twice pretreatment habit, dysuria, urgency not requiring medication | Frequency of urination or nocturia which is less frequent than every hour, dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium) | Frequency with urgency and nocturia hourly or more frequently, dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotic or gross hematuria with or without clot passage | Hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage, ulcération or necrosis |

| HEART                      | No change over baseline | Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease | Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease, treatment required | Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures |

| CNS                        | No change | Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed | Neurologic findings present sufficient to require home care / nursing assistance may be required, medications including steroids, anti-seizure agents may be required | Neurologic findings requiring hospitalization for initial management | Serious neurologic impairment which includes paralysis, coma or seizures > 3 per week despite medication, hospitalization required |

| HEMATOLOGIC WBC (X 1000)  | >= 4.0    | 3.0 - < 4.0 | 2.0 - < 3.0 | 1.0 - < 2.0 | < 1.0 |
| PLATELETS (X 1000)        | > 100     | 75 - < 100  | 50 - < 75   | 25 - < 50   | < 25 or spontaneous bleeding |
| NEUTROPHILS (X 1000)      | >= 1.9    | 1.5 - < 1.9 | 1.0 - < 1.5 | 0.5 - < 1.0 | < 0.5 or sepsis |
| HEMOGLOBIN (GM %)         | > 11      | 11 - 9.5    | < 9.5 - 7.5 | < 7.5 - 5.0 | 95 - 70 |
| HEMATOCRIT (%)            | >= 32     | 28 - < 32   | < 28        | Packed cell transfusion required | 28 - 32 |

**GUIDELINES:** The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease and treatment related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3,4 or 5* must be verified by the Principal Investigator.

*ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.
<table>
<thead>
<tr>
<th>ORGAN/TISSUE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
<td>Market atrophy; Gross telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &gt;10% linear measurement</td>
<td>Necrosis</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucous</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>Mild L’Hermite’s syndrome</td>
<td>Severe L’Hermite’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Mono, para quadriplegia</td>
</tr>
<tr>
<td>BRAIN</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
<td>Seizures or paralysis; Coma</td>
</tr>
<tr>
<td>EYE</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment; Severe glaucoma</td>
<td>Panophthalmitis / Blindness</td>
</tr>
<tr>
<td>LARYNX</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chorditis</td>
<td>Severe edema; Severe chondritis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>LUNG</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate asymptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
<td>Severe asymptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
<td>Severe respiratory Insufficiency / Continuous O2 / Assisted ventilation</td>
</tr>
<tr>
<td>HEART</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
<td>Tamponade / Severe heart failure / Severe constrictive pericarditis</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilatation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilatation required</td>
<td>Necrosis / Perforation Fistula</td>
</tr>
<tr>
<td>SMALL/ LARGE INTESTINE</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily; Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis / Perforation Fistula</td>
</tr>
<tr>
<td>LIVER</td>
<td>Mild icassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
<td>Necrosis / Hepatic coma or encephalopathy</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%; Creatinine 1.5-2.0 mg%; Creatinine clearance &gt;75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;30-60 mg%; Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension Persistent anemia (&lt;10g%); Severe renal failure; Urea &gt;60 mg%; Creatinine &gt;4.0 mg%; Creatinine clearance &lt;50%</td>
<td>Malignant hypertension Uremic coma / Urea &gt; 100%</td>
</tr>
<tr>
<td>BLADDER</td>
<td>Slight epithelial atrophy (microscopic hematuria)</td>
<td>Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt;150 cc)</td>
<td>Necrosis / Contracted bladder (capacity &lt;100 cc)</td>
</tr>
<tr>
<td>BONE</td>
<td>Asymptomatic; No growth retardation; Reduced bone density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
<td>Necrosis / Spontaneous fracture</td>
</tr>
<tr>
<td>JOINT</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
<td>Necrosis / Complete fixation</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

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

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

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

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

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

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

Investigational Agents

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

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330  FAX # 301-230-0159
i.  
**Phase I Studies Utilizing Investigational Agents**

- All deaths during therapy with the agent.  
  Report by phone within 24 hours to IDB and RTOG Headquarters. 
  **A written report to follow within 10 working days.**

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

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

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

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

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

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

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

**See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form**
APPENDIX VI (p.1)
Sample Treatment Diagram

Whole Pelvis
Sample Treatment Diagram

Parametrial Boost with 5-6 cm Midline Shield
APPENDIX VII

ICRU #38 Point Dose Definition

Definition of Point A, Point B, Rectal and Bladder Reference Points