

#88-032

GYNECOLOGIC ONCOLOGY GROUP • HEADQUARTER:

OPERATIONS OFFICE 1234 MARKET STREET • SUITE 1945 • PHILADELPHIA, PA 19107 • 215-854-0770
STATISTICAL OFFICE R.P.M.I. APTS • R.P.M.I. • 666 ELM STREET • BUFFALO, NY 14263 • 716-845-5702

PROTOCOL GOG #92

TREATMENT OF SELECTED PATIENTS WITH STAGE IB CARCINOMA OF THE
CERVIX AFTER RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY:
PELVIC RADIATION THERAPY VERSUS NO FURTHER THERAPY

(SPECIAL CATEGORY - 12 CREDITS PER ENTRY FOR RANDOMIZED PATIENTS)

STUDY CHAIRMAN

NAV1.954715.002

ALEX SEDLIS, M.D.
STATE UNIVERSITY OF NEW YORK
DOWNSTATE MEDICAL CENTER
450 CLARKSON AVENUE
BROOKLYN, NEW YORK 11203
(718) 270-2531

STUDY CO-CHAIRMEN

MARVIN ROTMAN, M.D.
STATE UNIVERSITY OF NEW YORK
DOWNSTATE MEDICAL CENTER
450 CLARKSON AVENUE
BROOKLYN, NEW YORK 11203
(718) 270-1591

RICHARD J. ZAINO, M.D.
HERSHEY M.S. MEDICAL CTR
OF THE PENNSYLVANIA
STATE UNIVERSITY
500 UNIVERSITY DRIVE
PO BOX 850
HERSHEY, PA 17033
(717) 531-8246

ACTIVATED FEBRUARY 8, 1988
ACTIVATED IN GOG FORMAT JULY 2, 1990

S C H E, M A

		R	
S		A	
T	Size of lesion	N	
R	1. > 4 cm	D	ARM 1: Pelvic RT (see section 6.0)
A	2. ≤ 4 cm	O	
T		M	
I	Capillary-Like Space	I	ARM 2: No Further Treatment
F	1. Positive	Z	
Y	2. Negative	E	

Depth of Invasion

1. Superficial
2. Middle Third
3. Deep Third

Eligible: Stage: IB confined to the cervix and corpus.
 Histology: Squamous, adenocarcinoma, adenosquamous.

Positive capillary - lymphatic (CL) space involvement and either deep third penetration, middle third penetration with clinical tumor ≥ 2 cm or superficial third penetration with clinical tumor ≥ 5 cm.

or

Negative CL space involvement and either deep or middle third penetration with clinical tumor ≥ 4 cm

APPENDIX IV

RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMYPurpose

- 1) Surgical cure of carcinoma of the cervix, upper vagina or endometrium.

Indications

- 1) Invasive cervical carcinoma clinically confined to the cervix or upper vagina.
- 2) Invasive vaginal carcinoma clinically confined to the upper vagina.
- 3) Endometrial carcinoma extending to the cervix.

Contraindications

- 1) More advanced stages of disease. (surgical or clinical).
- 2) Poor surgical risk patient.
- 3) Inadequate facilities and/or personnel.

Content of Procedure

A) Pelvic Lymphadenectomy

Bilateral removal of all nodal tissue and skeletonization of all vessels from the mid portion of the common iliac artery to the circumflex iliac vein; laterally, from the mid portion of the psoas muscle to ureter medially including the hypogastric artery and vein and from the obturator fossa anterior to the obturator nerve.

B) Radical Hysterectomy

Removal of the uterus and contiguous parametrial tissue to its most lateral extent along with para-vaginal tissue and upper 1/4 of the vagina along with the proximal utero-sacral ligaments. The uterine artery should be transected at its origin lateral to the ureter. The ureter must be unroofed from its entry into the broad ligament to its intramural portion in the bladder and dissected laterally from its attachment to the cardinal ligament.

APPENDIX IV

Radical Hysterectomy and Pelvic Lymphadenectomy
(Cont'd.)

ADVERSE EFFECTS THAT MAY BE ASSOCIATED
WITH AN UNEVENTFUL PROCEDURE

SYSTEM

GRADE
(up to and including)

Hematopoietic	2
Genitourinary	1
Gastrointestinal	1
Hepatic	1
Pulmonary	1
Cardiovascular	1
Peripheral Neurologic	1
Central Neurologic	0
Cutaneous	2
Lymphatics	1
Fever	2
Allergic	0

#88-032

Radiation Therapy Oncology Group

RTOG 87-06
GOG #92

TREATMENT OF SELECTED PATIENTS WITH STAGE 1B CARCINOMA OF THE CERVIX
AFTER RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY:
A RANDOMIZED COMPARISON OF PELVIC RADIATION THERAPY
VERSUS NO FURTHER TREATMENT

Schema

S T R A T I F Y	<p>Size of lesion</p> <ol style="list-style-type: none"> 1. > 4cm 2. ≤ 4cm <p>Capillary-Like Space</p> <ol style="list-style-type: none"> 1. Positive 2. Negative <p>Depth of Invasion</p> <ol style="list-style-type: none"> 1. Superficial 2. Middle Third 3. Deep Third 	R A N D O M I Z E	<p>ARM 1: Pelvic RT (see section 6.0)</p> <p>ARM 2: No Further Treatment</p>
--------------------------------------	--	---	--

Eligible:

Stage : IB confined to the cervix and corpus.
Histology: Squamous, adenocarcinoma, adenosquamous.

Positive capillary - lymphatic (CL) space involvement and either deep third penetration, middle third penetration with clinical tumor ≥ 2 cm or superficial third penetration with clinical tumor ≥ 5 cm.

or

Negative CL space involvement and either deep third penetration with clinical tumor ≥ 4 cm or middle third penetration with clinical tumor ≥ 4 cm.

1.0 BACKGROUND AND RATIONALE

Stage I cervical cancer has assumed increased importance for gynecologic oncologists because of the rising proportion of early stages among patients with invasive cervical cancer. According to the latest FIGO report¹, there has been a continuous increase in the proportion of Stage I disease, possibly because of improved early detection. Although the majority of patients with Stage I cancer are cured with radical hysterectomy and pelvic lymphadenectomy or with radiotherapy, the 20% mortality in these patients has not improved during the last two decades.

Some high risk factors responsible for treatment failure have been identified. Pelvic lymph node metastases, for example, have been known to decrease the five year survival from 82-90% in patients with negative nodes to 38-61% in patients with positive nodes².

Other high risk factors, although recognized have not been investigated as extensively as the positive lymph nodes (Table I). Large tumor size has been associated with a high incidence of recurrence^{3,4,5}. According to Chung et al³, a tumor size greater than 4 cm determined by preoperative clinical examination was associated with a five-fold increase in pelvic node metastases, a ten-fold increase in recurrence rates and a 50% decrease in survival when compared to tumors less than 4 cm in size.

Tumor size has also been measured as the depth of tumor penetration into the cervical stroma. In several studies^{3,6,7,8}, depth of penetration (measured either in millimeters or as a percent of the total thickness) has been shown to be associated with increasing frequency of pelvic node metastases and recurrence and poorer survival. Depth of penetration of the tumor measured directly on the histologic material is the most objective method of estimating tumor size and can be evaluated relatively easily by outside pathologists in a cooperative study group.

Vascular or lymph channel penetration by tumor has been recently identified as a high risk factor^{3,4,6,7,9}. It was found in association with the rise in the local recurrence rate from 5-8% to 25-34% and a decrease in the survival rate from 94% to 50-74%. In the GOG¹⁰ study of microinvasive carcinomas of the cervix, two of 31 patients with vascular invasion developed recurrences.

Corpus extension has also been suggested as a high risk factor. Perez¹¹ reported drop in survival from 84% to 50% in patients with corpus involvement. Boyce⁴ reported a five year survival of only 56% in patients with negative pelvic nodes and corpus extension.

When the pelvic nodes are negative, a single high risk factor does not worsen the prognosis sufficiently to justify irradiating all patients. Sedlis et al¹⁰ in the GOG study found 97% survival in subjects with vascular invasion but less than 5mm depth of invasion (microinvasion). Boyce et al⁴ reported that in 11 cases with stromal penetration greater than 10mm but no vascular invasion and in three cases with vascular invasion but less than 10mm penetration, there were no recurrences. However, if both deep penetration and lymphovascular invasion were present, there were recurrences in 30% and the five year survival fell to 80%. Therefore, in this protocol a patient will be eligible only if two high risk factors are present.

A preliminary analysis of the outcome of patients with Stage IB cancer of the cervix who were entered into GOG Protocol 49A and had a radical hysterectomy and pelvic lymph node dissection, has shown that in patients with cancer confined to the uterus, vascular invasion, deep invasion and large clinical size are all predictive of a poor outcome.

The results of fitting Cox's proportional hazard model to these data yielded 3 factors: capillary-lymphatic space involvement (C/L space), maximum clinical size of the tumor (clin. tumor) and the depth of penetration in thirds (penetration). It is important to note that the depth of penetration in millimeters was a prognostic factor by itself but the depth evaluated in the thirds was far superior. The three factors mentioned have special importance in that no other factors listed above could further discriminate risk of recurrence.

TABLE 1

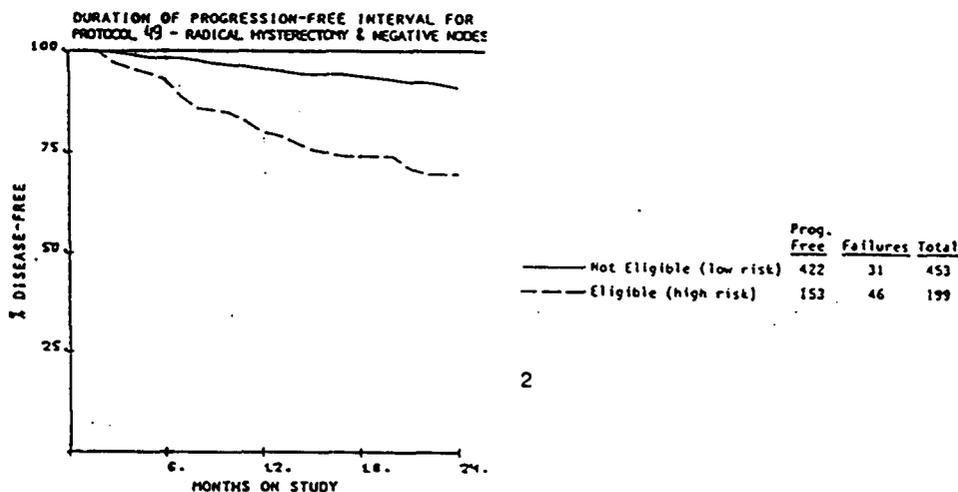
STAGE I CARCINOMA OF THE CERVIX: FACTORS INFLUENCING PROGNOSIS

Prognostic Factors	% Positive Nodes			Recurrence			Survival **				
	(3)	(4)	(5)	(3)	(4)	(5)	(3)	(4)	(5)	(11)	
CLINICAL SIZE											
> 4 cm			80%			40%				47%	
< 4 cm			16%			4%				92%	
DEPTH OF INVASION											
> 70% thickness			40%			27%				67%	
< 70% thickness			13%			4%				93%	
11-15 mm			33%			31%				72%	
< 11 mm			5%			4%				96%	
VASCULAR INVASION											
Present			63%	39%	34%	25%	31%	34%	50%	69%	73%
Absent			13%	4%	6%	5%	8%	8%	94%	94%	93%
CORPUS EXTENSION											
Present						56%			55%	50%	
Absent						3%			95%	84%	

- * Numbers in parentheses indicate studies referred to in bibliography.
- ** Five year survival, except for reference(3) which is two year survival.

Essentially, these three factors taken together contain all the information about prognosis that reside among all the factors above. The relative risk is essentially the chance of recurrence at any instant of time relative to the patient with no capillary-lymphatic space involvement, superficial third depth of penetration, and clinically occult tumor at the same instant of time. Discriminating between high and low risk is arbitrary; the only guide in this situation is to include as high risk those factors that indicate a significant chance of recurrence while at the same time keeping the high risk group large enough to make a randomized study feasible. However, as stated before the distinction between high and low risk is arbitrary. Thus, for convenience of eligibility, the tumor size should be rounded off to the nearest centimeter.

FIGURE 1



The patients with positive capillary-lymphatic space involvement and one of the following are at high risk:

- A. Deep third penetration
- B. Middle third penetration, clinical tumor ≥ 2 cm
- C. Superficial third penetration, clinical tumor ≥ 5 cm

The patients with negative capillary-lymphatic space involvement and one of the following are at high risk:

- A. Deep third penetration, clinical tumor ≥ 4 cm
- B. Middle third penetration, clinical tumor ≥ 4 cm

The progression free interval (PFI) for this high risk group 2 years is 69% which is almost a 1:3 chance of recurrence within 2 years.

2.0 OBJECTIVES

- 2.1 To determine the value of adjunctive pelvic radiation in the treatment of Stage IB carcinoma of the cervix, but with selected high-risk factors.
- 2.2 To determine the recurrence-free interval, survival and patterns of failure in these patients.
- 2.3 To determine the morbidity of adjunctive pelvic radiation following radical hysterectomy.

3.0 PATIENT SELECTION

3.1 ELIGIBLE PATIENTS

3.1.1 Patients with primary, histologically-confirmed invasive carcinoma of the uterine cervix Stage IB (Appendix II) who have undergone radical hysterectomy and pelvic lymphadenectomy including peritoneal cytology as described in Appendix IV.

3.1.2 The following histologic types of cancer are eligible:

- Squamous carcinoma
- Adenocarcinoma
- Adenosquamous carcinoma

3.1.3 Patients with carcinoma confined to the cervix and corpus.

3.1.4 Patients with the following characteristics (depth of stromal invasion and lymphovascular space involvement to be pathologically confirmed):

Positive Capillary-lymphatic space involvement and one of the following:

- A. Deep third penetration
- B. Middle third penetration, clinical tumor ≥ 2 cm
- C. Superficial third penetration, clinical tumor ≥ 5 cm.

or

Negative Capillary-lymphatic space involvement and one of the following:

- A. Deep third penetration, clinical tumor ≥ 4 cm
- B. Middle third penetration, clinical tumor ≥ 4 cm

3.1.5 Patients who have signed the informed consent.

3.1.6 Patients must have an Hgb ≥ 10 gm, WBC $\geq 3,000$ /ul, platelets $\geq 100,000$ /ul and creatinine ≤ 2.0 . Alkaline phosphatase, SGOT and bilirubin levels cannot be greater than 2 times normal range.

3.1.7 Patients must have a KPS ≥ 40 .

3.1.8 Patients should be randomized not prior to 3 weeks post-surgery but will not be acceptable for randomization more than 6 weeks post-surgery.

3.1.9 Patients who have met the pre-entry requirements listed in Section 11.0.

3.2 Ineligible Patients

3.2.1 Patients with histologic types other than squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix.

3.2.2 Patients with tumor in the parametria, pelvic lymph nodes or any other extra-uterine site or with surgical margins involved with tumor or positive peritoneal cytology.

3.2.3 Patients with past or concomitant cancer other than skin (except melanoma).

3.2.4 Patients with WBC $< 3,000$ /ul, Hgb < 10 gms, or platelet count $< 100,000$ /ul.

3.2.5 Patients with septicemia, or severe infection.

3.2.6 Patients with intestinal obstruction or gastrointestinal bleeding.

- 3.2.7 Patients with postoperative fistula.
- 3.2.8 Patients with cervix cancer who have received any previous radiation or chemotherapy.
- 3.2.9 Patients with significant impairment of hepatic or renal function (creatinine > 2, alkaline phosphatase, SGOT, or bilirubin levels which are > 2 x normal).
- 3.3.0 Patients whose circumstances do not permit completion of the study or the required follow-up.
- 3.3.1 Patients with renal abnormalities requiring modification of radiation fields (pelvic kidney, renal transplant, etc.).
- 3.3.2 Patients with a Karnofsky < 40.
- 3.3.3 Post-surgical period greater than 6 weeks.

4.0 PRE-TREATMENT EVALUATIONS

- 4.1 The following pre-treatment evaluations are mandatory:
 - History and physical examination
 - Tumor Measurements and clinical staging
 - Hemoglobin, WBC, Platelets
 - Creatinine, Alkaline Phosphatase, SGOT, Bilirubin
 - Chest X-ray, CT with contrast
- 4.2 The following pre-treatment evaluations are optional:
 - Proctoscopy
 - Cystoscopy
 - Barium Enema
 - IVP
 - Lymphangiogram

5.0 RANDOMIZATION

An original, signed Form HHS-596, indicating prior approval by the institution's Human Rights or Clinical Trials Committee for participation in this study must be forwarded to your group Operations Office before patient entries onto the study will be accepted. In addition, a copy of the informed consent being used (if it differs from the suggested form appended to the protocol) must accompany the HHS-596.

5.1 Telephone Entry/Randomization

When a candidate is suitable for protocol entry and has fulfilled the eligibility requirements according to Section 3.0, the institution should phone the randomization desk for its cooperative group and provide the following information;

Patient name
 Patient ID number
 Doctor's name
 Institution
 Eligibility check information
 Stratification information

RTOG Institutions: call (215)574-3191, Monday through Friday from 8:30 am to 5:00 pm ET.

GOG Institutions: Call the GOG Operations Office in Philadelphia via the "WATS" Line, 1-800-523-2917, Monday through Friday, 9 a.m. to 5 p.m. EST/EDT. In Pennsylvania, call 1-215 (where applicable) 854-0722. GOG will then relay this information to RTOG. RTOG will provide the treatment assignment and case number (see Appendix V).

RTOG will confirm all case numbers and treatment assignments by mail.

5.2 Treatment Plan

Patients who meet the eligibility requirements according to Section 3.0 will be assigned randomly to one of the two regimens:

Arm I: Pelvic Radiation Therapy (see Section 6.0)
Arm II: No further therapy

6.0 Radiation Therapy

- 6.1 All patients receiving radiation therapy should have therapy started within four to six weeks postoperatively or at time of complete healing.
- 6.2 Patients receiving whole pelvic irradiation will receive therapy within a range spreading from 46 Gy in 23 fractions of 2 Gy daily to 50.40 Gy in 28 fractions of 1.8 Gy daily, with the dose delivered homogeneously to the whole pelvis. Each patient will be given daily treatments (five fractions per week) and daily increments of 1.8 - 2 Gy calculated dose. Each field is to be treated at every fraction when using CO-60 or less than 10 MV photons. A maximum of 30.60 GY may be delivered to the pelvis through opposing anterior-posterior portals. A minimum of 19.80 Gy may be delivered through opposing lateral portals. The total period of treatment will be 4 1/2-6 weeks. Brief breaks from therapy are allowed for particular clinical problems, such as severe nausea, vomiting and acute diarrhea leading to dehydration, or WBC's less than 2,000. Treatment breaks should not total more than 1 week.
- 6.2.1 Doses should be calculated at the center of the target volume. For the following portal arrangements, the target dose shall be specified as follows:
- For two coaxial equally weighted beams: on the central ray at mid-separation of the beams.
 - For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.3 Radiation Therapy Delivery:

- 6.3.1 Radiation therapy will be delivered by means of Cobalt-60 teletherapy or other supervoltage treatment which allows treatment at 80 cm SSD or greater.
- 6.3.2 Treatment Volume: Should be simulated prior to the initiation of treatment. Obturator, hypogastric and external iliac lymphatics must be included in the treatment portal. The following boundaries shall be maintained:
- Superior - The upper margin of L5.
 - Inferior - The upper third of the obturator foramen.
 - Lateral - At least 1 cm beyond the lateral margins of the bony pelvis at the widest plane through the pelvis.
- Lateral Field Borders - Superior and inferior borders same as above. Anterior border - transverse line through pubic symphysis. Posterior border at least 4 cm. beyond cervical marker. The minimum anterior-posterior dimension of lateral field is 9 cm.
- NB: A marker should be placed at the vaginal apex to insure its inclusion in the field.
- 6.3.3 All fields treated require simulation and beam verification films. Copies of these are to be submitted to your cooperative group.
- 6.3.4 Treatment portals may be changed to include pelvic lymphatic visualized by lymphography which are not within routine portals.
- 6.3.5 An isodose distribution through the center of the pelvis will be obtained and submitted to your cooperative group.
- 6.3.6 Critical Structures - Bladder and Rectum. The base of the bladder and the anterior rectal wall of the rectum will, by necessity, receive the same dose as the cervix.

6.4 Expected Toxicity

- 6.4.1 Gastrointestinal: Nausea and vomiting may occur after pelvic treatments, especially after the first few treatments. Patients may be pretreated with an anti-emetic agent such as Tigan 250 PO mg before each daily treatment. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is rarely seen as a result of radiation therapy alone. If necessary the dose rate during pelvic radiation may be decreased to .3 Gy/min. to improve GI tolerance.
- Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic radiation. It is recommended that instructions be given to patients for low fiber, low fat, bland diet. Most patients will require antidiarrheal medications such as Lomotil or Immodium to control diarrhea.
- Should GI toxicity become severe enough to require hospitalization for IV fluid replacement, radiation treatment should be discontinued upto 1 week until the patient's condition improves.

6.4.2 Hematologic toxicity of a mild nature will be seen frequently with a decline in WBC and less often platelet count. CBC should be obtained weekly, and if WBC falls below 2000 or platelet count below 100,000, CBC should be obtained twice weekly. If neutrophil count falls below 1000 or platelet count below 50,000 then treatment should be temporarily discontinued to allow recovery of blood counts above these level.

6.4.3 Hepatic toxicity should rarely occur. When seen, it will usually appear as marked fatigue usually without other symptoms. SMA-12 will show significant elevations of alkaline phosphatase, LDH, and SGOT with hyperbilirubinemia. Should this occur, it may require cessation of upper abdominal treatment and aspirin therapy. Such an occurrence is extremely unlikely.

6.5 Rapid Turnaround Review

Radiation Therapy Oncology Group will review pretreatment films, calculations, and plan of treatment. The following information must be sent to your cooperative group within 1 week after radiation therapy begins:

- Plan of treatment (dose prescription)
- Initial calculations
- Representative film of initial field

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

All patients will have had a radical hysterectomy and pelvic lymphadenectomy (Appendix IV) including peritoneal cytology. Para-aortic lymphadenectomy is not required. Prior to (within 2 months) or after surgery the patient will have a chest x-ray and IVP. Prior to surgery, all patients will have a complete history and physical examination and blood studies (CBC, differential, platelet count, creatinine, SGOT, alkaline phosphatase and bilirubin). Optional tests include proctoscopy, cystoscopy, barium enema, CT scan and lymphangiogram before or after surgery.

8.1 Operative Note

The standard, typed, hospital Operative Note for the radical hysterectomy and pelvic lymphadenectomy must be submitted. The operative note must indicate a description of the findings on abdominal and pelvic exploration. The surgeon must dictate, preferably in his introductory paragraph of the operative note, his measurements of the lesion size in two dimensions, the location of the lesion and the clinical status of the lymph nodes. Estimated blood loss of surgery and surgical complications must be included.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

A central pathology review is planned for this study. Representative stained slides must be submitted to your cooperative group office which display the deepest point of stromal invasion by tumor (assessable in 1/3 of total thickness) and capillary or lymphatic vascular space involvement is present. In addition, the Pathology Report and Form must specify histologic type, the histologic grade, the depth of stromal penetration in thirds and the presence of lymphovascular space involvement, corpus involvement, the total number and sites of lymph nodes examined and the status of the cervical margins. A report of the peritoneal cytology is also required.

10.1 Pathology Reporting Requirements

The standard typed diagnostic pathology report for the biopsy and the surgical pathology report, including radical hysterectomy, pelvic lymphadenectomy and peritoneal cytology. Representative slides must be submitted for hysterectomy, lymphadenectomy and any positive peritoneal cytology.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Observations and tests to be performed and recorded before, during and after treatment.

<u>Tests & Observations</u>	<u>Prior to Surgery</u>	<u>Prior to Radiotherapy</u>	<u>Every</u>	
			<u>3 months</u>	<u>6 months</u>
			<u>1st 2 yrs</u>	<u>3-5 yrs</u>
Physical Examinations	x	x	x	x
Tumor Measurements	x		x	x
Palpable Lesions	x			
Clinical Staging	x			

Tests & Observations	Prior to		Every	Every
	Surgery	Radiotherapy	3 months 1st 2 yrs	6 months yrs 3-5
Hemoglobin	x	x	x	x
WBC	x	x	x	x
Platelets	x	x	x	x
Creatinine	x	or	x	x
Alkaline Phosphatase	x	or	x	x
SGOT	x	or	x	x
Bilirubin	x	or	x	x
Chest x-ray	x		x(a)	x(a)
IVP or CT with contrast	x	or	x	x(b)
<u>Optional</u>				
Proctoscopy	x	or	x	
Cystoscopy	x	or	x	
Barium Enema	x	or	x	
Lymphangiogram	x	or	x	

(a) yearly

(b) at 6 months and then yearly

11.2 EVALUATION CRITERIA

11.2.1 Objective Response

The major parameters of response will be time to recurrence, survival and sites of recurrence.

11.2.1.1 Time to Recurrence

Response will be assessed by time to recurrence which is defined as the interval from date of entry on protocol to date of reappearance of disease.

11.2.1.2 Survival

Survival will be defined as observed length of life from entry on protocol to death or, for living patients, the date of last contact regardless of whether this contact is on a subsequent protocol.

11.2.1.3 Sites of Recurrence

Response will be assessed by site(s) of recurrence, specifically, local, in pelvic regions or distant, in relation to the original disease pattern and the therapy

11.2.2 Subjective Response

Performance Status will be recorded on the patient's record according to the standard Karnofsky Performance Scale (Appendix III).

12.0 DATA COLLECTION

All data collection materials must be submitted to the institution's cooperative group within the time specified. The cooperative group will then forward the data on to RTOG.

<u>Item</u>	<u>Time of Submission</u>
On Study Forms (I1)	Within 2 weeks of randomization
Initial Dosimetry Information Treatment Plan (T2) Dose Calculations (T4) Large Field Localization Film (T3)	Within 1 week of Rx start

Diagnostic Pathology Report (P1)
Surgical Pathology Report
including peritoneal cytology (S5)
Operative Report (S2)
Pathology Form (P4)
Surgical Form (S1)
Discharge Summary (W4)

Within 3 weeks of randomization

Final Dosimetry Information
Radiotherapy Form (T1)
Treatment Record (T5)
Isodose Distribution (T6)

Within 1 week of completion of treatment

Follow-up Form (F1)

Upon completion of protocol treatment, at progression, death and routinely every 3 months for 3 years, every 6 months for 2 years then annually.

13.0 Statistical Considerations

- 13.1 Randomization with equal probability to each of the treatment regimens will be carried out by a computer algorithm based upon the permuted block design within strata with balance across strata. When the patient assignment is found in the block, the institution which entered the cases is then examined with respect to the balance of treatment regimens. If there is a serious imbalance of treatment regimens within institution, the patient is assigned to the other treatment and that assignment is noted within the block. A manual system exists for back-up in the event of a computer malfunction.
- 13.2 The endpoints of the study include time to recurrence, survival, patterns of failure, morbidity and survival.
- 13.3 The anticipated annual accrual is approximately 80 patients based on GOG and RTOG projections.
- 13.4 The primary objective of the study is to determine if adjuvant radiotherapy lengthens the recurrence-free interval. If a 58% recurrence-free interval at 3 years (GOG protocol #49) is assumed and an increase of 15% (to 73% at 3 years) is to be detected with a power of 90% and a Type I error of 5% (one-sided), 147 cases per treatment arm would be required. Assuming that 10% of the cases will be ineligible or inevaluable, the total required accrual is 324 patients. This estimate assumes an accrual period of 4 years (at 80 patients per year) and an additional 1 1/2 years of follow-up. If a 10% death from causes other than disease is assumed the power will drop to 87%.
- 13.5 Interim analysis will be done twice a year to correspond with RTOG semi-annual meetings.
- 13.6 The final analysis will be done 1 1/2 years after the accrual phase.