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RTOG 78-26: Revisions/Clarifications - September 11, 1979 713035

The following revisions have been made:

Schema, Item C will read as follows:

> Minimum of 2000 peak pion rad to the large field plus 1500 rad boost at 100 rad/day, calculated at the 80% isodose line (Maximum total 4375 at 125 rad/day at the 100% isodose line).

The above revisions also apply to Section 6.3 Pion Therapy, Paragraph I.

FILE BARCODE
00133290

To be attached to the front of the above named protocol.

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-26

PI MESON RADIOTHERAPY* OF T-3 and T-4 TRANSITIONAL CELL CARCINOMA OF THE BLADDER

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PI MESON RADIOTHERAPY OF T-3 and T-4 TRANSITIONAL CELL CARCINOMA OF THE BLADDER

SCHEMA

Stratify:

- Histologic Grade
  low, intermediate vs. high
- Lymphangiogram
  pelvic nodes positive vs. negative or equivocal
- Primary Tumor
  T-3 vs. T-4

RANDOMIZE

- Photon Radiotherapy
  6000 rad/6½-7 wks to bladder
  4500-5000 rad/5-6 wks to pelvis
  ±4500 rad/5 wks to para-aortic nodes[a]
- Pion Therapy[a, b, c]

[a]Included if pelvic nodes positive on lymphangiogram.

[b]Nodes may be treated with pions or conventional radiotherapy.

[c]Minimum of 2000 peak pion rad to initial large portal, followed by boost of minimum of 1300 peak pion rad to gross tumor, both at a minimum of 85 peak pion rad/day. The minimum dose is approximately 2 cm peripheral to the 90% isodose line.

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1.0 INTRODUCTION

1.1 Definition of the Problem.

Failure to locally control advanced (T_3-T_4 and B_2 - C Stages) carcinoma of the bladder remains disappointingly high, at least 50% in many published series (1). Although metastases are not uncommon, persistent disease tends to remain localized to the pelvis (bladder, soft tissues and lymph nodes). The therapeutic challenge of bladder cancer is predominantly one of obtaining local control. Table 1 summarizes the survival in several major series as a function of therapeutic approach. Survival rates in locally advanced (T_3, T_4 or B_2 and C) stages may range between 19-31%. Several authors (see Table 1) have shown that the prognosis in bladder cancer is closely dictated by the local extent of the disease.

Bladder cancers (squamous and transitional cell types) are difficult to cure using conventional radiotherapy modalities for at least three reasons as follows:

1.1.1 The normal surrounding structures (small bowel and rectum) limit the maximum safe dose which can be delivered with an acceptable morbidity.

1.1.2 The cancer deposits seem to become more resistant to photon therapy as the tumor cells extend deeply into the smooth muscle wall of the bladder proper.

1.1.3 Hypoxic areas develop as the mucosal tumor deposits increase in size.

It is anticipated that pi meson therapy may be effective in overcoming some or all of these problems, thereby improving local control and cure of these more advanced bladder cancers.

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Table 1: Summary of Survival Rates for Carcinoma of the Bladder.

Source	Stage	No. Cases	Survival
Whitmore & Marshall (1962) (Cystectomy) 3-year results (2)	0,A,B1	68	43%
	B2-C	140	22%
	D1	20	5%
Bowles & Cordonnier (1963) (Cystectomy) 5-year results (3)	0,A,B1	40	52%
	B2-C	30	30%
Riches (1958) (Partial Cystectomy)(4)	T0 and T1	17	58%
	T2	56	36%
	T3-4	15	0%
Finney & Jones (1962) (Radiation) (5)	T1	41	34%
	T2	72	17%
	T3	21	19%
Caldwell, et al. (1967) (Radiation) 3-year results (6)	0,A,B1	38	50%
	B2-C	77	31%
	D1	15	7%

1.2 Rationale for Pion Radiotherapy.

The rationale for pion radiotherapy is primarily related to two factors: 1) a different biological response in the stopping region of the pion beam from that seen in conventional radiation, and 2) the capability for localizing this differential response within the target volume, largely sparing normal surrounding tissues.

With high-linear-energy-transfer (high-LET) radiation (for example, neutrons, pions, and heavy ions), there is increased irreparable damage of critical molecules (i.e., double-strand breaks in DNA), as compared to the type of damage caused by low-LET radiation (e.g., x-rays, gamma rays of cobalt, electrons, and protons). In addition, cells exposed to low-LET radiation exhibit up to three times more resistance to injury if they are not well oxygenated. Thus, hypoxic cells, large numbers of which are usually present in tumors, are less sensitive to damage than are well oxygenated cells of the tumor and the surrounding normal tissue. The dense ionization of high-LET radiation overcomes the protective effect of hypoxia, killing those cells almost as effectively as well oxygenated cells. Further, cells are more resistant to low-LET radiation in certain phases of the cell cycle than in others. High-LET radiation reduces differences in cellular sensitivity due to cell cycle variations.

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Heavy charged particles, such as pions and heavy ions, distribute their dose with a Bragg peak, a region of intense radiation which can be located in the tumor volume. In contrast, neutrons, which have no charge, deposit dose in tissue exponentially, similarly to dose absorption of the gamma rays of cobalt.

Pions have the advantages of both high-LET and low-LET radiation, because they deposit a low-LET component in the stopping (tumor) region. Due to their negative charge, the stopping pions are absorbed by the positively charged nuclei of oxygen, carbon, and nitrogen atoms. This excess energy makes the nuclei unstable and they disintegrate, producing neutrons, protons, deuterons, tritons, alpha particles and heavy ions. These events increase the total dose in the pion stopping region and alter the biological effectiveness of the dose in that region because of the dense ionization produced by the alpha particles heavy ions and neutrons.

Results to date of Phase I-II studies of pion radiotherapy, being conducted at the Los Alamos Meson Physics Facility (LAMPF), by the University of New Mexico Cancer Research and Treatment Center, suggest therapeutic advantages in the treatment of many advanced solid tumors with pion radiotherapy. Patients with primary and metastatic tumors of the skin, head and neck, lung, abdomen and pelvis have been irradiated with pions to assess tolerance of normal tissues and tumor response. Early studies with metastatic tumor nodules in the skin established a relative biological effectiveness (RBE) of 1.42 for pions, as compared to 100 kVp x-rays, for acute skin injury (7). Subsequently, analysis of time to regrowth of 16 nodules (primary breast) in one patient participating in that study who could be followed for 346 days suggested the possibility of therapeutic gain of 37% for pions versus x-rays (8).

An analysis of 52 evaluable tumors in 20 patients (including those in the skin metastases series) treated with pions only and followed for 3 to 22 months showed 42 tumors completely

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regressed, 3 tumors partially regressed, and 7 tumors did not respond, although 5 of the 7 showed no growth for 10 months (9). A more recent report on 40 patients treated for large deep-seated lesions, all of whom were followed for 6 to 15 months, showed that pion radiotherapy was well tolerated at doses ranging from 1000 to 4600 peak pion rad, delivered generally in five fractions per week with daily fraction sizes of 110 to 140 peak pion rad maximum. Complete regressions occurred in approximately half those patients treated with pions alone at maximum doses of more than 2700 peak pion rad. No complete regressions occurred in patients treated with pions alone at doses under 2700 peak pion rad. Conventional radiation and/or surgery was well tolerated by those patients requiring those treatments after pion radiotherapy. Reactions in the normal tissues within the plateau and the peak regions have been relaatively mild, compared to those which would be expected with conventional radiation for similar tumor response. No patient with a pelvic tumor has exhibited any serious untoward radiation reaction over observation times ranging up to 26 months (10). However, one patient who had undergone surgical exploration and was found to be non-resectable one month prior to pion radiotherapy and was re-explored one month after pion radiotherapy and again found to be non-resectable. The patient suffered complications and expired two months after the re-exploration.

It is estimated that some 60,000 persons die in the United States each year because of lack of tumor control at the primary site. Pions are being tested on those types of large tumors which are not well managed by any other treatment or combination of treatments, to attempt to improve the survival in this group of patients. In addition, any large reduction in the body's total burden of tumor cells improves the chances for cure by conventional techniques (surgery, radiotherapy, and chemotherapy, alone or in combination). Thus, potentially additional patients can be helped by pion radiotherapy if their large tumor masses can be eliminated or significantly reduced.

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2.0 OBJECTIVES

The objectives of this study are to determine if pion radiotherapy can improve local control and survival in patients with carcinoma of the urinary bladder.

The study will evaluate the effects of pion radiotherapy upon:

2.1 Length of survival.

2.2 Quality of survival (Karnofsky ratings).

2.3 Radiation tolerance and complications.

2.4 Change in tumor size (clinically and on x-rays)

2.5 Incidence and response of metastasis in regional nodes.

2.6 Incidence of distant metastasis.

2.7 Incidence of local recurrence.

2.8 Radiotherapy effect upon normal tissues included within radiotherapy beam (bowel, rectum, etc.).

3.0 PATIENT SELECTION (ELIGIBILITY)

3.1 General Condition of Eligibility.

Only patients with transitional cell of the urinary bladder are eligible for this study. Their disease (according to AJC definition (see Appendix I) must be established as T3 or T4 primaries, with no metastases extending beyond the pelvic nodes.

3.2 Conditions for Patient Eligibility.

In addition to the above general condition, the following conditions must be met before a patient can be admitted to the study:

3.2.1 Biopsy proof of transitional cell carcinoma.

3.2.2 Performance of superficial fulguration, in indicated cases, will not be cause for exclusion. Patients explored for cystectomy and found to be non-resectable because of local extent or pelvic node metastases would be ideal candidates for this protocol.

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3.2.3 Reasonable expectation of completing the study treatment and the required follow-up examinations (including travel to and treatment at Los Alamos, as well as an annual follow-up examination at the study center in Albuquerque, if the patient is assigned to pion radiotherapy).

3.2.4 Agreement of the patient and his physician to the conditions of the study, including the diagnostic and therapeutic randomizations.

3.2.5 Agreement of the patient's physician to relinquish management of the patient's treatment to the study team.

3.2.6 Understanding by the patient of the provisions of the study and completion of the required investigational treatment consent form.

3.2.7 General medical condition sufficient to tolerate a full course of radiotherapy.

3.2.8 Age at diagnosis of $\geq$ 18 and $\leq$ 75 years.

3.2.9 Pulmonary function capacity sufficient to allow performance of bipedal lymphogram.

3.2.10 Karnofsky performance rating of 60 or greater (see Appendix II).

3.3 Conditions for Patient Ineligibility.

The following conditions are cause for exclusion of the patient from the study:

3.3.1 Evidence of metastasis beyond the pelvic lymph nodes.

3.3.2. Previous definitive therapy of the primary tumor and regional adenopathy, including prior definitive radiation therapy or potentially curative surgical procedures (except for superficial fulguration).

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3.3.3 Histologic type other than transitional cell types.

3.3.4 Previous chemotherapy, which, in the opinion of the study team, might compromise treatment or evaluation.

3.3.5 Previous radiotherapy to areas overlapping the projected treatment portals.

3.3.6 Active, uncontrollable infection in the area of contemplated irradiation.

3.3.7 Medical, psychological, or other contraindication to the contemplated diagnostic or therapeutic measures and their evaluation.

3.3.8 Evidence of a second malignancy, other than skin cancer. (For patients with second malignancies other than skin cancer, the disease-free interval must exceed eight years. For patients with skin cancer, the disease must have been under control for at least three years. Skin cancer, for purposes of this study, does not include melanoma or cancer of the lip.)

4.0 PRETREATMENT EVALUATION

Consistent with good medical practice, the following will be performed on initial evaluation prior to admitting the patient to the study. Results of the evaluation will be used to determine patient eligibility for the study and in management of the treatment regimen.

4.1 Medical History.

4.1.1 Age.

4.1.2 Sex.

4.1.3 Race.

4.1.4 Date of onset of symptoms (month and year in which the patient first noticed the onset of definite symptoms or signs which are later explained by the disease).

4.1.5 Date (month and year) of definite diagnosis of disease.

4.1.6 Description of symptoms (including pain).

4.1.7 Other illnesses.

4.1.8 Medications currently used.

4.1.9 Previous therapy (if any).

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4.3 Routine Laboratory Tests.

4.3.1 CBC.

4.3.2 BUN.

4.3.3 Creatinine.

4.4 Routine Imaging Procedures.

4.4.1 Chest x-ray (posterior-anterior and lateral).

4.4.2 Cystogram.

4.4.3 Intravenous pyelogram.

4.4.4 Lymphangiogram (lower extremity, bipedal).

4.4.5 CT scan if available; if not, this will be performed at the Study Center.

4.5 Optional Studies.

4.5.1 Cardiopulmonary assessment if indicated to tolerate 7000 feet altitude of Los Alamos.

4.5.2 Other studies as indicated.

4.6 Staging Procedures.

Staging for this protocol is derived from the AJC clinical staging system (Appendix I). As the urinary bladder is a deep-seated organ, the following examinations are mandatory: (1) cystoscopy, (2) bimanual examination under anesthesia, and (3) biopsy. A lymphangiogram will also be required for this study to assess spread of disease to beyond the pelvic lymph nodes.

4.6.1 Cystoscopy with biopsy of primary tumor. Since bladder carcinomas can be multifocal or spread by submucosal lymphatics to remote portions of the bladder, at least two biopsies from areas remote from the gross tumor are recommended.

5.0 ADMISSION TO STUDY AND RANDOMIZATION

Patients will be admitted to the study only after the pretreatment evaluation is completed and the eligibility criteria are met. Copies of all necessary forms will be forwarded to RTOG Headquarters.

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5.1 All therapy will be scheduled through the Cancer Research and Treatment Center in Albuquerque. It is planned to have all patients receive radiotherapy planning CT scans and localization in Los Alamos even if randomized to conventional treatment at the referring institution. Ophthalmologic examination to assess lens opacity will be performed upon admission to the study. The following steps must be completed:

5.1.1 Identification and registration (see 5.1.2) of all patients entering the participating institution with a diagnosis of carcinoma of the bladder.

5.1.2 Completion of RTOG initial registry form. (Patients who are determined by their physician ineligible will be eliminated at this point. The RTOG initial registry form must list the reason(s) for ineligibility and be forwarded to RTOG Headquarters for use in population control.)

5.1.3 Pretreatment evaluation.

5.1.4 Completion of the study entrance form (patient name and address, referring institution, referring physician, etc.).

5.1.5 Completion of patient consent form.

5.1.6 Notification of Dr. Kligerman or his designee (preferred 505/277-3539 or 505/667-7392) in Los Alamos, of potentially eligible patients who have agreed to participate in this study.

5.2 When a patient has been fully evaluated and determined to be eligible and the forms completed as specified in 5.1, Dr. Kligerman or his designee at the pion facility will complete and submit the on-study form and will phone RTOG Headquarters and relate the following information:

5.2.1 Patient's Name.

5.2.2 Institution and Radiotherapist.

5.2.3 Histologic Grade (Low, Intermediate, or High).

5.2.4 Lymphangiogram findings (negative para-aortic nodes).

5.2.5 Primary Tumor (T3 vs. T4).

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A project case number and one of the following treatments will be assigned by RTOG Headquarters:

(a) conventional therapy at their parent institutions, or

(b) mesons at the Los Alamos, New Mexico facility.

This will be confirmed by mail to Dr. Kligerman and the referring physician.

6.0 TREATMENT DETAILS

6.1 Target Volume.

The target volume will be a minimum of 1 cm beyond the boundary of the gross tumor volume or as large as needed to include that volume of tissue beyond which the radiotherapist believes microscopic tumor does not extend and the regional lymph nodes. The para-aortic nodes will be treated if the pelvic nodes are positive on lymphangiogram.

6.2 Conventional Radiotherapy.

6.2.1 Equipment. Equipment will be 4 MeV or greater, or Cobalt 60. Minimum SSD will be 80 cm or 80 cm to axis for SAD techniques.

6.2.2 Dose and Dose Time Factors. Dose to be specified at the midplane of the pelvis along the central axis for AP/PA opposed field techniques or at the intersection of the fields for alternative techniques. The dose will be 4500 rad in 25 fractions given in 5 weeks at 180 rad per day or 5100 rad in 30 fractions in 6 weeks at 170 rad per day, plus an additional 1000 to 1500 rad in 1 to 1½ weeks coned-down to the tumor and positive nodes for a minimum total dose of 6000 rad. The dose to the para-aortic area, if treated, shall be 4500 rad in 5 weeks at 180 rad per fraction. The dose across the target volume should not vary more than ± 10% from these values.

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6.2.3 Field Definition.

6.2.3.1 Pelvic Field. At minimum, the inferior extent should be the lower margin of the obturator foramen or 3 cm below the known inferior extent of the tumor. The superior extent should be at the level of the superior cortical plate of L5. One and one half cm lateral to the extent of the pelvic nodes will be sufficient to cover the nodes when visible on lymphangiogram or 1.5 cm lateral to the iliopectineal line when not visualized.

6.2.3.2 Bladder Boost. The coned-down boost should be adequate to cover the residual tumor and any positive lymph nodes.

6.2.3.3 Para-aortic Fields. When pelvic nodes are positive the para-aortic region will be included in the treatment volume with an appropriate gap above the superior border of the pelvic field. Alternatively, the pelvic para-aortic regions may be included in a composite shaped field. The superior margin of the para-aortic field shall be at the top of L1. Lateral borders will encompass the visible nodes plus 1.5 cm margins with a minimal field width.

6.2.4 Technique. The preferred technique of therapy should consist of a 4-field box technique. Alternative techniques may be used if the clinical situation demands. The boost should be delivered by a 3-field, 4-field, or rotational technique.

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6.2.5 Recommended Dose to Critical Tissues. Small bowel and rectal dose should be limited to 5000 rad in 6 weeks maximum, except for normal bowel segments located within the boost-volume fields.

6.2.6 Treatment Planning. Localizing films of each field will be taken and sent to the RTOG Office in the first week of therapy together with a copy of the treatment plan. Isodose distributions will be submitted to RTOG Headquarters with the Radiotherapy Form at the completion of radiotherapy.

6.2.7 Dosimetry Monitoring. The Radiological Physics Center in Houston will conduct field surveys to verify the accuracy of dosimetry at each participating institution.

6.3 Pion Therapy.

The tumor dose to the initial large field will be 2000 minimum peak pion rad at a daily minimum tumor dose of 85 peak pion rad. The target volume will be the same as described above under 6.2.3. The peak pion dose could be limited to the primary tumor and the local lymphatic spread in those instances where such lymphatic spread is contiguous with or near the gross tumor and which will be 2 cm from the 95% isodose line. In the latter case the remaining pelvic area and the para-aortic nodal area will be treated prophylactically with conventional radiation to the dose level described above for conventional radiation. Patients will then receive a peak pion cone-down to the primary tumor and any known gross disease to an additional minimum 1300 peak pion rad . The boost volume will be as described under 6.2.4 above. For the pion radiotherapy, split course treatment may be needed to conform to accelerator operating schedules.

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7.0 ENDPOINTS OF STUDY AND RESPONSE CRITERIA

Primary endpoints will be derived from:

7.1 Patient survival time.

7.2 Quality of survival

7.2.1 Karnofsky function assessment.

7.2.2 Subjective assessment.

7.3 Local Tumor Response.

The rate of regression of the primary tumor and regional nodes at each assessment will be determined by measurements of the primary tumor and any palpable nodes, in maximum dimensions and dimensions at right angles and when possible third dimensions; otherwise by subjective assessment of percentage regression. This assessment will be performed immediately after treatment and at each follow-up visit.

7.3.1 Complete response (CR) - Complete disappearance of all measurable and palpable tumor.

7.3.2 Partial response (PR) - Tumor shrinkage greater than 50% of the product of the perpendicular diameters of the two largest dimensions.

7.3.3 Minor response (MR) - Tumor shrinkage greater than 25% but less than 50% of the product of the perpendicular diameters of the two largest dimensions.

7.3.4 No change (NC) - 25% growth to 25% shrinkage of the product of the perpendicular diameters of the two largest dimensions.

7.3.5 Progressive disease (PD) - Growth of tumor greater than 25% of the product of the perpendicular diameters of the two largest dimensions.

7.4 Response of regional node metastasis.

7.5 Lymph node change as seen on repeat KUB or other follow-up x-ray studies, including CT scan or cystogram (or IVP).

7.6 Incidence of distant metastasis.

7.7 Incidence of local recurrence.

7.8 Acute and late response of normal tissue (see Appendix III).

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8.0 POST-TREATMENT EVALUATION

Parameters to be recorded at each follow-up evaluation while on study include:

8.1 Medical history data (see section 4.1), including Karnofsky status.

8.2 Physical examination including vaginal examination for female patients.

8.3 Laboratory tests, as indicated.

8.4 Imaging procedures, as indicated.

- 8.4.1 Chest x-ray (posterior-anterior and lateral).
- 8.4.2 Intravenous pyelogram (except for patients who are dye sensitive).
- 8.4.3 Repeat CT Scan.
- 8.4.4 Cystoscopy, as indicated.

8.5 Cystoscopy as indicated (when invasion of the bladder is involved).

8.6 Summary of Evaluation Parameters

	Pre-Treatment	At Completion	Follow-Up
History & Physical*	x	x	x
Performance Status	x	x	x
CBC	x		a
BUN, Creatinine	x		a
Cardiopulmonary Assessment	x		
CT Scan	x	a	a
Chest x-ray	x		a
IVP	x		a
LAG	x		b**
Cystogram	x		
Cystoscopy	x	x	a
Metastatic Surveys (liver, bone, brain, etc.)	a		a
Ophthalmologic Exam	c		c

* Vaginal Exam for Female Patients.

(a) If clinically indicated.

(b**) KUB or Plain abdomen/pelvis, radiograph as indicated.

(c) Prior to treatment and yearly thereafter.

(x) Required, consistent with good medical practice.

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9.0 FOLLOW-UP SCHEDULE

Patients receiving pion radiotherapy will receive an annual physical examination by a Study Center radiation oncologist at the study center in Albuquerque or at a regional clinic closer to the patient's home. Deaths of patients treated with either pion radiotherapy or conventional therapy will be reported.

The purpose of follow-up assessments is to determine:

9.1 Gross tumor response to treatment.

9.2 Time of distant spread and involved organs and nodes.

9.3 Long-term normal tissue effects of radiotherapy (see Appendix II).

9.4 Time and site of local recurrence (if any) as accurately as possible.

9.5 Patient functional status during survival; subjective appraisal of such symptoms as bleeding or pain.

9.6 Time of survival in years.

9.7 The first day of definitive treatment is considered Day 1. Follow-up assessments should be scheduled within two weeks of the specified times and will be reported:

- 9.7.1 Immediately after treatment, then monthly for six months counting from Day 1.
- 9.7.2 Every three months for the next 18 months.
- 9.7.3 Every six months for the next year (when patient survival time reaches three years after Day 1).
- 9.7.4 If data analysis warrants, patients will continue to be followed at six-month intervals until survival reaches five years after Day 1.

9.8 If a study patient cannot return to the participating hospital where he was entered on the study, arrangements will be made to have him examined at another hospital or by his private physician and a report of this examination submitted. The following information will be recorded on the follow-up form at each visit (unless indicated otherwise):

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9.8.1 Brief interim history (weight loss, abdominal pain, weakness, diarrhea, constipation, obstruction, other).

9.8.2 Physical examination (same as 4.2).

9.8.3 Performance status (Karnofsky function assessment).

9.8.4 Laboratory tests as indicated.

9.8.5 Imaging procedures as indicated (same as 8.4).

9.8.6 Ophthalmologic exam to assess lens opacity (annually).

9.8.7 Progress toward endpoints (complications, tumor response, etc.) will be recorded and reported at each follow-up visit. If a recurrence develops, a biopsy should be taken and the date of recurrence should be fixed as closely as possible. Patients receiving pion radiotherapy will receive an annual physical examination by a radiation oncologist at the Study Center in Albuquerque or at a regional clinic closer to the patient's home.

10.0 PATHOLOGY

10.1 Pathology data will be derived from:

10.1.1 Biopsy Specimens. Biopsy specimens will be examined by pathologists at the participating institutions to substantiate the diagnoses. Representative slides for patients entered onto the study will be forwarded to RTOG Headquarters for review by the study pathologist. Copies of biopsy reports will be submitted to RTOG Headquarters and the referring and/or follow-up physician.

10.1.2 Surgical Specimens. Any tissue surgically removed from anatomic sites will be examined by pathologists at the participating institutions where the surgery was performed. A description of the surgical specimen and microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist.

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10.1.3 Autopsies. Autopsies should be performed on all study patients by pathologists at the participating institutions. The postmortem study should include a description of irradiated tissues and pattern of tumor spread (see Appendix IV). Autopsy reports and representative microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist.

11.0 FORMS

A copy of each study form must be submitted to RTOG Headquarters. Data will be recorded on standard forms to be supplied to each participating institution. The following records will be generated by the study team and participating institutions for storage, retrieval, and analysis:

11.1 RTOG initial registry form (submitted for both eligible and ineligible patients entering each participating institution).

11.2 On study form.

11.3 Treatment prescription.

11.4 Localization films.

Localization films of each field will be taken and sent to the RTOG office in the first week of therapy together with a copy of the treatment plan.

11.5 Treatment summary form.

11.5.1 Radiation therapy administered (type of energy, daily schedule of treatment, maximum dose, complications during radiation therapy, a description of the lesion at the end of treatment, patient's weight at the end of treatment, performance at end of treatment, complications following therapy and their management, copies of port films and isodose curves, etc.). Isodose distributions should be attached.

11.5.2 Operative procedures and findings, if applicable (extent of disease, presence of metastases, type and extent of surgery performed, etc.).

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11.5.3 Postoperative data (complications following surgery, patient weight at time of discharge, performance at time of discharge, etc.).

11.5.4 Drugs administered, if any (a description of type and dose of any drugs administered, duration and purpose, including any chemotherapy administered in the event of lack of tumor control).

11.6 Follow-up assessment form (see Section 9.0).

11.7 Pathology forms (see Section 10.0).

11.8 Summary of forms submission.

Form	Due
Initial registry	Within two weeks of evaluation
On study form Study entrance form Radiotherapy prescription Copies of localization films Pathology slides and report	Within two weeks of randomization
Treatment summary form Copy of radiotherapy record Copy of boost fields Isodose distribution	Within two weeks of completion of radiotherapy
Follow-up assessment	Within two weeks of times in 9.7
Surgery form Pathology slides and report	Within one month of surgery
Death form	Within one month of death

12.0 ADDITIONAL THERAPY ALLOWED

Therapy is to be administered as detailed in section 6.0. Subsequent therapy shall proceed at the discretion of the patient's responsible physician. Indications for subsequent therapy and the therapy performed should be documented in the patient's follow-up records.

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13.0 STATISTICAL CONSIDERATIONS

Based on available literature and the likelihood that only patients with more advanced tumors will be referred, members of the Committee on Human Trials of Pion Radiation Therapy, UNM/LASL have determined that a cumulative five-year survival rate of about 14 percent is currently experienced by patients to be treated in this study.

The committee further determined that an improvement of 100 percent (or, survival of about 30 percent) should be sought for patients assigned to pion radiotherapy, compared with results for the conventional treatment control group.

The following table shows the statistical power (i.e., the probability of detecting the desired improvement, if it exists) as a function of the accrual rate, the period of patient accession and the years of additional follow-up. It assumes a one-sided test of significance (P=0.05) and survival times which follow a negative exponential distribution.

ACCRUAL (Pts/Year)	Years of Accession	Additional Years of Follow-Up 1	2	3	4
40	2	42%	51%	57%	61%
	3	60%	69%	74%	77%
	4	75%	82%	85%	88%
50	2	49%	59%	65%	69%
	3	69%	77%	82%	85%
	4	83%	88%	91%	93%
60	2	55%	66%	72%	76%
	3	76%	83%	88%	90%
	4	89%	93%	95%	96%

As the table shows, a total of 150-200 patients will, if accrued quickly enough, provide an adequate evaluation of pion therapy in this disease.

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14.0 PATIENT CONSENT AND PEER JUDGMENT

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 (see Appendix V).

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APPENDIX I

AJC STAGING

(1977)

TNM Categories: The following are TNM categories established for the bladder by the AJC:

1. Primary Tumor (T)
The suffix "m" should be added to the appropriate T category to indicate multiple lesions. Papilloma is classified as "T0".

TX Minimum requirements cannot be met.

T0 No evidence of primary tumor.

TIS Sessile carcinoma in situ.

Ta Papillary noninvasive carcinoma.

T1 On bimanual examination a freely mobile mass may be felt; this should not be felt after complete transurethral resection of the lesion and/or there is papillary carcinoma without microscopic invasion beyond the lamina propria.

T2 On bimanual examination there is induration of the bladder wall, which is mobile. There is no residual induration after complete transurethral resection of the lesion and/or there is microscopic invasion of superficial muscle of bladder.

T3 On bimanual examination there is induration or a nodular mobile mass is palpable in the bladder wall which persists after transurethral resection.

T3a Microscopic invasion of deep muscle.

T3b Invasion through the full thickness of bladder wall.

T4 Tumor fixed or invading neighboring structures and/or there is microscopic evidence of invasion of the prostate and in the other circumstances listed below at least muscle invasion.

T4a Tumor invading substance of prostate, uterus, or vagina.

T4b Tumor fixed to the pelvic wall and/or infiltrating the abdominal wall.

2. Nodal Involvement (N)
The regional lymph nodes are the pelvic nodes just below the bifurcation of the common iliac arteries. The juxtaregional lymph nodes are the inguinal nodes, the common iliac, and para-aortic nodes.

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NX Minimum requirements cannot be met.

N0 No involvement of regional lymph nodes.

N1 Involvement of a single homolateral regional lymph node.

N2 Involvement of contralateral, bilateral, or multiple regional lymph nodes.

N3 There is a fixed mass on the pelvic wall with a free space between this and the tumor.

N4 Involvement of juxtaregional lymph nodes.

Note: Subsequent data regarding the histologic assessment of the regional lymph nodes may be added to the clinical "N" category thus: "N-" (minus) for nodes with no microscopic evidence of metastasis, or "N+" (plus) for those with microscopic evidence of metastasis, for example, N0+, etc.

3. Distant Metastasis (M)

MX Not assessed

M0 No (known) distant metastasis

M1 Distant metastasis present
Specify _____

Specify sites according to the following notations:

Pulmonary	-	PUL
Osseous	-	OSS
Hepatic	-	HEP
Brain	-	BRA
Lymph Nodes	-	LYM
Bone Marrow	-	MAR
Pleura	-	PLE
Skin	-	SKI
Eye	-	EYE
Other	-	OTH

<u>Clinical Stage Groupings</u>: AJC clinical stage classifications of carcinoma of the bladder are:

Stage I	T1	NX	M0
Stage II	T2	NX	M0
Stage III	T3	NX	M0
Stage IV	T4	NX	M0
	T1	NX	M1

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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 sign or symptoms of disease.
70	Cares for self, unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated, although death not imminent.
20	Very sick; hospitalization necessary; active support treatment is necessary.
10	Moribund; fatal process progressing rapidly.
0	Dead.

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APPENDIX III

ACUTE/LATE EFFECTS SCORING

Normal Tissue Reaction Grades

1. Skin

00 Nil
01 Threshold erythema
02 Erythema < ½ field
03 Erythema ≥ ½ field
04 Dry desquamation < ½ field
05 Dry desquamation ≥ ½ field
06 Moist desquamation < ½ field
07 Moist desquamation ≥ ½ field
08 Small necrotic ulcer or slough
09 Massive acute skin necrosis
10 Unknown

2. GI Tract

0 Nil
1 Transient change of bowel habit
2 Definite change: mucosa normal
3 Minimal tenesmus and/or reddening of mucosa
4 Moderate tenesmus with mucus
5 Severe tenesmus with mucus
6 Severe tenesmus with bleeding
7 Intractable hemorrhage requiring transfusion and/or fecal diversion
8 Necrosis
9 Unknown

2a. Proctoscopic Findings

0 Nil
1 Injection
2 Dusky mucosa
3 Edema
4 Punctate hemorrhage
5 Gross bleeding

3. GU Tract

0 Nil
1 Frequency
2 Dysuria
3 Burning
4 Hematuria
5 Unknown

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LATE EFFECTS

0 None
1 Lymphedema
2 Fibrosis
3 Pain
4 Ulcer
5 Pneumonitis
6 Pericarditis
7 Necrosis
8 Trismus
9 Xerostomia
10 Chronic enteritis
11 Fistula
12 Myelitis
13 Atrophy
14 Induced tumor
15 Other (specify)

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APPENDIX IV

AUTOPSY PROTOCOL FOR PATIENTS TREATED WITH PION RADIATION

Histopathological data on the effects of pi mesons on normal as well as neoplastic tissues is still not extensive. For this reason these patients have enormous clinical research importance. This communication is designed to explain the basic questions we would like to try to answer and to serve as a guideline to help you in obtaining the most appropriate tissues as easily and efficiently as possible. We believe that a relatively small group of selectively localized blocks will yield more information than numerous random tissue samples.

Basically four types of specimens need to be collected of which two deal with the neoplasm per se and two with normal tissues from the treatment field. In the first place you will naturally want to assess the effects of therapy on the neoplasm within the central portion of the treatment field. Secondly it will be desirable to compare tissues from this area with those more peripherally situated at or near the margins of the treatment fields. This information will allow the therapists and physicists to assess the accuracy of localization of the field and to draw conclusions relative to dosimetry on the basis of semiquantitative histopathology.

Radiation effects upon normal tissues and organs are equally important because of potential complications of therapy. Once again there is a need to obtain separate specimens from within the treated volume and others from similar but peripheral organs or tissues that were calculated to have received a relatively low dose of radiation.

Initially we felt that the pathologist, provided with the therapy chart, could select appropriate blocks on the basis of his own judgment. In practice this has not been the case since the details of therapy, while recorded in the chart, have seldom been collated into a workable form, i.e., size and shape of fields, relative dose levels etc. Thus, on the

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basis of meetings with the Human Trials Committee it was decided that the pathologist must be provided with a simplified "map" that will enable him to obtain proper sections with confidence in the course of performing his usual autopsy procedure. It is clear that this document can only be prepared by the radiation therapist and physicists during or at the conclusion of the patient's therapy.

The accompanying form includes an extremely simplified summary of therapy details together with fairly specific suggestions for tissue sampling. These suggestions are broken down into four categories as explained: 1) Several blocks from the epicenter of the treated tumor; 2) Blocks from the perimeter of the tumor; 3) Blocks from organs situated within the treated volume; 4) Blocks from tissues or organs intercepting radiation but external to the treatment field per se. A set of lettered labels is available corresponding to individual tissue sites in the lettered column as identified by the radiation therapist. The center of the form has been left blank for line drawings by the therapists. These drawings might indicate external landmarks such as tattoos or represent internal cross sections to include metal clips etc. (Initially we attempted to construct anatomically precise horizontal line drawings for each tumor included in the pi meson protocols but believe there is too much individual patient variability with regard to tumor size, configuration and orientation of treatment fields to make this practical.)

Please be assured that we will share any information generated by these studies as they pertain to this patient or to the effects of pi mesons on tissues in the most general sense. As in the case of the radiation therapists, there are pathologists from many institutions involved and we sincerely wish this to be a mutually informative effort with wide dissemination of information and findings.

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PATIENT'S NAME: _____

SUMMARY OF THERAPY:	Total Dose	Date Completed	Adjuvant Chemotherapy?
High LET	_____	_____	
Low LET	_____	_____	
Other	_____	_____	

RADIATION THERAPIST: _____

PHYSICIST: _____

BLOCKS

T_C (Tumor, Central Treatment Area)

T_P (Tumor, Peripheral Treatment Area)

	OTHER SITE	ESTIMATED DOSE
A	_____	_____
B	_____	_____
C	_____	_____
D	_____	_____
E	_____	_____
F	_____	_____
G	_____	_____
H	_____	_____

T_C	A
T_C	B
T_C	C
T_C	D
T_P	E
T_P	F
T_P	G
T_P	H

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APPENDIX V

PATIENT CONSENT FORM FOR

RADIATION TREATMENT OF BLADDER CANCER*

PATIENT'S NAME: _____

ADDRESS: _____

HOSPITAL/CLINIC: _____

HOSPITAL/CLINIC I.D. NUMBER: _____

1. I, _____, agree to take part in a research study
(Name of Patient)
to test the use of radiation to treat cancer of the bladder. Dr. Morton M. Kligerman, Dr. _____, and doctors they
(Name of Physician)
have chosen will do this study. Persons helping them will be supervised by a doctor at all times while treatment is being given.

2. The treatment to be given to me has been described to me by Dr. _____. It is as follows:

   a. I might receive x-ray or cobalt treatments to my abdomen and pelvis (from the top of my stomach to the top of my legs). These treatments might be given to me at the _____
   (Name of Institution)

   b. I might receive negative pi meson (pion) treatments to my abdomen and pelvis (from the top of my stomach to the top of my legs). These treatments might be given to me at the Los Alamos Meson Physics Facility, Los Alamos, New Mexico.

   c. If I agree to take part in the study, I must agree to go to Albuquerque and Los Alamos, New Mexico, for tests so that my doctors can plan the best possible treatment for me.

   d. If I am chosen for pion treatment, I must agree to stay the needed time (about eight weeks) in Los Alamos for treatment.

   e. I must agree to return to the University of New Mexico Cancer Research and Treatment Center in Albuquerque for needed follow-up exams, if I am chosen for pion treatment.

   f. I understand that I will be chosen by chance for either x-ray, cobalt or pion treatment, and that my doctors cannot tell me ahead of time which treatment I will be chosen to receive.

*Sample Consent Form Submitted by the Study Chairman.

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3. Dr. _____ has told me that I might not feel well after these radiation treatments. Some of the things that might happen to me are:

   a. I might lose my appetite.

   b. I might have diarrhea or constipation. This is usually temporary.

   c. I might have pain when I pass water or need to pass water more often. This is usually temporary.

   d. My skin might get red and peel in the treatment area.

   e. I might lose hair in the treatment area.

   f. I might get pain or swelling in the treatment area.

   g. The number of my blood cells might be less. This could make it easier for me to get a disease caused by germs, but my blood will be tested often so that any problems can be treated quickly.

   h. I might get a narrowing in my stomach or intestine (bowel), or even a hole (not expected), but this can usually be helped by an operation.

   i. I might have weakness in my legs or lose the ability to move them, although this is not expected to happen.

   j. If I am a man, I might not be able to have sex or to father children.

   k. If I am a woman who still has monthly periods, my menstrual flow may stop and I amy not be able to have children.

   l. If I am a woman, I may have a discharge from my vagina.

4. Dr. _____ has told me about the good things this research research study might do for me and for other people. It will help to find out which kind of radiation is better in treating bladder cancer.

5. Dr. _____ has told me about other treatments for me.
   a. X-ray or cobalt treatment and drugs.
   b. X-ray or cobalt treatment and an operation.

6. Dr. _____ will answer any questions I have during the treatment.

7. I know that the treatment could harm me. No one has said that it wouldn't. I can stop treatment at any time I want to.

8. Dr. _____ is in charge of my treatment. He can change the treatment at any time, or stop it.

9. If my body is injured by the research treatment, more than or different from that explained above, I understand that any emergency medical care I need will be given to me at no cost, but I will not be paid any money. Payment for medical costs will not continue after the emergency treatment is finished.

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10. I understand that by signing this paper I am not giving up my legal rights. State laws exist which may help people who think they have been treated carelessly. For information, write or call the Risk Management Division, Room 24, Lamy Building, Santa Fe, New Mexico 87503.

Date: _____ Time: _____ Place: _____

Signed: _____ Witness: _____

_____ Witness: _____
(Parent or Guardian When Indicated)

Original: Patient Chart
cc: Patient
RTOG Headquarters

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