FAST NEUTRON RADIOTHERAPY FOR LOCALLY ADVANCED PROSTATE CANCER: UPDATE OF A PAST TRIAL AND FUTURE RESEARCH DIRECTIONS

John N. Krieger, M.D.[1]
John M. Krall, Ph.D.[2]
George E. Laramore, Ph.D., M.D.[3]
Kenneth J. Russell, M.D.[3]
Frank S. Thomas, M.D.[4]
Moshe H. Maor, M.D.[5]
Frank R. Hendrickson[6]
Thomas W. Griffin, M.D.[3]

[1] Department of Urology,
University of Washington School of Medicine,
Seattle, WA 98195

[2] Statistical Divison, Radiation Therapy Oncology Group,
American College of Radiology, 925 Chestnut Street,
Philadelphia, PA 19107

[3] Department of Radiation Oncology,
University of Washington School of Medicine RC-08
Seattle, WA 98195

[4] Department of Radiation Therapy
Cleveland Clinic Foundation
Cleveland, OH 44106

[5] Department of Radiation Therapy
M.D. Anderson Hospital
Houston, TX 77030

[6] Neutron Therapy Department
Fermi National Accelerator Laboratory
Batavia, IL 60511

Correspondence: [1] Department of Urology RL-10
University of Washington School of Medicine
Seattle, WA 98195
Telephone: (206) 543-3640

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ABSTRACT

Between June, 1977 and April, 1983 the Radiation Therapy Oncology Group (RTOG) sponsored a Phase III study comparing fast neutron radiotherapy as part of a mixed beam (neutron/photon) regimen with conventional photon (x-ray) radiotherapy for patients with locally advanced (stages C and D_1) adenocarcinoma of the prostate. A total of 91 analyzable patients were entered into the study with the two treatment groups being balanced in regard to all major prognostic variables. The current analysis is for a median follow-up of 6.7 years (range 3.4-9.0). Actuarial curves are presented for local/regional control, overall survival and "determinantal" survival. The results are statistically significant in favor of the mixed beam group for all of the above parameters. At 5 years the local control rate is 81% on the mixed beam arm compared to 60% on the photon arm. Histologic evidence of residual prostatic carcinoma was documented in six patients with no clinical evidence of disease on both treatment arms. The actuarial overall survival rate at 5 years is 70% on the mixed beam compared to 56% on the photon arm. The determinantal survival at 5 years was 82% on the mixed beam arm compared to 61% on the photon arm. The type of therapy appeared to be the most important predictor of both local tumor control and patient survival in a step-wise Cox analysis. There was no difference in the treatment related morbidity for the two patient groups. Mixed beam therapy may be superior to standard photon radiotherapy for treatment of locally advanced prostate cancer.

INTRODUCTION

External beam radiotherapy has been a therapeutic option for patients with locally advanced carcinoma of the prostate for over 60 years. During the 1920's and 1930's, orthovoltage equipment was employed with disappointing results because the deliverable tumor dose was severely limited by radiation damage to surrounding tissues.[1] Megavoltage therapy using photons generated by cobalt units or linear accelerators became the standard care in the 1950's and 1960's. The largest series with long term follow-up was from Stanford University.[2,3] The actuarial survival of patients with clinical stage C disease was 60% at 5 years, 36% at 10 years and 22% at 15 years (based on analysis of 24 patients for the 15-year follow-up). Only 14-18% (depending on the radiation portals) of patients with stage D_1 disease survived for more than 5 years without evidence of cancer.[4] Furthermore, some patients with no clinical evidence of active cancer had histological evidence of residual prostate carcinoma but the significance of this is uncertain.[5,6]

Recent data clearly demonstrate that there has been considerable variation in the efficacy of "conventional" photon radiotherapy delivered in the United States. The "Patterns of Care in Radiotherapy" study surveyed 574 patients treated at 163 randomly chosen radiotherapy centers between January, 1973 and June, 1976. Local control strongly correlated with the radiation dose

delivered to the primary tumor bed, the paraprostatic region, and the pelvic sidewall.[7,8] For stage C lesions at least 6500-7000 cGy to the prostate bed was necessary for optimal tumor control. It also was necessary to deliver a similar dose to a point 4 cm lateral to the center of the gland. Many series which are often used as benchmarks for the efficacy of radiotherapy did not adhere to these standards.

Recent studies evaluated the optimal volume to treat with photons in patients with locally advanced prostate cancer. The Radiation Therapy Oncology Group (RTOG) conducted a randomized study with 523 analyzable patients with stage C tumors to determine whether para-aortic irradiation would improve survival.[9] The answer was "no". Because appropriate photon treatment standards are now reasonably well established, interest has turned to evaluating other types of radiotherapy for patients with prostate cancer.

Mixed-beam radiotherapy,[10] using a combination of fast neutrons and photons, became available at a limited number of centers in the 1970's. Based on theoretical considerations, fast neutrons should be advantageous for treating slow-growing tumors. This conclusion was further supported by the experimental observations of Batterman *et al*[11] on pulmonary metastases from human tumors. In general, prostate cancer tends to fall into the category of

slow-growing tumor systems. This report updates the results of a prospective, randomized study comparing a mixed-beam (neutron/-photon) treatment schedule to standard megavoltage photon radiotherapy for patients with locally advanced (stages C and D_1) carcinoma of the prostate and presents new information on post-treatment biopsies on these patients. The two treatment arms adhere to the doses and field geometries defined as optimal by previous photon studies.

METHODS

1. Patient selection and randomization. Between June 1, 1977 and April 30, 1983, the RTOG sponsored a study (RTOG 77-04) to test the efficacy of mixed beam radiotherapy for advanced adenocarcinoma of the prostate. To be eligible for inclusion, patients had to be less than 80 years old and have an initial Karnofsky score greater than 40. Patients were excluded if they had a history of previous pelvic radiation, extensive pelvic surgery or prior carcinoma (excluding non-melanoma skin cancer). The eligible tumor stages were C or D_1 using the Whitmore-Jewett staging system.[12,13] Patients were considered to have stage D disease if they had evidence of invasion of adjacent organs such as the bladder, or extension to the pelvic lymph nodes. A total of 95 patients were entered onto the study. Four patients were subsequently excluded from analysis (three were ineligible by virtue of inappropriate histology or stage and one refused the assigned treatment). Thus, there were 91 analyzable cases.

Mandatory prerandomization studies included: a positive prostatic biopsy, complete history and physical examination, chest X-ray, complete blood count, serum chemistries (enzymatic acid and alkaline phosphatase, liver function tests and calcium) and a radionuclide bone scan. Pelvic lymphadenectomy and/or bipedal lymphangiography, were performed in 41 cases. CT scans of the pelvis

were not routine at the time the study was initiated but were done in approximately 50% of cases. Patients were staged based on clinical criteria in conjunction with the mandatory studies.

Following informed consent, patients were randomized to receive either photon (control) radiotherapy or mixed-beam radiotherapy. At the time of randomization patients were stratified according to tumor histology (Mustofi schema), prior hormonal therapy, and status of pelvic nodes (No_1, N_+, N_x). The randomization process was purposefully unbalanced (60-40%) to favor the experimental therapy arm. This resulted in 55 analyzable cases on the mixed beam arm and 36 cases on the photon arm.

2. Radiotherapy. The mixed beam irradiation was a mixture of 40% neutrons plus 60% photons in terms of the expected biological effects to normal tissues. The study was designed to use a combination of both neutrons and photons rather than fast neutrons alone because of the limited penetration characteristics of the neutrons available at some treatment facilities. The radiation portals included the pelvic nodes as well as the prostate, and there was concern about treating this large volume of tissue with neutrons alone. The protocol is described in more detail in a previous communication,[10] but in brief, 50 Gy-equivalent was given to the large pelvic field and an additional 20 Gy-equivalent boost given to the prostate and other areas of gross tumor.

The cumulative dosage of radiation to surrounding organs was to be restricted to 60 Gy-equivalent for the bladder, 55 Gy-equivalent to the posterior rectal wall, and 55 Gy-equivalent to the small bowel.

Portal films for each field and computer isodose calculations through both the central axis plane of the pelvis and through the prostate were obtained in all cases. The beam films, isodose calculations, and treatment records of all patients were reviewed centrally for all patients on the study. Based on this review, five patients on the photon arm and eight patients on the mixed-beam arm were determined to have major protocol deviations. Most deviations resulted from prolonged treatment time course (>75 days). The remaining deviations were due to too low a neutron dose in mixed-beam group ($\leq$ 25% instead of the planned 40% of total dose). A prior analysis[10] of the study showed no differences in either local/regional control or survival for the patients with or without those types of protocol violations. Therefore, the analyses in this paper will include the entire group of 91 patients to avoid inadvertent "selection bias".

3. Follow-up studies: Patients were evaluated monthly for the first three months after treatment, at 3-month intervals for the next 3 years and, subsequently at 6-month intervals. At each

visit, the patients had a complete history and physical examination and measurement of serum acid phosphotase level (prior to rectal examination). Additional laboratory studies were performed as clinically indicated.

An effort was made to have all patients who survived at least 2 years after completion of treatment, undergo repeat prostate biopsies. As this was not part of the original protocol, both the physicians and the patients at each institution had to agree to this procedure. All post treatment specimens were obtained by a single urologist who evaluated the patients and performed the biopsies with no prior knowledge of the treatment received by the patients. Following informed consent, the patient was placed in the dorsal lithotomy position, premedicated with 5-10 mg of intravenous diazepam, suitably prepared and draped in sterile fashion. The perineal body was infiltrated with 1% Lidocaine, then a Tru-cut (R) biopsy needle (Travenol) was used to obtain at least three cores of tissue from both sides of the prostate, including all suspicious areas. A total of 11 patients were evaluated in this manner.

4. Statistical methods. The patient data were analyzed using the chi-square test of independence, the Kaplan-Meier method of plotting failure curves[14] and the Mantel-Haenszel test[15] of statistical significance. At the time of analysis the median follow-up time was 6.7 years (range 3.4-9.0).

A chi-square test was used to determine whether or not the two treatment arms were balanced according to major prognostic variables not controlled in the stratification process. The two groups were balanced according to age, tumor grade (according to both the Mostofi[16] and Gleason[17] schemes), stage (C vs. D_1), method of diagnosis (TURP vs. needle biopsy),[18] proportion of patients having lymphangiograms, pelvic node dissection or other methods of nodal evaluation, initial elevation of enzymatic serum acid phosphatase, evidence of seminal vesicle invasion, Karnofsky performance status, race, prior hormonal therapy, cardiac disease status and other intercurrent disease status. The sizes of the tumors were estimated from the product of the major diameters as determined on rectal examination. On the photon arm 58% had a "size" <16 cm^2, 25% had a "size" between 16-25 cm^2, and 17% had a "size" >25 cm^2. On the mixed beam arm 73% had a "size" <16 cm^2, 10% had a "size" between 16-25 cm^2, and 17% had a "size" >25 cm^2. This apparent difference was not significant (p=0.16). Concomitant benign prostatic hypertrophy was more common in the mixed-beam group (marginally significant at p=0.06). With the exception of the Gleason scores, all parameters were determined at the time of entry into the study. The Gleason scores were determined retrospectively by central review of 73/91 cases for which the original biopsy material was available.

RESULTS

The major endpoints of this study were local/regional tumor control and patient survival. Secondary endpoints were complications of therapy and tolerance of surrounding tissues to irradiation. The graphs in this section were calculated using the actuarial method,[14] with times determined from the initiation of treatment. Given the long natural history of prostate cancer, it is important to evaluate the number of patients at risk as a function of time for each of the graphs shown in this section. This information is summarized in Table 1.

1. Tumor control. Local/regional tumor control is the critical measure of local treatment modalities such as radiotherapy or surgery. The fraction of patients exhibiting local/regional control as a function of time is shown in Figure 1. Because many patients initially had persistent abnormalities on rectal examination, a post-treatment abnormality was not counted as a treatment failure unless there was obvious progression. This analysis is in keeping with the clinical observation that prostate cancer responds slowly to radiation therapy and often does not regress fully until many months following completion of treatment. For construction of the curves in Figure 1, local/regional failure was defined as either: (1) product of tumor major diameters at least 25% larger than at the time of entry into the study, (2) a

positive biopsy after 2 years, (3) new extension of tumor beyond the prostatic capsule or re-extension after becoming temporarily negative, (4) new local extension of the tumor or extension after temporary regression, or (5) evidence of active disease in the pelvic nodes. Serum acid phosphatase level alone was not considered evidence of tumor progression, but was used as an indication for additional evaluation. The total number of treatment failures is 9 on the mixed-beam arm compared with 13 on the photon arm.

Although repeated biopsy of the prostate was not part of the initial protocol, it has become apparent that, following radiotherapy, some patients may have no clinical evidence of failure yet still have histologic evidence of active tumor at the primary site. In order to assess this possibility, we performed repeated prostate biopsies on 11 patients who had survived for at least 2 years after completion of therapy. Ten of these were felt to be in local clinical remission. Five (63%) of eight patients in the mixed-beam-treated group had histological evidence of prostate cancer, including two patients with solitary focii of well differentiated carcinoma. Due in part to a reduced survival rate only 2 patients in local clinical remission were available from the photon-treated group and one (50%) had active tumor. Unfortunately, for a variety of reasons it has not been possible to biopsy the other surviving patients. Thus, one can only conclude

that there is no obvious difference between the two forms of treatment in the histological appearance of those tumors that have been in clinical remission after treatment. These failures were incorporated in the analysis leading to Figure 1. At 7 years the local control rate is approximately 75% on the mixed beam arm compared with 30% on the photon arm. Since the significance of a positive biopsy in the face of clinical remission is uncertain at present, the failure analysis was redone using clinical tumor progression as the endpoint. These results are shown in Figure 2. At 7 years the local control rate is approximately 80% on the mixed beam arm compared with approximately 60% on the photon arm. These numbers that should probably be compared with other photon results reported in the literature as routine biopsies have seldom been done for patients in clinical remission.

2. Patient survival. Overall patient survival as a function of time is summarized in Figure 3. The patients who received mixed-beam radiotherapy did significantly better than those who received standard photon therapy ($p=0.01$). At 7 years the actuarial survival was approximately 60% for patients treated with mixed-beam therapy compared with approximately 25% for patients treated with photons only ($p=0.01$).

Using overall patient survival as an endpoint is associated with problems since this is an elderly population with many deaths due

to diseases other than prostate cancer. In an attempt to avoid this problem, modified determinantal survival curves were constructed in which failure was defined as clinical evidence of active cancer at the time of death. These curves are shown in Figure 4. Deaths without evidence for active disease were treated as censored observations. Again the mixed-beam group did significantly better than the photon group ($p=0.02$). These curves probably are a more accurate assessment of the effect of treatment on survival than the ones shown in Figure 3.

Non-cancer related deaths in the control group included three cardiovascular events and four deaths due to unknown causes. Non-cancer related deaths in the mixed-beam group included three cardiovascular events, three deaths coded as "not cancer related" and one death coded as "unknown causes". All patients who died of non-cancer related causes had tumor control. In addition, there was one treatment-related fatal complication on each arm.

3. Systemic treatment failures. Distant metastases were documented in 23/55 (42%) mixed-beam-treated patients and in 18/36 (50%) photon-treated patients. There was also a slightly longer interval to the development of distant metastases on the mixed beam arm. However, none of these differences were statistically significant.

4. Secondary endpoints. Most patients experienced some toxicity associated with treatment but this was predominantly the expected side effects of nausea, diarrhea and urinary urgency. Since neutrons penetrate tissues less readily than photons, mild skin and subcutaneous reactions were more common among patients treated with mixed-beam irradiation. However, the incidence of complications graded "severe or greater" was only 9% on the mixed beam arm and 14% on the photon arm. Thus, improved local control and survival for the mixed beam group did not come at the expense of increased treatment-related morbidity.

DISCUSSION

Many urologists[19] view all external beam radiotherapy for prostate cancer as equivalent while radiation oncologists tend to do the same regarding surgical series. It is time that each specialty begin to appreciate what the other has to offer. The "Patterns of Care Study" clearly demonstrated the need for adequate tumor doses delivered using high energy linear accelerators.[7,8] Other work[9,18] showed the importance of stratifying by transurethral prostatic resection versus transperineal needle biopsy in subsequent development of distant metastases. The current study was balanced in all of these factors--only the type of radiation used was different.

In this randomized study, mixed-beam therapy was compared to standard high-dose photon therapy in a group of patients with stage C or stage D_1 disease. Judged by overall survival, "determinantal" survival or local/regional tumor control, patients in the mixed-beam group did significantly better than those treated with photons alone. Including positive random biopsies in clinically controlled patients, the local control rate at 5 years was 81% and at 7 years was 75% on the mixed beam arm compared with 60% at 5 years and 30% at 7 years on the photon arm. Using only clinical progression as the failure endpoint, the local control rate at 5 years was 86% and at 7 years was 80% on the mixed beam

arm compared with 60% at both intervals on the photon arm. The later figure is not too different from other reported photon series[20-22]. The actuarial 5- and 7-year survival rates were 64% for patients on the mixed beam arm versus about 56% and 25%, respectively, for patients on the photon arm. The determinantal survival curves showed a 7-year survival of approximately 80% on the mixed-beam arm compared with approximately 55% on the photon arm. Therefore, improved local tumor control appears to correlate with improved survival. This important finding supports further efforts to improve local/regional forms of therapy for prostate cancer.

The conclusion that mixed-beam therapy is superior to standard photon therapy for carcinoma of the prostate fits well with current concepts of radiobiology. In laboratory studies, fast neutrons are characterized by a high linear energy transfer (LET) in tissue. Typically, fast neutrons deposit 20-100 times more energy in tissue per unit path length than photons generated from megavoltage x-ray equipment. The important biological effects of radiation largely correlate with LET.[23] Particles with high LET, such as fast neutrons, are less dependent on the presence of oxygen to accomplish their cell-killing effects than are low LET X-rays and, thus, are more effective killers of the hypoxic cells found in large tumor masses. This property is termed the oxygen enhancement ratio (OER). The OER for fast neutrons is approximately 1.6 compared to an OER of 2.5-3.0 for high energy photons.

It has also been shown that the type of damage inflicted by neutrons is less readily repaired by tumor cells.[24] This reduced ability to repair both potentially lethal and sublethal damage may be especially important for slow growing tumors, such as prostate cancer, which may have a large proportion of cells in the "resting" or G_0 phase. Finally, there appears to be less variation in radiosensitivity of tumor cells across the cell cycle with neutrons than with conventional X-rays. These and other properties support the concept that neutrons should possess a high relative biological effectiveness in slow growing, photon-resistant tumors,[11] including carcinoma of the prostate.

A step-wise Cox analysis[25] was used to identify important parameters relating to local tumor control.[10] The most important variable was the type of treatment with "other disease status" being the next most significant. A similar analysis was used to identify important patient parameters relating to overall survival.[10] Age, stage and serum acid phosphatase level also correlated with survival. However, the most important predictor of survival was the type of radiotherapy ($p<0.01$).

There are a number of caveats to the conclusion that mixed-beam therapy is superior to conventional therapy for locally extensive prostate cancer. This study included a relatively small number of patients and the follow-up was short. Considering the entire

group of 91 evaluable cases (55 on the mixed-beam arm, and 36 on the photon arm), the differences in all parameters were significant based on analysis using either the Mantel-Haenzel or Wilcoxon test. The issue of overall patient survival is complex due to the number of deaths from other intercurrent diseases in our elderly patient population. Because they eliminate the "noise" due to nontumor-related deaths the determinantal survival curve in Figure 4 may be the best measure of the advantage of mixed-beam therapy over conventional photon radiotherapy.

A second reservation is the issue of the staging of disease in our patients. Although most cases were stage C, 5/36 patients on the photon arm and 6/55 patients on the mixed beam arm had proven metastases to the pelvic nodes. Without question, the prevalence of occult nodal involvement was substantially higher. Surgical staging has shown that 40-60% of patients with clinical stage C disease have lymph node metastases[26-28]. Lymphangiography was used to stage many patients, but this test may be of limited value for diagnosis of metastases because the obturator and hypogastric groups are not well visualized by this procedure[28].

Another caveat concerns the difference in survival of patients treated with photons in this study from other series of patients receiving similar treatment. Despite the inclusion of internal controls, it is important to compare the results of this study

with previous investigations. The actuarial local/regional clinical failure rate at 5 years in this study was 40% for photon therapy compared to only 14% for mixed-beam therapy. Neglia et al[20] report a local/regional failure rate of 5 years of 15.1% for patients with advanced stage C disease. Perez et al[21] report a 5-year local failure rate of 20% for patients receiving between 65-70 Gy. Ranglia et al[22] found a 5-year local failure rate of 24% for a combined group of stage B and C patients. The "Patterns of Care Study" showed a 19% local failure rate[7] after treatment for patients with stage C lesions receiving more than 65 Gy. In the present series 5/36 photon-treated patients had documented involvement of the pelvic nodes and 6/55 mixed-beam-treated patients had documented pelvic node involvement. Hence, our patients were likely more advanced than those in other series noted above. It is therefore possible that the apparent survival advntage may result, in part, from increased ability of mixed-beam treatment to sterilize or to retard progression of disease in the pelvic nodes.

The remaining reservation concerns the results of repeated histological evaluation of patients after definitive radiotherapy. Most patients with clinical evidence of treatment failure were documented by positive biopsies. In this situation the meaning of a positive biopsy is clear. However, in photon treated patients with no clinical evidence of disease 2 years after completion of

treatment, the meaning of a positive biopsy is uncertain. Freiha et al[5] claim that this is the harbinger of a more ominous prognosis while Leach et al[6] claim it has no clinical significance. Our results indicate that histological evidence of residual carcinoma may also occur in asymptomatic patients after mixed-beam therapy. Whether these patients, particularly those with single foci of well differentiated carcinoma, will suffer adverse consequences of their disease is as yet unknown.

This study demonstrates that a local/regional therapy can indeed affect the disease free and actuarial survival of patients with locally advanced prostate cancer. A new generation of treatment facilities is now available with the capability of administering treatment with fast neutrons alone. These facilities utilize neutron beams having depth-dose properties comparable to photon beams produced by megavoltage linear accelerators. Initially, patients with advanced pelvic malignancies were entered onto a randomized dose-searching study (RTOG 84-14) to determine the normal tissue tolerance dose for this region of the body. The "rapid" fractionation schema of Catterall at Hammersmith Hospital, London, England was utilized in this work. It appears possible to safely deliver 20.4 $Gy_{n\gamma}$ in 12 fractions over 4 weeks using a "shrinking field" technique. In a group of 43 patients there was only one serious acute complication which was a severe diarrhea. There were no life-threatening or fatal complications.

These results are comparable to the acute toxicities experienced by patients in both arms of the present series. Unfortunately, no late effects data are currently available from the dose-searching study. However, data analysis[29] from a joint RTOG/EORTC tumor registry indicates that this dose will be safe for the high-energy neutron beams in current use. Clearly this dose fractionation schema is unsafe if primitive, low-energy treatment machines are used.[30]

The RTOG recently initiated a new randomized study comparing fast neutrons alone to conventional photon therapy for patients with locally-advanced prostate cancer (RTOG 85-23). The intent of this study is to try to improve local tumor control and survival by increasing the percentage of radiation delivered with fast neutrons. The study was designed to better document pelvic nodal status by "encouraging" patients to undergo a staging lymphadenectomy and then stratifying the treatment arms according to this variable. Patients with negative nodes will undergo local field (prostate bed) radiotherapy only, while patients with documented positive pelvic nodes or those who refuse staging lymphadenectomy will receive pelvic irradiation followed by a prostatic boost. A post-treatment biopsy of the prostate gland will be <u>mandatory</u> at 2 years post therapy.

TABLE 1. Number of patients at risk for failure as a function of follow-up time (years) for the parameters of local/regional control (with and without biopsy for clinically-controlled disease) survival, and determinental survival. "M" refers to the mixed-beam group and "p" refers to the photon group.

		Years at Risk								
Endpoint	Arm	0	1	2	3	4	5	6	7	8
Local Control (with biopsy)	M	55	53	51	43	35	23	12	4	3
	P	36	33	28	19	14	6	4	1	1
Local Control (without biopsy)	M	55	53	51	43	37	23	12	4	3
	P	36	34	28	19	14	6	4	1	1
Survival	M	55	54	53	46	39	26	15	5	3
	P	36	36	33	24	20	9	6	2	1
Determinental Survival	M	55	54	53	46	39	26	15	5	3
	P	36	36	33	24	20	9	6	2	1

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Figure 1: Local tumor control as a function of treatment with positive tumor biopsies in patients in local clinical remission being included as failures. The dashed curve represents the mixed-beam treated patients and the solid curve represents the photon treated patients. The two curves are different at the $p \leq 0.01$ level.

Figure 2: Local tumor control as a function of treatment using clinical assessment of tumor as the endpoint. Patients with clinical local control and positive biopsies are not counted as failures. The dashed curve represents the mixed-beam treated patients and the solid curve represents the photon treated patients. The two curves are different at the $p \leq 0.01$ level.

Figure 3: Patient survival as a function of treatment. The dashed curve represents the mixed-beam-treated patients and the solid curve represents the photon-treated patients. The two curves are different at the $p=0.01$ level.

Figure 4: Patient survival as a function of treatment using active cancer (local or distant) at the time of death as the endpoint. Deaths due to intercurrrent disease with cancer controlled are treated as "censored" observations. The dashed curve represents the mixed-beam-treated patients and the solid curve represents the photon-treated patients. The two curves are different at the p=0.02 level.