

Radiation Therapy Oncology Group

NON-RANDOMIZED STUDY OF THE VALUE OF RADIATION THERAPY USING NEUTRONS
ALONE OR WITH PHOTONS (i.e., MIXED) OR OF EITHER IN COMBINATION WITH
SURGERY FOR THE TREATMENT OF CLINICAL STAGE B1, (GRADE III OR IV)
OR STAGE B2, C and D1 (ANY GRADE) URINARY BLADDER CARCINOMA

RTOG 77-05

closed

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REPOSITORY Fermi Lab NTF
COLLECTION Neutron Therapy Experimental
Protocols
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SCHEMA

CLINICAL STAGE B1 (GRADE III OR IV), OR STAGE B2, C and D1 (ANY GRADE) URINARY BLADDER CARCINOMA

	C*	
I	H	Preoperative Mixed Beam Irradiation **
II	O	Preoperative Neutron Irradiation
	O	
III	S	Mixed Beam Therapy Alone **
IV	E	Neutron Therapy Alone

* Groups have chosen:
MANTA - I
MDA - III
NAL - II, IV
Seattle - I, III

Doses -

Preoperative - 5000 rad eq. in 5-6 weeks. to bladder and pelvic lymph nodes.

Radiotherapy only - 5000 rad eq. in 5-6 weeks, to pelvic lymph nodes, 6500-7000 rad eq. in 6½-7 weeks to bladder.

** 3 photon, 2 neutron fractions per week

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1.0 INTRODUCTION

The anticipated 5 year survival rate of patients with clinical stage B1 (Grade III and IV), B2, or C bladder cancer at present is less than 30% whether treated primarily with resection (up to and including radical cystectomy) or irradiation. The demonstration of muscle invasion indicates that an aggressive tumor, with a potentially ominous outlook, is present. The final event in regional progression, that of multiple pelvic lymph node metastases, is an ever-escalating one as the depth of muscle invasion increases.

Efforts to extend the survival of these patients by performing extensive pelvic surgery were first systematically employed by Dr. Victor F. Marshall. Subsequently, as megavoltage energy radiations became available and were employed by skilled radiotherapists in patients with bladder carcinoma, it became evident that some patients were curable if treated by irradiation alone (Table 1). Differences in staging techniques and selection of patients, however, still make comparison of results of radiotherapy with those of resection inaccurate, if not impossible. It is clear, however, that for patients with advanced-stage tumors, neither approach yields a satisfactory control rate.

RESULTS OF IRRADIATION (5yr. Survival)

TABLE I

	<u>Clinical Stage 0, A, B1</u>	<u>Clinical Stage B2, C</u>
Dick (64 pts.) ²	71%	9%
Ellis (152 pts.) ³	36%	7%
Crigler, Miller, et al (126 pts.) ⁴	32%	18%
Finney (67 pts.) ⁵	28%	13%
Caldwell, Bagshaw, Kaplan (73 pts.) ⁶	50%	20%
Goffinet, et al (384 pts.) ⁷	40%	25%

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Because the results of irradiation or resection alone are not satisfactory, various combinations of both have been tried by clinicians in the hope that additive therapeutic effects might be obtained. 8-13 The results of these preliminary studies have been reported and the authors exhibit varying degrees of enthusiasm for the regimens they have selected. The studies are difficult to interpret because of poor study design, unrandomized selection of patients, exclusion of a high percentage of patients following entry into the protocol, small numbers of patients, small fields of irradiation, low doses of irradiation, etc.

The study of Miller and Johnson⁹ differs from the others, in that they clinically staged their patients and then randomly assigned them either to definitive irradiation or preoperative radiotherapy plus cystectomy. Their preliminary results indicate a clear benefit with the integrated approach as compared to irradiation alone (Table 2). Van der Werf-Messing's reports¹² have shown an apparent advantage for preoperative irradiation in conjunction with cystectomy in patients with advanced cancers. An excellent survival rate is seen by her in the patients whose tumors regressed clinically following pre-operative doses of 4000 rads in 4 weeks (5 fractions per week) to a "small pelvic field" although patient selection actually should have biased her statistics towards unfavorable results.

RESULTS OF TREATMENT WITH PREOPERATIVE IRRADIATION + CYSTECTOMY VS.
 IRRADIATION ALONE - RANDOMIZED CLINICAL STAGE (1964 - 1970) B2
 AND C DISEASE (MILLER & JOHNSON⁹)

TABLE 2

	<u>S U R V I V A L</u>	
	<u>3 Year</u>	<u>5 Year</u>
Preoperative Irradiation* + Cystectomy (35 pts.)	50%	50%
Irradiation Only (32 pts.)	25%	20%

*Includes 2 patients rescued by cystectomy.

A study by the Urologic Cancer Research Group, headed by Dr. George Prout⁸ has been interpreted as showing a benefit for preoperative irradiation plus appropriate operation versus appropriate operation alone. The question that the Bladder Cancer Collaborative Group A is now attempting to answer (this study also led by Dr. George Prout) is to see whether preoperative irradiation followed by cystectomy (or less than a cystectomy in some instances) is better therapy than irradiation alone. Dr. Prout and the other cooperating urologists believe that irradiation probably is as effective in curing bladder cancer as an operative approach alone (and without morbidity associated with loss of the urinary bladder)¹⁴, but want to document this. Also the expectation is that a improvement in survival with integrated therapy will result which will more than compensate for the added morbidity of that approach (and hopefully some patients may need less than a cystectomy with combined therapy).

Controversy obviously still exists as to how to best approach bladder cancer which invades the muscle.^{16 17} Irradiation alone is held by some as a valid option and others feel strongly that combined therapy is indicated. Cancer which extends beyond the bladder (D1) is generally treated by radiation alone and control of these extensive tumors is extremely poor. Furthermore, in order to enhance the possibility of local control using radiation therapy, the use of neutron therapy should be investigated.

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.

Because conventional treatment combinations for bladder cancer remain to be studied and since the most suitable method of using neutrons in the treatment of this disease is uncertain, information must be gathered to properly design a randomized study. RTOG protocol 76-12 will eventually provide some information concerning the use of conventional radiation therapy and surgery in the treatment of bladder carcinoma. This non-randomized study hopefully will provide the required information concerning the use of neutrons in this disease so that a randomized study can be proposed in 12 to 18 months. Each of the four neutron facilities will treat eligible patients according to one of the radiotherapy schemes while two of the facilities will also include patients who will have pre-operative radiotherapy followed by cystectomy for Stages B and C.

2.0 OBJECTIVES OF THE STUDY

- 2.1 To determine the morbidity for each treatment.
- 2.2 To gather information concerning neutron treatment to design a randomized study.

3.0 SELECTION OF PATIENTS

The basis of selection will be histologically-proven primary transitional or squamous cell carcinoma of the bladder.

3.1 CONDITIONS OF ELIGIBILITY

All patients must be

- 3.11 70 years of age or younger.
- 3.12 With clinical Stage B1 (with Grade III or IV histology) or clinical Stage B2, C, or D1 (any histologic grade disease) See Appendix I.

- 3.13 Considered suitable for high dose radiotherapy.
- 3.14 With a complete work-up as indicated in 4.0.
- 3.15 With informed consent to participate in the study.

3.2 CONDITIONS FOR INELIGIBILITY:

- 3.21 Any patient with prior pelvic irradiation
- 3.22 Any patient with prior open pelvic surgery excluding relatively minor and uncomplicated procedures such as appendectomy and excluding urinary diversion.
- 3.23 Any patient with a previous or concomitant malignancy other than skin cancer.
- 3.24 Any patient who is unlikely to be available for regular follow-up, with a Karnofsky status less than 50%, or who is considered a prohibitive risk for radiotherapy.
- 3.25 Any patient with para aortic lymph node involvement.

4.0 STAGING WORK-UP

4.1 MANDATORY STUDIES

- 4.11 History and physical examination
- 4.12 Histologic proof of squamous or transitional cell bladder carcinoma.
- 4.13 SMA-12.
- 4.14 Urinalysis
- 4.15 Chest x-ray: PA, lateral.
- 4.16 CBC
- 4.17 Excretory urogram (IVP) and/or retrograde studies.
- 4.18 Staging examination under anesthesia (urologist and radiotherapist to stage patient whenever feasible). See Appendix I.
- 4.19 Cystourethroscopy and transurethral resection of the bladder tumor for histological examination.

4.2 OPTIONAL STUDIES

- 4.21 Bipedal lymphangiography.
- 4.22 Barium enema in patients with history of diverticulitis or other G.I. disease.
- 4.23 Urine cytology.
- 4.24 Small bowel studies for bowel mobility.

5.0 TREATMENT SELECTION AND PATIENT REGISTRATION

5.1 Patients will be treated according to one of the following plans:

- 5.11 Pre-operative irradiation of the pelvis and bladder using a mixed beam.
- 5.12 Pre-operative irradiation of the pelvis and bladder using neutrons.
- 5.13 Definitive Irradiation of the pelvis and bladder using a mixed beam.
- 5.14 Definitive Irradiation of the pelvis and bladder using neutrons.

5.2 A facility may participate in one of the pre-operative options and/or one of the irradiation only options. Facilities have initially selected the following treatments:

- 5.21 MANTA: Pre-operative mixed beam therapy.
- 5.22 MD Anderson: Definitive mixed beam therapy.
- 5.23 NAL: Pre-operative neutron therapy and definitive neutron therapy.
- 5.24 Seattle: Pre-operative mixed beam therapy and definitive mixed beam therapy.

5.3 There will be no randomization in this study. Once a patient has been found acceptable for this study by all investigators, the RTOG operational office (215-574-3191) must be called to register the patient. The following information must be given to the Operations Office:

Protocol Identification
Investigator
Patient's Name
Treatment Assignment

A case number will be assigned. This subsequently will be confirmed by mail.

6.0 RADIATION THERAPY

A urinary diversion may be done prior to the preoperative irradiation.

6.1 Portals - A contrast cystogram is required for localization:

6.11 Preoperative irradiation: The entire pelvis will be uniformly irradiated with opposed beams or a four field technique the lateral portals are at least 11 x 14 cm. in size and the anterior margin of the field is at least to the anterior border of the pubis (planning films may show the bladder even anterior to this in some patients). Anterior and posterior fields must be at least 14 x 14 cm. in size, encompassing all of the pelvic lymph nodes at risk. The lower border should be at least to the bottom of the obturator foramen, at the top of the L5-S1 interspace, and the lateral margins should extend 1 cm. lateral to the maximum width of the osseous pelvis. Boost therapy to a small field may be indicated if the lymphangiogram is positive.

6.12 Definitive Irradiation: The pelvis should be treated as in 6.11. Bladder boost therapy can be with multiple fields. The minimum field size permitted is 7 x 7 cm. and the bladder should be emptied before each treatment.

6.2 DOSE

6.21 Preoperative therapy.
5000 rad equivalent of neutrons or neutrons

plus photons (mixed beam) to the pelvis in 5 to 6 weeks with the dose calculated at the midplane of the central axis. Small field boost therapy to an additional 1,000 rads to positive areas on the lymphangiogram is permitted.

- 6.22 Definitive Irradiation:
Neutron equivalent or neutron plus photon (mixed beam) equivalent of 5,000 rads to the pelvis in 5 to 6 weeks followed by an additional six to eight fractions to the bladder using smaller fields, giving an estimated total equivalent dose of 6,500 to 7,000 rads in 6 1/2 to 7 weeks.

6.3 PHYSICAL PARAMETERS

- 6.31 Portal films will be obtained for each treatment field and must be submitted for review.
- 6.32 Isodose distributions for the treatment technique used will be calculated and submitted.
- 6.33 At least weekly check films are encouraged.
- 6.34 Neutrons therapy will use four fractions per week. (250 rad equivalent per fraction).
- 6.35 Mixed beams therapy will use 3 photon and 2 neutron fractions per week (200 rad equivalent per fraction).

External Radiation Sources

- 6.361 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 SSD of 80 cm. or greater.

6.362 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 125cm.

6.37 Fractional neutron doses considered equivalent to 250 rad photon irradiation are:

MANTA	78 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 when only neutrons are used.

6.38 Fractional neutron doses considered equivalent to 200 rad photon irradiations are:

MANTA	63 rads
NAL	65 rads
SEATTLE	60 rads
TAMVEC	65 rads

The neutron contribution shall not be less than 30% of the total external beam tumor dose when a mixed beam is used.

6.4 CRITICAL STRUCTURES AND TOLERANCE

6.41 Rectum: The dose to the rectum in its entirety should not exceed 5,500 rads equivalent neutron dose. Portions of the anterior wall of the rectum will receive the same dose as the bladder.

6.42 Small Bowel: The dose to any segment of the small bowel should not exceed 5,000 rads equivalent neutron dose. Efforts should be made to exclude the small bowel from the true pelvis by such maneuvers as treating the patient in a prone position, equipment permitting. Evaluation of small bowel location in patients with previous small bowel disease or previous abdominal surgery should be made by barium studies.

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6.43 Bone Marrow: The bone marrow will be unavoidably irradiated in all field arrangements. The percentage of bone marrow radiated will be about 20% with pelvic irradiation. The dose to these bone marrow areas will produce decreased function for at least two years.

6.5 IRRADIATION AND TIME OF OPERATIVE PROCEDURE WITH INTEGRATED THERAPY

6.51 Following preoperative irradiation, the operative procedure (see 7.0) should be performed within 4 to 6 weeks.

6.6 DOSE MODIFICATION

Daily doses may be reduced or treatment interrupted for treatment related signs or symptoms such as diarrhea, urinary frequency or urodyma. If interruption of treatment does not allow fulfillment of dose-time requirements (6.2), the patient will be kept on protocol and analyzed separately from other protocol patients.

7.0 STANDARD OPERATIVE PROCEDURE

Each surgeon should perform the operative procedure he considers best for each patient. This should be done between 4 and 6 weeks after the conclusion of irradiation. During the operation, information concerning metastases to lymph nodes and other organs should be sought and recorded. The exact anatomical site of all tissues removed should be identified and the specimens separately submitted. Silver clips should be used to mark suspicious areas. Operative findings will be recorded on the appropriate RTOG form.

- a. Simple cystectomy includes removal of the bladder, peritoneum, and perivesical fat as well as the prostate and seminal vesicles in the male. It may include portions of the vagina, cervix, uterus, tubes and ovaries in the female when their removal seems indicated. Isolated pelvic nodes may be removed without systematic lymphadenectomy.

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b. Radical cystectomy in the male includes removal of the peritoneum fat and lymph nodes of an area within the pelvis subtended by the medial border of the psoas to a point level with the mid-portion of the common iliac artery on either side of the pelvis and extending down into the cul-de-sac so that the bladder, seminal vesicles, prostate and ends of the ureter as well as all of the associated peritoneum and perivesical fat are removed en bloc. Lymphadenectomy should include the obturator space and the nodes of the hypogastric and external iliac vessels at a minimum. A portion of the penile urthra should be included.

In the female, in addition to the peritoneum, fat and lymph nodes of the vessels and spaces mentioned above, the bladder, anterior and lateral wall of the vagina as well as the uterus, tubes and ovaries will be included in the surgical specimen. This is a minimal dissection to qualify for radical cystectomy.

c. Segmental resection includes removal of the full thickness of bladder wall, perivesical fat, peritoneum without node dissection. Ureteroneocystotomy may be necessary in some cases.

8.0 STUDY PARAMETERS

<u>Parameter</u>	<u>Before Therapy</u>	<u>End of Therapy</u>	<u>At Follow-up</u>	<u>At 6 months, then yearly or on indication</u>
History	X	X	X	
Rectal exam	X		X	
SMA-12	X			X
Urinalysis	X			X
Chest x-ray	X			
Plain film of abdomen		X(a)	X(a)	
Excretory urogram (IVP and/or retrograde)	X			X

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<u>Parameter</u>	<u>Before Therapy</u>	<u>End of Therapy</u>	<u>At Follow-up</u>
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Cystoscopy	X		X(b)
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Performance status	X	X	X
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(a) if lymphogram done

(b) if irradiation only option

every 3-4 months post treatment for 2 years;

intervals extended to every 6 months

2 years after treatment.

9.0 SPECIFIC ENDPOINTS TO BE MEASURED:

9.1 Local control of tumor

9.2 Urinary complications or morbidity

9.3 G.I. complications or morbidity

9.4 Pathologic findings at surgery; degree of penetration of tumor through bladder wall, location of positive lymph nodes.

10.0 FOLLOW-UP EXAMINATION

10.1 Every month following onset of treatment until conclusion of treatment regimen..

10.2 Every 3-4 months, after conclusion of treatment, for 2 years.

10.3 Every 6 months thereafter for the rest of the patient's life.

11.0 TREATMENT FAILURE

With proven recurrence of disease or the development of distant metastases, the patient is eligible for any additional appropriate therapy.

12.0 STATISTICAL CONSIDERATIONS

This is a non-randomized study in which all eligible patients will be treated according to the treatment option selected by each of the facilities. It is estimated that the objectives of the study (i.e., treatment tolerance and short term complications) require 10 - 15 patients per treatment arm and that this can be completed within 18 months.

13.0 PATIENT CONSENT FORM

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

14.0 STATISTICAL FORMS

Data will be submitted to the Operations Office in the following manner:

Bladder On-study Form & Treatment Planning Information	Within 1 week of registration
Bladder Radiotherapy Form & Treatment sheets	At the end of radiotherapy
Bladder Surgery Form	One week post-surgery, if applicable
Bladder Follow-up Form	At each stipulated follow-up visit (see Section 10.0) & at recurrence/ relapse
Bladder Death Form	At death

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APPENDIX I

STAGING CLASSIFICATION FOR BLADDER TUMORS:

Comparison of Marshall-Jewett and UICC Systems

MARSHALL-JEWETT

UICC

- | | |
|--|--|
| A - Microscopically, the tumor does not extend beyond the lamina propia | T1 - On bimanual examination, a freely-mobile mass may be felt: this should not be felt after complete transurethral resection of the lesion. |
| B1 - There is microscopic invasion of superficial muscle. | T2 - On bimanual examination, there is induration of the bladder wall which is mobile. There is not residual induration after complete transurethral resection of the lesion. |
| B2 - There is microscopic invasion of deep muscle | T3 - On bimanual examination induration <u>or</u> a nodular mobile mass is palpable in the bladder wall which persists after transurethral resection of the exophytic portion of the lesion. |
| C - There is extension through the bladder wall | T4 - Tumor fixed or invading adjacent structures |
| D1 - There is microscopic evidence of tumor invading prostate, uterus or vagina. | |
| D2 - There is microscopic evidence of tumor fixed to the pelvic wall and/or infiltrating the abdominal wall. | |

In this protocol, the Marshall-Jewett system is used; although it is primarily a surgical system, it has a clinical and pathologic correlate with the UICC TNM system in the T Category.

APPENDIX II

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 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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