RADIATION THERAPY ONCOLOGY GROUP

RTOG 0116

A TWO-PART PHASE I/II STUDY OF EXTENDED FIELD EXTERNAL IRRADIATION AND INTRACAVITARY BRACHYTHERAPY COMBINED WITH CHEMOTHERAPY *(WEEKLY CISPLATIN–ARM 1)* AND AMIFOSTINE *(WEEKLY CISPLATIN AND AMIFOSTINE-ARM 2)* IN CARCINOMA OF THE CERVIX WITH POSITIVE PARA-AORTIC OR HIGH COMMON ILIAC LYMPH NODES

Study Chairs

Radiation Oncology	William Small Jr., M.D. Northwestern Memorial Hospital 251 E. Huron, Suite LC-178 Chicago, IL 60611 *(312)* 926-6810 FAX # *(312)* 926-6374 *w-small@northwestern.edu*
Gynecologic Oncology	Charles Levenback, M.D. *(713)* 745-2563 FAX# *(713)* 792-7586 *clevenba@mdanderson.org*
Radiology	Revathy Iyer, M.D. *(713)* 792-5043 FAX# *(713*) 745-1399 *riyer@mdanderson.org*
Dermatology	Sharon R. Hymes, M.D. *(713)* 745-1113 FAX# *(713)* 745-3597 *srhymes@mdanderson.org*

Activation Date:	**August 1, 2001**
Update Date:	**August 13, 2004**
Version Date:	**July 15, 2004** **Broadcast Date: July 23, 2004** **(Includes Revision 1- 6)**

This protocol was designed and developed by the Radiation Therapy Oncology Group *(RTOG)* of the American College of Radiology *(ACR)*. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

INDEX

Schema

Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Pathology

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status
Appendix III - Staging System
Appendix IV - Toxicity Criteria/Management of Skin Reactions
Appendix V - Management of Fever
Appendix VI - RTOG/EORTC Late Radiation Morbidity Scoring Scheme
Appendix VII - Adverse Reaction Reporting Guidelines
Appendix VIII - Amifostine Shipping Form
Appendix IX - HDR Intracavitary Brachytherapy Guidelines
Appendix X - ICRU #38 Point Dose Definition

RADIATION THERAPY ONCOLOGY GROUP (4/30/04)
RTOG 0116

A TWO PART PHASE I/II STUDY OF EXTENDED FIELD EXTERNAL IRRADIATION AND INTRACAVITARY BRACHYTHERAPY COMBINED WITH CHEMOTHERAPY *(WEEKLY CISPLATIN–ARM 1)* AND AMIFOSTINE *(WEEKLY CISPLATIN AND AMIFOSTINE-ARM 2)* IN CARCINOMA OF THE CERVIX WITH POSITIVE PARA-AORTIC OR HIGH COMMON ILIAC LYMPH NODES

SCHEMA (8/1/03)

R	**T**	**Arm 1**
		Extended field external radiation[a] to the para-aortic region and pelvis,
E	**R**	intracavitary irradiation[b] with concurrent weekly cisplatin[c]
G	**E**	**Arm 1 is followed by evaluation of toxicity; Arm 2**
		proceeds only if toxicity in Arm 1 is within expected parameters.
I	**A**	
		Arm 2
S	**T**	Extended field external radiation[a] to the para-aortic region and pelvis,
		intracavitary irradiation[b] with concurrent weekly cisplatin[c] and amifostine[d]
T	**M**	
E	**E**	
R	**N**	
	T	

a. 1.8 Gy daily for five weeks for a total dose of 45 Gy; involved lateral parametrium and/or pelvic nodes should be boosted for a total dose (*including intracavitary treatment*) of 60 Gy ± 5%
b. LDR: cesium in one to two intracavitary applications, within two weeks of completion of external radiation **OR** HDR: starting as early as week two of external radiation for a minimum cumulative external and intracavitary dose of 85 Gy (*LDR equivalent; See Appendix IX for HDR dosing and fractionation*); if patient has extensive tumor precluding intracavitary treatment, shrinking field technique should be performed to bring GTV to a minimum of 65 Gy.
c. cisplatin 40 mg/m^2 given weekly with external radiation and once with LDR brachytherapy *(**OR** once prior to HDR brachytherapy)* for total of six doses
d. amifostine daily, delivered before each RT

Eligibility: *(See Section 3.0 for details)* **[8/1/03]**
- Squamous cell, adenocarcinoma, or adenosquamous cancer of the uterine cervix
- Evidence of positive para-aortic or high common iliac lymph nodes *(See Section 4.1.6)*
- Zubrod Performance Status 0-1
- Life expectancy ≥ 6 months
- WBC ≥ 3000/mm^3 *(ANC ≥ 1800/mm^3)*; platelets ≥ 100,000 mm^3; creatinine ≤ 1.5; bilirubin ≤ 1.5 mg/dl; ALT ≤ 2x normal, corrected calcium level within normal limits
- No metastatic disease outside pelvis *(except to para-aortic nodes)*
- No prior tumor-directed surgery, other than lymph node biopsies/staging
- No previous chemotherapy, or pelvic radiation therapy
- No prior *(within last 3 years)* or simultaneous malignancies *(other than basal cell carcinoma or non-invasive tumors)*
- Patients with insulin dependent diabetes are ineligible.
- Due to possible harmful effects to the unborn child, pregnant patients are ineligible.
- Patients must sign a study-specific informed consent form prior to study entry.

Required Sample Size: Arm 1: 27; Arm 2: 39; Total: 66

RTOG Institution # _____

RTOG 0116 **ELIGIBILITY CHECK** **(8/1/03, Date)**

Case # _____ *(Page 1 of 2)*

_____(Y) 1. Does the patient have squamous cell, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix?

_____(Y) 2. Is there evidence of para-aortic or high common iliac lymph node involvement, and has this been confirmed in accordance with Section 4.1.6?

_____(N) 3. Is there evidence of distant metastasis outside the pelvis other than para-aortic lymph nodes?

_____(Y) 4. Is the Zubrod Performance Score 0-1?

_____(N) 5. Does the patient have any significant medical contraindications that may preclude the administration of the full chemotherapy dose?

_____(Y) 6. Does the patient have adequate bone marrow, liver function, renal function, and a normal corrected calcium level as outlined in Section 3.1.5?

_____(N) 7. Is there any prior *(within the last 3 years)* or simultaneous malignancy, other than basal cell carcinoma or non-invasive tumors?

_____(N) 8. Is the patient's life expectancy less than 6 months?

_____(N) 9. Has the patient had prior tumor-directed surgery other than lymph node biopsies/staging ?

_____(N) 10. Does the patient have insulin dependent diabetes?

_____(N) 11. Has the patient had any prior pelvic irradiation or systemic chemotherapy?

_____(N) 12. Is the patient pregnant or lactating?

_____(Y) 13. If the patient is of childbearing potential, is she using an adequate method of contraception?

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

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

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

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

_____ 5. Patient's Name

(continued on page 2)

RTOG Institution # _____

RTOG 0116 **ELIGIBILITY CHECK** *(8/01/01, Date)*

Case # _____ *(Page 2 of 2)*

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Social Security Number

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code

_____ 14. Patient's Insurance Status

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

_____ 16. Treatment Start Date

_____ 17. Will the patient receive IMRT?

_____ 18. Medical Oncologist

_____ 19. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Cervical Cancer

It is estimated that there will be 12,800 new cases of invasive carcinoma of the cervix in 1999.[1] While the mortality rate from this cancer has been decreasing over the last twenty years, this is predominantly due to improved screening programs and early diagnosis. For early stage disease, either radical surgery or pelvic radiation can result in a five-year survival of 85-90%. Nevertheless, nearly 5,000 women die annually in the United States from invasive carcinoma of the cervix, and a great majority of these present initially with large advanced lesions. [1]

The NCI Consensus Conference of 1996 concluded that chemotherapy did not provide additional benefit to radiation therapy alone to the pelvis for patients with bulky tumors or advanced stage disease. However, the recent results of five randomized phase III trials were announced in an NCI Clinical Announcement recommending that chemoradiation be used to treat cervical cancer. Concurrent chemoradiation demonstrated a 30-50% reduction in risk of death.[2]

1.2 Radiation with Concurrent Chemotherapy in Cervical Cancer

The use of radiation therapy with concurrent administration of cytotoxic and radiosensitizing agents has become increasingly well accepted, especially in patients with advanced squamous carcinomas. Recently, there have been five randomized trials that have shown an improved efficacy to a combination of cisplatin-based chemotherapy with pelvic radiation. These trials all excluded patients with para-aortic metastases.[3-7]

GOG 120 randomized patients between radiation with weekly cisplatin vs. 5-FU, cisplatin and hydroxyurea vs. hydroxyurea. The results noted similar efficacy in each of the cisplatin arms. The arm containing cisplatin alone was associated with less leukopenia and gastrointestinal toxicity.[5]

GOG 123 was a randomized trial between weekly cisplatin and radiation vs. radiation alone followed by extrafascial hysterectomy. This trial also demonstrated a survival benefit in patients with bulky stage cervical carcinoma receiving cisplatin and radiation.[7]

These two trials note weekly cisplatin to be a highly efficacious treatment. GOG 120 noted weekly cisplatin to be as efficacious as a triple drug combination with reduced toxicity. The reduced toxicity will be important in an extended field trial.

1.3 Extended-Field Radiation Alone

A number of authors have noted the ability of extended field radiation to cure patients with para-aortic lymph node metastasis. *(Table 1)* Lovecchio et al. noted a 50% 5-year survival in patients who had histologically confirmed para-aortic lymph node metastasis treated with 45Gy.[10] In the Lovecchio trial, all clinically involved nodes were resected. Burman, Nori and Twefik also noted the ability of radiation to cure patients with para-aortic metastasis, although they noted a lower five-year survival of approximately 25%.[8,11,12]

Goodman et al. reported the results of a number of studies demonstrating an overall 40% five-year survival in patients with para-aortic metastasis treated with extended field radiation.[13]

Table 1: Results of Extended Field Radiation in Patients with Positive Para-aortic Metastasis

Author	**Number of Patients**	**Pelvic/Para-aortic Control *(%)***	**5-Year Survival *(%)***
Berman[8]	98	50	25*
Leptano[9]	36	76	33
Lovecchio[10]	36	42	50
Nori[11]	27	NS	29
Tewfik[12]	23	65	23
TOTALS	**220**	**55**	**30**

* 3 Years

1.4 Extended Field Radiation and Concurrent Chemotherapy

Combining cytotoxic chemotherapy with extended field radiation is the next step in improving the outcome of patients with positive para-aortic nodes. However, high rates of toxicity have been observed.

GOG 125 investigated the tolerance of extended field radiation with concomitant 5-FU and cisplatin during weeks one and five of external beam. A total of 86 cervical carcinoma patients with para-aortic metastases were included in the trial. Late morbidity was noted in 14% of the patients, primarily from rectal complications with no small bowel obstructions observed. The three-year overall survival was 39%. This study utilized a relatively low dose of cisplatin *(50mg/m^2)* for the two cycles. The radiation field was limited to L1/L2 and the para-aortic region received 150 cGy/fx. The point A dose was 8,000 cGy with no chemotherapy during the implants.[14]

In an effort to intensify the radiation treatment RTOG 9210 was designed as a phase II study investigating the use of hyperfractionated extended-field external radiation and intracavitary brachytherapy and chemotherapy *(5-FU and cisplatin)* in patients with positive para-aortic lymph nodes. An unacceptable incidence of toxicities *(31% experienced grade 4 nonhematologic toxicity and 1 death)* was attributed to this regimen.[15]

Table 2 reviews pertinent trials for patients with para-aortic metastasis treated with extended field radiation with chemotherapy.

Table 2: Results of Extended Field Radiation and Chemotherapy in Patients with Positive Para-aortic Metastasis

Author	**Number of Patients**	**Pelvic/Para-aortic Control *(%)***	**5-Year Survival *(%)***	**Toxicity ≥ Grade 3 *(%)***
Varia [14]	95	68.6 *	39**	37.7
Grigsby[15]	29	51***	47***	76
Maltefano[16]	13	100	69	0
Podczaski[17] ****	33	51	31	6
TOTALS	**170**	**65**	**42**	**43**

* Pelvic Control – Para-aortic control N.S., ** 3-Years, *** 2-Years,
**** Only 6 patients treated with chemotherapy.

1.5 WR-2721 *(amifostine)* (8/1/03)

The compound WR-2721 *(amifostine)* is a phosphorylated aminothiol demonstrating cytoprotection of normal tissues in the face of chemotherapy and radiation treatment.[18] Amifostine is a drug that undergoes dephosphorylation by cellular bound alkaline phosphatase to an active metabolite, WR-1065. Cytoprotection is believed to result from elimination of free radicals produced by the interaction of ionizing radiation and water molecules, as well as radicals produced by certain cytotoxic drugs.[18,19,20] A separate amifostine metabolite, WR-33278, has also been shown to protect cells from radiation induced cytotoxicity.[21] In addition, the active metabolite WR-1065 can reverse platinum-DNA adducts when administered concurrently with cisplatin.[22]

The protection afforded by amifostine appears limited to normal and not neoplastic tissues. A number of potential mechanisms have been described for selective cytoprotection. Dephosphorylation of amifostine to the active WR-1065 metabolite occurs at the cellular level by membrane bound alkaline phosphatase. Normal tissue appears to have greater alkaline phosphatase activity over neoplastic tissue, allowing for selective production of WR-1065 about normal cells.[23,24] Another selective mechanism centers about the relatively acidic pH found in cancer cells. This favors alkaline phosphatase production of WR-1065 in normal cells with a neutral pH.[25]

A growing body of literature has documented the tissue protective effects of amifostine in patients receiving radiation therapy, with no apparent loss of tumor control.[26] A phase I trial by McDonald, et al. evaluated the use of amifostine in patients receiving radiation for cancer of the head and neck.[28,29] Amifostine was administered before each radiation treatment at a dose of 200 mg/m2 without significant adverse effect. Preservation of salivary gland function was observed, with a return of 54% of baseline parotid gland saliva flow eighteen months after treatment. A prospective randomized trial by Liu, et al. in 100 patients with advanced rectal cancer compared the use of radiation versus radiation and amifostine

treatment.[19] All patients received 4500 cGy pelvic radiation followed by a conedown of 720 cGy over four days. Unresectable cases received an additional 720 cGy conedown. Patients in the amifostine arm received 340 mg/m^2 fifteen minutes before each pelvic radiation fraction. Moderate to severe late effects of radiation were experienced in 13.5% of patients treated with radiation alone, versus no patients receiving amifostine *(p = 0.03)*. Importantly, there was no evidence of diminished anti-tumor effect in either treatment arm *(16% versus 10% complete response rate).*

An important, recently published phase III trial utilized amifostine at a dose of 200 mg/m^2 *i.v.* daily before head and neck radiotherapy compared to untreated controls. There was a significant reduction in acute and chronic xerostomia. The local regional control and overall survival were not significantly impacted by the use of amifostine.[29]

Given the cytoprotective effects of amifostine in the setting of radiation and chemotherapy treatment, the protection of normal tissues during combination chemoradiation treatment would be expected.[30] Buntzel, et al. reported a randomized trial of radiation and carboplatin chemotherapy in head and neck cancer patients, with and without amifostine.[31] Carboplatin, 70 mg/m^2, was administered before radiotherapy on days 1-5 and 21-25 during radiotherapy. Patients randomized to receive cytoprotection also received amifostine 500 mg. intravenously, prior to carboplatin. Reductions in grade 3-4 mucositis *(86% versus 0%)* and grade 2 xerostomia *(100% versus 12%)* were noted with amifostine pretreatment. In addition, carboplatin induced grade 3-4 thrombocytopenia was reduced from 29% to 0%.

Cytoprotection has not been well studied in the combined modality treatment of cervical cancer. Wadler, et al. reported their experience with the use of amifostine in patients receiving cisplatin and radiotherapy for stages IIB to IVA cervical cancer. A phase I trial was initiated to determine the maximal amifostine dose when using a five-day cisplatin regimen. Patients were treated with a 4-field technique to a pelvic dose of 39.6 Gy using 1.8 Gy fractions. This was followed by two intracavitary implants for a total dose of 80 Gy to point A. Extended field therapy was employed for cases with para-aortic adenopathy. Cisplatin was administered during teletherapy at 20 mg/m^2/day for five days on days one and twenty-two. In addition, cisplatin 100 mg/m^2 was administered after each brachytherapy treatment. Amifostine at doses of 340 to 910 mg/m^2/day was infused intravenously over fifteen minutes, immediately before cisplatin. The maximum tolerated dose was 825 mg/m^2/day for five days in this setting, with hypotension being the dose limiting toxicity.[32] In addition, the authors noted less radiation-related mucosal toxicity in the current study compared to their earlier experience in combined modality therapy without amifostine.[33]

Several reports suggest dosing regimens for amifostine. Potential dose-limiting side effects with the compound include transient hypotension, nausea, and vomiting.[34] Phase I/II clinical trials in patients receiving cisplatin every three to four weeks have evaluated amifostine at doses of 740 to 910 mg/m^2 as a thirty-minute infusion prior to chemotherapy[34,35]. In the study by Kemp, et al. utilizing 910 mg/m^2 of amifostine, 61.5% of patients experienced reduction in their systolic blood pressure requiring interruption in the amifostine infusion. Severe nausea and vomiting was not more common in patients receiving amifostine versus chemotherapy alone. In addition, pretreatment with amifostine reduced the hematologic, renal, and neurologic toxicities associated with the chemotherapy regimen.[34] Glover, et al. reported on the use of amifostine 740 mg/m^2 administered *i.v.* over fifteen minutes before single agent cisplatin given every three or four weeks.[35] The authors reported that amifostine was well tolerated among their study group, with hypotension occurring in 1% of treatments, and nausea and vomiting occurring in 56% of courses.[35]

Wadler, et al. recommended an amifostine dose of 825 mg/m^2 when administered daily during a five-day cisplatin regimen. No patients required interruption of drug infusion due to hypotension.[32] Tannehill, et al. reported on the use of amifostine in the treatment of unresectable non-small cell lung cancer with *sequential* chemotherapy and radiation therapy. Patients received amifostine at doses of 740 mg/m^2 or 910 mg/m^2 fifteen minutes prior to cisplatin 120 mg/m^2 on days one and twenty-nine. This was followed by daily fractionated radiation therapy beginning on day fifty, which was proceeded by amifostine at doses of 340 mg/m^2 for four days or 200 mg/m^2 for five days. The authors noted a dose-related decrease in systolic blood pressure, with no long-term side-effects. A total of 96% of patients completed amifostine during cisplatin, and 72% during radiation[36]. The study by Buntzel, et al. as discuss above, administered amifostine prior to each chemotherapy dose during combined chemotherapy and radiation treatment, consisting of five day cisplatin treatment on days one and twenty-one.[31]

1.6 Rationale for Subcutaneous Amifostine (8/1/03)

1.6.1 *Subcutaneous Experience with Amifostine*

The subcutaneous *(SC)* administration of amifostine has been investigated in four clinical trials, including two bioavailability trials *(WR-A057 and WR-A064)* and two Phase II trials *(WR-B060* [37, 38] *and Koukorakis, et al.* [39]*)*. In addition, two groups have recently reported their experiences with SC administration. [40-41].The SC formulations used in these trials are summarized as follows:

Study	Amifostine SC Dose and Formulation
WR-A057	500 mg dissolved in 2.5 mL of normal saline solution
WR-A064	500 mg dissolved in 2.5 mL of 0.9% sodium chloride 500 mg + 1 mg sodium deoxycholate dissolved in 2.5 mL 0.9% sodium chloride 500 mg dissolved in 20 mg/mL sorbitol/20 mg/mL edetate disodium (EDTA)
WR-B060 [37-38]	500 mg dissolved in 2.5 mL of normal saline solution*.
Koukourakis[39]	500 mg diluted in 2.5 mL normal saline solution
Daly [40]	500 mg diluted in 3.0ml normal saline solution*.
Samuels [41]	500 mg diluted in 3.0ml normal saline solution*.
* Administered as two fixed SC injections of 250 mg each.	

In 1996, a Phase I safety and pharmacokinetic study was performed to determine the relative bioavailability of SC and oral *(PO)* doses of amifostine as compared to IV amifostine *(WR-A057).* Twelve healthy male subjects were randomized to receive amifostine for 3 successive days as an IV infusion *(200 mg/m^2 as a 7.5 minute infusion),* a PO solution *(500 mg),* or an SC injection *(500 mg).* Plasma concentrations of amifostine *(parent drug)* and serum concentrations of WR-1065 *(active metabolite)* were measured in blood samples obtained prior to and up to 4 hours after receiving amifostine. Following a 200-mg/m^2 IV infusion, there was rapid uptake of amifostine within < 1 minute of drug administration. The maximum concentration *(C_{max})* of amifostine was approximately 130 μM 8 to 10 minutes after IV administration that dropped below 10 μM approximately 45 minutes after drug administration. Following a 500-mg SC injection, there was a slower rise in plasma/serum concentrations of amifostine as compared to IV administration. A C_{max} of approximately 15 μM was observed 15 minutes after SC administration and was maintained for approximately 30 minutes. Thereafter, concentrations of amifostine fell below 10 μM approximately 50 minutes after SC administration. Thirty minutes following administration of 200 mg/m^2 IV amifostine and 500 mg SC amifostine, the plasma/serum concentration-time curves of amifostine *(parent drug plus active metabolite)* were identical. The relative bioavailability of amifostine *(parent drug plus active metabolite)* following a 500-mg SC dose was 67% of the 200 mg/m^2 IV dose, with a dose-normalized bioavailability of 50%.

In 1999, a Phase I safety and pharmacokinetic study was conducted to determine the qualitative pharmacokinetics and relative bioavailability of three formulations of SC amifostine as compared to IV amifostine *(WR-A064).* This study was designed as a randomized, open-label, four-way crossover study. Healthy male subjects were randomized to receive either amifostine *(200 mg/m^2)* as a 3-minute IV infusion *(Treatment A)* or one of three formulations of SC amifostine *(500 mg)* administered on day 1. All subjects received the other formulations of amifostine on days 2, 3 and 4. The three formulations of SC amifostine were as follows: Treatment B - amifostine *(500 mg)* dissolved in 2.5 mL of 0.9% sodium chloride; Treatment C - amifostine *(500 mg)* plus 1 mg sodium deoxycholate dissolved in 2.5 mL of 0.9% sodium chloride; and Treatment D - amifostine *(500 mg)* dissolved in 2.5 mL of 20 mg/mL sorbitol and 20 mg/mL edetate disodium *(EDTA).*

Following the three-minute IV infusion of 200 mg/m^2 *(Treatment A),* the pharmacokinetic parameters obtained are consistent with prior investigations of amifostine pharmacokinetics. The mean half-life *($T_{1/2}$)* of 7.5 *(± 5.7)* minutes and the systemic clearance of 2.3 *(± 0.9)* L/min are consistent with the very rapid systemic clearance and short half-life of the parent drug previously observed in cancer patients and healthy volunteers. In contrast, the pharmacokinetic parameters of the three SC formulations *(Treatments B, C, and D)* reveal a much lower C_{max} *(12.7, 10.9, and 11.1 μmol/L, respectively)* compared to that of the IV formulation *(142 μmol/L)* but detectable concentrations for a much longer period of time *(90, 102.5, and 76.3 minutes, respectively),* compared to an average of 29 minutes for the IV formulation. The relative bioavailabilities of amifostine *(parent drug plus active metabolite)* following

three 500-mg SC formulations were 58% *(Treatment B),* 64% *(Treatment C),* and 54% *(Treatment D)* of the 200-mg/m^2 IV dose.

A Phase II trial of SC amifostine and RT was recently completed in 55 patients with SCCHN to assess the effectiveness of SC amifostine in protecting against the oral radiation reactions associated with standard fraction radiotherapy *(WR-B060).* In this study, patients received amifostine as two 250-mg SC injections 60 minutes *(± 15 minutes)* prior to RT *(1.8 to 2.0 Gy/day for 25 to 35 fractions).* The SC formulation used in this study was amifostine dissolved in 2.5 mL of 0.9% sodium chloride *(saline diluent).* Assessment of acute radiation toxicities *(i.e., xerostomia and mucositis)* was determined by RTOG criteria. Preliminary results *(see table below)* in 54 evaluable patients showed that the incidence of Grade 2 or higher acute xerostomia in this study was similar to that observed in the Phase III head and neck cancer trial *(WR-0038).* [29]

	WR-B060 [37-38]	**WR-0038** [29]		
	SC Amifostine	**IV Amifostine + RT**	**RT**	**p-value (RT ± IV amifostine)**
N	54	148	153	
≥Grade 2 acute xerostomia				
Incidence All patients Patients receiving ≥60 Gy RT	 56% 49%	 51% 51%	 78% 78%	 <0.0001 <0.0001
Median time to onset	40 days	45 days	30 days	0.0001
Median cumulative RT dose to onset	58 Gy	60 Gy	42 Gy	0.0001

In terms of safety, there were no reports of Grade 3 hypotension or Grade 3 nausea/vomiting following SC amifostine. In contrast, these events were reported by 3% and 7% of patients, respectively, receiving IV amifostine in WR-0038. Grade 1 or 2 local injection site reactions were observed in 40% of patients. Generalized cutaneous reactions were reported by 23.6% of patients *(all grades);* Grade 3 generalized cutaneous reactions *(characterized by rash, pruritus,* rash *erythematous, or rash maculopapular)* occurred in 11% of patients treated with SC amifostine as compared to 3% of patients with IV amifostine in WR-0038.

Recently, Koukourakis et al. [39] reported results of a randomized Phase II study in which amifostine was given by SC injection at a dose of 500 mg 20 minutes prior to RT in patients receiving treatment for pelvic carcinoma *(n=40),* lung carcinoma *(n=60),* or head and neck carcinoma *(n=40).* Compared to control groups, there was significantly reduced severity of symptoms related to oral, esophageal, and rectal mucosa *(p<0.05).* Amifostine-related side effects included Grade 1 nausea in 20/70 *(28.5%)* patients lasting for 1 to 4 hours after injection *(despite premedication with antiemetic)* and Grade 2 vomiting in 2/70 patients *(3%);* hypotension was negligible, with 2 patients *(3%)* having transient Grade 1 hypotension after radiotherapy. In 6 patients *(9%),* treatment was discontinued due to possible hypersensitivity reaction *(rash with or without fever).*

In addition to these two trials, there have been two recent reports of the use of subcutaneous amifostine in a group of diverse patients. In a trial reported by Daly et al., amifostine was reconstituted with 3ml of normal saline and given as two SC injections. Thirty-five patients were treated with the most common effect being local skin reactions. 3 patients' *(8%)* treatment was discontinued related to a systemic rash.[40] In a similar trial by Samuels et al., 18 patients were treated with SC amifostine administered in 2 1.5ml injections. Local injection site reactions were again the most common side effect noted.[41]

Taken as a group, these trials give strong support to the efficacy of the SC administration of amifostine. The side effect profile is favorable as compared to IV therapy, and the efficacy seems to be similar. In addition, SC administration is much more practical in a radiotherapy department compared to IV therapy. For these reasons, we have elected to use SC administration in this trial.

1.7 Rationale for Two Part Study Design

The toxicity of extended field radiation and chemotherapy is formidable – especially as delivered in RTOG 92-10. There has been no large trial evaluating the toxicity of extended field radiation combined with weekly cisplatin. This regimen offered similar efficacy as the CDDP/5-FU arm in GOG 120 with an improved toxicity profile. This trial is designed in two parts. Arm 1 will involve the use of extended field radiation, intracavitary irradiation, and cisplatin. The goal is to accurately define the toxicity of such a treatment. After accrual is reached for Arm 1, accrual to the study will be suspended until the acute toxicity rate for Arm 1 is determined. If the toxicity rate is in an acceptable range, accrual will begin to Arm 2, which will add amifostine as a radioprotectant to determine amifostine's ability to reduce the combined therapy toxicity.

1.8 Future Applications

If amifostine is determined to increase the therapeutic ratio of patients receiving chemotherapy and extended field radiation, this drug may have future applications allowing intensification of treatment either with increased radiation dose possibly utilizing intensity modulated radiation, or new chemotherapeutic agents.

2.0 OBJECTIVES (8/1/03)

2.1 To determine the feasibility and tolerance of extended-field external radiotherapy to the pelvis and para-aortic region and intracavitary irradiation combined with weekly cisplatin.

2.2 To determine the feasibility and tolerance of extended-field external radiotherapy to the pelvis and para-aortic region and intracavitary irradiation combined with weekly cisplatin in combination with amifostine.

2.3 To evaluate the efficacy of extended-field and intracavitary irradiation with weekly cisplatin +/- amifostine in improving pelvic and para-aortic tumor control and distant metastasis in carcinoma of the uterine cervix with positive para-aortic or high common iliac lymph nodes.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (8/1/03)

3.1.1 Patients must have carcinoma of the uterine cervix with evidence for positive para-aortic or high common iliac lymph nodes *(See Section 4.1.6).* Patients remain eligible if the involved lymph nodes have been completely resected or if gross residual tumor involvement of a lymph node remains.

3.1.2 Patients with squamous cell, adenocarcinoma, and adenosquamous carcinoma are eligible.

3.1.3 Patients must have no evidence of metastatic disease outside of the pelvis *(except to the para-aortic nodes).*

3.1.4 Patients must have a Zubrod Performance Status 0-1 and no significant medical contraindications to the administration of full dose chemotherapy.

3.1.5 Adequate bone marrow function: WBC $\geq$ 3000/mm^3 *(ANC $\geq$ 1800/mm^3);* platelets $\geq$ 100,000 mm^3; Adequate renal function: creatinine $\leq$ 1.5 mg/dl *(urinary diversion is permitted to improve renal function)*; patients must have bilirubin $\leq$ 1.5 mg/dl, ALT $\leq$ 2 x normal, corrected calcium level within normal level.

3.1.6 Signed study-specific informed consent prior to study entry

3.2 Ineligibility Criteria (8/27/02)

3.2.1 Prior (*within the last 3 years*) or simultaneous malignancies *(other then cutaneous basal cell carcinoma or non-invasive tumors)*

3.2.2 Patients with the following histologies are excluded: small cell, carcinoid, glassy cell, clear cell and adenoid cystic.

3.2.3 Life expectancy < 6 months

3.2.4 Patients with insulin dependent diabetes

3.2.5 Prior tumor-directed surgery, with the exception of lymph node biopsies/staging

3.2.6 Previous systemic chemotherapy; No pelvic radiation therapy is permitted other than transvaginal irradiation to control bleeding.

3.2.7 As radiation and cytotoxic agents are contraindicated in pregnancy, pregnant women are ineligible and those of childbearing potential should practice contraception.

4.0 PRETREATMENT EVALUATIONS

4.1 Required Evaluations (8/1/03)

4.1.1 History and physical examination including height, weight, body surface area, and Zubrod Performance Status. 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 a radiation oncologist.

4.1.2 Histologic proof of carcinoma. All patients will have confirmation of diagnosis by cervical biopsy.

4.1.3 All patients will undergo complete blood count with differential and platelets; Serum creatinine, bilirubin, transferase *(ALT)*, electrolytes, magnesium level, and corrected calcium levels.

4.1.4 Chest x-ray *(PA and lateral).*

4.1.5 IVP *(not needed if CT or MRI with contrast has been performed).*

4.1.6 Evaluation of para-aortic lymph nodes is required by bipedal lymphangiogram, surgical exploration, MRI, or CT scan. Lymphangiogram, MRI, or CT scan is recommended prior to staging surgery in order to avoid unnecessary procedures in patients with para-aortic metastases. CT and MRI criteria for presumed para-aortic node involvement is size greater than 1.5 cm. FDG-PET scanning can be used to supplement cross sectional imaging. If PET scanning is suggestive of positive high common iliac and/or para-aortic metastasis and the abnormality is correlated with cross sectional imaging, the patient will be considered eligible for the trial. The cross sectional imaging does not need to meet the 1.5 cm criteria if the lymph node is positive on FDG-PET imaging and extended field radiotherapy is planned. Histologic proof of metastasis is not required as long as extended field radiation was planned. Staging laparotomy with sampling of para-aortic lymph nodes may be performed as outlined in Section 8.0.

4.1.7 Pregnancy test for premenopausal women.

4.1.8 CT scan or MRI of the abdomen and pelvis should be performed in order to delineate tumor volume and location.

4.2 Optional Tests

4.2.1 Barium enema.

4.2.2 Metastatic evaluation *(CT, MRI, nuclear studies)* as indicated.

4.2.3 AST

5.0 REGISTRATION PROCEDURES (9/15/03)

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

5.2 **For Arm 2 only:** Each institution must submit a Study Agent Shipment Form *(Appendix VIII)* to the CTSU Regulatory Office *(Fax 215-569-0206)* as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case **to Arm 2**. The shipment form is only submitted once. Allow adequate processing time *(7-10 days)* before calling to register the first case **to Arm 2**.

6.0 RADIATION THERAPY

Treatment Plan: 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 headquarters data management and dosimetry.

6.1 External Beam (8/1/03)

Pelvic and para-aortic regions will be treated to a total dose of 45 Gy in 5 weeks. Four-field technique *(AP-PA and lateral opposed fields)* is recommended, particularly when treatment is delivered with a beam energy of < 15 MV. Patients will be treated once a day, 5 days a week with a daily fraction size of 1.8 Gy.

- If the patient has extensive tumor which precludes intracavitary treatment, shrinking field technique should be performed to bring the gross tumor volume with adequate margins to a minimum of 65 Gy.
- 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 the intracavitary treatment)* of 60 Gy±5%. See Section 6.3 on parametrial fields. Sites of known non-pelvic lymph node metastasis may receive an additional external boost to a total dose of 54-59.6 Gy.

6.1.1 *Physical Factors*

A megavoltage beam of 4 MV or greater, with a minimum source-axis distance of 100 cm and a minimum source-to-skin distance of 80 cm will be used.

6.1.2 *Radiation Therapy Fields* **(8/1/03)**

All fields treated require simulation and portal verification on the treatment unit. Copies of these films will be submitted to RTOG Headquarters. Treatments may be delivered in the prone or supine position. At simulation, techniques to limit irradiation of the small bowel should be employed including treatment with a full bladder. If a 4-field technique is used, use of a bellyboard and contrast opacification of the small bowel are to be considered. The distal-most aspect of cervico-vaginal disease should be marked using radio-opaque seeds or using a radio-opaque vaginal tampon. Barium or other radio-opaque treatment device may be used to localize the rectum. CT scan (including treatment planning CT) or MRI must be used in pre-treatment planning. The tumor volume including gross nodal disease should be indicated on the simulation films or digitally reconstructed radiographs if CT planning is utilized *(AP and lateral films).*

6.2 Pelvic/Para-Aortic Field

6.2.1 *AP-PA Portals*

Superior border: a transverse line between T11 and T12

Inferior border: transverse line below the obturator foramen or 3 cm below the most distal vaginal disease, to include the introitus if necessary

Lateral border: 2 cm lateral to widest true pelvic diameter unless the distal 1/3 of the vagina is involved; then the inguinal lymph nodes should also be treated

Custom blocking: to shield small bowel and femoral heads while maintaining a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina; a midline block may be added after 20 Gy if patient is being treated AP/PA.

6.2.2 *Lateral Portals* **(8/1/03)**

Superior/Inferior borders: Identical to AP-PA fields

Anterior border: A line drawn anterior to the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4-L5

Posterior border: A line through the posterior sacrum to include the cervical disease with a margin of 3-4 cm; blocking should split the T12-L5 vertebral bodies to shield posterior soft tissue and may split the sacrum to provide adequate margin for presacral nodes; posterior blocking should be designed so that gross disease is encompassed by at least a 3 cm margin.

Custom blocking: to shield small bowel and posterior soft tissue *(which may split the sacrum)*

6.3 Reduced Fields: Parametrial/Nodal Boost

6.3.1 *Parametrial Boost*: AP-PA fields with inferior and lateral borders identical to pelvic fields. Superior border: 1 cm above the inferior aspect of the sacro-iliac joints; central blocking should measure at least 4.5 cm in width at midplane and should be tailored to the position of the intracavitary system.

6.3.2 *Treatment Technique:* Initial pelvic/para-aortic field will be irradiated with a 4-field *("box")* technique. If the external beam energy is ≥ 15 MV photons, AP-PA fields alone may be used. All fields will be treated on a daily basis.

6.3.3 *Dose Specifications:*

4-Field Technique: dose to be prescribed at the isocenter of the beams; the maximum and minimum doses in the target volume should be within ± 5% of the dose at the isocenter.

AP-PA fields: The dose will be prescribed on the central ray at mid-separation of the coaxial equally weighted beams.

6.3.4 Isodose distributions are required at the central axis, 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 Applications (8/1/03)

6.4.1 Intracavitary Protocol Compliance: The first intracavitary implants performed on two patients *(both LDR and HDR)* at each institution will be reviewed directly by the Radiological Physics Center *(RPC).* The following data needs to be submitted to the RPC: for HDR, submit a completed protocol compliance form *(Appendix IX),* treatment plan, isodose plots, treatment tapes and films *(AP and lateral);* for LDR, submit a completed protocol compliance form *(Appendix IX),* treatment plan, isodose plots, source activity, source loading, treatment time and films *(AP and lateral).* The films and dosimetry will be sent within 2 working days to the RPC at MD Anderson Cancer Center:

Low dose rate *(LDR)* and high dose rate *(HDR)* brachytherapy will be employed in this study. If the plan is found to be compliant, a letter will be sent to the institution indicating that that treatment plan was found to be protocol compliant. If the plan is not complaint, a phone call will be made to the institution from one of the reviewers. All subsequent patient data will be sent directly to RTOG.

6.4.2 *LDR Brachytherapy:* Cesium will be used with standard intracavitary systems preferably in one or 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 will be given within two weeks of the completion of external irradiation. If tumor and normal tissue anatomy permit acceptable intracavitary geometry, treatment may be performed during external beam therapy. The interval between the two applications will be one to three weeks. It is recommended that the total course of treatment be completed in less than eight weeks.

6.4.3 *HDR Brachytherapy* **(8/1/03)**

6.4.3.1 See High Dose Rate Intracavitary Brachytherapy Guidelines *(Appendix IX)* for guidelines of dosing, fractionation, vaginal surface dose, normal tissue tolerances, packing and imaging.

6.4.3.2 *Timing*

HDR brachytherapy may start as early as week two. When HDR brachytherapy begins, at least one insertion will be performed per week with no external beam therapy or chemotherapy given on the day of the insertion. If the majority of the external beam radiation has been given, then two insertions per week could be done separated by at least 48 hours in order to complete all treatment within eight weeks. Chemotherapy may be given with one HDR fraction delivered after the completion of all the external beam irradiation.

6.4.3.3 *HDR Instruments*

It is strongly recommended that tandem and ovoids be used for HDR brachytherapy. A tandem and cylinder is allowed only for patients where tandem and ovoid application is not possible due to extent of disease. A tandem and ring also are acceptable.

6.5 Intracavitary Radiotherapy Dosimetry (8/1/03)

6.5.1 Intra-uterine tandems and vaginal applicators such as the Fletcher-Suit-Delclos afterloading system is recommended. The dose to points A, B, rectum, bladder, and vaginal vault must be calculated and reported *(See Appendix X)*.

6.5.2 *Point A*: Measure 2 cm along the intrauterine tandem from the cervical os or flange of the tandem and 2 cm laterally in the plane of the intracavitary system.

6.5.3 *Point B*: Measure 5 cm lateral from a point 2 cm vertically superior to the cervical os or flange of the central tandem along the patients' midline.

6.5.4 *Bladder Dose:* calculated at the center *(in the superior-inferior plane)* of a contrast-filled balloon of a Foley catheter and closest to the applicator system on a lateral view, as defined by ICRU 38.

6.5.5 *Rectal Dose:* Calculate the dose at a point 0.5 cm posterior to the vaginal ovoid or vaginal packing in the lateral projection, defined by ICRU 38.

6.5.6 *Vaginal Surface Dose:* calculated at the vaginal surface lateral to the midpoint at the surface of the ovoid

6.5.7 *Maximum Doses to Sensitive Structures for Patients Treated with LDR Implant*

Normal Tissue	Specified	Per Protocol
Spinal Cord	Maximum Dose	45 Gy
Bladder	ICRU Point	80 Gy
Rectum	ICRU Point	75 Gy
Vaginal Surface	Lateral Surface of Ovoid or cylinder	135 Gy
Kidney	At least 2/3 of renal parenchyma	18 Gy
Maximum Dose to Small Bowel	Estimated dose based on Computed Tomography planning and/or 2D simulations with small bowel series	60 Gy
Maximum dose to an area measuring 10 X 10 cm	Estimated dose based on Computed Tomography planning and/or 2D simulations with small bowel series	45 Gy

6.5.8 *Determination of Normal Tissue Tolerance for HDR*

Maximum doses to the rectum should be less than 70% of the point A dose. Maximum dose to the bladder should be less than 80% of point A dose. In order to stay below an LDR equivalent of 75 Gy to the rectum for six HDR insertions, including the 45 Gy contribution from the external beam radiation, the rectum should receive less than 70% of the prescribed dose to Point A. The dose to the bladder should be less than 80% of the prescribed dose to Point A. As in LDR brachytherapy, every attempt should be made to deliver tumoricidal doses, even if the late responding tissues receive a slightly higher dose.

6.6 Dosimetry to be Reported

6.6.1 Total dose to point A
6.6.2 Total dose to point B
6.6.3 Total dose delivered to involved para-aortic lymph nodes
6.6.4 Maximum dose to small intestine
6.6.5 Maximum dose to an area of small bowel measuring 10 x 10 cm
6.6.6 Total bladder dose
6.6.7 Total rectal dose
6.6.8 Total vaginal surface dose
6.6.9 Central axis isodose curve
6.6.10 Mid para-aortic isodose curve
6.6.11 Mid pelvic isodose curve

6.7 Radiation Toxicities

Side effects expected from radiation therapy include fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, darkening of skin in the treatment portal, low blood counts. Common long-term effects include vaginal narrowing and shortening and dyspareunia. Long-term side effects, although uncommon, may include rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, vaginal vault necrosis. Rare long-term effects include bowel obstruction, ureteral obstruction, vesicovaginal or rectovaginal fistula. All toxicities will be recorded on data collection forms.

6.8 Premedication Before Radiation (8/1/03)

Given that significant amounts of the stomach may be in the radiation field, proton pump inhibitor therapy *(i.e., Prilosec)* should be instituted with radiotherapy. Anti-emetics will be at the discretion of the investigator.

6.9 Radiotherapy Dose Modifications (8/1/03)

There will be no specific guidelines regarding the holding of radiotherapy for toxicities including cytopenias. This will be left to the discretion of the treating radiation oncologist. Any radiotherapy treatment interruptions should be recorded including the reason for the treatment break. The radiation oncologist is encouraged to keep treatment breaks to a minimum. Usually radiotherapy will continue if cisplatin is held for mild/moderate cytopenias.

7.0 DRUG THERAPY

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

7.1 Treatment Plan (8/1/03)

7.1.1 *Cisplatin*: cisplatin and external beam treatment should be initiated on a Monday if possible and given concurrently. Cisplatin will be given weekly with external beam radiation therapy and once with brachytherapy for a total of six doses.

7.1.2 Cisplatin will be given in a sixth and final course as described above with cisplatin started after the insertion of the applicator or before an HDR application. If the patient does not have an absolute neutrophil count $\geq$ 1500 mg/m^3, a platelet count $\geq$ 100,000 mm^3, or experiences more than one toxicity (See Section 7.4), chemotherapy will be held, and brachytherapy will proceed as indicated.

7.1.3 **In Arm 2 of the study**, amifostine will be delivered before each radiation treatment.

7.2 Treatment Schema (8/1/03)

Week	Day	External Radiation	Chemotherapy, Arm 1	Chemotherapy, Arm 2
1	1	+	cisplatin 40 mg/m^2	amifostine 500mg, cisplatin 40 mg/m^2
	2	+		amifostine 500mg
	3	+		amifostine 500 mg
	4	+		amifostine 500mg
	5	+		amifostine 500mg
	6	0		
	7	0		
2	8	+	cisplatin 40 mg/m^2	amifostine 500mg, cisplatin 40 mg/m^2
	9	+		amifostine 500mg
	10	+		amifostine 500mg
	11	+ or HDR		amifostine 500mg
	12	+		amifostine 500mg
	13	0		
	14	0		
3	15	+	cisplatin 40 mg/m^2	amifostine 500mg, cisplatin 40 mg/m^2
	16	+		amifostine 500mg
	17	+		amifostine 500mg
	18	+ or HDR		amifostine 500mg
	19	+		amifostine 500mg
	20	0		
	21	0		
4	22	+	cisplatin 40 mg/m^2	amifostine 500mg, cisplatin 40 mg/m^2
	23	+		amifostine 500 mg
	24	+		amifostine 500 mg
	25	+ or HDR		amifostine 500 mg
	26	+		amifostine 500 mg
	27	0		
	28	0		
5	29	+	cisplatin 40 mg/m^2	amifostine 500mg, cisplatin 40 mg/m^2
	30	+		amifostine 500mg
	31	+		amifostine 500mg
	32	+ or HDR		amifostine 500mg
	33	+		amifostine 500mg
	34	0		
	35	0		
Week	**Day**	**External Radiation**		**Chemotherapy, Arm 2**
6	36	LDR brachytherapy # 1 and, cisplatin 40mg/m^2 *(if eligible)* **OR** HDR and cisplatin 40 mg/m^2		LDR brachytherapy #1, 500 mg amifostine, cisplatin 40 mg/m^2 **OR** HDR, cisplatin 40 mg/m^2 and amifostine 500 mg
	38			
	39			
	40			
	41			
	42			

Week	Day	External Radiation	Chemotherapy, Arm 1	Chemotherapy, Arm 2
7	43	+ *(Parametrial Boost)*		amifostine 500mg
	44	+ or		amifostine 500mg
	45	+ *(Nodal Boost)*		amifostine 500mg
	46	+		amifostine 500mg
	47	+		amifostine 500mg
	48	0		
	49	0		
8	50			
	51	LDR Brachytherapy # 2, cisplatin 40 mg/m^2 **OR** HDR and cisplatin 40 mg/m^2 *(if eligible and not given with first fraction)*		LDR Brachytherapy # 2, 500 mg amifostine, cisplatin 40 mg/m^2 *(if eligible and not given with first fraction)* **OR** HDR and amifostine 500 mg
	52			
	53			
	54			

Note: the radiation treatments should be completed as quickly as possible with no planned breaks.

7.3 Drug Information

7.3.1 Cisplatin

7.3.1.1 *Chemistry*

Cisplatin *(cis-diamminedichloroplatinum II)* has the empiric formula N2CL2 PtH6. It is a planar inorganic compound with a molecular weight of 300; soluble in water at a concentration of 1 mg/ml. The *(II)* nomenclature denotes the *(active)* valence state of the platinum. The interatomic distance of the chlorides is 3.3A, which is different from the 5-7A interatomic distance of the classic alkylating agents. Only the dis-isomer is therapeutically active.

7.3.1.2 *Mechanism of Action*

Primarily causes inhibition of DNA synthesis and, to a lesser degree, inhibition of RNA and protein; it has not been shown to be cell cycle specific.

7.3.1.3 *Pharmaceutical Data*

10 mg/ vial

7.3.1.4 *Administration Guidelines*

Patients will be prehydrated with two liters of D5/1/2 NS and 40 mEq KCL or NS. Cisplatin is given over 30-60 minutes followed by 1L of D5/1/2/NS. Patients should receive at least three liters of fluids over the ensuing 24 hours either parenterally or orally. The anti-emetic regimen for this combination is to be determined by the local investigator.

7.3.1.5 *Animal Tumor Data*

shown to be effective against sarcoma 180, Leukemia L1210, Dunning ascitic leukemia, Walker 256 carcinoma, DMBA induced mammary tumors and ascitic B16 melanosarcoma

7.3.1.6 *Animal Toxicology*

High doses of the drugs have been shown to cause severe vomiting, anorexia, abdominal tenderness, diarrhea, and alterations in kidney function, including acute tubular necrosis. Destroyed circulatory lymphocytes and lymphoid atrophy, hypoplasia of the bone marrow, and ototoxicity manifested as vestibular toxicity and high frequency hearing loss have been observed.

7.3.1.7 *Human Pharmacology*

Highest concentrations were found in kidney, liver, spleen, and lowest concentrations were in the brain. Plasma contained less than 10% of dose at 1 hour and the peak urinary excretion was 22-32% in forty-eight hours. It has a biphasic mode half-life; the initial phase of 25-49 minutes and the secondary, 58-73 hours. The drug was 79% protein bound with intracellular leukocyte levels 6.1% of plasma levels. There was incomplete urinary excretion, 27-45% of the radioactive drug in the first

five days. It has been found to be a very significant immunosuppressive drug with single doses being more effective than divided doses.

7.3.1.8 *Toxicities*

Impairment of renal function, myelosuppression, high-frequency hearing loss, nausea and vomiting. Mannitol-induced diuresis can decrease toxicity. Peripheral neuropathy with chronic use has been reported and may be reversible.

7.3.1.9 *Supply*

This drug is commercially available.

7.4 Cisplatin Dose Modification

7.4.1 A patient with grade 2 or greater platinum-related neuropathy or grade 2 or greater ototoxicity will not receive further cisplatin.

7.4.2 Dose will be modified on the serum creatinine and/or creatinine clearance immediately prior to each cisplatin dose. If the serum creatinine is $\leq$ 1.5, creatinine clearance is not necessary for treatment with full dose, 40 mg/m^2. If the serum creatinine is > 1.5, a creatinine clearance should be obtained by urine collection with GFR as per the Cockroft-Gault formula: [(140-age)(kg wt) divided by [(serum creatinine) x (72)] or nomogram calculation *(valid only if serum creatinine is not changing rapidly),* and the dose modified as indicated.

Serum Creatinine	Creatinine Clearance	Cisplatin Dose
≤ 1.5	or 50 cc/min	40 mg/m^2
> 1.5	and 40-50 cc/min	25 mg/m^2
> 1.5	< 40 cc/min	0

7.4.3 Cisplatin will be held if the absolute neutrophil count is < 1500 mg/m^3 or platelet count is < 100,000 mm^3.

7.4.4 Cisplatin will be held if bilirubin is ≥ 2 or if ALT is ≥ 3 x ULN.

7.5 Amifostine (*Arm 2*) (8/1/03)

7.5.1 *Formulation*

Amifostine *(Ethyol)* is an organic thiophosphate cytoprotective agent known chemically as ethanethiol, 2-[3-aminopropyl)amino]-, dihydrogen phosphate *(ester)*.

$H_2N(CH_2)_3NH(CH_2)_2S\text{-}PO_3H_2$

Amifostine is a white crystalline powder that is freely soluble in water. Its empirical formula is $C_5H_{15}N_2O_3PS$, and its molecular weight is 214.22. Amifostine is supplied as a sterile lyophilized powder mixture that requires reconstitution for subcutaneous administration. Each single-use 10 mL vial contains 500 mg of amifostine *(anhydrous base).*

7.5.2 *Preparation, Storage, and Stability*

Preparation: Prior to subcutaneous injection, amifostine for injection must be reconstituted with 2.9 mL of sterile Sodium Chloride for Injection, USP, 0.9%. No further dilution is necessary. The compatibility of amifostine with solutions other than 0.9% sodium chloride for injection, or sodium chloride solutions with other additives, has not been examined. The use of other solutions is not recommended.

Storage: Intact, unreconstituted vials of amifostine may be stored at room temperature

Stability: When reconstituted to 2.9 ml h, for subcutaneous administration, the solution is chemically stable for 5 hours at room temperature and up to 8 hours when stored at refrigerated temperature *(2-6* ^{o}C).

Caution: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if cloudiness or precipitate is observed.

7.5.3 *Administration*

Patients should receive premedication regimen as described below. They also should be adequately hydrated prior to amifostine injection and kept in a supine or reclined position during administration. Amifostine will be given as two equally-divided subcutaneous injections, each approximately 1.7ml. The subcutaneous injection sites should be rotated.

7.5.4 *Toxicities*

7.5.4.1 Hemodynamic: amisfostine administration has been associated with hypotension in patients who are dehydrated or otherwise indisposed. Predisposing factors include the use of antihypertensive medications or diuretics.

7.5.4.2 Hematologic: none.

7.5.4.3 Gastrointestinal: nausea, vomiting.

7.5.4.4 Heart: none.

7.5.4.5 Neurologic: drowsiness.

7.5.4.6 Allergy: sneezing, flushing, allergic reaction.

7.5.4.7 Skin: local skin reactions, systemic rash

7.5.4.8 Other: hypocalcemia.

7.5.5 *Supplier* **(9/15/03)**

MedImmune, Inc. will supply amifostine to Specialty Pharmacy Services *(SPS)* for distribution. RTOG members must submit the Study Agent Shipping Form *(Appendix VIII)* with the institution's State Board of Pharmacy License OR the Principal Investigator's DEA License to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first patient **to Arm 2** of this study.

After registration, RTOG will notify MedImmune to initiate shipment of 35 vials of amifostine to the institution. The supply will not be patient-specific and may be used as needed for study patients. Drug inventory logs must be kept by the institution for review by RTOG upon request. At the completion of the study, remaining amifostine supplies will be inventoried and destroyed on site.

For questions regarding supply and distribution, contact **(8/13/04)**:

Craig Mincheff
MedImmune Medical Science Liaison
Central Region
651-775-6617
mincheffc@medimmune.com
or
Sydney Skilskyj
240-632-4108
skilskyjs@medimmune.com

7.5.6 *Precautions*

1) Amifostine should be administered in a supine position. 2) Patients will receive *i.v.* hydration *(chemo days)* or 2 cups of oral fluids *(non-chemo days)*. 3) Anti-hypertensive/diuretic medications should not be taken until after the amifostine infusion is completed.

7.5.7 *Premedication and Amifostine Infusion Schema, Chemotherapy Days*

Amifostine will be administered before each chemotherapy dosing. Since amifostine and cisplatin infusion have been associated with nausea and vomiting, patients should receive premedication prior to amifostine administration.

- 1 hour: Ondansetron *(32 mg i.v.)* or granisetron *(1 mg)* in 50 ml D_5W i.v. over fifteen minutes; dexamethasone *(20 mg i.v.)* and cimetidine *(300 mg i.v.)*.
- 0: Amifostine *(500 mg sc)* in two equally-divided subcutaneous administrations. Patient should remain supine during the injections and for fifteen minutes after amifostine administration.
- Within + 15 minutes: Start cisplatin 40mg/m^2 *i.v.,* to be infused over one hour.
- Within + 90 minutes: Radiation *(except during brachytherapy when radiation will be ongoing during amifostine and cisplatin).*

7.5.8 *Premedication and Amifostine Infusion Schema, Non-Chemotherapy Days*

Amifostine will be administered before each radiation treatment.

- 90 minutes: Compazine 10 mg and/or Ondansetron 8mg PO.

- 15 to 30 minutes: Two cups of oral fluids.

- 0: Amifostine *(500 mg sc)* in two subcutaneous injections . Patient should remain supine during the infusion and for fifteen minutes after amifostine administration.

- Within + 30 - 60 minutes: Radiation *(except during brachytherapy when radiation will be ongoing during amifostine).*

7.5.9 *Blood Pressure Monitoring*

Blood pressure (BP) should be monitored by taking a baseline BP prior to the first amifostine injection and then 10 minutes after the injection. An additional BP may also be taken prior to the patient ambulation for treatment.

7.6 Management of Localized or Generalized Skin Reaction (8/1/03)

Cutaneous evaluations should precede every Amifostine injection. Particular emphasis should be placed on the lips, mucosa, palms, soles of the feet, and other cutaneous reactions of the trunk. Amifostine should be permanently discontinued for any cutaneous reaction considered to be erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, exfoliative dermatitis, or any cutaneous reaction associated with fever or constitutional symptoms. If a cutaneous reaction occurs outside the injection site and is not related to another etiology, Amifostine should be withheld and dermatologic consultation with appropriate therapy initiated. Any grade 2 or higher injection site reaction or any non-injection site dermatologic reaction not associated with another etiology should be discussed with Dr. Hymes at *(713)* 745-1113. Re-initiation of Amifostine after a non-injection site reaction will be at the clinician's discretion after dermatologic consultation and discussion with Dr. Hymes. Amifostine will not be re-initiated for reactions felt to be erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, exfoliative dermatitis, or any cutaneous reaction associated with fever or constitutional symptoms[41]. Local injection site skin reactions should be graded and treated as per Appendix IV.

7.7 Management of Fever (8/1/03)

An oral temperature should be taken before each Amifostine injection. If a fever occurs, other causes, i.e., infection, should be ruled out before attributing the fever to Amifostine. If the fever is associated with a cutaneous reaction, mucosal reaction or constitutional symptoms not know to be due to another etiology the Amifostine should be permanently discontinued. See Appendix V for an algorithm for the management of Amifostine related fever.

7.8 Management of Hypocalcemia (8/1/03)

Hypocalcemia should be supplemented with oral Calcium. Amifostine should be held for Grade 3 or 4 hypocalcemia or symptomatic hypocalcemia. Amifostine may be restarted after correction, with the exception of hypocalcemia associated with arrhythmia that resulted in cardiovascular compromise or that required hospitalization *(grade 4).*

7.9 Toxicity Reporting

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

7.9.1.1 Any ADR which is both serious *(life-threatening, fatal)* and unexpected.

7.9.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.9.1.3 Any death on study if clearly related to the commercial agent*(s)*.

7.9.1.4 Acute myeloid leukemia *(AML)*. The report must include the time from original diagnosis to the development of AML, characterization such as subtype, cytogenetics, etc, and protocol identification.

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

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

7.9.3 Special Reporting for this study: FAX (215) 928-0153

7.9.4 All ≥ grade 3 nonhematological toxicities must be reported to RTOG within 24 hours.

8.0 SURGERY

8.1 Patients may undergo surgical staging prior to initiation of therapy. The primary goal of this surgery is to establish the status of the para-aortic nodes. Aortic node sampling should be performed by a retroperitoneal approach. Enlarged or suspicious nodes should be excised or biopsied if unresectable. If bulky, incompletely dissected disease is encountered, a clip should be placed at the superior, lateral *(2)*, and inferior margins. The nature of the dissection and the location of the clips should be noted in the operative note. An intraperitoneal exploration is permissible to document the presence of peritoneal disease.

8.2 Operative Note: the standard typed hospital operative note for the exploration and lymph node biopsies must be submitted. The operative note must indicate a description of the findings on abdominal and pelvic exploration.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank

10.1.1 The following must be provided in order for the case to be evaluable for the RTOG Tissue Bank:

10.1.1.1 One H&E stained slide

10.1.1.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **NOTE**: A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.1.1.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.1.1.4 A Specimen Transmission Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; the form must include the RTOG protocol number and patient's case number.

10.1.2 Submit materials to:

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

10.2 Reimbursement

RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue, $200 per case for a block or core of material, or $100 per case for unstained slides. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.3 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details.)

10.3.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified

investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.3.2 Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (8/1/03)

		Interval in weeks during treatment							
	Pre-Entry	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Clinical Examination	X	X	X	X	X	X	X	X	X
Cervical or para-cervical biopsy/tumor measurements	X[a]								
CBC; diff; platelets	X	X	X	X	X	X	X	X	X
Serum creatinine; bilirubin; ALT; electrolytes; Mg++, Ca++[c]	X[b]	X	X	X	X	X	X	X	X
Chest X-ray *(PA and lateral)*	X								
CT scan of abdomen and pelvis *(or MRI)*	X								X[g]
Evaluation of para-aortic lymph nodes[d]	X								
IVP[e]	X								
Pregnancy test[f]	X								

a. Tumor measurements should be taken at the time of each isotope insertion.
b. Also prior to each course of cisplatin
c. Electrolyte abnormalities, including hypocalcemia, will be corrected as needed or treatment held, as described in Section 7.8.
d. By bipedal lymphangiogram, surgical exploration, CT scan, or MRI. FDG-PET also may be used as a supplement to cross-sectional imaging.
e. Not necessary if CT or MRI with contrast has been performed
f. For premenopausal women
g. To be performed 8-12 weeks after treatment then as necessary

11.2 Evaluation During Treatment (8/1/03)

11.2.1 All patients will undergo weekly clinical examinations. Pelvic examinations will be done as needed but are not required during external beam radiotherapy. Studies such as CT and MRI evaluation will be performed as indicated by the patient's tumor status.

11.2.2 Complete blood counts with differential and platelet count will be performed weekly; transfusion may be given if felt to be necessary. The use of hematologic growth factors *(i.e., G-CSF and/or Epogen)* will be at the investigator's discretion. Any transfusions or hematopoietic growth stimulants used during therapy should be recorded and reported to RTOG. Hematopoietic growth stimulants *(i.e., G-CSF and Procrit®)* can be given at the investigator's discretion.

11.2.3 Serum chemistry including creatinine, ALT, electrolytes, Mg++, Ca ++, and bilirubin will be performed prior to each course of cisplatin. If cisplatin is not being delivered, weekly calcium levels will still need to be obtained while patients are receiving amifostine.

11.2.4 At the time of each isotope insertion, additional physical examinations, including pelvic examinations, will be performed to document the presence of disease.

11.3 Evaluation of Response and Toxicity

11.3.1 Every attempt should be made to histologically document tumor recurrence. Patients will be followed for disease status and for the appearance of chronic toxicity with history, physical examination, and indicated laboratory and radiologic tests according to the schedule in Section 12.1.

11.3.2 *Toxicity Evaluation* **(8/1/03)**

11.3.2.1 Myelosuppressive toxicity shall be reported as the lowest observed WBC, absolute granulocytes, and platelet count. Anemia, red blood cell transfusions, and the use of hematologic growth factors will be noted.

11.3.2.2 Renal and hepatic toxicity will be reported as changes in creatinine, ALT, and bilirubin during treatment course.

11.3.2.3 Any other treatment toxicities will be reported.

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

11.4 Criteria for Response

11.4.1 *Complete Clinical Remission*: Disappearance of all clinical evidence of active tumor for a minimum of four weeks. The patient must be free of all symptoms.

11.4.2 *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 measured lesions or the appearance of new metastatic lesions.

11.4.3 *No Change*: No change in the tumor size *(< 50% decrease, or <25% increase).*

11.4.4 *Progressive Disease*: Increase > 25% in the size of any measured lesions or the appearance of new metastatic lesions.

11.5 Criteria for Discontinuing Study Treatment

11.5.1 Increasing disease as defined in Section 11.4.4 after two weeks of therapy

11.5.2 The development of unacceptable toxicity

11.5.3 Patient request

12.0 DATA COLLECTION (8/1/03) (7/15/04)

Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Pathology Slides/Blocks **(P2)**	Within 2 wks of study entry
Preliminary Dosimetry Information: RT Prescription *(Protocol Treatment Form)* **(T2)** Films *(simulation and portal)* **(T3)** Calculations **(T4)**	Within 1 wk of start of RT
Final Dosimetry Information: Radiotherapy Form **(T1)** Daily Treatment Record **(T5)** Isodose Distribution **(T6)** Intracavitary Dose Form **(I9)** Supplementary Calculations *(HDR/LDR)* **(TL)** Intracavitary Films **(T0)**	Within 1 week of RT end
Treatment Summary Form **(TF)**	Two weeks from start of treatment, *(to include pre-tx labs and first dose of chemo)*, then at completion of chemotherapy
Initial Follow-up Form (**FS**)	At day 90 *(week 13)* to include all acute treatment toxicities
Follow-up Form **(F1)**	Every 3 months for 2 years, then every 4 months for 1 year then every 6 months for 2 years. Also at progression/relapse and at death.
Long Term Follow-up Form (**FF**)	Annually after 5 years

AUTOPSY REPORT (D3) **AS APPLICABLE**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 *Primary Endpoints*

- To determine the feasibility and tolerance of extended-field external radiotherapy to the pelvis and para-aortic region and intracavitary irradiation combined with weekly cisplatin. *(Arm 1)*
- To determine if the addition of amifostine to extended-field external radiotherapy to the pelvis and para-aortic region and intracavitary irradiation combined with weekly cisplatin reduces acute grade 3 and 4 toxicity. *(Arm 2)*

13.1.2 *Secondary Endpoints*

- Pelvic tumor control
- Distant metastases

13.2 Sample Size Determination (8/1/03) (7/15/04)

There is not enough data concerning the feasibility and tolerance of extended-field external radiotherapy to the pelvis and para-aortic region and intracavitary irradiation combined with weekly cisplatin; therefore, this study is being done in two parts. The first arm of the study is designed to evaluate the feasibility and tolerance of extended-field external radiotherapy to the pelvis and para-aortic region and intracavitary irradiation combined with weekly cisplatin. Given that the toxicity from the first arm is in an acceptable range, the second arm will determine if the addition of amifostine lowers the acute grade 3 and 4 toxicity rate, excluding grade 3 leukopenia. These outcomes given the radiotherapy field and cisplatin may be expected and not considered life threatening.

Based on the acute grade 3 and 4 toxicity rates from RTOG 90-01[4], 92-10[15], and GOG 125[14], the expected acute grade 3 and 4 toxicity rate in the first arm of this study is 40%. Under this assumption, with a sample size of 24, a one-sided 97.5% confidence interval for the acute grade 3 and 4 toxicity rate *will have an upper bound of 0.62*. If the acute toxicity rate from the first arm is > 62.5%, then the study will not proceed to Arm 2 due to excessive toxicity. If the acute toxicity rate from the first arm of the study is < 30%, then the study will not proceed to Arm 2, due to the sample size that would be required to detect a meaningful difference.

Based on an acute grade 3 and 4 toxicity rate of 0.40 from Arm 1, Arm 2 is designed to detect an acute grade 3 and 4 toxicity rate of 0.20 with the addition of amifostine. This arm of the study is designed using Simon's minimax two-stage design[42] with a one-sided significance level of 0.05 and 80% power. If five or more of the first thirteen evaluable patients experience an acute grade 3 or 4 toxicity, then the study will be stopped and it will be concluded that there is not enough evidence that the addition of amifostine results in a reduction of the acute grade 3 and 4 toxicity rate. If fewer than five out of the first thirteen evaluable patients experience an acute grade 3 or 4 toxicity, then the study will continue until there are thirty-five evaluable patients. The sample size and the maximum number of patients allowed to experience an acute grade 3 or 4 toxicity in order to reject the null hypothesis for Arm 2 will be increased if the acute toxicity rate from Arm 1 is less than 0.40. The maximum sample size needed for this arm is 55 patients, which would correspond to an acute toxicity rate of 0.30 from Arm 1.

Sample Sizes for Arm 2 Based on Toxicity Rate from Arm 1

Arm 1 Toxicity Rate	Alternative Hypothesis Toxicity Rate	% Reduction	Absolute Reduction	Sample Size*	Time to Accrue (months)
0.40	**0.20**	**50%**	**0.20**	**59**	**~ 18**
0.60	0.30	50%	0.30	18	~ [illegible]
0.50	0.25	50%	0.25	25	[illegible]
0.30	0.15	50%	0.15	55	[illegible]

* Includes additional 10% for ineligible/no data cases.

Revised Below

The acute Grade 3 and 4 toxicity rate, excluding Grade 3 leukopenia, from the first stage of this study was 77%. Although this exceeded the upper limit of 62.5% originally set in the protocol, after careful

consideration, it was decided that the study would continue on to the amifostine portion. This RT and chemotherapy regimen is the standard of care for this patient population and, given the excessive toxicity it causes, continuing this study to determine the effect that amifostine may have on decreasing the toxicity rate is warranted. Let p = Grade 3 and 4 toxicity rate, excluding Grade 3 leukopenia. The hypotheses to be tested are: Ho: p = 0.77 vs Ha: p = 0.46. This corresponds to a 40% reduction in toxicity and an absolute reduction of 31%. With a one-sided alpha level of 0.05, 16 patients will provide 80% power to detect a 40% reduction in the toxicity rate as defined above. To allow for a 10% ineligibility rate, 18 patients will be accrued.

Arm 1 Toxicity Rate	Alternative Hypothesis	Toxicity Rate % Reduction	Absolute Reduction	Sample Size*	Time to Accrue (months)
0.77	0.46	40%	31%	18	~18

* Includes additional 10% for ineligible/no data cases.

There will be a total accrual of 45 patients to this study, 27 patients from the first stage and 18 in the second.

13.3 Accrual and Duration

Based upon RTOG 92-10, monthly accrual will be approximately two to three patients. Arm 1 should accrue in approximately 12 months. After the last patient is entered onto Arm 1, accrual to the study will be suspended until acute toxicity information is collected and the acute toxicity rate for Arm 1 is determined. If the acute toxicity rate for Arm 1 is in the acceptable range, accrual to Arm 2 may begin. Arm 2 should accrue in approximately 18 months. The trial should be completed in approximately 3 years. If at any time a grade 5 toxicity occurs, the case will be reviewed by the study chair. For the efficacy of the treatment, additional follow ups after the closure of the accrual are needed. With an additional one year of follow up, we will have better estimates of two-year rates for the secondary endpoints.

13.4 Analysis Plan (7/15/04)

13.4.1 *Interim Reports*

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

- patient accrual rate with projected completion date,
- pretreatment characteristics of patients accrued,
- the frequencies and severity of toxicity due to chemotherapy and radiation therapy,
- compliance rate of treatment per protocol

13.4.2 *Arm 1 Analysis*

The analysis of Arm 1 will be performed approximately three months after the last patient has been entered and acute toxicity information has been reported. If the acute grade 3 and 4 toxicity rate falls in *(0.20, 0.60)*, then it will be concluded that the treatment of extended-field radiotherapy to the pelvic and para-aortic region and intracavitary irradiation combined with weekly cisplatin is feasible with acceptable toxicity and the study will proceed to Arm 2.

13.4.3 *Arm 2 Analysis: Stage 1*

The analysis of Arm 2, stage 1, will be performed after acute toxicity information has been reported for the first thirteen evaluable patients entered onto the second arm of this study. If five or more out of the first thirteen evaluable patients experience an acute grade 3 or 4 toxicity, then the study will be stopped and it will be concluded that there is not enough evidence that the addition of amifostine results in a reduction of the acute grade 3 and 4 toxicity rate. If fewer than five out of the first thirteen evaluable patients experience an acute grade 3 or 4 toxicity, then the study will continue until there are thirty-five evaluable patients.

13.4.4 *Arm 2 Analysis: Stage 2*

If ten or more out of thirty-five evaluable patients experience an acute grade 3 or 4 toxicity, then we will conclude that there is not enough evidence to reject the null hypothesis of an acute grade 3 and 4 toxicity rate of 0.40. If fewer than ten out of thirty-five evaluable patients experience an acute grade 3 or 4 toxicity, then we will reject the null hypothesis of an acute grade 3 and 4 toxicity rate of 0.40 and conclude that this toxicity rate is decreased with the addition of amifostine.

Revised Below

13.4.3 *Arm 2 Analysis:*

If nine or more out of sixteen evaluable patients experience an acute Grade 3 or 4 toxicity (excluding grade 3 leukopenia), then we will conclude that there is not enough evidence to reject the null hypothesis of an acute Grade 3 or 4 toxicity rate of 0.77. If eight or fewer out of sixteen evaluable patients experience an acute Grade 3 or 4 toxicity, then we will reject thenull hypothesis of an acute Grade 3 and 4 toxicity rate of 0.77 and conclude that this toxicity rate is decreased by at least 40% with the addition of amifostine.

The probabilities of pelvic failure and distant metastasis will be estimated using the cumulative incidence method to provide the efficacy measurement.

13.5 Inclusion of Minority (7/15/04)

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the possible difference in any of the above endpoints between whites and non-whites will be investigated. RTOG cervix cancer trial 9001 accrued approximately 52% non-whites. With the proposed number of evaluable patients, there will not be enough statistical power to detect the difference in the primary endpoint between race groups. Nonetheless, the descriptive statistics for each of these groups will be reported. The projected minority accruals are shown below:

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other Or Unknown	Total
Arm 1 Female	0	0	7	6	0	13	1	27
Arm 2 Female	0	0	5	4	0	8	1	18
Total	0	0	12	10	0	21	2	45

REFERENCES (8/1/03)

1. Cancer Statistics 1999. *CA Cancer J. Clin.* 49: 8-31, 1999.
2. Concurrent chemoradiation for cervical cancer. *National Cancer Institute Clinical Announcement*. February 1999.
3. Whitney CW, Sause W, Bundy BN et al. A randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes. A Gynecologic Oncology Group and Southwest Oncology Group Study. *J. Clin Oncology* (in press).
4. Morris, M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med.* 340: 1137-43, 1999.
5. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 340: 1144-53, 1999.
6. Peters WA III, Liu PY, Barrett RJ, et al. Cisplatin and 5-Flrorouracil plus radiation therapy are superior to radiation therapy as adjunctive in high-risk early-stage carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: report of a phase III intergroup study (manuscript in submission).
7. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical cancer. *N Engl J Med.* 340: 1154-61, 1999.
8. Berman M, Keys H, Creasman W, et al. Survival and patterns of recurrence in cervical cancer metastatic periaortic lymph nodes. *Gynecologic Oncology.* 19: 8-16, 1984.
9. Lepanto P, Littman P, Mikuta, et al. Treatment of para-aortic nodes in carcinoma of the cervix. *Cancer.* 35: 1510-13, 1975.
10. Lovecchio JL, Averette HE, Doinato D, et al. 5-Year survival of patients with periaortic nodal metastases in clinical stage IB and II cervical carcinoma. *Gynecol Oncol*. 34:43-45, 1989.
11. Nori D, Valentine E, Hilaris B. The role of paraaortic node irradiation in the treatment of cancer of the cervix. *Int J Radiat Oncol Biol Phys.* 211: 1469-73, 1985.
12. Tewfik H, et al. Para-aortic lymph node irradiation in carcinoma of the cervix after exploratory laparotomy and biopsy-proven positive aortic nodes. *Int J Radiat Oncol Biol Phys.* 8:13-18, 1982.
13. Goodman HM, Bowling MC, Nelson JH. Cervical malignancies. In: Knapp RC, Berkowitz RS, eds. *Gynecologic Oncology*. New York: Macmillan; 1986: 225-273.
14. Varia M, et al. Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group Study. *Int J Radiat Oncol Biol Phys.* 42: 1015-1023, 1998.
15. Grigsby PW, Lu JD, Mutch DG, Kim RY, Eifel PJ. Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: Phase II study of the Radiation Therapy Oncology Group 92-10. *Int J Radiat Oncol Biol. Phys.* 41: 817-22, 1998.
16. Maltefano J, Keys H. Aggressive multimodality treatment for cervical cancer with paraaortic lymph nodes metastases. *Gynecologic Oncology.* 42: 44-47, 1991.
17. Podczaski E, Stryker J, Kaminski P, et al. Extended-field radiation therapy for carcinoma of the cervix. *Cancer.* 66: 251-58, 1990.
18. Capizzi, R.L. The preclinical basis for broad-spectrum selective cytoprotection of normal tissues from cytotoxic therapies by amifostine. *Seminars in Oncology*. 26: 3-21, 1999.
19. Liu, T. Liu, Y. He, S. Zhang, Z. Klingerman, M.M. Use of radiation with or without WR-2721 in advanced rectal cancer. *Cancer.* 69: 2820-2825, 1992.
20. Myers, C.E. McGuire, W.P. Liss, R.H. et al. Adriamycin: The role of lipid peroxidation in cardiac toxicity and tumor response. *Science*. 197: 165-167, 1977.
21. Shigematsu, N. Schwartz, J.L. Grdina, D.J. Protection against radiation-induced mutagenesis at the hprt locus by spermine and N,N"-(dithiodi-2,1-ethanediyl) bis-1,3-propane-diamine (WR-33278). *Mutagenesis*. 9: 355-360, 1994.

22. Treskes, M. Nijtmans, L.G. Fichtinger-Schepman, A.M. et al. Effects of the modulating agent WR-2721 and its main metabolites on the formation and stability of cisplatin-DNA adducts in vitro in comparison to the effects of thiosulfate and diethyldithio-carbamate. *Biochem Pharmacol.* 43:1013-1019, 1992.

23. Romanol, F.L. Bannister, R.G. Histochemistry: Localized areas of high alkaline phosphatase activity in endothelium of arteries. *Nature*. 195: 611-612, 1962.

24. Yang, G.L. Fernandez, D.J. Speicher, L. et al. Biochemical determinants of the cytoprotective effect of amifostine. *Proc Am Assoc. Cancer Res*. 36:290, 1995 (abstract).

25. Calabro-Jones, P.M. Aquilera, J.A. Ward, J.F. et al. Uptake of WR-2721 derivatives by cells in culture: Identification of the transport form of the drug. *Cancer Res*. 48:3634-3640, 1988.

26. Wasserman, T. radioprotective effects of amifostine. *Seminars in Oncology*. 26:89-94, 1999.

27. Mcdonald, S. Meyerowitz, c. Smudzin, T. et al: Preliminary results of a pilot study using WR-2721 before fractionated irradiation of the head and neck to reduce salivary gland dysfunction. *Int J Radiat Oncol Biol Phys*. 29:747-754, 1994.

28. Mcdonald, S. Meyerowitz, c. Smudzin, T. et al: Amifostine preserves the salivary gland function during irradiation of the head and neck. *Eur J Cancer*. 31A:415, 1995 (suppl 5) (abstract).

29. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol*. 18(19): 3339-3345, 2000.

30. Mehta, M.P. Amifostine and combined-modality therapeutic approaches. *Seminars in Oncology*. 26:95-101,1999.

31. Buntzel, J. Kuttner, K. Rusell, L. et al. Selective cytoprotection by amifostine in the treatment of head and neck cancer with simultaneous radiochemotherapy. *Proc Am Soc Clinc Oncol*. 16:393, 1997 (abstract).

32. Wadler, Scott. Beitler, J.J. Rubin, J.S. Haynes, H. et al. Pilot trial of cisplatin, radiation, and WR2721 in carcinoma of the uterine cervix: A New York Gynecologic Oncology Group Study. *J Clin Oncol*. 11:1511-1516, 1993.

33. Runowicz, D.D. Wadler, S. Rodriguez-Rodriguez, L. Concomitant cisplatin and radiotherapy in locally advanced cervical cancer. *Gynecol Oncol*. 34:395-401, 1989.

34. Kemp G, Rose P, Lurain J Berman, M et al: Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: Results of a randomized control trial in patients with advanced ovarian cancer. *J Clin Oncol*. 14:2101-12, 1996.

35. Glover D, Glich, JH, Weiler Clare, et al: WR-2721 and high-dose cisplatin: An active combination in the treatment of metastatic melanoma. *J Clin Oncol*. 5:574-578, 1987.

36. Tannehill SP, Mehta MP, Larson M, et al. Effect of amifostine on toxicities associated with sequential chemotherapy and radiation therapy for unresectable non-small-celllung cancer: Results of a phase II trial. *J Clin Oncol*. 15:2850-2857, 1997.

37. Anne P, Curran W, Machtay M, et al. A phase II trial of subcutaneous amifostine and radiation therapy in patients with head and neck cancer (WR-B060). *In J Radiat Oncol Biol Phys.* 51:84, 2001 (abst).

38. Anne P. Phase II trial of subcutaneous amifostine in patients undergoing radiation therapy for head and neck cancer. *Sem in Oncol.* 29: 80-83. 2002.

39. Koukourakis MI, Kyrias, G, Kakolyris, S, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomixed phase II study. *J Clin Oncol*. 18: 2226-2233, 2000.

40. Daly C, Ameen D, Holloway N. Subcutaneeous administration of amifostine prior to radiation therapy. *Proc Amer Soc Clin Oncol*, 2002.

41. Samuels MA, Mesko T, Keisch, ME, et al. Safety and feasibility of subcutaneous administration prior to radiation therapy. *Int J Radiol Biol Phys*. 54: 287, 2002.

42. Simon, Richard. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*. 10:1-10, 1989.

APPENDIX I (4/30/04)

RTOG 0116

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A TWO PART PHASE I/II STUDY OF EXTENDED FIELD EXTERNAL IRRADIATION AND INTRACAVITARY BRACHYTHERAPY COMBINED WITH CHEMOTHERAPY *(WEEKLY CISPLATIN –ARM 1)* AND AMIFOSTINE *(WEEKLY CISPLATIN AND AMIFOSTINE-ARM 2)* IN CARCINOMA OF THE CERVIX WITH POSITIVE PARA-AORTIC OR HIGH COMMON ILIAC LYMPH NODES

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have cancer of the cervix. You have the right to know about the procedures in this study, so you can decide whether or not to take part after knowing the risks, benefits, and alternatives involved. This consent form is an effort to make you better informed so you may give or withhold your consent to participate.

WHY IS THIS STUDY BEING DONE? (12/3/01)

The study is designed in two parts. The first part is designed to find out the side effects of chemotherapy combined with radiation for women who have cervical cancer. If this treatment is found to have acceptable toxicity, then the second part of the study will be done. Treatment in the second part will add amifostine to test this drug's ability to reduce side effects from the combination of radiation and chemotherapy.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 27 people will participate in the first part of this study, and about 39 people will participate in the second part of the study.

WHAT IS INVOLVED IN THE STUDY? (8/1/03)

If you take part in this study, you will undergo careful evaluation. This will include physical examination, blood tests, urinalysis, and special x-ray tests, such as CT scan, MRI, PET scan, or scan of lymph glands, to evaluate the amount of tumor present. Some patients also may be evaluated under anesthesia with biopsies of lymph glands to which the cancer may have spread.

The treatment you receive will depend on when you enter the study. Following the initial evaluation, if you are among the first 27 patients enrolled in the study, you will receive an external radiation treatment lasting a few minutes a day, five days a week, for a period of five weeks. Along with the radiation therapy, you will receive chemotherapy (as an outpatient) consisting of cisplatin through a tube in your vein (intravenously) over a one-hour period.

Depending upon the size of the tumor, you may get additional external radiation treatments or one to two radioactive insertions (placement of radioactive "seeds" in hollow tubes) into your uterus and vagina two to three weeks apart. The insertions will require a two to three day hospital stay. An alternative could include having six insertions as an outpatient. Your doctor will discuss these options with you.

If the second part of the study is done, and you are among the 39 patients enrolled in that part of the study, you will receive the same treatment described above for part one, but you will also be given amifostine as two injections under your skin prior to each radiation treatment, Monday through Friday, to help decrease any side effects from radiation therapy and any additional side effects of chemotherapy. Your blood pressure will be checked before and after the amifostine.

If you take part in this study, you will have the following tests and procedures:

Prior to Treatment:

- History and weekly pelvic exams by two doctors
- Blood tests
- Chest X-Ray
- CT scan or MRI of the abdomen and pelvis or scan of lymph glands
- PET scan, if indicated by your doctor
- Surgery under anesthetic-- biopsies of lymph glands if indicated by your physician
- Pregnancy test, if applicable

During Chemotherapy, External Radiation Treatment, and Radioactive Insertions (**Part 1**):

- Weekly clinical exams
- A pelvic exam at the time of each radioactive insertion
- Blood tests weekly and before each chemotherapy treatment
- Additional X-rays and/or biopsies depending upon tumor size

During Chemotherapy, External Radiation Treatment, Radioactive Insertions, and Amifostine (Part 2)

- Frequent checking of blood pressure before, during, and after amifostine injections
- Weekly clinical exams
- A pelvic exam at the time of each radioactive insertion
- Blood tests weekly and before each chemotherapy treatment
- Additional X-rays and/or biopsies depending upon tumor size

At Completion of Treatment:

- Blood tests
- Additional X-rays depending upon tumor size

During Follow-up:

- Clinical exam and blood tests every 3 months for the first 2 years, then every 4 months for the 3rd year, every 6 months for the next 2 years, then annually
- CT scan or MRI of the abdomen and pelvis will be performed 8-12 weeks after treatment then as necessary to check for disease.
- PET scan, if indicated by your doctor
- Biopsies as necessary to check for disease

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

HOW LONG WILL I BE IN THE STUDY? (8/27/02)

During the approximately seven to eight weeks of treatment, you will have weekly clinical exams and blood tests (approximately two teaspoons of blood will be drawn). Follow-up visits will be every three months for the first two years, every four months for the third year, every six months for the fourth and fifth year, then annually.

Your doctor may decide to take you off this study if your disease becomes worse, the side effects of treatment become very severe, new scientific developments occur that indicate the treatment is not in your best interest, or if your doctor feels that this treatment is no longer in your best interest.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks associated with Radiation Therapy to the Pelvis

Very Likely

Low blood counts causing easy bruising
Shortening and narrowing of the vagina
Pain with sexual intercourse
Tiredness near the end of treatment
Diarrhea
Nausea and/or vomiting
Stomach pain that feels like bad heartburn or an ulcer and that may make eating or drinking difficult; if you become dehydrated, you may need to receive fluids through your vein
Poor digestion of food
Weight loss; if this is severe, you may need a tube placed into your stomach to provide nutrition
Rectal irritation
Urinary frequency and difficulty
Loss of pubic hair
Reddening and irritation of the skin in the treatment area

Less Likely But Serious

Rectal ulcer
Bleeding or narrowing of the rectum
Bloody urine
Pain, bleeding, and/or blockage of the stomach or other parts of the digestive system
Ureteral (tube connecting kidneys to the bladder) obstruction
Fistula (opening) forming between pelvic tissues

Reproductive 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 you prior to the initiation of this study. Ask about counseling and more information about preventing pregnancy. You should not nurse your baby while on this study.

Radiation to the pelvis will cause sterility, and you will not be able to become

pregnant after treatment. Young women will go through menopause, and medication will be given to help with the symptoms of menopause.

Risks Associated with Cisplatin

Very Likely

Decrease in blood counts which can lead to a risk of infection and bleeding.
Loss of appetite and/or taste; metallic taste in your mouth
Nausea and/or vomiting
Fatigue
Hearing loss or ringing in the ears
Numbness or tingling in the hands or feet

Less Likely

Muscle cramps or spasm
Loss of coordination
Involuntary movements or shaking
Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet
Facial swelling

Less Likely, But Serious

A decrease in the kidneys' ability to handle the body's waste, which may be permanent.
Allergic reactions which can cause difficulty breathing, fast heartbeat, and sweating
Decrease in liver function
Another cancer called Acute Leukemia

Risks Associated with Amifostine (part two only) [8/1/03]

Very Likely

Lowering of blood pressure
Decrease of calcium levels in the blood
Nausea and/or vomiting
Warm or flushed feeling
Tiredness
Chills or feeling cold
Sneezing
Dizziness
Sleepiness
Hiccups
A metallic taste in the mouth
Local skin reactions, such as redness, itching, pain, and/or swelling
Rash
Fever

Less Likely But Serious

Allergic reactions

Low blood calcium level, which could lead to tingling, muscle spasms, twitching, and in very rare cases, life threatening spasms of the throat, seizures, and/or heart failure

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. 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 your tumor and prolongation of your life, but this is not guaranteed.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: *(1)* radiation therapy; *(2)* chemotherapy; *(3)* no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG).* Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration *(FDA),* the National Cancer Institute *(NCI),* qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

The amisfostine in part two will be provided free of charge for study patients by the pharmaceutical company.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

_____	_____
Name	Telephone Number

For information about this study, you may contact:

_____	_____
Name	Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

_____ _____
Name Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

Visit the NCI's Web sites for comprehensive clinical trials information
http://cancertrials.nci.nih.gov or for accurate cancer information including PDQ
http://cancernet.nci.nih.gov.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol *(full study plan)*.

_____ _____
Patient Signature *(or legal Representative)* Date

TISSUE AND BLOOD TESTING *(RTOG 0116) (4/30/04)*

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

☐ Yes ☐ No

_____ _____
Patient Signature *(or legal Representative)* Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

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

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

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

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20)*.

APPENDIX III

STAGING FOR CERVIX CANCER
(AJCC, 1997)

TNM CATEGORIES
Primary Tumor *(T)*

TNM	FIGO	DEFINITION
TX	**-**	Primary tumor cannot be assessed
T0	**-**	No evidence of primary tumor
T*is*	**0**	Carcinoma *in situ*
T1	**I**	Cervical carcinoma confined to uterus *(extension to corpus should be disregarded)*
T1a	**IA**	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.
T1a1	**IA1**	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread.
T1a2	**IA2**	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less.
T1b	**IB**	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2.
T1b1	**IB1**	Clinically visible lesion 4.0 cm or less in greatest dimension.
T1b2	**IB2**	Clinically visible lesion more than 4.0 cm in greatest dimension.
T2	**II**	Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina
T2a	**IIA**	Tumor without parametrial invasion
T2b	**IIB**	Tumor with parametrial invasion
T3	**III**	Tumor extends to the pelvic wall, and/or involves the lower third of the 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

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	T*is*	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
	T2	N1	M0
	T3a	NI	M0
	T3b	Any N	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

APPENDIX IV

NCI Common Toxicity Criteria for Local/Generalized Cutaneous Skin Reactions				
	Grade			
	1	**2**	**3**	**4**
LOCAL REACTIONS:				
Injection site reaction	Pain or itching or erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe or prolonged, or requiring surgery	---
GENERALIZED REACTIONS:				
Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	Symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	Generalized exfoliative dermatitis or ulcerative dermatitis
Pruritus	Mild or localized, relieved spontaneously or by local measures	Intense or widespread, relieved spontaneously or by systemic measures	Intense or widespread and poorly controlled despite treatment	---
Urticaria (hives, welts, wheals)	Requiring no medication	Requiring PO or topical treatment or IV medication or steroids for <24 hours	Requiring IV medication or steroids for ≥24 hours	---
Erythema multiforme	---	Scattered, but not generalized eruption	Severe or requiring IV fluids (e.g., generalized rash or painful stomatitis	Life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support

APPENDIX IV (Continued)

Management of Local Skin Reactions Following Subcutaneous Amifostine

NCI CTC Grade	Toxicity Management Schema	Schedule of Amifostine
Grade 1	**Consult dermatologist**; rotate injection site, treat with local measures (warm moist compress). Treat with daily administration of oral antihistamine *(such as diphenhydramine, Zyrtec® or other antihistamine of choice)*[a]	Continue
Grade 2	**Consult dermatologist**; treat with PO or IV glucocorticoids *(with or without antihistamines)* until recovery to Grade 1 or 0, then continue to treat with daily administration of oral antihistamine[a,b]	Continue
Grade 3 or 4	**Consult dermatologist**; treat with appropriate dressings, debridement etc, and as needed for secondary infection, phlebitis, etc. Typically, treatment of these patients would include IV glucocorticoids, with or without antihistamine.	Discontinue[b]

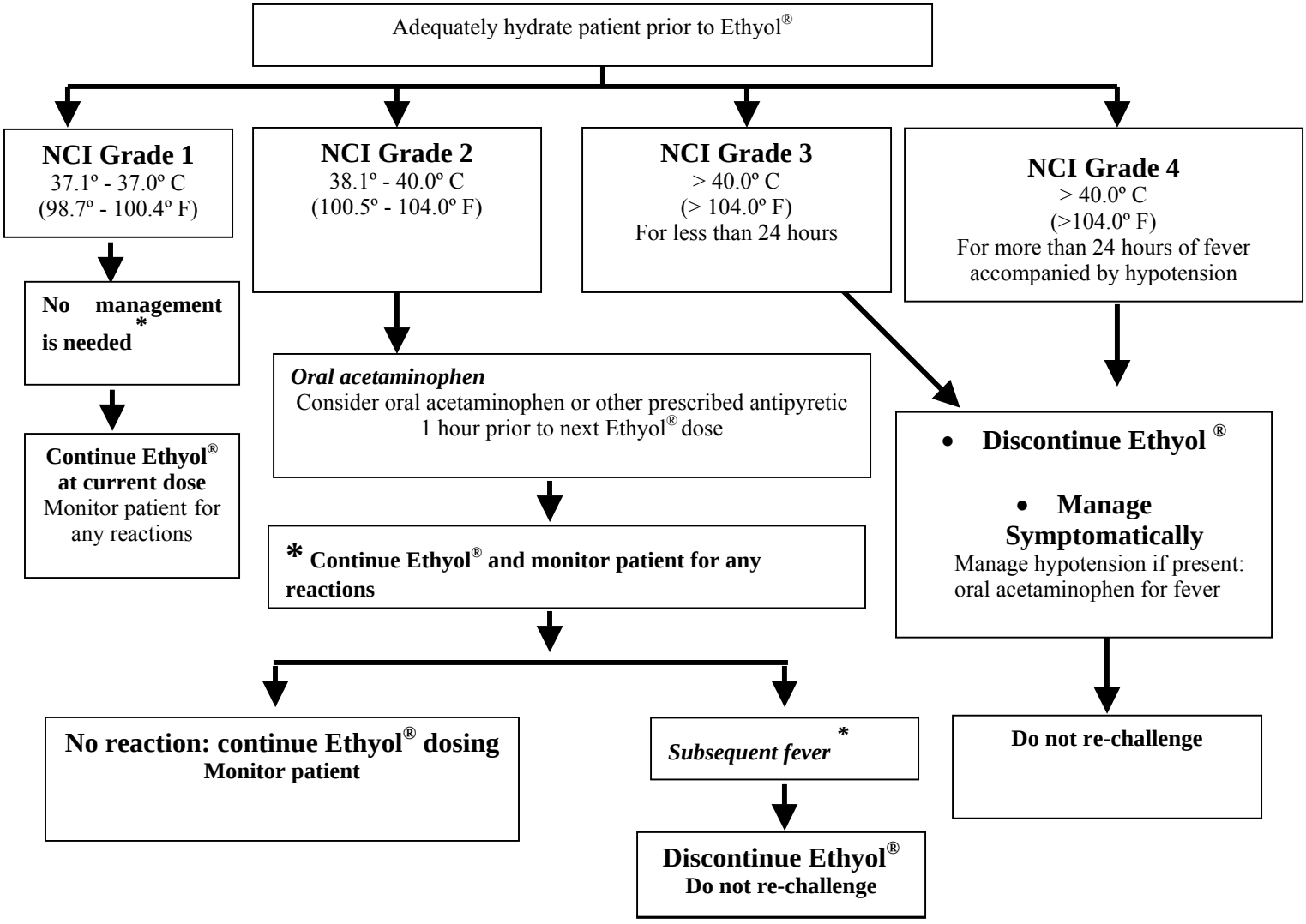
[a] Continue daily administration of PO antihistamine until discontinuation of amifostine or completion of amifostine treatment.

[b] Continue scheduled radiation treatment, if indicated.

APPENDIX V

MANAGEMENT OF FEVER*

Side Effects Associated with Ethyol® Administration



*Amifostine should be permanently discontinued for any cutaneous reaction associated with fever or any constitutional symptoms not known to be due to another etiology.

APPENDIX VII (8/1/03)

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

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

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

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

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

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

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

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

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

Investigational Agents

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

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

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **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 10 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 VIII (9/15/03, 4/30/04)

RTOG 0116

STUDY AGENT SHIPMENT FORM *(For Patients Registered to ARM 2)*

Specialty Pharmacy Services *(SPS)* will ship amifostine only to institutions who have completed this form and returned it to the CTSU Regulatory Office with the institution's State Board of Pharmacy License OR the Principal Investigator's DEA License to as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first patient **to Arm 2** of this study. Allow adequate processing time *(7-10 days)* before calling to randomize your first patient **to Arm 2**.

SHIP TO:

Name: _____

Address: _____
(No P.O. Box numbers)
_____
_____
_____

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____
(Attach copies of the institution's State Board of Pharmacy License OR the Principal Investigator's DEA License)

Investigator *(PI)* Signature _____ Date: _____

Investigator Name *(Print)* _____

Investigator NCI # *(Required)* _____

Return to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
(Fax 215-579-0206)

RTOG Headquarters Approval _____ Date: _____

APPENDIX IX (8/1/03, 4/30/04)

RTOG 0116

High Dose Rate Intracavitary Brachytherapy Guidelines

I. Schedule

1. HDR brachytherapy may begin as early as week two of external beam radiotherapy.

2. HDR procedures can be performed once or twice per week with a minimum separation of two days. It is important to avoid prolongation of the overall treatment time beyond fifty-six days. Whether one or two HDR fractions are given per week, the external beam irradiation to the whole pelvis should not be given the same day as the HDR fraction.

II. Dose Specification

1. Localization orthogonal x-rays of the applicator system should be obtained for each fraction for dosimetry calculations and dose optimization without and with rectosigmoid contrast.

2. Dose per fraction for the HDR brachytherapy course will be specified at POINT A.

3. The vaginal surface dose shall be defined opposite the dwell positions in each ovoid at a distance equal to the radius of the ovoid. For the ring applicator, the surface dose points on the ring are measured 6 mm laterally from each dwell position on each side of the ring. For the tandem and cylinder, the dose will be calculated at the cylinder surface, which generally has a radius between 1.0 and 2.0 cm.

4. Normal tissue dose points will include one rectal dose point. A point adjacent to the applicator system at 0.5 cm posterior to the vaginal applicator in the lateral projection as has previously been described in the RTOG protocols. Bladder dose may be calculated at a point on the surface of a contrast-filled balloon of a Foley catheter closest to the system on a lateral view.

III. Brachytherapy Dose

1. The recommended HDR brachytherapy dose in this study will be 6.0Gy for 5 fractions to point A. Other schedules are provided in Table #1, (below) if a midline block is utilized. If a midline block is used the dose to point A will be based on the external beam dose.

2. The vaginal surface dose should be approximately 140% of the point A dose.

3. Maximum doses to the rectum should be less than 70% of the point A dose. Maximum doses to the bladder should be less than 80% of point A.

IV. Treatment Data Requirements

1. AP and lateral x-rays without and with rectosigmoid contrast of each brachytherapy fraction are required.

2. Copies of dosimetry and computer data for each brachytherapy fraction are required.

APPENDIX IX (Continued)

Table 1-Equivalent Doses for Tumor and Late Effects for Doses of EBRT and HDR Brachytherapy used in Cervical Cancer if midline block is utilized

EBRT (Gy) @ 1.8 Gy/fx	# of HDR fractions	HDR dose/fx
19.8	7	6.7
19.8	6	7.4
39.6	5	6.6
39.6	6	5.8
45	5	6.0-6.5*
45	6	5.3-5.8*
50.4	4	7.0*
50.4	5	6.0*
50.4	6	5.3*

*these doses are used in treating larger, more advanced tumors

APPENDIX IX (Continued)

RTOG GYNECOLOGICAL BRACHYTHERAPY PROTOCOL COMPLIANCE FORM

Institution Name:_____ RTOG #:_____ Protocol:_____

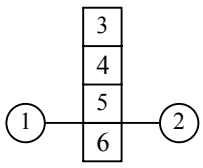
	Name	Phone #	E-mail address
Oncologist:		( )	
Physicist:		( )	
Dosimetrist:		( )	
Data Manager:		( )	

External Beam:
Start date of external beam: __/__/__ End date of external beam:__/__/__.
Whole pelvis dose: _____(Gy)
Boost dose: _____(Gy)
Non-pelvic lymph node boost dose: _____(Gy)

Brachytherapy:
Treatment Type: ☐ LDR ☐ HDR Number of insertions:_____
Nuclide: ☐ Cs^{137} ☐ Ir^{192} ☐ Other _____

Insertion #	Date	A_R (Gy)	A_L (Gy)	B_R (Gy)	B_L (Gy)	Rectum (Gy)	Bladder (Gy)	Magnification Factor AP Film	**Lat. Film**
_____	__/__/__	___.___	___.___	___.___	___.___	___.___	___.___	_____	_____
_____	__/__/__	___.___	___.___	___.___	___.___	___.___	___.___	_____	_____
_____	__/__/__	___.___	___.___	___.___	___.___	___.___	___.___	_____	_____
_____	__/__/__	___.___	___.___	___.___	___.___	___.___	___.___	_____	_____
_____	__/__/__	___.___	___.___	___.___	___.___	___.___	___.___	_____	_____
	Total Dose:	___.___	___.___	___.___	___.___	___.___	___.___		

Source loading for LDR implants:



Source	Activity (mgRaeq)	**Total Hours** (hrs.)	**Active Length** (mm)	**Physical Length** (mm)	**Spacer Length** (mm)
Oviods					
1	_____	_____	_____	_____	_____
2	_____	_____	_____	_____	_____
Tandem					
3	_____	_____	_____	_____	_____
4	_____	_____	_____	_____	_____
5	_____	_____	_____	_____	_____
6	_____	_____	_____	_____	_____

Submit the following information:

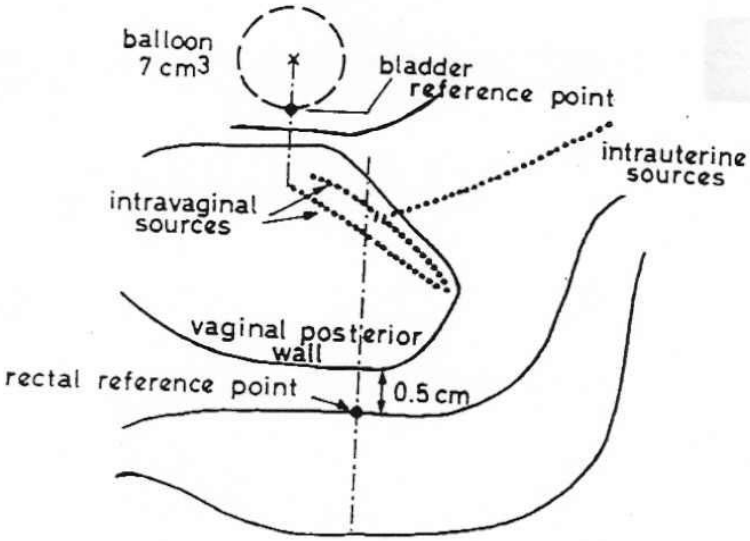
- ☐ AP and lateral orthogonal films for all insertions.
- ☐ Treatment plans for all insertions.(i.e. isodose distributions, all calculations)
- ☐ Activity, dwell times, dwell positions. (HDR only)

APPENDIX X (4/30/04)

RTOG 0116

ICRU #38 Point Dose Definition

Description of ICRU Bladder/Rectal Dose Reporting Points

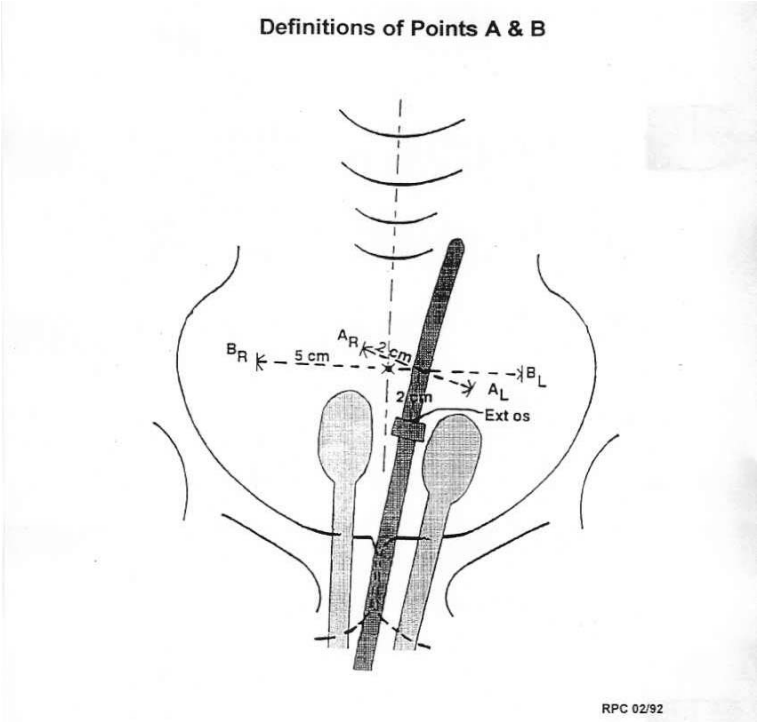


The *bladder reference point* is obtained as follows. A Foley catheter is used. The balloon must be filled with 7 cm^3 of radio-opaque fluid. The catheter is pulled downwards to bring the balloon against the urethra. On the lateral radiograph, the reference point is obtained on an anterio-posterior line drawn through the center of the balloon. The reference point is taken on this line at the posterior surface of the balloon. On the frontal radiograph, the reference point is taken at the center of the balloon.

The *point of reference for the rectal dose* is obtained as follows. On the lateral radiograph, an anterio-posterior line is drawn from the lower end of the intrauterine source (or from the middle of the intravaginal sources). The point is located on this line 5 mm behind the posterior vaginal wall. The posterior vaginal wall is visualized, depending upon the technique, by means of an intravaginal mould or by opacification of the vaginal cavity with a radio-opaque gauze used for the packing. On the AP radiograph, this reference point is at the lower end of the intrauterine source or at the middle of the intravaginal source(s).

ICRU REPORT 38, March 1, 1985

APPENDIX X (4/30/04) (Continued)

RTOG 0116

ICRU #38 Point Dose Definition