

RTOG 76-08  
RADIATION THERAPY ONCOLOGY GROUP

NEUTRON THERAPY  
IN THE TREATMENT OF  
SQUAMOUS CELL CARCINOMA OF THE  
UTERINE CERVIX

*closed*

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NEUTRON THERAPY

Carcinoma of the Uterine Cervix

S T R A T I F Y

R A N D O M I Z E

Stage *IB*  
IIIA  
IIIB  
IVA

Paraaortic Nodes on  
lymphangiogram

Negative  
Equivocal

Institution

Total pelvis treatment:

- A. Photons only: 5000 rad/5-5½ wks.
- B. Mixed: 5000 rad equivalent/5-5½ wks.  
3 photon - 2 neutron fractions/wk.
- C. Photons: ~~3000 rad/3-3½ weeks, then~~  
Neutrons: ~~2000 rad equivalent/2 wks.~~
- D. Neutrons only: ~~5000 rad equivalent/5-5½ wks.~~

1. All randomizations to be followed by intracavitary radium  
4000-5000 mg - hrs. with a Fletcher applicator or  
3000-4000 rad at 2 cm lateral to the cervical canal using other applicators.

2. Or if intracavitary radium not possible

1000-1600 rad or rad equivalent boost using randomized modality (neutrons for randomization C)

3. Field size - mid L5 to 2 cm below known disease (at least mid obturator foramen)

4. Photons: 180-200 rad/fraction (900-1000 rad/wk); 5 fractions/wk.  
5. An institution may select 2, 3, or 4 options but all must include A; geographic subsets may be selected within an institution.

6. 600 rad to involved side with reduced anterior and posterior fields (optional).

## 1.0 INTRODUCTION

1.1 Rationale for Combined Neutron & Photon Radiotherapy: In the past 25 years, advances in the field of radiotherapy have resulted in a substantial improvement in local control, while the incidence of normal tissue complications has declined. Nevertheless, a significant number of tumors continue to be locally incurable at doses within tissue tolerance, and improved control rates are achieved only at the cost of increased radiation sequelae. In the management of human cancer, both the duration and quality of survival are important. Fast neutrons have been proposed as a means of improving the control of bulky tumors while keeping radiation injury to a minimum.

The principal rationale for fast neutron radiotherapy is related to the hypoxic cell problem. Numerous radiobiological studies have shown that hypoxic cells are 2.5 to 3.0 times (OER\*) more resistant to the effects of conventional X and gamma irradiation than are well oxygenated cells. While the cells in most normal tissues are well oxygenated, most solid tumors have hypoxic regions which have outgrown their vascular supply. It has been postulated that these cells remain viable and provide a focus for local recurrence. With neutrons, radiosensitivity is less dependent upon the state of oxygenation.

\*Oxygen enhancement ratio (OER) refers to the ratio of the radiation dose required to produce a specified biologic effect under anoxic conditions to the dose required to produce the same effect under well oxygenated conditions.

Although fast neutrons are theoretically superior to photons radiobiologically, the physical properties of neutron beams are significantly inferior to those of high energy photon beams:

- 1) Poor skin sparing and depth dose - The dosimetric properties of the clinical neutron beams are compared with those of high energy photon beams in Table I. The depth dose and skin sparing qualities of the most energetic neutron beams are approximately the same as those of  $^{60}\text{Co}$  - a beam which is marginal at best for the treatment of advanced pelvic neoplasms.
- 2) Horizontal beam - All current neutron facilities employ a horizontal beam. Therefore, patients must be treated in a standing position which results in an increased patient diameter. This makes a poor penetration of neutron beams even more significant.
- 3) Increased absorption in fat - Bewley (<sup>1</sup>) has shown that fat absorbs approximately 18% more energy with neutrons than water density tissue. This factor could lead to increased subcutaneous fibrosis.

Castro et al (<sup>2</sup>) have shown that doses of 6000-7000 rads are required to achieve even modest control rates of extensive carcinomas of the cervix. Fast neutron doses equivalent to 6000-7000 rads would result in significant subcutaneous fibrosis and a high risk of major complications. Consequently, any radiobiological advantage of fast neutron beams might be masked by the poor dose distribution.

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This protocol therefore uses a mixed beam of neutrons and high energy photons in one arm in an attempt to improve the local control rate of advanced cervical carcinoma. The objectives are: 1) to take advantage of the radiobiological properties of neutrons by irradiating with neutrons twice weekly throughout the course of treatment; and 2) to take advantage of the dose distribution properties of high energy photons by irradiating with photons three times weekly. In this manner the study will use conventional five times weekly fractionation.

TABLE I.

	<u>Neutrons</u> (Deuteron energy-MeV)				<u>Photons</u>		
	<u>16</u>	<u>21.5</u>	<u>35</u>	<u>50</u>	<u><sup>60</sup>Co</u>	<u>10MeV</u>	<u>25MeV</u>
Depth of D max (cm) (10x10cm Fld)	.2	.3	.5	1.0	.5	2.4	3.9
Depth of 50% dose	8.3	9.6	12.1	13.0	11.4	18.	22.

1.2 Scope of the Problem: Locally advanced carcinomas of the uterine cervix are among the more suitable tumor populations for a clinical trial of fast neutron therapy. The local control rate for patients with stage III-IV carcinoma of the cervix with conventional radiotherapy continues to be low and

death is usually due to local failure. Of approximately 10,000 deaths due to cervical cancer in 1968, 60% of the patients had local failure as the major cause of death. In addition, these tumors are frequently ulcerated and necrotic and would be expected to contain a significant hypoxic compartment. Local recurrences usually occur within 2 years, allowing an early appraisal of results.

A pilot study at the M.D. Anderson Hospital included 51 patients with Stage IIB, IIIA, IIIB or IVA carcinoma of the cervix who were treated with either neutrons alone, photons followed by a neutron boost or a mixed beam (3). Preliminary results indicate a slight superiority for the mixed beam treatment although this may be due to a greater number of patients with earlier stage tumors in the treatment category. Preliminary radiobiological experiments in animals at the University of Washington indicate that there may be an increased therapeutic ratio between tumor and normal tissue effects for the mixed beam. These studies support the need to study the mixed beam treatment option.

- 1.3 Neutron Therapy Equipment: The two machines showing potential for fast neutron radiotherapy are the large cyclotrons and the deuterium on tritium neutron generators (D-T). The large cyclotron is the best presently available source of fast neutrons for radiotherapy. At most cyclotron facilities

fast neutrons are produced by bombarding a beryllium target with deuterons ( $\text{Be}^9(d,n)\text{B}^{10} + 4.36 \text{ MeV}$ ). This results in a spectrum of neutron energies ranging from zero to the deuteron energy plus 4 MeV. The features of prime importance to this study are the high ion energies and beam intensities that can be obtained. With the 50 MeV<sub>d-Be</sub> beam at TAMVEC dose rates of 60 rads per minute at 140 cm SSD have been achieved without difficulty. The dosimetric properties of the 50MeV beam are similar to those of 4-6 MeV x-rays (better than  $^{60}\text{Co}$ , but inferior to 22 MeV x-rays).  $D_{\text{max}}$  occurs at 1.0 cm and the depth dose at 10 cm is 65%.

The D-T generators of the future will never match the skin sparing or the excellent and variable depth doses which can be obtained with the large cyclotrons, and it is unlikely that they will ever duplicate their output.

1.4 Staging: Patients will be staged according to the system derived by FIGO: (Appendix I)

1.41 Comparison with other staging systems: Although the FIGO staging system will be the official staging system for this protocol, other staging systems are included for comparison (Appendix II).

## 2.0 OBJECTIVES

2.1 Assessment will be made of the primary endpoints.

2.11 Local control. Absence of persistent or recurrent tumor in the pelvis.

2.12 Length of survival

2.13 Distant metastases

2.14 Complications of treatment

2.15 Assessment of functional status. The Karnofsky scale will be used.

## 3.0 SELECTION OF PATIENTS

3.1 Eligibility Criteria: Only patients with a diagnosis of squamous cell carcinoma of the uterine cervix are eligible for the study. Their disease must be established as Stage III or IVA by the FIGO classification (MDAH: IIIA, IIIB, IVA; AJC: IIIA, IIIB, IV).

3.11 All patients will have a lymphangiogram and those with positive paraaortic nodes on lymphangiogram will be excluded unless a selective lymphadenectomy (performed at the discretion of the institution) is negative.

3.12 Biopsy proof of squamous cell carcinoma.

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- 3.13 Reasonable expectation of completing the study treatment and the required follow-up examinations.
- 3.14 Agreement of the patient and her physician to the conditions of the study, including the diagnostic procedures and therapeutic randomizations.
- 3.15 Understanding by the patient of the provisions of the study and the treatment category options.
- 3.16 Completion of the required investigational treatment consent forms and the proper execution of the instrument of informed consent.
- 3.2 Ineligibility criteria: The following are cause for exclusion of the patient from the study:
- 3.21 Medical contraindication to lymphangiography (see 3.11). Medical, psychological or other contraindications to contemplated diagnostic and/or therapeutic measures and their evaluation.
- 3.22 Fifty or less on the Karnofsky performance scale.
- 3.23 Evidence of paraaortic nodal metastasis.

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- 3.24 Evidence of extrapelvic cancer and/or distant metastasis.
- 3.25 Pregnancy at the time of diagnosis, or immediately postpartum.
- 3.26 Previous radiation therapy, chemotherapy and/or surgical procedure for cancer in the pelvis.
- 3.27 Simultaneous or prior tumor at another site except for controlled skin and lip carcinoma other than melanoma.
- 3.28 Active, uncontrolled infection in the area of contemplated irradiation.
- 3.29 Patients who are extremely obese, such that their pelvic diameters during a treatment set-up will result in a depth dose distribution of 40% or less.
- 3.30 An occasional patient may be excluded for other reasons; these exclusions are expected to be 5% or less of the eligible patients.

#### 4.0 STAGING WORK-UP

- 4.1 The pretreatment evaluation will be performed prior to admitting the patient to the study. Results of the evaluation will be

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used to determine patient eligibility for the study and in management of her treatment regimen.

4.11 Staging should include but not be limited to:

- 4.111 A history and physical examination
- 4.112 Cystoscopy
- 4.113 Proctosigmoidoscopy
- 4.114 Biopsies (4-quadrant, endocervical and endometrial aspiration biopsies recommended).
- 4.115 Pelvic examination and diagram of pelvic findings.

4.12 An assessment of the performance status (Karnofsky function assessment-Appendix III)

4.13 Drawing of primary tumor and regional adenopathy (with centimeter dimensions) and photographs, if possible

4.14 Laboratory tests:

- 4.141 Complete blood count (with white count and differential and platelet count)
- 4.142 Urinalysis
- 4.143 Chemical battery: alkaline phosphatase, BUN, SGOT, glucose, protein, albumin.
- 4.144 Others, as indicated by the individual patient.

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4.15 Imaging procedures:

- 4.151 Chest x-ray (posterior-anterior and lateral)
- 4.152 Lymphangiogram (lower extremity)
- 4.153 Intravenous pyelogram
- 4.154 Barium enema
- 4.155 Barium studies for small bowel mobility
- 4.156 Others, as indicated (e.g. inferior vena cavagram, etc.)

5.0 RANDOMIZATION

5.1 Patients will be stratified according to the following factors:

5.11 Stage of tumor

5.12 Interpretation of paraaortic nodes on lymphangiogram as either negative (i.e. no metastases) or equivocal. Those with positive nodes on lymphangiogram are only eligible if, at selective lymphadenectomy, the nodes are negative. These patients will be stratified with the negative nodes group.

5.13 Institution

5.2 Procedure of Randomization

(1) Call RTOG Operations Office:

215-829-6719 between 9:00 a.m.-5:00 p.m. Eastern Time,  
Monday through Friday.

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(2) The following information will be required:

- i) Principal investigator's name
- ii) protocol identification
- iii) Institution name
- iv) Patient's name
- v) Stage of tumor
- vi) Status of paraaortic nodes on lymphangiogram

The Operations Headquarters will give the treatment assignment and the project case number. The randomization will be confirmed by mail.

5.3 A facility may choose to randomize patients among 2, 3 or all 4 options but all must include A - Photons only. Specific referring physicians or clinics within a facility (geographic subsets) may choose different randomizations but these must be stated prior to initiating the study at a facility.

## 6.0 Radiation Therapy Program

### 6.1 External Radiation Sources

6.11 Photons: X-ray generators capable of producing photon beams with a peak photon energy of 4 MeV or greater or Cobalt 60 shall be required. The output of the unit must be adequate to permit the use of an SSD of 80 cm or greater.

6.12 Neutrons: For neutron irradiation cyclotrons using neutron beams of 21.5 MeV or greater deuteron energy, or 14 MeV D-T neutron generators shall be required. The minimum acceptable SSD is 125 cm.

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## 6.2 General Treatment Plan and Radiation Doses

### 6.21 Photon Radiation Therapy

Patients allocated to this treatment category will initially receive 5000 rad total pelvis irradiation at a rate of 180-200 rad per fraction (900-1000 rad per week). Patients will be reevaluated in the 5th week for completion of treatment with either:

- a) supplementary intracavitary irradiation (radium, cesium, or cobalt) if the residual disease can be adequately treated with an intracavitary application.

If an intracavitary application can be performed after the basic dose of 5000 rad an additional 600 rads external megavoltage irradiation may be given to the involved pelvic side wall if clinically indicated (optional).

- b) supplemental megavoltage radiotherapy to a reduced volume confined to the residual disease (boost therapy) if an intracavitary application is not feasible due to the extent of the tumor, patient geometry or other factors. An additional 1000-1600 rad should be delivered in one to two weeks.

### 6.22 Neutron Radiation Therapy

General Treatment Plan and Radiation Doses. Patients

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allocated to this treatment category will initially receive a dose equivalent to 5000 rad in 20 to 24 fractions in 5-6 weeks (5000 rad eq/20 fx/5wks) using neutrons. Fractional doses considered equivalent to 250 rad photon irradiation are:

MANTA	80 rads
NAL	80 rads
SEATTLE	75 rads
TAMVEC	80 rads

The neutron contribution shall not be less than 90% of the total external beam tumor dose.

The patient will be reevaluated in the 5th week of treatment for completion with either:

a) supplemental intracavitary irradiation

If an intracavitary application can be performed after the basic dose of 5000 rad<sub>eq</sub> dose, an additional 600 rad<sub>eq</sub> dose in three fractions may be given with external radiotherapy to the involved pelvic side wall if clinically indicated (optional).

b) supplemental neutron radiotherapy to a reduced volume confined to the residual disease (boost therapy) if an intracavitary application is not feasible due to the extent of the tumor, patient

geometry, or other factors. An additional 1000-1600 rad<sub>eq</sub> should be delivered in one to two weeks.

6.23 Photon radiation therapy followed by Neutron Radiation Boost: Patients allocated to this treatment category will initially receive a dose of 3000 rad/15-17 fractions/3-3 1/2 weeks with conventional megavoltage irradiation. The patient will then be transferred to neutron therapy and will receive an additional dose equivalent to 2000 rad/8-10 fractions/2-2 1/2 weeks. The fractional dose considered equivalent to 250 rad photon irradiation are:

MANTA	80 rad
NAL	80 rad
SEATTLE	75 rad
TAMVEC	80 rad

The neutron contribution shall not be less than 30% nor more than 50% of the total external beam tumor dose.

The patients will be reevaluated in the 5th week for completion of treatment with either:

a) supplemental intracavitary irradiation.

If an intracavitary application can be performed, an additional 600 rad<sub>eq</sub> dose in three fractions may be given with an external radiotherapy to

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the involved pelvic side wall if clinical indicated (optional).

- b) supplemental neutron radiotherapy to a reduced volume confined to the residual disease (boost therapy) if an intracavitary application is not feasible due to the extent of the tumor, patient geometry, or other factors.

An additional 1000-1600 rad<sub>eq</sub> should be delivered in one to 2 weeks.

6.24 Combined neutron and photon radiation therapy: Patients allocated to this treatment category will initially receive a dose equivalent to 5000 rad in 25 fractions and 5 weeks (5000 rad<sub>eq</sub>/25 Fx/5 wks) using combined fast neutrons (2 fractions per week) and conventional radiotherapy (3 fractions per week). The fractional doses considered equivalent to 200 rad photon irradiation are:

MANTA	65 rad
NAL	65 rad
SEATTLE	60 rad
TAMVEC	65 rad

The neutron contribution shall not be less than 30% nor more than 50% of the total external beam tumor dose.

The patients will be reevaluated in the 5th week for completion of the treatment with either:

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a) supplemental intracavitary irradiation.

If an intracavitary application can be performed, an additional 600 rad<sub>eq</sub> dose in three fractions may be given with external radiotherapy to the involved pelvic side wall if clinically indicated (optional).

b) supplemental neutron and photon radiotherapy to a reduced volume confined to the residual disease (boost therapy) if an intracavitary application is not feasible due to the extent of the tumor, patient geometry, or other factors. An additional 1000-1600 rad<sub>eq</sub> should be delivered.

6.25 Supplemental intracavitary brachy-radiotherapy applications.

Radium sources or the equivalent of cesium or cobalt are to be used for intracavitary brachy-radiotherapy applications with long intrauterine tandems and vaginal applicators such as the Fletcher-Suit afterloading applicators.

If intracavitary brachy-radiotherapy applications can be performed after the basic total pelvic dose of 5000 rad, or 5000 rad<sub>eq</sub> the total radium dose to be delivered is 4000-5000 mg hours using a Fletcher applicator (3000-4000 rad calculated at 2 cm from the cervical canal using

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other applicators). If the patient geometry permits a satisfactory application of the tandem-vaginal ovoid system, the total radium dose can be given in one application of 72 hours. This application should be done within 21 days of completing external beam radiotherapy. To allow for further regression of central disease in some patients two 48-hour insertions may be performed with a rest period of 2-3 weeks in between. If there is an anatomical limitation for an ideal application, the type of insertion can be individualized (example: 72-hour ovoid insertion plus 48-hr tandem insertion as the first application - rest period of 2 weeks - 2nd tandem insertion of 24-48 hrs).

6.26 Transvaginal cone irradiation. For exophytic and/or bleeding cervical lesions, 500 rad given dose, each dose x 2-3 of 125-300 KeV x-rays, may be given prior to or during external radiotherapy as necessary. This dose shall be ignored and the calculation of the total dose planned for the entire treatment.

### 6.3 Treatment portals

6.31 Total pelvis irradiation shall include all of the clinically apparent disease, the entire uterus, the paracervical,

parametrial, the utero-sacral regions as well as the iliac, hypogastric, and obturator lymph nodes. If a four field box technique is used, a minimum field size of 15 x 15 cm anterior, posterior portals 15 x 9 cm lateral portals will be required. However, other treatment configurations will be accepted, e.g. rotational therapy or lateral arc rotations. The following boundaries are recommended: Superior border - mid L 5. Inferior border - mid obturator foramen or 2 cm caudad to the lowest extent of the disease as marked by vaginal localizer or inert silver or gold seeds: lateral border - at least 1 cm beyond the lateral margin of the bony pelvis or at least 7 cm from the mid line. Two opposing portals will be treated each day.

6.32 Portal or simulator films with the localizer or seeds in place will be taken and copies or these forwarded to RTOG Headquarters. A squeeze device may be used to reduce pelvic diameters.

6.33 For patients receiving an intracavitary brachy-radiotherapy application an additional 600 rad or  $rad_{eq}$  may be given to the involved pelvic side wall through reduced anterior and posterior fields. These portals will usually measure 15 x 6 cm, 12 x 6 cm, or 10 x 6 cm in size, depending on the extent of the disease.

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#### 6.4 Dosimetry

6.41 Total pelvis doses will be calculated at the pelvic midplane on the central axis.

6.42 The minimum dose delivered to the pelvic sidewall (at the boney margin of the widest part of the true pelvis) will be 5500 rads.

#### 7.0 STUDY PARAMETERS AND FOLLOW-UP

7.1 Parameters to be recorded on study forms and submitted to Operation Headquarters include:

Parameter	Prior to Radiotherapy	Completion of Radiotherapy	At Each follow-up
Tumor measurements	X	X	X
CBC, platelets	X		
Urinalysis	X		
Chemistries	X		
Chest x-ray	X		X*
Lymphangiogram	X		
IVP	X		X**
Cystoscopy	X		
Proctoscopy	X		
Photographs of the treated area	X		X*

\* every 6 months

\*\* yearly

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## 7.2 Follow-up

7.21 Follow-up reports will be forward to RTOG Operation Headquarters at the completion of treatment; then every three months for 3 years; then every six months for the fourth and fifth year; and annually thereafter. The data reported should include:

7.22 Patient alive or dead. If dead, the date and cause of death should be noted (Autopsy report whenever possible, and material of post-mortem examination should be sent to RTOG Headquarters).

7.23 Clinical evaluation of tumor activity at the primary site (when there is histological confirmation of tumor activity or local control, the pathology report and slides should be sent to RTOG Headquarters).

7.24 Tumor activity anywhere within the pelvis.

7.25 Distant metastases (two x-rays of the chest and one IVP per year; skeleton x-ray whenever bone pain is present).

7.26 A form recording the reactions produced during the treatment period up to the first follow-up visit will be kept on each patient chart. These will include an evaluation of diarrhea, proctitis, dysuria, skin reactions, vaginal and cervical reactions.

## 7.3 Measurement of Specific Endpoints.

Criteria of response shall be measured as follows:

7.31 Local control of the primary tumor and regional metastases.

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7.32 Frequency and severity of complications (normal tissue tolerance).

7.33 Patient survival time.

7.34 Quality of survival (as determined by Karnofsky's function assessment).

7.35 Incidence of regional and distant metastases.

#### 7.4 Records

7.41 Initial evaluation form - mandatory

7.42 Drawings of tumor and regional adenopathy on diagrams are mandatory each visit.

7.43 Treatment summary

7.44 Follow-up evaluation form - mandatory each visit.

7.45 Photographs optional

7.46 Death report

### 8.0 STATISTICAL CONSIDERATIONS

In obtaining estimates of the number of patients required for this study, the following assumptions have been made:

- a) That an increase to a 50% 2-year survival rate (from the current rates (estimated) of 30%) is desirable.
- b) That an improvement of this magnitude should be detected with a high degree of certainty, i.e., at least 80% using a significance level of  $p=0.05$ .
- c) That some treatment comparisons e.g. that using photons

only versus that using mixed beams, will be possible sooner than others, depending on the treatment options chosen by each participating institution; the calculations below relate to the photon-only versus mixed beam comparison.

- d) The investigators in three of the institutions in question have stated that the following numbers of patients will be available:

- (1) 20/year
- (2) 8-10/year
- (3) 25/year

It is anticipated that institutions (1) and (2) will randomize patients between the "photon-only" and the "mixed-beam" arms and that institution (3) will divide patients between "photon-only" and "neutron-only" irradiation.

With these projections, it is anticipated that the treatment arms will, in a period of 3 years, accrue the 50-60 patients per arm necessary to meet the objectives stated above.

#### 9.0 ADDITIONAL THERAPY

Whenever possible, unless there is rapid tumor progression, a biopsy or surgical procedure should not be performed prior to 100 days after the start of radiation therapy. If the primary tumor is not controlled at the primary site, subsequent therapy should proceed at the discretion of the patient's responsible physician.

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Clinical evidence of lack of tumor control should be documented in the patient's follow-up records.

In the event that surgery or a biopsy is performed, the excised tissue or biopsy specimen should be carefully examined by a pathologist at the participating institution, with representative slides forwarded to RTOG Operations Headquarters for review by the study pathologist.

#### 10.0 PATHOLOGY

Representative sections of tumor should be forwarded to the study pathologist. Unstained extra slides or parafin blocks are acceptable. All initial histologies, follow-up biopsies and/or autopsy specimens should be made available to the study pathologist.

#### 11.0 PATIENT CONSENT AND PEER JUDGEMENT FORMS

All institutional, Food and Drug Administration, and National Cancer Institute regulations requiring submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study at any time if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form.

## REFERENCES

1. Bewley, D.K.: Pretherapeutic experiments with the fast neutron beam from the Medical Research Council Cyclotron-II. Physical aspects of the fast neutron beam. Br. J. Radiol. 36:81-88, 1963.
2. Castro, J.R., Issa, Philippe, and Fletcher, G.H.: Carcinoma of the cervix treated by external irradiation alone. Radiology 95:163-166, 1970.
3. Caderno, J.B., Hussey, D.H., Fletcher, G.H., Sampiere, V.A., Johnson, D.E. and Wharton, J.T.: Fast neutrons Radiotherapy for Locally Advanced Pelvic Cancer. Cancer 37:2620-2629, 1976.

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APPENDIX I:

FIGO Staging System

Stage I	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded).
Stage IA	The cancer cannot be diagnosed by clinical examination (i) Early stromal invasion and (ii) occult cancer.
Stage IB	A-1 other cases of Stage I.
Stage II	The carcinoma extends beyond the cervix but has not extended on to the pelvis. The carcinoma involves the vagina but not the lower third.
Stage IIA	No obvious parametrial involvement.
Stage IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended on to the pelvic wall. On rectal examination there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina.

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Stage IIIA

No extension on to the pelvic wall.

Stage IIIB

Extension on to the pelvic wall.

Stage IV

The carcinoma has extended beyond the true pelvis or has involved mucosa of the bladder or of the rectum. A bullous edema as such does not permit allotment of a case to Stage IV.

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APPENDIX II

MDAH Staging System

Stage I <sub>A</sub>	Micro-invasive
Stage I <sub>B</sub>	-1 cm diameter or two or more positive quadrant biopsies
State I <sub>C</sub>	-1 positive quadrant biopsies
Stage II <sub>A</sub>	Lateral parametrial involvement (with or without upper vaginal extension); or massive involvement of corpus (barrel-shape)
Stage III <sub>A</sub>	One pelvic wall or lower one-third vagina Favorable: One wall involved -- not massively, and primary not too massive. Unfavorable: More disease than above -- still confined to this stage.
Stage III <sub>B</sub>	Both pelvic walls <u>OR</u> one wall plus lower one-third of vagina or, both pelvic walls and entire vagina.
Stage IV <sub>A</sub>	Carcinoma involving the urinary bladder and/or rectum histologically proven.

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TNM categories (AJC staging system). The following TNM categories are established for the uterine cervix by AJC:

- TIS Pre-invasive carcinoma (carcinoma in situ)
- T<sub>1</sub> Carcinoma confined to the cervix:
- T<sub>1</sub>A Preclinical invasive carcinoma (i.e., cases which can be diagnosed only histologically).
- T<sub>1</sub>B Clinical invasive carcinoma. (Microscopic extension to the corpus as demonstrated by dilation and curettage does not influence the stage classification of this tumor).
- T<sub>2</sub> Carcinoma extending beyond the cervix but not reaching the pelvic wall, or carcinoma involving the vagina but not the lower third.
- T<sub>2</sub>A The carcinoma has not infiltrated the parametrium.
- T<sub>2</sub>B The carcinoma has infiltrated the parametrium.
- T<sub>3</sub> Carcinoma involving either the lower third of the vagina or reaching the pelvic wall. (There is no free space between the tumor and the pelvic wall.) (The presence of hydronephrosia or a nonfunctional kidney due to stenosis of the ureter by growth allots the case to T<sub>3</sub>, even if, according to the other findings, the case should be allotted to a lesser category.)
- T<sub>4</sub> Carcinoma extending beyond the true pelvis, or involving the mucosa of the bladder or of the rectum (the presence of bullous edema is not sufficient evidence to classify the tumor as T<sub>4</sub>):

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T<sub>4A</sub> Carcinoma involving the bladder or the rectum only and histologic proven.

T<sub>4B</sub> Carcinoma extending beyond the true pelvis. (Enlargement of          so that it becomes palpable by abdominal examination does not constitute grounds for assignment to T<sub>4</sub>).

N<sub>X</sub> Not possible to clinically assess pelvic lymph nodes.

N<sub>0</sub> No deformity of regional nodes as shown by available diagnostic methods such as lymphography.

N<sub>1</sub> Regional nodes deformed, as shown by available diagnostic methods.

N<sub>2</sub> There is a fixed palpable mass on the pelvic wall, with a free space between this mass and the tumor.

M<sub>0</sub> No evidence of distant metastases.

M<sub>1</sub> Distant metastasis present, including nodes above the bifurcation of the common iliac arteries.

Clinical stage groupings for AJC: Patients will be staged according to the system derived by the American Joint Committee on Cancer Staging and End Res Reporting.

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APPENDIX III

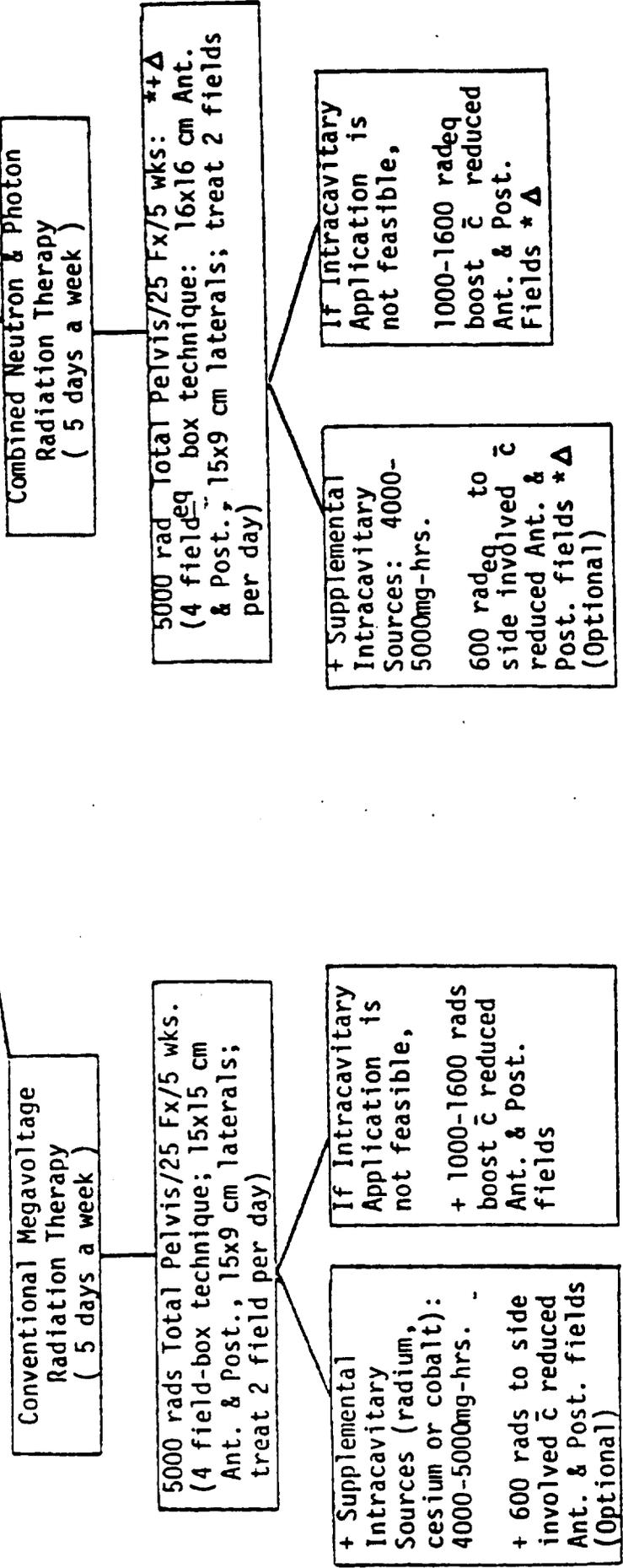
R.T.O.G. (KARNOFSKY) PERFORMANCE STATUS

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 signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to 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 process progressing rapidly.
0	Dead

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SCHEMA OF RADIATION DOSES & CERVIX TECHNIQUES

RANDOMIZATION



\* Determination of equivalent dose: for 35 and 50 Mev F.N., 65 rad<sub>n</sub> is equivalent to 200 rads conventional irradiation (RBE=3.1); for 21.5 Mev F.N., 55 rad<sub>n</sub> is equivalent to 200 rads conventional irradiation (RBE=3.6).

Δ Neutron XRT will be delivered twice weekly, and the photon XRT 3x weekly. The neutron contribution shall not be less than 30% of the total external beam tumor dose.

+ Transvaginal cone therapy for bleeding - can be given with 125-300 KeV x-rays to doses of 500 rads given dose x 3; this shall be ignored in the calculation of the above external and intracavitary doses.

+ + Δ on XRT will be delivered four times weekly ( neutron contribution shall not be less than 90% of the total external beam tumor dose. )

Neutron Radiation  
Therapy  
( 4 days/week )

5000 radeq Total Pelvis/25-29 Fx/ 5-6 wks

If Intracavitary  
Application is  
not feasible,  
1000-1600 radeq  
boost c reduced  
Ant. & Post.  
fields \*Δ<sup>++</sup>

+ Supplemental  
Intracavitary  
Sources: 4000-  
5000mg - hrs.  
600 radeq to  
side involved c  
reduced Ant. &  
Post. fields \*Δ<sup>++</sup>

Photon XRT followed  
by neutron XRT  
( 4 days / week )

3000 rad conventional XRT/15-18 FX/3-3 1/2 wks.  
+  
200 radeq FN (total pelvis)

If Intracavitary  
Application is  
not feasible,  
1000-1600 radeq  
boost c reduced  
Ant. & Post.  
fields \*Δ

+ Supplemental  
Intracavitary  
Sources: 4000-  
5000 mg-hrs.  
600 radeq to  
side involved c  
reduced Ant. &  
Post. fields \*Δ

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Description

Stage

Stage 0

Stage 0

Stage I

Stage I

Stage II

Stage II

Stage III

Stage III

TIS

T1 NX M0

T1a

T1b

T2 NX M0

T2a

T2b

T3 (stenosis of the ureter by growth allots the case to T3 even if according to the other findings the case should be allotted to a lesser category)

Pre-invasive (carcinoma in situ)

Confined to the Cervix (disregard extension to corpus) Pre-clinical invasive carcinoma (histological dx)

Clinical invasive Ca

Carcinoma extending beyond the cervix but not reaching the pelvic wall, or carcinoma involving the vagina but not the lower 1/3

Carcinoma has not infiltrated the parametrium

Carcinoma has infiltrated the parametrium

Carcinoma involving either the lower 1/3 of the vagina, or reaching the pelvic wall. There is no free space between the tumor and the pelvic wall.

0

I

Ia

Ib

Ic

II

IIa

IIb

III

IA

IB (1 cm or less d)

IC (more than 1 cm or 2 or more + quadrant bx)

Ia\*

Ib

-

IIa

IIb

\*\*IIA (medial parametrial involve and/or spread upper 2/3 vag

IIB (lateral parametrial involve w/ or w/o upper vaginal extension or massive involvement of corpus barrel shape)

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var( )  
 IIIb (Both pelvic wall  
 or one wall +  
 lower 1/3 vagina)

IIIb

( T3 ( ) )  
 ( T1b N2 MO ) \*\*\*  
 ( T2a N2 MO )  
 ( T2b N2 MO )

Stage IV

Stage IV

T4\*\*\*

IVA

IVB

IIIa ( Carcinoma involves the lower  
 1/3 of the vagina but has not  
 extended on to the pelvic wall

IIIb Carcinoma has extended on to  
 the pelvic wall

IV Carcinoma involving the mucosa of  
 the bladder or rectum histolo-  
 gically proven or extending be-  
 yond the true pelvis. The pre-  
 sence of bullous edema is not  
 sufficient evidence to classify  
 the tumor as T4 or Stage IV

IVA Carcinoma involving the bladder  
 or the rectum only and histolo-  
 gically proved

IVB Carcinoma extending beyond the  
 true pelvis

T4a NX MO  
 N2 MO

T4b any M1

\* Includes Stage Ia-post-surgical (microscopic focus found in the removed uterus).  
 \*\* Except IC and IIA; Includes bulky exophytic lesions, or unfavorable anatomy for radium system  
 (narrow vault-short uterine canal, asymmetrical fornices).  
 \*\*\* T1a N2 can not exist.  
 \*\*\*\* Enlargement of the uterus alone does not constitute grounds for assignment to T4.

Distant Metastases (UICC & AJC)

MO - No evidence of distant metastases.  
 M1 - Distant metastases present, inclu-  
 ding nodes above the bifurcation of  
 the common iliac arteries.

Regional Lymph Nodes (UICC & AJC)

NX - When it is not possible to assess the regional  
 lymph nodes, the symbol NX will be used permitting  
 eventual addition of histological information thus:  
 NX- or NX+.  
 N1 - Regional nodes deformed as shown by available  
 diagnostic methods.  
 N2 - There is a fixed palpable mass on the pelvic wall  
 with a free space between this and the tumor.