Fast Neutron Radiotherapy for Advanced Carcinomas of the Urinary Bladder and Prostate Gland: Results of RTOG Clinical Trials

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Introduction

Tumors of the lower genitourinary tract constitute a significant medical problem throughout the world. In 1984, the American Cancer Society (25) estimates that there will be approximately 38,700 new cases of bladder cancer and 76,000 new cases of prostate cancer in the United States alone. There will be approximately 10,700 deaths due to bladder cancer and 25,000 deaths due to prostate cancer in spite of aggressive medical management. In the case of bladder cancers that have deeply invaded the musculature, e.g., stages B_2 and C (a), the majority of patients in the United States are treated with preoperative megavoltage photon irradiation followed by a radical cystectomy. With this technique, 3-year survival rates are in the range of 40% to 50% (3, 19, 22, 28, 29, 30). Unfortunately, distant metastases are a major failure mode, and so there is a growing tendency to use radiation alone and to reserve cystectomy for the subgroup of patients who first fail locally (5, 9, 26). In the case of prostate cancer, patients with locally advanced disease (stages C and D_1) are usually treated with definitive megavoltage photon irradiation. However, studies to date do not conclusively demonstrate that this form of local/regional treatment alters the survival of this subgroup of patients. The clinical course of the disease can be quite variable, and patients must be followed for at least 5 years to accurately evaluate the effect of a given form of treatment.

The Radiation Therapy Oncology Group (RTOG) has recently completed two studies that test the efficacy of fast neutron radiotherapy as used in a mixed beam (neutron/photon) fractionation schedule for advanced tumors of the bladder and prostate. The mixed beam form of treatment refers to delivering 2/5 of the doses with neutrons and 3/5 of the doses with photons in daily doses of approximately equal biologic effectiveness. Treatments were given at daily dose rates of 1.8-2.0 Gy-equivalent. This method of treatment was chosen because many of the participating neutron facilities had relatively low energy beam, and there was concern about treating large volumes of tissue in the pelvis with neutrons alone. With the new generation of higher energy facilities that have recently become available in the United States, this will not be as great a problem, and the next generation of studies will likely involve using neutrons alone as the "experimental" form of treatment for pelvic malignancies. Hence, now is an

opportune time to review the results of these earlier studies. The bladder study (RTOG 77–05) has been previously analyzed (13), but the work presented in the present paper is an updated summary that includes as well some additional patients treated on an "aborted" protocol (RTOG 81–10). The prostate study (RTOG 77–04) has also been analyzed in detail (14). This was a randomized study which compared the mixed beam form of treatment with conventinal photon irradiation and demonstrated a significant improvement both in local control and survival for the mixed beam form of treatment. Because of space limitations the discussion of many of the technical points relating to the details of treatment delivery and data analysis will be somewhat abbreviated, and the reader is referred to the original manuscripts (13, 14) for further information.

Bladder cancer

RTOG 77–05 was open from June 1977 through March 1981. It was non-randomized in nature, and patients were assigned by the treatment facilities to receive either preoperative mixed beam radiation to a dose of 50 Gy-equivalent to the pelvis (bladder and regional nodes) followed by a cystectomy in 4–6 weeks, or to receive definitive mixed beam irradiation which consisted of 50 Gy-equivalent to the pelvis followed by an additional 15–20 Gy-equivalent boost to the bladder. Areas of proven positive adenopathy could also receive an additional 10 Gy-equivalent through small boost fields. A small group of 4 patients received only neutron irradiation, but these will not be further discussed here. Treatments were delivered 5 days per week, and the bladder was to be emptied prior to each daily treatment. The dose to the posterior rectal wall was limited to $\leqq 55$ Gy-equivalent and the dose to small bowel was limited to $\leqq 50$ Gy-equivalent. Following this study the RTOG attempted to mount a randomized study (RTOG 81-10) which compared preoperative mixed beam irradiation with preoperative photon irradiation. This study was open from March 1981 through September 1984 and was then closed both because of actual lack of compliance with the assigned treatment. The patients who were randomized to the preoperative mixed beam treatment tended to refuse the assigned surgery (after receiving the planned preoperative dose) and then were treated definitively with mixed beam irradiation. Three patients completed a definitive course of radiotherapy in this manner and will be added to the subgroup of patients treated definitively on protocol RTOG 77–05.

The following table summarizes the staging information according to the type of treatment the patient received.

Table 1
Staging information according to treatment received

	Definitive Mixed Beam	Preoperative Mixed Beam + Surgery
B_1	2	0
B_2	5	10
C	5	3
D	17*	0
Total	29	13

* Includes 8 patients with tumor fixed to the pelvic sidewall, sacrum or symphsis pubis

There were 1 patient in the preoperative subgroup and 2 patients in the definitive subgroup with squamous histologies; the other patients all had transitional cell carcinomas.

The major endpoints of the study were local control rates, survival and complication rates. All analyses are carried out using the actuarial method (12), with times being measured from the date of entry onto the study.

In the group of patients undergoing preoperative mixed beam irradiation followed by cystectomy, the incidence of down-staging for the primary tumor was quite high. Only 12 of the 13 patients actually underwent the planned cystectomy, and 7/12 (58%) were completely downstaged to P_0 (i.e., no tumor in the operative specimen). One other patient had only microscopic residual tumor in the operative specimen. One patient's surgery was cancelled due to fixation of tumor to adjacent pelvic structures. This patient initially had a very advanced tumor (although technically a stage C) and probably should not have been initially entered on the preoperative treatment arm. With conventional photon irradi-

ation in the range of 40-50 Gy, the expected rate of downstaging to P_0 is in the range of 25-35% (3, 18, 22, 30). Only one patient has subsequently developed a regional recurrence, and this occurred approximately 10 months after surgery.

Based upon follow-up cystoscopies and biopsies as well as CT scans of the pelvis, 21/29 (72%) of the group treated definitively with mixed beam irradiation were believed to have been cleared of tumor at some point, but 10 patients ultimately exhibited a relapse in the bladder. However, only 4/10 of these exhibited solely a relapse in the bladder and would have been potential candidates for salvage cystectomies. The other 6/10 patients exhibited regional and/or distant metastases as well. Salvage cystectomies were carried out in 3 cases without significant postoperative complications. An additional 2 patients required cystectomies because of a shrunken, irritable bladder due to the complications of treatment. Of the original 29 patients, 6 (21%) exhibited no local disease and an adequately functioning bladder at either death or last follow-up.

Fig. 1 plots survival by treatment for the subgroups treated definitively and preoperatively. Median survival is approximately 14 months for the definitively-treated group and 26 months for the preoperatively-treated group. 4 of the preoperatively-treated patients are still alive and free of disease, and 3 more were disease-free at the time of death. Distant failures dominated the recurrence pattern. The subgroup of patients treated definitively obviously had much more advanced disease than the preoperatively-treated group, and this accounts in large part for the difference in median survival.

Fig. 2 shows the survival for the definitively-treated group as a function of disease stage. The median survival for those patients with stage B and C lesions is 38 months compared with 13 months for those patients with D_1 disease. More importantly, the "long-term" survival for the subgroup with stage B and C lesions is about 48% which is actually greater than that for those patients treated with preoperative mixed beam irradiation followed by cystectomy.

With the exception of skin reactions, acute treatment reactions were about the same as expected for megavoltage photon irradiation to comparable dose levels. The more severe skin reactions were likely due to the poorly penetrating nature of the neutron beams that were utilized by many

Figure 1
Actuarial survival as a function of the treatment received for bladder cancer. The solid curve represents those patients treated with preoperative mixed beam irradiation folllowed by a cystectomy, and the dashed curve represents those patients treated with definitive mixed beam irradiation.

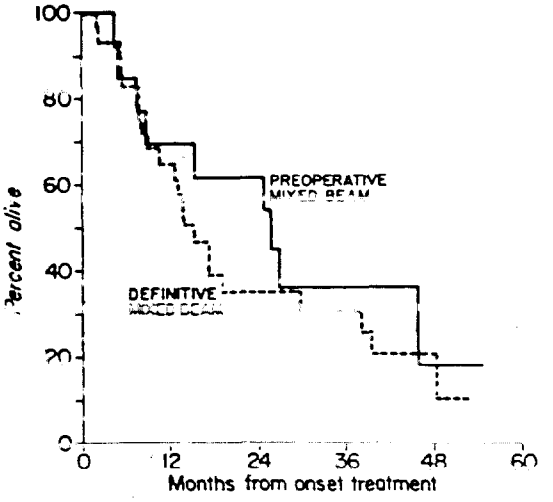
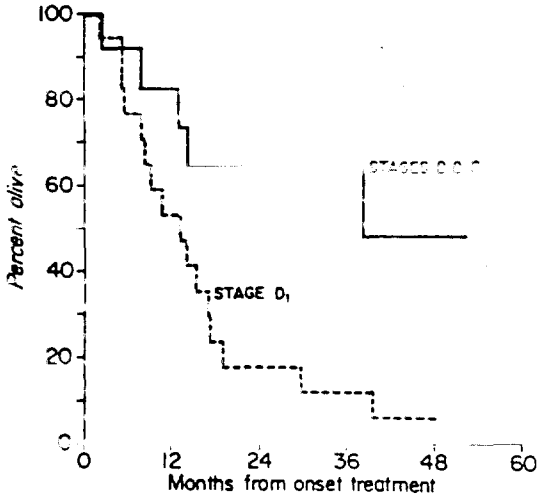


Figure 2
Actuarial survival curves for the subgroup of patients with bladder cancer that received definitive mixed beam irradiation as a function of the initial stage of disease. The solid curve represents those patients with stages B_1, B_2 and C disease, and the dashed curve represents those patients with stage D_1 disease.



of the facilities. Late reactions tended to be more severe than the acute effects. Utilizing the joint EORTC/RTOG scoring scheme, 2 patients in the preoperative group had worst reactions graded as "moderate," 1 patient had a reaction graded as "life-threatening," and 1 patient had a "fatal" complication. The "life-threatening" complication was a generalized peritonitis with perforation of the small bowel and radiation enteritis of small bowel, colon, and urinary bladder. The "fatal" complication was severe atherosclerotic change in the major pelvic blood vessels that appeared to have been accelerated by the radiation. Following the surgery there was a bowel obstruction, and the cause of death was reported as being due to radiation and additional surgery (an attempted bypass for the obstruction). In the group that received definitive mixed beam irradiation, the worst reaction was graded as "moderate" in 4 cases and "severe" in 5 cases. Those cases that required a cystectomy for a malfunctioning bladder are included in the "severe" category.

Prostate cancer

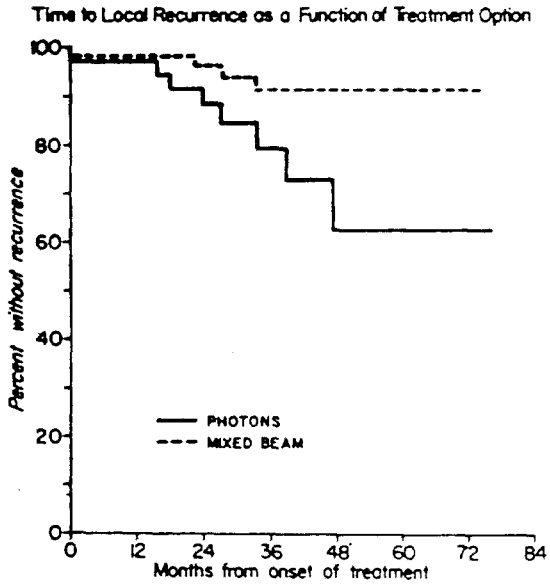
From June 1977 through April 1983, the RTOG conducted a randomized study for patients with locally-advanced prostatic cancer. Eligible patients had biopsy-proven adenocarcinoma of the prostate gland and were either stage C or D_1. The control group was treated with conventional megavoltage photon irradiation and received 50 Gy to the pelvis (prostate and nodes) followed by a 20 Gy boost to the prostate and any areas of proven, bulky, extraprostatic disease. Mixed beam treated patients received the same doses in Gy-equivalent. The radiation dose to the entire bladder was restricted to 60 Gy-equivalent, and the doses to the posterior rectal wall and small bowel were restricted to 55 Gy-equivalent. Patients were to be treated with the bladder distended. The randomization was purposefully unbalanced (60-40%) in favor of the experimental arm. A total of 91 analyzable patients were accrued to this study - 55 patients on the mixed beam arm and 36 patients on the control arm. At the time of analysis the mean follow-up time was 54 months (range 14-80) with 85 patients at risk for times ≥ 3 years and 48 patients at risk for times ≥ 5 years. There were 6 patients with documented positive pelvic nodes on the mixed beam arm and 5 patients with documented positive pelvic nodes on the photon control arm. Operative staging series (1, 7, 17) of patients with clinical stage C disease show an actual incidence of nodal involvement ranging from 40-60%, and so the actual incidence of positive pelvic nodes was likely much higher than documented. Prior to the analysis, one of us (G.E.L.) visited RTOG headquarters and reviewed all of the records for the patients entered onto the study. Based upon this review, 8 patients on the mixed beam arm and 5 patients on the photon arm were felt to exhibit major deviations from treatment protocol – largely because of prolonged treatment times ($\geq$ 75 days) or too low a neutron dose ($\leq$ 25% rather than the prescribed 40%). To avoid problems with inadvertent biases due to patient exclusion, the analysis presented here will be for the entire group of 91 analyzable cases. A parallel analysis is presented for both the entire group of 91 analyzable cases and the 78 cases treated within strict protocol guidelines in the original report (14).

Based upon the chi-square test of independence, the two patient groups were balanced according to age distribution, tumor grade, stage (C vs. D_1), method of diagnosis (TURP vs. needle biopsy), percent of patients having lymphangiograms, laparotomies, or other methods of nodal evaluation, initially elevated serum acid phosphatase levels, degree of seminal vesicle involvement, Karnofsky performance status, race, prior hormonal therapy status, cardiac performance status, other intercurrent disease status, and Gleason grade (8). The presence of concomitant, benign, prostatic hypertrophy was greater on the mixed beam arm ($p=0.06$). Tumor size based upon the product of the clinically-assessed major diameters was somewhat larger on the photon arm ($p<0.05$).

The major endpoints of the study were local/regional control and survival, with complication rates and normal tissue tolerance being secondary endpoints.

Fig. 3 shows the fraction of patients exhibiting local/regional control as a function of time. In this analysis, a post-treatment abnormality was assumed to be of unknown significance in the period immediately following irradiation and

Figure 3
Actuarial curves showing local/regional control for prostate cancer. The subgroup treated with mixed beam irradiation is shown as the dashed curve, and the photon-treated subgroup is shown as the solid curve. The difference between the two curves is statistically significant at the $p < 0.05$ level.

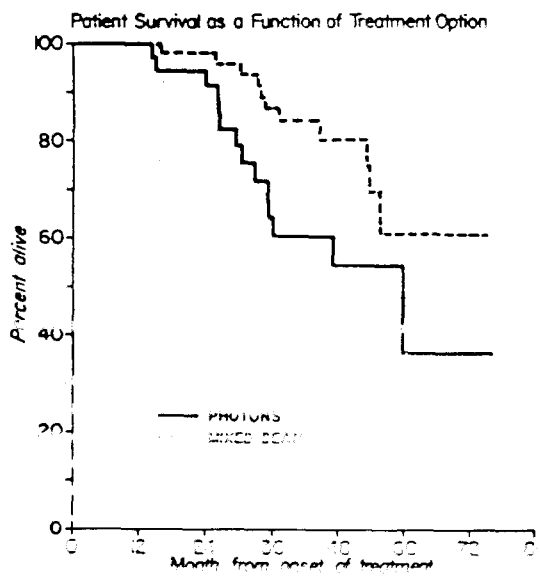


was not counted as a failure until progression was noted.

This method of analysis was chosen because of the notoriously slow rate of regression of prostate cancer and is the reason these curves start at the 100% level. The failure rate at 5 years is about 7% for the mixed beam group compared with about 38% for the photon group. Using the Mantel-Haenszel (16) and the Wilcoxon (10) tests, the mixed beam group does significantly better ($p < 0.05$). Failure rates reported in the literature (15, 20, 21, 23) for photon treated patients with advanced stage C disease are in the range of 15-24%.

Fig. 4 shows the percent of patients surviving as a function of time. At 5 years the actuarial survival rate is approximately 60% for the mixed beam subgroup compared with approximately 40% for the photon-treated patients. The difference between the two curves is statistically significant ($p < 0.05$) using both the Mantel-Haenzel (16) and the Wilcoxon (10) tests. Survival rates for photon-treated patients with stage C lesions have been reported in the literature (11, 21, 27) to be as high as 55-60% at 5 years. However, Neglia et al. (20) report a definite dependence of patient survival on primary tumor size, with less advanced stage C lesions having a 5-year survival of approximately 60% compared with approximately 45% for the more advanced lesions. This may be a factor in the somewhat low 5-year survival noted for our photon-treated patients.

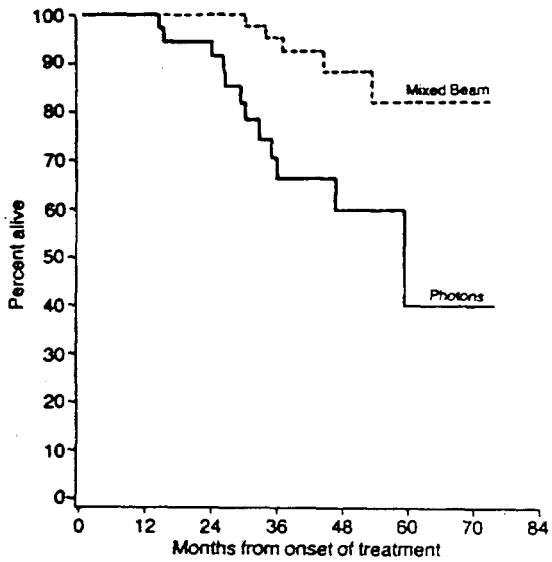
Figure 4
Actuarial curves showing patient survival for prostate cancer. The subgroup treated with mixed beam irradiation is shown as the dashed curve, and the photon-treated subgroup is shown as the solid curve. The difference between the two curves is statistically significant at the $p < 0.05$ level.



The problem with using patient survival as an endpoint is that patients with prostate cancer tend to be elderly and often die of intercurrent disease. In an attempt to avoid this problem, we have constructed modified determinantal survival curves which define active cancer present at death as failure and treat patients who die of intercurrent disease with no cancer present at the time of death as "censored" observations. These curves are shown in Fig. 5.

Using both the Mantel-Haenszel (16) and the Wilcoxon (10) tests, the mixed beam subgroup does significantly better ($p < 0.01$). The non-cancer deaths in the photon subgroup included 1 cardiovascular

Figure 5
Actuarial curves for prostate cancer showing patient survival as a function of time using active cancer present at death as the failure endpoint. Deaths due to intercurrent disease with cancer controlled are treated as "censored" observations. The subgroup treated with mixed beam irradiation is shown as the dashed curve, and the photon-treated subgroup is shown as the solid curve. The difference between the two curves is statistically significant at the $p < 0.01$ level.



event and 1 coded a "unknown" causes, while the non-cancer deaths in the mixed beam subgroup included 2 cardiovascular events, 2 coded as "not cancer related" and 2 coded as "unknown" causes.

Stepwise Cox analyses (4) were used to identify the important patient parameters relating to local/regional control and survival. In each case the type of treatment given was the most important, with age, stage of lesion, and elevation of serum acid phosphatase being less important factors.

Treatment-associated complications in most cases were mild. Acute reactions were primarily the expected side effects of nausea, diarrhea, dysuria, and urinary urgency. Because of the poorly penetrating beam qualities of several of the neutron facilities, skin and subcutaneous reactions were more common in the mixed beam group of patients. However, the incidence of severe complications was not significantly different between the two treatment groups, being 9% for the mixed beam group and 7% for the photon group. No chronic bladder complications have been reported. The only fatal complication was a severe proctitis that required surgical intervention that occurred in a photon-treated patient. Wound complications and sepsis were the cause of death

Discussion

We have described the results of RTOG studies testing the efficacy of fast neutron irradiation as used in a mixed beam treatment schedule for locally-advanced carcinomas of the urinary bladder and prostate gland. The bladder study was non-randomized in nature (initially), and the analysis indicated a tumor clearance rate that was higher than expected with conventional photon irradiation. However, a subsequent, randomized, preoperative study failed for lack of patient accrual. Combining the patient groups treated definitively on both these studies, the initial clearance rate was 72% and the long term clearance rate was 31%. For the subgroup of patients with stage B and C disease, the long term clearance rate was about 33%. There have been two other reported series of patients with advanced bladder cancer treated with fast neutrons. Battermann and Breur (2) report on 22 patients with stage T_{4b} tumors treated with a neutron-only schedule using the beam from a dT generator. They found complete tumor regression in 11 patients (50%) but noted a 2-year survival of only 23%. This is comparable to the patients with D_1 lesions treated in our definitive mixed beam series. They noted a 23% (5/22) severe complication rate that led to death in 3 instances and to a colostomy in the other 2 cases. Duncan et al. (6) report on a randomized series of patients treated at Edinburgh with either conventional photon irradiation or fast neutron irradiation using the beam generated by a 15 MeV d-Be reaction. No difference was noted in terms of local control, but the neutron-treated group did show a higher incidence of late effects and, in particular, more pelvic fibrosis. Although our treatment fields were larger than those used by Battermann and Breur (2) and Duncan et al. (6), we did not see the problems they reported. This may be due to our using a mixed beam scheme rather than treating with neutrons alone. It remains to be seen whether or not the higher energy beams of

the next generations of neutron therapy machines will obviate this problem.

Our patients with locally advanced prostate cancer are the first reported group with this tumor type that has been treated with neutron irradiation. This was a randomized study, and the subgroup treated with mixed beam irradiation showed a significantly higher local control rate and survival than the photon-treated subgroup. It is also significant to note that there was no increased morbitity associated with the mixed beam form of treatment. Clearly, prostate cancer is a tumor where one would not expect a significant hypoxic cell fraction. However, it is a slowly-growing, better-differentiated type of tumor (in general), and the other radiobiological properties of fast neutron irradiation might be of importance here. These other properties are a reduced ability of cells to repair sublethal and potentially lethal damage and less variation in radiosensitivity across the cell cycle when compared with the effects of low LET radiation.

In the immediate future, patients with advanced pelvis malignancies will be placed on a neutron dose-searching study which will randomize them to receive either 16, 18, or 20 Gy with neutrons alone. Once the maximum tolerated dose to the pelvis is established, randomized studies will be developed for specific tumor histologies. The new prostate study will compare a neutron-alone arm with the same mixed beam arm that proved better than conventional photon irradiation on the previous study. The specific form of the bladder study is less certain, but it may involve randomizing patients to treatment with either neutrons alone and surgery held in reserve for salvage vs. a "standard" treatment arm that would consist of conventional, preoperative photon irradiation followed by a planned cystectomy.