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Radiation Therapy Oncology Group Phase I-II Study on Fast Neutron Teletherapy for Carcinoma of the Bladder

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From June 1977 through March 1981, the Radiation Therapy Oncology Group sponsored a Phase I-II study (RTOG 77-05) on the use of fast neutrons for treating carcinomas of the urinary bladder. Patients entered on the study had Stage B1 (grade III or IV histology) or Stage B2, C, or D1 (any grade histology) disease. Thirteen patients received preoperative mixed-beam (neutron/photon) irradiation to 50 photon Gy-equivalent, and in 12 of these a cystectomy was performed in 4 to 6 weeks. The incidence of pathologic downstaging to Po was 58% in the cystectomy specimens. The projected survival at 30 months is 32%. Twenty-six patients were treated definitively with mixed-beam irradiation consisting of 50 photon Gy-equivalent to the pelvis followed by a 20 photon Gy-equivalent boost to the bladder itself. Eighteen of 26 patients (69%) achieved tumor clearance at some time during their follow-up but 8/18 (44%) of these ultimately exhibited some component of local failure. The projected survival at 30 months for this group of patients is 34%. However, the subset of patients with Stage B or C disease had a projected survival at 30 months of 60%. Four patients received definitive neutron irradiation alone and 3/4 achieved tumor clearance at some time during their follow-up. Actuarial curves are presented for patient survival and duration of local control, and results are compared with comparably staged patients treated with megavoltage photon irradiation. Treatment-related morbidity is also discussed.

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In 1982 the American Cancer Society estimated¹ that in the United States alone there would be over 10,000 deaths due to carcinoma of the bladder. This is in spite of very aggressive treatment for most patients. Once the tumor has deeply invaded the bladder musculature, the majority of patients are treated with preoperative megavoltage photon irradiation followed by a cystectomy, but nevertheless, the best reported 3-year survival rates²⁻⁹ with this technique are in the range of 40% to 50%. Distant

metastases are a major failure mode, and so there is a growing trend to use radiation alone and reserve cystectomy for the subgroup of patients who first fail locally.¹⁰⁻¹² The hope is that this technique will spare a large number of patients the need for a cystectomy—both the group of patients who have their bladder tumor successfully treated with radiation alone and the group of patients who achieve adequate local palliation until they ultimately die of distant metastases. However, series of patients treated definitively with radiation therapy alone show survival rates^{7,13,14} at 5 years that are in the range of 20% to 26% which is substantially less than the best reported series utilizing a planned combined approach.²⁻⁹ This argues that local control of bladder cancer with conventional radiotherapeutic techniques is suboptimal and new approaches need to be explored.

One possible avenue to improved local control is to test the use of high-linear energy transfer (LET) particle irradiation for this tumor system. This has several potential advantages over conventional photon irradiation. The higher energy deposition as the particle traverses the cell means that one is less dependent on an "indirect" free-radical mediated mechanism for cell killing. This results in a better ability to kill hypoxic cells.¹⁵ The fast neutrons in particular, oxygen enhancement ratios are approximately 1.6 compared with 2.5 to 3.0 for high

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energy photons. Moreover, the type of damage inflicted by high LET irradiation is less readily repaired by the tumor cells. There are at least two aspects to this: (1) a reduced ability to repair sublethal damage manifests itself as a reduction of the shoulders on cell survival curves¹⁵; and (2) there is reduced ability to repair potentially lethal damage¹⁶ which could be important for cells in a "resting" or G₀ phase. Finally, there is less variation in radiosensitivity across the cell cycle than for conventional photon irradiation.¹⁷

While the above points are important radiobiological considerations, their applicability for any given tumor system must be determined by clinical trials. The Radiation Therapy Oncology Group (RTOG) has recently completed such a clinical trial (RTOG 77-05) testing the efficacy of fast neutron irradiation for carcinoma of the bladder. This article constitutes a report on the local control rates and survival data for the patients entered onto this study.

Materials and Methods

The study was open from June 1977 through March 1981, and accrued a total of 46 patients. Eligible patients had histologically-proven primary transitional or squamous cell carcinomas of the bladder that were localized to the pelvis. The tumors were staged according to the classical Jewett-Strong-Marshall^{18,19} system which is summarized in Table 1. Only patients with clinical Stage B1 (grade III or IV histology) or Stage B2, C, or D1 (any grade histology) were accepted into the study. In addition, patients had to be ≤ 70 years of age, have an initial Karnofsky status of ≥ 50 , be considered suitable for high-dose radiotherapy, could not have had prior pelvic irradiation or extensive prior pelvic surgery, and could not have had a history of a prior malignancy (excluding non-melanoma skin cancer). Informed consent was given by all patients entered on the study. The mandatory initial evaluation consisted of a history and physical examination, complete blood count, blood chemistry studies including liver function tests, urinalysis, chest x-ray, IVP and/or retrograde studies, staging examination under anesthesia, and cystourethroscopy with resection of adequate tumor for histologic examination. A bone scan or bone survey and bipedal lymphangiogram and/or CT scan of the pelvis were performed in the great majority of patients.

The study was nonrandomized with one of three treatment options selected by the neutron therapy facility: (1) preoperative irradiation of the pelvis and bladder using a "mixed-beam" schedule (2 neutron fractions and 3 photon fractions per week) followed by either a simple cystectomy or a radical cystectomy (at the discretion of the urological surgeon) at a 4- to 6-week time interval

TABLE 1. Staging System for Carcinoma of the Bladder

Jewett-Strong-Marshall Clinical Stage	
0	Carcinoma in situ; papillary tumor without invasion
A	Invasion of the lamina propria
B1	Superficial muscle invasion
B2	Deep muscle invasion
C	Tumor extends beyond bladder into perivesical fat
D1	Tumor extends beyond bladder but confined to pelvis; may invade prostate, uterus, vagina; lymph nodes in pelvis may be positive
D2	Positive lymph nodes outside pelvis; distant metastases

after completing therapy; (2) definitive irradiation of the pelvis and bladder using a "mixed-beam" schedule as noted above; or (3) definitive irradiation of the pelvis and bladder using neutrons alone. Although a fourth treatment option consisting of preoperative irradiation of the pelvis and bladder using only neutrons was allowed by the protocol, no patients were entered on this last option. Definitive neutron irradiation was to be delivered on a 4-day-a-week basis due to restrictions on the use of the neutron generators at the treatment facilities. Patients were placed on the study by calling RTOG headquarters.

The following neutron treatment facilities participated in the study: the University of Washington in Seattle, Washington (SEATTLE), the Great Lakes Neutron Therapy Association in Cleveland, Ohio (GLANTA), the Texas A & M variable energy cyclotron in College Station, Texas, M. D. Anderson (TAMVEC), and the Fermi National Accelerator Laboratory in Batavia, Illinois (FERMI). The neutron beams from these various facilities were all somewhat different in terms of their relative biological effectiveness (RBE) compared with megavoltage photon irradiation. Table 2 summarizes the reactions used to produce the neutron beams at the various facilities and the RBEs used in this particular protocol to scale their respective neutron doses to a photon equivalent dose. In all cases the gamma ray contaminant was included in the measured neutron dose, *i.e.*, Gy_{n γ} .

At the time of simulation for the radiation portals it was required that a contrast agent be injected into the bladder. In the treatment of the "whole pelvis" either a four-field "box" technique or parallel opposed antero-

TABLE 2. Participating Neutron Treatment Facilities, Reactions Used to Produce Neutron Beams, and RBE Factors Used to Approximately Scale Neutron Dose to Photon Equivalent Dose

	Relative biological effectiveness
SEATTLE (22 MeV d - Be)	3.3
GLANTA (25 MeV d - Be)	3.5
TAMVEC (50 MeV d - Be)	3.1
FERMI (50 MeV d - Be)	3.0

RBE: relative biological effectiveness

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TABLE 3. Staging Information According to Treatment Received

	Definitive mixed beam	Mixed beam + surgery	Definitive neutron	Total
B1	2	0	1	3
B2	5	10	0	15
C	3	3	1	7
D1	16*	0	2	18
Total	26	13	4	43

* Eight patients with disease fixed to sidewall, sacrum, or symphysis pubis.

posterior-posteroanterior (AP-PA) fields could be used. The fields were to encompass the bladder and the pelvic nodes at risk. The AP-PA fields were required to be at least 14 × 14 cm in size but generally were somewhat larger, extending from the top of the sacrum to the bottom of the obturator foramen and laterally 2 cm beyond the borders of the osseous pelvis. If lateral fields were used, they were required to be at least 11 × 14 cm in size with the anterior margin of the field at least to the anterior border of the pubis (or beyond if indicated by the position of the bladder). Barium contrast was generally injected into the rectum and the posterior border of the lateral fields adjusted to spare the posterior rectal wall. A total of 50 Gy-equivalent was delivered to the midplane of the pelvis along the central axis over 5 to 6 weeks. In addition, it was permissible to deliver an additional 10 Gy-equivalent to positive nodal areas through small boost fields. For the subgroup of patients receiving definitive radiotherapy the whole pelvis phase of radiotherapy was followed by an additional 15 to 20 Gy-equivalent to the bladder using boost fields having a minimum size of 7 × 7 cm. The bladder was to be emptied prior to each daily treatment.

Portal films were obtained for each treatment field, and were reviewed at RTOG headquarters. Isodose calculations in the central axis plane were required and submitted to RTOG headquarters. In the mixed-beam treatment schedule the low LET photon portion of therapy had to be delivered with x-ray generators with a peak photon energy of ≥ 4 meV or equivalently a Cobalt-60 apparatus could be used. The treatment apparatus furthermore had to utilize a source-skin distance (SSD) ≥ 80 cm. The dose to the posterior rectal wall was limited to ≤ 55 photon Gy-equivalent, and the dose to the small bowel was generally limited to ≤ 50 photon Gy-equivalent. The photon portion of the irradiation was delivered with the patient in the usual prone position, but given the fixed horizontal beams at the neutron facilities, many of the neutron radiation treatments were delivered with the patient in a standing position.

Patients were seen for follow-up visits every 3 months for the first 2 years after treatment, and then every six months thereafter. At these visits laboratory parameters,

additional treatment (if any), and disease status (primary regional lymph nodes, and/or other metastatic disease) were recorded. In the subgroup of patients receiving definitive radiotherapy, frequent cystoscopic examinations (with biopsies of suspicious areas) and follow-up pelvic CT scans were performed. Reporting forms were initially reviewed by a data manager at RTOG headquarters and then again by the study data manager. Sixteen months after the study was closed, the on-study and follow-up forms for each patient on the study were reviewed by the study chairman. Questions concerning the data base were resolved by direct contact with the investigators at the various participating institutions.

Based on this review, three patients were declared ineligible (one had a history of a prior malignancy, one had prior extensive pelvic surgery, and one had metastatic disease outside the pelvis at the time of entry onto the study). Table 3 summarizes the staging distribution of the remaining 43 patients according to the treatment they received. Twenty-six patients were treated definitively with mixed beam irradiation, and of these, 16 had stage D1 disease, and 8 of these latter patients had very extensive tumors fixed in the pelvis. Thirteen patients were treated with preoperative mixed beam irradiation followed by cystectomy, and only four patients were treated definitively with neutron irradiation. These latter four patients all received their treatment using the high energy neutron beam at the FERMI facility. The other characteristics of the patients in this study are summarized in Table 4. The section on tumor location refers to the sites of tumor involvement at the time of entry into the study and not to the site of tumor origin.

Results

The major end points of the study were local control rates, survival, complication rates, and tolerance of the surrounding normal tissues to mixed-beam or neutron irradiation. The plots in this section are calculated using the actuarial method,²⁰ with times being measured from the date of entry onto the study.

Figure 1 plots survival by treatment for the definitive mixed-beam and preoperative mixed-beam groups. The median survival is 14.7 months for definitively treated patients, and 24.1 months for the preoperative group. Although there appears to be some difference between the two curves for times in the range of 15 to 25 months, the curves come together at longer follow-up times. The neutron group is not plotted since a survival curve for four patients is not very informative. Of these four, two patients died between 9 and 10 months, one died at 23 months, and the last one was last reported alive at 25 months.

In view of the advanced nature of the tumors in the group of patients treated with definitive mixed-beam irradiation, we decided to separately analyze the subgroup

TABLE 4. Patient Characteristics by Treatment

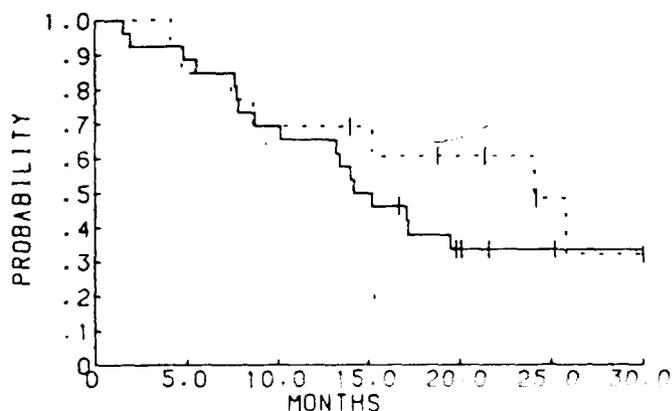
	Preoperative mixed beam		Definitive mixed beam		Definitive neutron		Total	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Sex								
Male	11	85%	20	77%	2	50%	33	77%
Female	2	15%	6	23%	2	50%	10	23%
Age								
Younger than 60 yr	7	54%	4	15%	2	50%	13	30%
60 or older	6	46%	22	85%	2	50%	30	70%
Karnofsky status								
60-needs some assistance	0	0%	1	4%	0	0%	1	2%
70-cares for self/can't work	0	0%	2	8%	0	0%	2	5%
80-some disease symptoms	1	8%	7	27%	1	25%	9	21%
90-minor signs of disease	4	31%	13	50%	0	0%	17	39%
100-no signs of disease	8	61%	3	11%	3	75%	14	33%
Institution								
Seattle	6	46%	12	46%	0	0%	18	42%
Fermi	0	0%	2	8%	4	100%	6	14%
M. D. Anderson	0	0%	9	35%	0	0%	9	21%
GLANTA	7	54%	3	11%	0	0%	10	23%
Race								
White	11	85%	22	85%	4	100%	37	86%
Black	2	15%	3	11%	0	0%	5	12%
Other	0	0%	1	4%	0	0%	1	2%
Histologic type								
Transitional cell	12	92%	24	92%	3	75%	39	91%
Squamous cell	1	8%	2	8%	1	25%	4	9%
Histologic grade								
I	0	0%	2	8%	0	0%	2	5%
II	0	0%	5	19%	0	0%	5	12%
III	8	62%	11	42%	1	25%	20	46%
IV	5	38%	5	19%	2	50%	12	28%
Unknown	0	0%	3	12%	1	25%	4	9%
Location								
Trigone	5	38%	5	19%	2	50%	12	28%
Right wall	7	54%	9	35%	1	25%	17	40%
Left wall	1	8%	8	31%	2	50%	11	26%
Posterior wall	5	38%	7	27%	0	0%	12	28%
Dome	2	15%	5	19%	0	0%	7	16%
Not determinable	0	0%	2	8%	0	0%	2	5%

with B and C-disease from the subgroup with D-disease. This would provide a more accurate basis of comparison with reported series of photon-treated patients. Figure 2 shows the survival for these two subgroups. Although the number of patients with B-stage and C-stage disease is small, the long-term survival levels out at 60%.

Of the 13 patients given preoperative mixed beam irradiation, 12 underwent cystectomy as planned. The other patient's surgery was cancelled due to fixation of the tumor to adjacent structures. This patient initially had a very advanced tumor (although technically a Stage C), and probably should not have been entered on the preoperative treatment arm. Pathologic examination found no evidence of viable disease in seven of the operative specimens. Thus, the proportion of patients achieving complete downstaging to Po was 54% (7/13) in terms of the entire

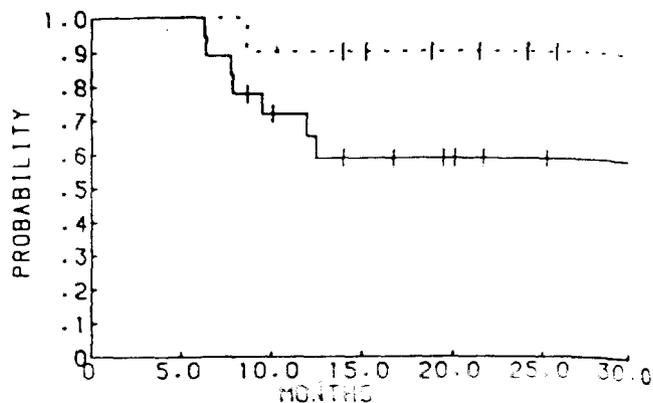
group of patients, or 58% (7/12) in terms of the patients actually undergoing cystectomy. In addition, the cystectomy specimen in one other case showed only microscopic evidence of disease.

Based on follow-up cystoscopies and biopsies as well as CT scans of the bladder and pelvis, 69% (18/26) of the mixed-beam treated group were believed to have cleared of tumor at some time during their follow-up but 7 patients ultimately recurred. Note that clearance and recurrence refer to disease within the irradiated volume. Two patients in the mixed-beam treated group eventually underwent a "salvage" cystectomy. In one case the specimen showed no evidence of disease (patient initially staged B2) and in the other case (patient initially staged D1) persistent disease was found. Breaking down this group according to the nature of their disease, 80% (8/



TREATMENT	ALIVE	DEAD	TOTAL	MEDIAN
— MIXED BEAM	6	20	26	14.7
... MIXED + SGY	6	7	13	24.1

FIG. 1. Survival by treatment. Actuarial plot of patient survival for the indicated treatment arms. Solid curve represents the group of patients treated definitively with mixed-beam irradiation, and dotted curve represents the group of patients on the preoperative mixed beam irradiation-cystectomy arm.

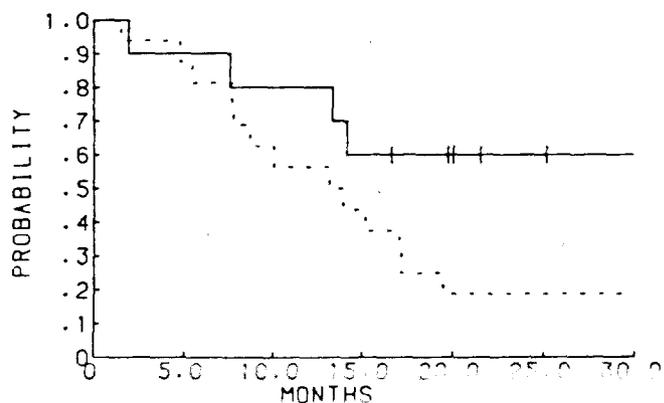


TREATMENT	CLEAR	RECUR	TOTAL	MEDIAN
— MIXED BEAM	11	7	18	UNDEF
... MIXED + SGY	9	1	10	UNDEF

FIG. 3. Time to clinical recurrence by treatment (responders only). Actuarial plot of tumor control within the irradiated volume for patients who exhibited a clearance of their disease. Solid curve represents patients treated definitively with mixed-beam irradiation, and dotted curve represents patients treated with preoperative mixed-beam irradiation followed by cystectomy.

10) patients with B-stage and C-stage disease cleared of their tumor, and three patients subsequently exhibited a local recurrence. The long-term clearance rate with mixed-beam irradiation alone was 50% (5/10) for this group. For the patients with Stage D1 disease, 63% (10/16) cleared of their tumor, and 4 patients ultimately exhibited a local recurrence for a 38% (6/16) long-term clearance rate.

The times to clinical recurrence for the complete responders on the two treatment arms are illustrated in



STAGE	ALIVE	DEAD	TOTAL	MEDIAN
— B1 B2 AND C	6	4	10	UNDEF
... D1	0	16	16	13.6

FIG. 2. Survival by stage. Actuarial plot of patient survival for patients treated definitively with mixed-beam irradiation. Solid curve represents the patients with Stage B and C disease, and dotted curve represents the patients with Stage D1 disease.

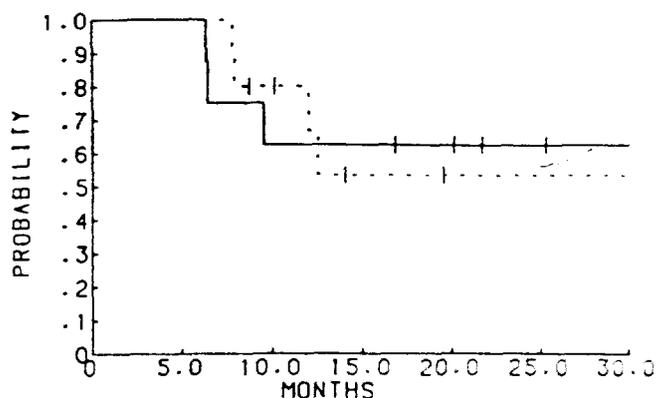
Figs. 3 and 4. All of the local failures were manifested within the first year.

In the small group of patients treated definitively with neutron irradiation, 3/4 were thought to have achieved local clearance of their disease at some time during their follow-up, and one patient ultimately exhibited a local recurrence.

Table 5 shows the relapse pattern for the groups of complete responders in the three treatment arms. In the group treated with preoperative mixed-beam irradiation followed by cystectomy, there was one regional failure (in the pelvic lymph nodes) and two distant failures. In the group treated definitively with mixed-beam irradiation, at first relapse there was a component of local failure in 8/18 (44%) cases but only 3 of these failed in the bladder alone. Presumably only these three would have been potential candidates for a salvage cystectomy. Seven of 18 patients (39%) had some component of distant failure which argues for the need for effective chemotherapy for this disease.

The acute treatment reactions are summarized in Table 6. Except for the skin reactions which were in large part due to the poorly penetrating properties of the neutron beams used in the study (for example, the SEATTLE and OLIVIA beams had depth-dose curves approximating a ¹⁰Cs unit), the reactions were about as expected for megavoltage photon treatments. The medication required for the "bladder complication" was Pyridium, and antispasmodics such as Lomotil were the medications required for the "rectal" complications. In only one instance

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STAGE	CLEAR	RECUR	TOTAL	MEDIAN
— B1 B2 AND C	5	3	8	UNDEF
--- D1	6	4	10	UNDEF

FIG. 4. Time to clinical recurrence by stage. Actuarial plot of tumor control within the irradiated volume for patients treated definitively with mixed-beam irradiation who exhibited a clearance of their disease. The solid curve represents patients with Stage B and C disease, and dotted curve represents patients with Stage D1 disease.

was a treatment break required, and this patient had severe nausea assigned to a "small bowel" reaction. Some patients were scored as having more than one reaction. In the preoperative mixed beam group, three patients had a "worst" reaction graded as "minimal" and four patients had a worst reaction that required some form of medication; and in the definitive mixed-beam group, seven patients had a worst reaction graded as minimal, seven patients had a worst reaction that required medication, and one patient had a reaction that required a break in treatment.

A characteristic of high LET irradiation is the dissociation between "acute" and "late" effects. The latter are summarized in Table 7 and tended to be more severe than the acute effects. As for the acute effects, some patients were scored for more than one reaction. In the preoperative mixed beam group, two patients had a worst reaction graded as "moderate," and two patients had a worst reaction graded as "life-threatening"; in the definitive mixed-beam group, three patients had a worst reaction graded as moderate, and four patients had a worst reaction graded as "severe"; and in the definitive neutron group, one patient had a worst reaction graded as moderate, one patient had a worst reaction graded as severe, and one patient had a worst reaction graded as life-threatening. The life-threatening complications were as follows: the small bowel complication in the preoperative mixed beam group was reported as generalized peritonitis with perforation of small bowel and radiation enteritis of small bowel, colon, and urinary bladder. The neutron-treated patient's life-threatening small bowel complications con-

TABLE 5. Disease Status at Time of First Relapse for Patients Clinically Cleared of Their Disease

	Preoperative mixed beam	Definitive mixed beam	Definitive neutron
Responders	10	18	3
NED at autopsy	2	—	1
Alive NED at last report	5	6	1
Primary	—	3	1
Regional	1	—	—
Primary and regional	—	2	—
Distant	2	4	—
Regional and distant	—	2	—
Primary, regional, and distant	—	1	—

NED: no evidence of disease.

TABLE 6. Acute Treatment Reactions

Site/degree	Preoperative mixed beam	Definitive mixed beam	Definitive neutron
Skin			
Minimal	6	9	0
Medication required	1	1	0
Bladder			
Medication required	0	1	0
Rectum			
Minimal	3	2	0
Medication required	4	7	0
Small bowel			
Minimal	2	1	0
Treatment interruption required	0	1	0
Bone marrow depression			
Minimal	0	2	0

sisted of obstruction and fistula with adhesions throughout the entire abdomen. Bladder cancer and extensive intraabdominal fibrosis and adhesions were found at au-

TABLE 7. Late Complications by Treatment Arm

Site/degree	Preoperative mixed beam	Definitive mixed beam	Definitive neutron
Bladder			
Moderate	0	3	1
Severe	0	1	0
Rectum			
Moderate	1	2	0
Severe	0	2	0
Small bowel			
Severe	1	0	1
Life-threatening	1	0	1
Large bowel			
Moderate	0	1	0
Severe	0	1	0
Other			
Moderate	1	3	1
Life-threatening	1	0	0

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TABLE 8. Incidence of Downstaging to Po in Cystectomy Specimens for Various Preoperative Series of Patients With B1, B2, and C Stage Disease Who Completed Their Planned Therapy.

	Percent Po
Mixed beam (50 Gy-equivalent)	58%
Photons	
Miller ⁶ (50 Gy)	29%
Chan and Johnson ⁹ (50 Gy)	35%
Prout <i>et al.</i> ² (45 Gy)	32%
Werf-Messing ³ (40 Gy)	30%
Shipley <i>et al.</i> ²¹ (40 Gy)	24%

topsy. The "other" life-threatening complication seen in a preoperative mixed-beam patient was atherosclerotic change in major pelvic vessels that appeared to be accelerated by radiotherapy. This patient had prior extensive atherosclerotic disease, but there was a quantitative change in its nature within the irradiated volume. The cause of death was reported as complications of radiotherapy or adjacent surgery (an attempted bypass for obstruction).

Discussion

We have reported the results of a Phase I-II study (RTOG 77-05) testing the efficacy of fast neutron radiotherapy for carcinomas of the urinary bladder. Patients were treated according to one of the following treatment schemes: preoperative mixed-beam irradiation followed by cystectomy, definitive mixed-beam irradiation, or definitive neutron irradiation. This study was designed to gain information about tumor control and morbidity in order to decide whether randomized Phase III studies were warranted.

In the preoperative group the incidence of downstaging to Po in the cystectomy specimen was 58% which is substantially higher than expected based on reports in the literature for photon-treated patients having comparable stage disease.^{2,5,6,9,21} Representative incidences of downstaging to Po are summarized in Table 8 for the indicated radiation doses.

Our preoperatively treated patients, however, did not show an increase in survival compared with photon-

TABLE 9. Survival Data for Various Series of Patients With Stage B and C Disease Treated With Preoperative Irradiation Followed by Cystectomy

	Actuarial survival
Mixed Beam	32% (30 mo)
Photons	
Miller and Johnson ¹³	50% (36 mo)
Chan and Johnson ⁹	50% (36 mo)
Wallace and Bloom ⁷	41% (36 mo)
Prout <i>et al.</i> ²	45% (36 mo)
Werf-Messing ⁴	50% (36 mo)

TABLE 10. Survival Data for Various Series of Patients With Indicated Disease Stage Treated Definitively With Radiotherapy

	Actuarial survival
Mixed Beam	
B, C, D1	34% (30 mo)
B, C	60% (30 mo)
D1	18% (30 mo)
Photons	
Miller and Johnson ¹³ (B2, C, D1)	22% (36 mo)
Wallace and Bloom ⁷ (B2, C)	28% (36 mo)
Prout <i>et al.</i> ² (B2, C, D1)	40% (36 mo)
Goffinet <i>et al.</i> ¹⁴ B2	43% (36 mo)
C	35% (36 mo)

treated patient groups^{2,4,7,9,13} as summarized in Table 9. Notice that the figures refer to actuarial projections with the mixed-beam group being at a time of 30 months and the photon groups being at times of 36 months. Our projected survival is 32%, compared with 41% to 50% for the photon-treated patients. Since the number of patients in our series is small and not matched to the photon-treated patients, this may simply represent intrinsic differences in the patient populations. We note that after the preoperative treatments, the surgery successfully cleared the tumor in only 10/15 (77%) cases, but all 13 cases are included in our analysis.

A comparison between the survival data for our definitively treated patients and representative results for photon-treated patients^{2,7,13,14} is made in Table 10. Again notice that the mixed-beam data is projected at 30 months whereas the photon-treated patients are projected at 36 months. Our survival is comparable to that shown in the photon series even though we have a very high percentage (62%) of patients with D1 disease. For our patients with Stage B and C disease the 30-month survival projects out at approximately 60% which is somewhat higher than for comparable photon series.

Various European centers have also investigated the use of fast neutron radiotherapy for carcinomas of the bladder but have tended to treat with neutrons alone rather than with a mixed neutron/photon schedule. Bartolman and associates^{22,23} used a "six-field" technique for a 14 meV neutron beam from a DT generator. They noted several instances of small and large bowel damage and found steep dose response curves for both tumor control and normal tissue damage. The total dose delivered to the tumor volume varied between 18.17 to 22.20 Gy_n/20 fractions/4 weeks. A total of 22 patients with Stage D1 bladder tumors fixed to the pelvic wall (Stage T4B) were treated, and at 2 years 50% of these patients were believed to have persisting local control of their tumor although severe pelvic fibrosis made evaluation difficult. The frequency of severe complications was 5/22 (23%). Three of these patients died, and the other two

required a colostomy. Duncan²⁴ has reported his experience using a neutron beam produced by a $^{15}\text{MeV } \alpha - \text{Be}$ reaction for a randomized study comparing neutron irradiation with photon irradiation for bladder cancer. Thirty-three patients were treated with neutrons, and 34 patients were treated with photons. Small, multiport fields, 11×11 cm, 3 photon fields or 6 neutron fields, treatment techniques were used. His local control rates at 6 months were 60.6% for neutrons and 64.7% with photons. He noted comparable acute morbidities for the two treatment methods, but a greater degree of pelvic fibrosis in the neutron-treated patients. His follow-up time was too short to accurately evaluate any differences in late effects. The higher complication rates reported by Batterman and coworkers^{22,23} are likely due in part to the poorly penetrating beam that they used, but nevertheless, caution must be used in treating pelvic tumors with high dose neutron irradiation alone.

A randomized, prospective study (RTOG 81-10) studying preoperative mixed beam versus preoperative photon irradiation to 50 Gy-equivalent followed by a cystectomy in 4 to 6 weeks is currently underway. This study will allow us to compare the two forms of treatment in terms of downstaging, survival, and morbidity in comparable patient populations. It is hoped that the higher energy neutron beams from the clinical neutron facilities (42, 48 MeV $\alpha - \text{Be}$ reactions) sponsored by the National Cancer Institute will enable us to improve the promising Phase I-II results reported in this study by both increasing the neutron component of the total irradiation schedule and by decreasing the morbidity associated with the poorly penetrating beams from the current physics-laboratory-based cyclotrons. These questions will be addressed in future randomized clinical trials.

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