RADIATION THERAPY ONCOLOGY GROUP

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RTOG 77-04

PROTOCOL TO STUDY
THE VALUE OF RADIATION THERAPY USING NEUTRONS IN COMBINATION WITH PHOTONS IN THE TREATMENT OF CLINICAL STAGE C ADENOCARCINOMA OF THE PROSTATE

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Schema

STRATIFY

Histology
- Well differentiated
- Poorly differentiated

Previous Orchiectomy -
- Yes
- No

Pelvic Nodal Status No, Nx, N+

RANDOMIZE

- Pelvic irradiation with photons[a]
- Pelvic irradiation with mixed beam[ab]

a Includes boost to the prostate.

b 3 photons, 2 neutron fractions per week.

Doses for all arms: Pelvic - 5000 rad or eq/5 wks.
Prostate - 6500 rad or eq/6-1/2 wks to 7000 rad or eq/8 wks.

1.0 INTRODUCTION

Carcinoma of the prostate has been treated with surgical resection, hormonal manipulation and radiation therapy. Unfortunately, by the time of diagnosis, very few patients with carcinoma of the prostate are candidates for curative surgical procedures (Flocks). Estrogen therapy is effective in the treatment of inoperable and metastatic carcinoma of the prostate (Nesbit et al.), although in high doses, it was found to increase the risk of cardiovascular disease (The Veterans Administration Cooperative Research Group). Radiation therapy has been shown to be effective, by itself, in the treatment of inoperable carcinoma of the prostate when confined to the pelvis (Bagshaw, del Regato, George, Rubin).

It has also been shown that there is early spread of disease to the pelvic and para-aortic lymph nodes in all stages of carcinoma of the prostate (Grossman et al., Flocks et al.) There is growing interest in the value of lymphangiograms and staging laparotomies in early and inoperable carcinomas of the prostate (Grossman et al., Bagshaw et al.)

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

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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 oxygenated.

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 Co^{60} - a beam which is marginal at best for the treatment of advanced pelvic neoplasms.

TABLE I

	Neutrons (Deuteron Energy MeV)				Photons		
	16	21.5	35	50	Co^{60}	10 MeV	25 MeV
Depth of D Max (cm) (10x10 cm Fld)	12	.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.

*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.

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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 pelvic diameter. This makes a poor penetration of neutron beams even more significant.
3. Increased Absorption in Fat - Bewley has shown that fat absorbs approximately 18% more energy with neutrons than water density tissue. This factor could lead to increased subcutaneous fibrosis.

Fast neutron doses equivalent to 6000-7000 rads may 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.

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. 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.

A current RTOG protocol (RTOG 76-06) is studying pelvic versus pelvic and para-aortic nodal irradiation in the treatment of locally advanced (Stage C) prostate carcinoma. The current study will use an identical arm as RTOG 76-06 so that comparisons may be possible between the two studies.

2.0 OBJECTIVES OF THE STUDY

2.1 To determine whether mixed beam radiotherapy is superior to megavoltage photons in the treatment of Stage C carcinoma of the prostate as measured by relapse free survival and total survival.

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3.0 SELECTION OF PATIENTS

The basis of selection will be histologically-proven adenocarcinoma of the prostate.

3.1 Conditions for Eligibility.

3.1.1 Any patient with Stage C adenocarcinoma of the prostate who has had curative surgery or previous irradiation.

3.1.2 Patients with informed consent to participate in the study.

3.1.3 Adequate bone marrow (WBC > 4,000/mm3, Hct > 35 and platelets > 100,000) and renal (BUN < 30 mg%) functions.

3.1.4 Hormonal treatment does not exclude the patients but must be reported.

3.2 Conditions for Ineligibility.

3.2.1 Previous radiation therapy, except for skin cancer irradiated outside potential treatment fields.

3.2.2 Previous or concurrent cancers other than skin cancer.

3.2.3 Major medical or psychiatric illness which the investigator's opinion would prevent completion of the protocol requirements.

3.2.4 Patients not available for regular follow-up.

3.2.5 Performance status below 40% on Karnofsky scale.

3.2.6 Over 80 years of age.

3.2.7 Previous curative prostatic surgery.

4.0 STAGING AND WORK-UP

4.1 Mandatory.

4.1.1 History and physical examination.

4.1.2 Histologic proof of adenocarcinoma.

4.1.3 SMA-12.

4.1.4 Serum acid phosphatase.

4.1.5 Chest x-ray: PA, lateral.

4.1.6 IVP and/or retrograde pyelogram.

4.1.7 Bone scan (positive areas should have further radiographic investigation).

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4.2 Optional.

4.2.1 Bone marrow biopsy and bone marrow acid phosphatase.

4.2.2 Bipedal lymphangiogram - STRONGLY ADVISED.

4.2.3 Laparotomy - At the time of laparotomy, biopsy and clipping of any lymph nodes suspicious at lymphangiogram or at surgery. If done, bone marrow biopsy and acid phosphatase can be done at this time.

4.2.4 Examination of the histologic specimen for hormonal receptors.

4.2.5 Rectal probe isotopic assessment of the prostate.

4.2.6 Skeletal survey.

4.2.7 Small bowel studies for bowel mobility.

5.0 STRATIFICATION AND RANDOMIZATION

5.1 Stratification will include:

5.1.1 Histology: well-differentiated vs. poorly differentiated.

5.1.2 Previous orchiectomy: Yes vs. No.

5.1.3 Lymph nodes: Positive pelvic lymph nodes vs. negative pelvic lymph nodes (as determined by lymphangiogram and/or laparotomy) or unevaluated.

5.2 Randomization will be to one of the following options:

5.2.1 Mixed beam therapy to pelvis with boost to prostate.

5.2.2 Conventional radiation therapy to pelvis with boost to prostate.

5.3 Randomization will be with RTOG Headquarters (215-574-3191, Monday-Friday; 9:00 a.m. - 5:00 p.m., ET) once a patient has been found acceptable by all the investigators and the patient has consented to participate in the study. The following information must be given to the Operations Office:

a) Protocol Name

b) Institution

c) Physician

d) Patient Name

e) Histology

f) Whether orchiectomy was performed

g) Lymph node status

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The physician will receive a treatment assignment that will later be confirmed by mail.

6.0 RADIATION THERAPY PROGRAM

6.1 Doses.

6.1.1 With photons the dose rate will be 180 to 200 rads/day, 5 days/week. Mixed beams will consist of three photon and two neutron fractions per week with a weekly equivalent dose of 1000 rad. The total mid-plane dose will be 5000 rads or rad equivalent in 5 weeks to the pelvis with an additional 1500-2000 rad or rad equivalent to the prostate using reduced fields. A minimum total dose of 6500 rad/6-1/2 weeks to 7000 rad/8 weeks should be delivered to the prostate.

6.2 Radiation Portal.

6.2.1 Pelvic Fields.

Inferior border - 2 cm below the inferior border of the prostate or the lower border of the ischial tuberosity, whichever is lower.

Lateral borders - At least 1 cm lateral to the medial rim of the ilium.

Superior border - The interspace of the 5th lumbar vertebra and the first sacral vertebra.

Such shaping of the fields as necessary to protect bone marrow is encouraged. Coplanar opposed anterior and posterior fields will be used with each field being treated at each session. A four field technique is optional.

6.2.2 Prostatic Boost Fields.

A field large enough to give an adequate margin around the prostate, usually 6 x 6 cm to 8 x 8 cm will be centered on the prostate.

Any field arrangement delivering the prescribed dose to the prostate is acceptable, although coplanar opposed anterior-posterior fields are less

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satisfactory than alternative plans because of the high dose delivered to the bladder and rectum. Alternative arrangements include coplanar opposed lateral fields, 4 field cross-fire and oblique fields. In any case, all fields will be treated at each session.

6.3 Physical Parameters.

6.3.1 Localization films will be obtained for each treatment field and must be submitted for review.

6.3.2 Isodose distributions for the pelvis, one for a transverse section through the center of the field, and one for a transverse section through the prostate will be obtained and submitted with the on-study form.

6.3.3 External Radiation Sources

6.3.3.1 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.

6.3.3.2 Neutrons: The neutron beam shall have such a penetrating power that for a 10 x 10 cm field the depth at which the maximum dose per monitoring unit is reduced to half of its value is 9.0 cm or greater as measured in tissue equivalent fluid at the standard SAD or SSD used at the institution.

Fractional neutron doses (for mixed beam) considered equivalent to 200 rad photon irradiation are:

MANTA	63 rad
FERMI	66 rad
SEATTLE/CHICAGO/GLANTA	60 rad
TAMVEC	65 rad

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The neutron contribution shall not be less than 30% of total external beam tumor dose for mixed beam radiation.

6.4 Critical Structures and Tolerance.

6.4.1 Bladder: The dose to the entire bladder should not exceed 6,000 rad or rad equivalent. The dose to the trigone and portions of the posterior wall should not exceed the dose to the prostate.

6.4.2 Rectum: The dose to the rectum in its entirety should not exceed 5,500 rad or rad equivalent. Portions of the anterior wall of the rectum will receive the same dose as the prostate.

6.4.3 Small bowel: The dose to any segment of the small bowel should not exceed 5,500 rad or rad equivalent. Efforts should be made to exclude the small bowel from the true pelvis by such maneuvers as treating the patient in a prone position. Evaluation of small bowel location in patients with previous small bowel disease or previous abdominal surgery should be made by barium studies.

6.4.4 Bone marrow: The bone marrow will be unavoidably irradiated in all field arrangements. The percentage of bone marrow irradiated will be about 25% with pelvic irradiation. The dose to these bone marrow areas will produce decreased function for at least 1 to 2 years.

6.5 Additional Treatment.

A TUR is to be avoided unless absolutely necessary, since previous experience suggests that post-TUR patients tolerate radiation therapy less well than those managed with lesser procedures. Prior to a TUR, attempt one week of drainage via a silastic catheter while treating with antibiotics, and/or radiation; if upon removal of the catheter, after one week of drainage, there is still obstruction, then a TUR is permissable. After the TUR, start or resume therapy as soon as possible (1 week). Do not adjust the dose of radiation. Estrogen therapy does not exclude a patient but must be reported on the appropriate forms.

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7.0 STUDY PARAMETERS

Parameter	Prior	Monthly for 3 months (post-randomization)	At Follow-Up	At 1 Year
History	X	X	X	
Rectal Examination	X	X	X	
SMA-12	X			
Serum Acid Phosphatase	X	X(b)	X	X
Chest x-ray PA & Lateral	X			X
IVP	X			X
Bone Scan	X			X
Trans-rectal Biopsy				X
Plain Film of Abdomen		X(a)	X(a)	

(a) = If lymphogram done
(b) = Not required during radiation therapy

8.0 SPECIFIC ENDPOINTS TO BE MEASURED

8.1 Tumor response (as determined by palpation and biopsy):

8.1.1 Primary tumor response will be measured by palpation in the following way. Estimate length (apex to base) and width of each nodule or tumor mass by the examining finger and record on anatomic diagrams. The following definitions of response will be used:

(A) Complete regression of primary: complete disappearance of primary tumor and local non-nodular extension.

(B) Partial regression of primary: at least a 50% decrease in the product of the length and width of the tumor mass or nodule (in the case of more than one nodular tumor mass, the sum of the products will be used).

(C) No change in primary: changes too small to qualify for partial regression or progression.

(D) Progression of primary: at least a 25% increase in the product of perpendicular diamters of measurable disease; (or the sum or the products if more than one nodule or mass is measurable).

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Biopsy information, when available, will be used to evaluate primary tumor response.

8.1.2 Lymph node response using lymphangiogram: If sufficient dye remains to evaluate lymph nodes, or if patient has a repeat lymphogram, then status will be graded as:

(A) Abnormal

(B) Normal

8.2 Effectiveness of local control (primary + direct extension).

8.3 Time to first metastases, as detected by radiograph or bone scan; biopsy proof as needed.

8.4 Loss of potency.

8.5 Urinary complications.

8.6 Rectal complications.

8.7 Late normal tissue reactions should be recorded at the time of each follow-up according to the scale in Appendix II.

9.0 FOLLOW-UP EXAMINATION

9.1 Once/month for the first 3 months following onset of treatment.

9.2 Every 3 months for the remainder of the first year, plus years 2 & 3.

9.3 Every 6 months for the remainder of the patient's life.

9.4 Additional visits as necessary.

10.0 TREATMENT FAILURE

With proven recurrence of disease or the development of distant metastases, the patient is eligible for any additional appropriate therapy or inclusion in other investigative protocols, but should still be followed in order to document survival and late effects of treatment.

11.0 CENTRAL PATHOLOGY REVIEW

Central pathology review is desirable but has not been formalized.

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12.0 STATISTICAL CONSIDERATIONS

The major endpoint will be the frequency and duration of local disease control. Furthermore, it is assumed that patient survival will follow an exponential distribution.

The null hypothesis (of equal ability to control local disease) will be tested against the alternative that employing neutron therapy can increase the frequency and duration of control.

It is assumed that patient accrual will continue for 2-3 years and that a statistical analysis will be made after the last patient entered has been followed for 2-3 years.

Using an anticipated entry rate of approximately 50 patients per year, and using a one-sided test of significance (P=0.05), it should be possible to declare the following therapeutic improvements as being statistically significant:

PROBABILITY OF DETECTION

Improvement	Probability of Detection
An increase of 20% in the percentage of tumors that are controlled.	80%
An increase from 5 year survival of 40% to 5 year survival of 60%.	75%

These estimates are subject to revision based on the actual accrual.

13.0 FORMS

Data will be submitted to RTOG Headquarters in the following manner:

Prostate On-study Form, treatment planning information and localization films	Within 1 week of randomization
Prostate Radiotherapy Form and films of boost fields	At end of radiotherapy
Prostate Follow-Up Form	Monthly for 3 months, every 3 months for the rest of year 1, 2, 3, then every 6 months.
Prostate Death Form	At death

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14.0 PATIENT CONSENT FORM

All institutional, federal and state requirements concerning human investigation will be satisfied.

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APPENDIX I

STAGING SYSTEM FOR ADENOCARCINOMA OF THE PROSTATIC GLAND

1. UICC (Union International Contre le Cancru, Geneva, 1968). The determination of extent of disease should be based on clinical examination, radiography, and endoscopy. The diagnosis must be confirmed by either:

   (a) Microscopy (either by cytological or histological examination), or

   (b) Combined radiography and biochemical tests (providing the serum acid phosphatase is raised on two different occasions).

   The regional lymph nodes are the intra-abdominal subdiaphragmatic nodes.

T - PRIMARY TUMOR

TX Incidental findings of carcinoma in operative specimen.

T0 No evidence of primary tumor.

T1 Tumor occupying less than one half of the prostate and surrounded by palpably normal gland.

T2 Tumor occupying one half or more of the prostate but not producing enlargement or deformity of the gland.

T3 Tumor confined to the prostate but producing enlargement or deformity of the gland.

T4 Tumor extending beyond the prostate.

N - REGIONAL LYMPH NODES

NX When it is impossible to assess the regional nodes, the symbol NX will be used, permitting eventual addition of histological information, thus: NX- or NX+.

N0 No deformity of the reginal nodes on lymphography.

N1 Regional nodes deformed on lymphography.

N2 Fixed palpable abdominal nodes.

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M - DISTANT METASTASES

M0 No evidence of distant metastases.

Distant metastases present:

M1A bone metastases only.

M1B Other metastases with or without bone metastases.

2. AJCCS (American Joint Committee on Cancer Staging).

Anatomical Staging:

Stage A: Occult cancer.

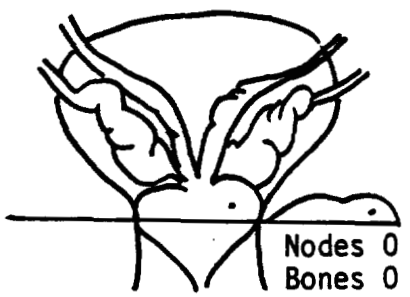
Stage B: Cancer nodule confined within prostatic capsule.

Stage C: Cancer with extracapsular extension into surrounding structures or confined within capsule with elevation of serum acid phosphatase. Pelvic nodes may be involved.

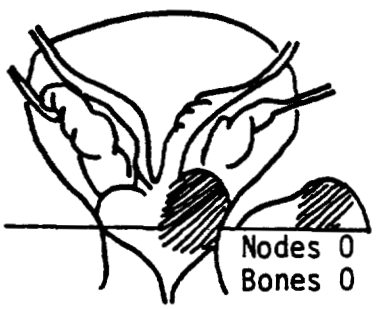
Stage D: Demonstrated bone or extrapelvic involvement.

A COMPARISON OF THE TWO STAGING SYSTEMS CAN BE DEMONSTRATED AS FOLLOWS:

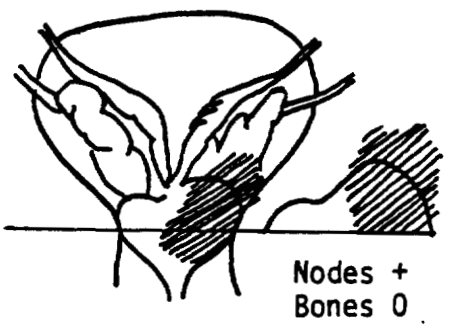
A. $T_xN_xM_0$



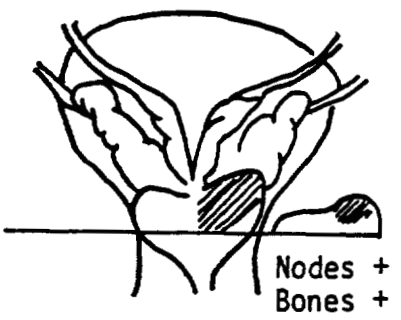
B. $T_1T_2T_3N_-M_0$



C. $T_4N_{\pm}M_0$



D. T_1-$T_4N_+M_1$a or b



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Appendix II

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Organ/Tissue	0	1 Mild	2 Moderate	3 Severe	4 Life Threatening	5*
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patchy atrophy Moderate telangiectasia Total hair loss	Marked atrophy Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture (< 10% linear reduction)	Severe induration and loss of subcutaneous tissue Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANES	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucus	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness Poor response on stimulation	Complete dryness No response on stimulation	Necrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono or para quadriplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headache Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or Paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panophthalmitis Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever. Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency Continuous oxygen Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion and ST changes Sinus tachycardia > 110 (at rest)	Moderate angina of effort Mild pericarditis Normal heart size Persistent abnormality T wave and ST changes Low QRS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade Severe heart failure Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilatation required	Necrosis Perforation, Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping. Bowel movement < 5 times daily. Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement > 5 times daily. Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation, Fistula	
LIVER	None	Mild lassitude, nausea dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis Hepatic coma or Encephalopathy	
KIDNEY	None	Transient albuminuria No hypertension Mild impairment renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine Clearance > 75%	Persistent moderate albuminuria (2+) Mild hypertension. No related anemia. Moderate impairment renal function Urea > 36-60 mg% Creatinine 2.5-4.0 mg% Creatinine Clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (< 10g%) Severe renal failure Urea > 60 mg% Creatinine > 4.0 mg% Creatinine Clearance < 50%	Malignant hypertension Uremic coma Urea > 100 mg%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized telangiectasia (often with petechiae). Frequent hematuria. Reduction in bladder capacity (< 150 cc)	Necrosis Contracted Bladder (capacity < 100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Retardation of growth Irregular bone sclerosis	Severe pain or tenderness Complete arrest bone growth Dense bone sclerosis	Necrosis Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis Complete fixation	

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*... related to radiation late effects