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Fast Neutron Radiotherapy for Locally Advanced Prostate Cancer

Final Report of a Radiation Therapy Oncology Group Randomized Clinical Trial

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Between June 1977 and April 1983 the Radiation Therapy Oncology Group (RTOG) sponsored a Phase III randomized trial investigating the use of fast neutron radiotherapy for patients with locally advanced (Stages C and D_1) adenocarcinoma of the prostate gland. Patients were randomized to receive either conventional photon radiation or fast neutron radiation used in a mixed-beam (neutron/photon) treatment schedule. A total of 91 analyzable patients were entered into the study, and the two patient groups were balanced with respect to the major prognostic variables. Actuarial curves are presented for local/regional control and "overall" survival. Ten-year results for clinically assessed local control are 70% for the mixed-beam group versus 58% for the photon group ($p = 0.03$) and for survival are 46% for the mixed-beam group versus 29% for the photon group ($p = 0.04$). This study suggests that a regional method of treatment can influence both local tumor control and survival in patients with locally advanced adenocarcinoma of the prostate gland.

Key Words: Neutron radiotherapy—Prostate cancer.

According to American Cancer Society estimates, in 1991 there were 122,000 new cases of prostate cancer and 32,000 deaths due to this disease in the United States alone (1). Prostate cancer is now the most common cancer in men in the United States, excluding non-melanoma skin cancer. The clinical course of this disease is quite variable, and long term follow-up is necessary to assess the true efficacy of any new form of treatment.

In the 1970s, the Radiation Therapy Oncology Group (RTOG) launched a series of randomized Phase III trials comparing fast neutron radiotherapy with conventional photon radiotherapy for various tumor systems. One such trial was RTOG 77-04 for locally advanced prostate cancer. Preliminary analyses of the data from this trial at the 5- and 8-year end points showed a benefit to the fast neutron form of treatment, both in terms of local/regional control and survival (2,3). In this article we present the final 10-year data from this study—data that are especially important given the long natural history of this disease. The data show a statistically significant improvement in both clinically assessed local/regional tumor control and survival from fast neutron radiotherapy and suggest that a regional form of treatment can favorably affect outcome in locally advanced prostate tumors.

MATERIALS AND METHODS

RTOG 77-04 was open between June 1977 and April 1983 with a total of 95 patients entered. Four patients were ultimately excluded from analysis (three were ineligible and one refused the assigned treatment), leaving 91 analyzable patients. All patients had either Stage C

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or D_1, biopsy-proven, adenocarcinoma of the prostate gland (4). For a complete discussion of the eligibility criteria, patient evaluation procedure, and treatment protocol, the reader is referred to the original report (2).

At the time of the present analysis the median time at risk for the patients is 10.8 years (range: 7.5–13). Statistical methods used to analyze the data include the chi-square test, the Mantel-Haenszel test (5), and the Kaplan-Meier method of plotting survival curves (6). Based on the chi-square test of independence, the two treatment groups were balanced according to the following prospectively gathered variables: age distribution; tumor grade (Mostofi schema (7)); Stage (C versus D_1); method of tumor diagnosis (transurethral prostate resection (TURP) versus needle biopsy); percentage of patients having lymphangiograms, laparotomies, or other methods of nodal evaluation; initially elevated acid phosphatase level; degree of seminal vesicle involvement; Karnofsky performance status; race; prior hormonal therapy; cardiac disease status; and other intercurrent disease status. The presence of concomitant, benign prostatic hypertrophy was unbalanced at a marginally significant level ($p = 0.06$) and occurred more frequently in the mixed-beam group. Tumor size based upon the product of the clinically assessed major diameters was somewhat larger in the photon group ($p < 0.05$). Gleason scores (8), which were retrospectively obtained on 73 of 91 patients for whom the biopsy material could be retrieved, were centrally reviewed and were balanced on the two arms.

RESULTS

The major end points of this study are local/regional tumor control and survival. Treatment-related complication rates are a secondary end point.

Figure 1 shows the proportion of patients exhibiting local/regional control as a function of time. In the assessment of control, a post-treatment abnormality was assumed to be of unknown significance in the immediate postirradiation period and was not counted as a failure until progression was noted. This method of failure determination was selected since prostate cancer is slow to respond to radiation therapy and often does not regress completely until several months after treatment is finished. Figure 1 shows the results for *only* clinical failures. Clinical local/regional failure was defined as either (a) product of tumor major diameters being at least 25% greater than at the time of entry onto the study, (b) new extension of tumor beyond the prostate capsule or re-extension after becoming temporarily negative, (c) new local extension of tumor or extension of tumor after an initial regression, (d) pelvic

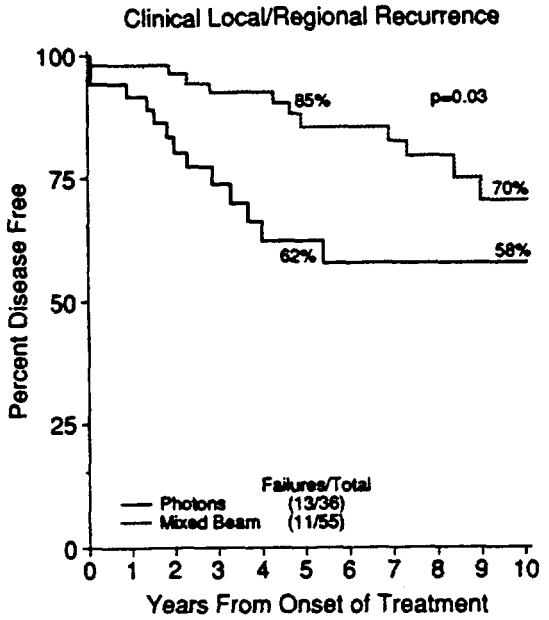

FIG. 1. Time to local/regional tumor progression using only clinical criteria. The mixed-beam group is shown as the dotted line, and the photon group is shown as the solid line. The difference between the two curves is statistically significant at the $p = 0.03$ level. The numbers in parentheses indicate the fraction of patients exhibiting a "failure" at the time of analysis.

nodes either becoming newly positive or again becoming positive after becoming temporarily negative, or (e) clinical evidence of tumor progression, such as obstructive symptoms, followed by a positive biopsy either via needle or TURP. As part of the program to evaluate tumor status in more detail, 11 patients who were treated at the Seattle facility and were clinically NED with normal serum acid phosphatase underwent an investigative procedure whereby two random biopsies were taken of each lobe of the prostate. The results were positive for four mixed-beam patients and one photon patient. Considerable sampling error was involved since there were more than twice as many mixed-beam patients surviving at the time the biopsies were performed. The significance of a positive biopsy in a patient in clinical remission is uncertain (9–11). Of these five "pathologic-only" failures, one was treated with DES, one was treated with an orchiectomy, and three were left untreated. All five have been free of local disease progression for more than 5 years. One other mixed-beam patient exhibited a "biopsy-only" failure initially and 3 years later showed clinical evidence of tumor progression. At the 10-year point, clinically assessed local/regional control is 70% for the mixed-beam group compared to 58% for the photon group. The difference between the curves is significant at the $p = 0.03$ level. All but one of the local/regional

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failures had a component in the prostate gland itself. The later patient who was treated with photons failed only in the regional nodes. If we were to include the "pathologic-only" failures in our analysis, the local control rates at 10 years would be 61% for the mixed-beam patients and 52% for the photon patients.

Actuarial survival for the two patient groups is shown in Fig. 2. There is a 17% survival advantage for the mixed-beam form of treatment at both the 5- and 10-year end points—70% versus 53% and 46% versus 29%. The difference between the two curves is significant at the p = 0.04 level.

Distant metastases have been documented in 49% (27 of 55) of the mixed-beam-treated patients and in 55% (20 of 36) of the photon-treated patients. There was no significant difference noted in the time to development of these distant metastases.

Most treatment-related complications were mild and consisted of the expected side effects of nausea, diarrhea, dysuria, and urinary urgency. Because of the poorly penetrating qualities of the neutron beams, skin and subcutaneous tissue reactions were more severe for the mixed-beam group. Table 1 lists the significant side effects, which were graded severe or greater using the joint RTOG/EORTC (European Organization for Research on Cancer Treatment) scoring scheme. A total of five photon-treated patients and seven mixed-beam-treated patients suffered such complications

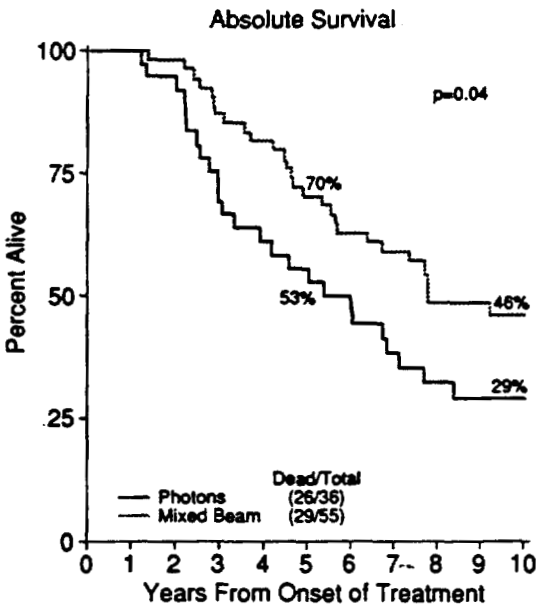

FIG. 2. Overall patient survival as a function of time. The mixed-beam group is shown as the dotted line, and the photon group is shown as the solid line. The difference between the curves is statistically significant at the p = 0.04 level. The numbers in parentheses indicate the fraction of dead patients at the time of analysis.

TABLE 1. *Toxicities scored severe or greater according to the RTOG/EORTC scoring schema*

Toxicity	Photon	Mixed beam
Skin	—	2
Urinary	3	2
Rectal	1[a]	2
GI	1	2 (1)[a]

[a] Fatal complications.

(some patients had more than one such complication). As noted in Table 1, there was one treatment-related fatality in each arm. In each case, surgery was required for a complication, and the patient died of sequelae following it. There is no statistical difference in the rate of significant complications in the two arms.

DISCUSSION

This article reports 10-year results of a prospective, randomized study comparing mixed-beam (neutron/photon) radiation therapy to conventional photon irradiation for patients with locally advanced adenocarcinoma of the prostate gland. The mixed-beam group of patients appears to fare better than the photon control group in regard to all major end points: local/regional control and survival. Most of the patients entered into this study had Stage C disease but 5 of 36 patients in the photon group and 6 of 55 patients in the mixed-beam group had proven metastases to the pelvic lymph nodes. These patients would have been excluded from clinical trials that were restricted to patients with Stage C tumors, which makes comparison with other series difficult.

Table 2 summarizes our 10-year results for both local control and survival and compares these figures with other reports in the literature (12–17). The mixed-beam

TABLE 2. *Ten-year actuarial local control rates and survival for various patient series*[a]

	Patient number	Local control (%)	Survival (%)
Present study—Stages C & D_1			
Mixed beam	55	70	46
Photons	36	58	29
Photon series—Stage C			
Stanford (13)	385	—	36
Syracuse (16)	63	—	30
MDAH (17)	551	81	47
Mallinckrodt (15)	328	—	38
University of Florida (12)	111	63	38
Patterns of Care (14)	296	65	38

[a] Except for the present study, all series are restricted to patients with Stage C disease.

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result of 70% is somewhat better than the University of Florida (12) and Patterns of Care (14) results, but is worse than the reported series from M.D. Anderson Hospital (17); our photon results are worse than all three. In regard to actuarial survival, our mixed-beam result is comparable to the M.D. Anderson results (17) and is better than the other series, whereas our photon result is comparable to that reported from Syracuse (16) and worse than the other series. Differences in patient population most likely account for the differences among the nonrandomized photon series shown in Table 2. This contention can be supported by comparing the outcome for the Stage C patients entered by M.D. Anderson on the present study with the M.D. Anderson results of Zagars et al. (17) for their Stage C patients. Ten Stage C patients from M.D. Anderson were treated with the mixed-beam regimen, and 11 were treated with photons on our randomized trial. At 5 and 10 years, local/regional control rates for this subset of patients were, respectively, 68% and 44% for the mixed-beam groups compared to 44% and 0% for the photon group. In regard to survival, the 5- and 10-year rates were, respectively, 70% and 60% for the mixed-beam group compared to 60% and 9% for the photon group. Clearly, the values for the photon-treated patients are markedly inferior to those reported by Zagars et al. (17). This finding demonstrates the role of patient selection even in reports from a single institution and further underscores the necessity of randomized trials. It is important to note that our study was randomized and the two treatment groups were balanced in regard to the major prognostic variables. Hence, our comparison of the results of the mixed-beam and photon forms of treatment should be valid.

This study seems to indicate that a local/regional form of treatment can favorably affect survival for locally advanced prostate cancer. Although the end point differences achieve statistical significance, the number of patients in the trial is relatively small. Recognizing this and also the large number of patients who present each year with locally advanced tumors, in 1986 the Neutron Therapy Collaborative Working Group (NTCWG) elected to repeat the essence of this trial using the newly available neutron therapy facilities that had been sponsored by the National Cancer Institute. In NTCWG 85-23 neutron radiation alone was used as the experimental arm, and photon radiation in the same manner as described herein was used as the control arm. Eligible patients had biopsy-proven Stage B_2 (Gleason $\geq$ 7), C, or D_1 tumors. Surgical staging of lymph nodes was encouraged and used as a stratification variable. Routine biopsy of the prostate was mandated 18 months after treatment. This study has just closed after accruing 178 patients, and the data will require several years to mature. If the results confirm the present study, then fast neutron radiotherapy may become the treatment of choice for patients with locally advanced prostate cancer.

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