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Fast Neutron Irradiation of Locally Advanced Prostate Cancer

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THE MANAGEMENT OF locally advanced prostate cancer remains a topic of considerable controversy in the oncologic community. While the hormonal treatment of patients presenting with metastatic disease engenders little debate, and while there is solid data to confirm the efficacy of radical prostatectomy and megavoltage photon irradiation in the control of early lesions localized within the gland itself,[1] the treatment of Stages C and D1 presentations is not well agreed upon. A number of studies have yielded long-term survival data for patients treated with megavoltage photon irradiation for these presentations, and appear to favor this approach.[2-6] Other investigations have yielded data to support the thesis that photon irradiation does not substantially alter the natural history of the disease in the same group of patients.[7,8] The study described in this article was designed to explore the role of fast neutrons in the treatment of patients with Stages C and D1 disease.

The theoretical advantage of neutrons over photons in the treatment of malignancies relates to the far greater energy deposition by neutrons in soft tissues. Considered "high LET" irradiation (LET, Linear Energy Transfer), neutrons deposit as much as 20 to 100 times more energy per centimeter of tissue traversed than photons. The biological consequences of this enhanced energy deposition are multiple, and the result is an enhanced relative biologic effectiveness (RBE) of neutrons compared with photons, as measured in both laboratory models and in human studies. When compared with conventional x-rays, neutrons: (1) are better able to sterilize hypoxic cells; (2) allow for less repair of potentially lethal damage; (3) allow for less repair of sublethal damage, and (4) exhibit less variation in cell killing ability across the cell cycle. A study comparing the relative biological effectiveness of neutrons with cobalt-60 gamma rays for human tumors metastatic to lung was performed by Batterman et al, who found that neutrons were particularly advantageous for treating slowly growing, radioresistant tumors.[9] While prostate cancer was not explicitly studied, it tends to fall into this general category.

MATERIALS AND METHODS

Ninety-five patients were entered in a prospective, randomized study comparing fast neutrons delivered in a mixed beam treatment regimen with conventional external beam photon radiation therapy between June 1977 and April 1983. Four patients have been excluded from the analysis (three were ineligible by the original protocol criteria, and one refused the assigned treatment arm). Of the remaining 91 patients, all had biopsy confirmation of adenocarcinoma and were staged as C or D1 lesions. Additional eligibility criteria required patients to be <80 years old, have an initial Karnofsky performance score of >40, and no prior history of pelvic irradiation, extensive prior surgery, or cancer (excepting non-melanoma skin cancer). Prior hormonal treatment was permitted, and 25% of the photon patients had received prior hormones *v* 11% of the mixed beam patients. Informed consent was obtained from all patients.

All patients underwent a pretreatment staging evaluation including history and physical examination, complete blood counts and serum chemistries, liver function tests, alkaline and acid phosphatases, chest x-ray, and a radionuclide bone scan. Computerized tomographic scans (CT) of the pelvis were performed in approximately one-half of the patients, and bipedal lymphangiography was performed on 41 patients. Three (8%) photon patients and 5 (9%) mixed beam patients underwent surgical node sampling.

Patients were randomized to receive either photon irradiation alone or mixed beam irradiation. Mixed beam treatment involved twice weekly irradiation with neutrons and thrice weekly irradiation with photons. The randomization of patients was purposely unbalanced (60% to 40%) to allow larger numbers of patients on the experimental mixed beam arm (55 *v* 36). The study design is illustrated in Fig 1.

Neutron treatment was delivered at the following institutions: the University of Washington, the Great Lakes Neutron Treatment Association, the M.D. Anderson Hospital

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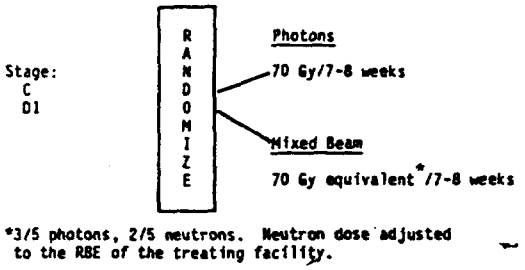

Fig 1. Study design: patients were stratified by stage, grade, and treating institution.

and Tumor Institute at the University of Texas, and the Fermilab. Neutron doses at each facility were adjusted according to the measured RBE of the neutrons from each accelerator. As neutron irradiation contains a small percentage of photon contamination, this photon component was included in the specified neutron dose.

The decision to make the experimental arm a neutron/photon mix rather than neutrons alone arose from the poor depth-dose characteristics of the neutron beams available at the time this study was conducted. All of these neutron beams were produced by accelerators located in nuclear physics laboratories. The poor penetration of many of these beams would have resulted in unacceptably high radiation doses to pelvic subcutaneous tissues and bowel in the process of treating the deep seated primary tumors and lymph nodes to tumoricidal doses with neutrons alone. The resulting complications would have been unacceptable. To avoid this problem, it was decided to dilute the neutrons with better penetrating photons, resulting in the mixed beam treatment delivered in this study.

Patients treated with photon irradiation alone received a dose of 5000 cGy to a field encompassing the prostate and pelvic lymph nodes at a daily rate of 180 to 200 cGy per fraction, with a subsequent boost of 2000 cGy (same fractionation) to the prostate and areas of proven bulky extraprostatic disease. Patients treated with mixed beam irradiation received a dose of 5000 cGy photon equivalent (neutron dose multiplied by the institutional RBE, and summed with the photon dose), plus a similar 2000 cGy photon equivalent boost, as before. A fractionation scheme of 180 to 200 cGy photon equivalent was administered per day, and all patients were treated 5 days per week. Photon or photon equivalent radiation doses to the posterior rectum were limited to 5500 cGy, and the entire bladder to 6000 cGy.

Computer generated isodose calculations and plots were obtained in all patients, and portal films confirming the accuracy of the treatment were obtained for each treatment field.

Following completion of treatment all patients were seen in follow-up at monthly intervals for the first 3 months, at 3 month intervals for the next 2¾ years, and every 6 months thereafter.

Statistical methods used to analyze patient data include the chi-square test of independence, the Kaplan-Meier method of plotting failure curves, the Mantel-Haenzel test, and the Wilcoxon test.[10,11,12]

RESULTS

Data analysis has been performed on 91 patients. Although review of patient records revealed that 13 patients were treated with major deviations from protocol (five photon and eight mixed beam), usually involving excessively long times to complete treatment, no statistical differences in survival or local control could be confirmed for protocol violators, as reported in an earlier analysis.[13] Consequently, the results of treatment for the entire 91 patients have been included in this report. At the time of this analysis, the median follow-up period was 6.7 years. The minimum follow-up period was 4 years, and the maximum follow-up period was 9.8 years.

Using chi-square analysis, the two groups proved to be balanced according to age, stage (C *v* D), presence of seminal vesical invasion, tumor grade (both Mostofi grade and Gleason pattern score), Karnofsky performance status, prior hormonal therapy, method of diagnosis (needle biopsy *v* transurethral resection), percentage of patients having nodal evaluation radiographi-

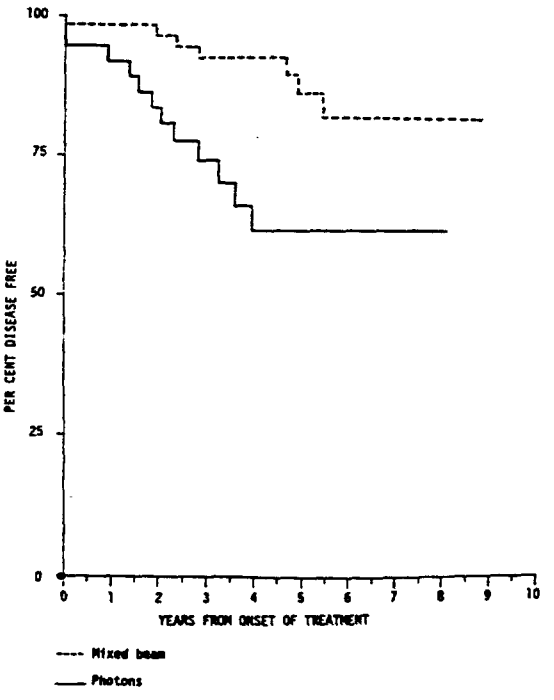

Fig 2. Freedom from local/regional tumor recurrence. The two curves are different at the $P < 0.01$ level.

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cally or surgically, and percentage of patients with elevated serum acid phosphatase at presentation.[14,15] Tumor size, derived from the product of the perpendicular diameters assessed on digital examination, was larger in the photon treated group, and concomitant benign prostatic hypertrophy was more frequent in the mixed beam group. Excepting Gleason scores, which were determined retrospectively by review of 73 of 91 cases for which biopsy material was available, all parameters were scored at the time each patient entered the study.

Fig 2 depicts the clinical freedom from local/regional tumor recurrence rates for the two treatments. Criteria defining clinical local tumor recurrence were: (1) increase in the product of tumor dimensions by 25% following treatment; (2) new extension of the tumor after initial regression; (3) radiographic or clinical evidence of progression in the pelvic nodes. Eighty-one percent of the neutron treated patients remained clinically free of local tumor recurrence compared with 61% of the patients treated with photons alone. This difference is statistically significant ($P < 0.01$). Although no standard approach to routine posttreatment biopsy was mandated in this study, 11 patients had their prostates rebiopsied a minimum of 2 years after treatment while in clinical remission. Combining the pathologic criterion of a positive biopsy with the clinical criteria, 77% of the neutron treated patients *v* 31% of the photon treated patients remained free of local disease. These differences remain statistically significant ($P < 0.01$).

Survival data are graphically displayed in Fig 3. Sixty-three percent of the neutron treated group are alive at 8 years as opposed to 13% of the photon only treated cohort ($P = 0.01$). When one excludes intercurrent deaths from causes other than prostate cancer, the corresponding determinantal survival data are summarized in Fig 4. The determinantal survival ratio for the neutron treated group of patients at 8 years is 82% compared with 54% for the photon only treated group. The difference remains statistically significant ($P = 0.02$). A stepwise Cox analysis has been used to identify the important patient parameters relating to overall survival in

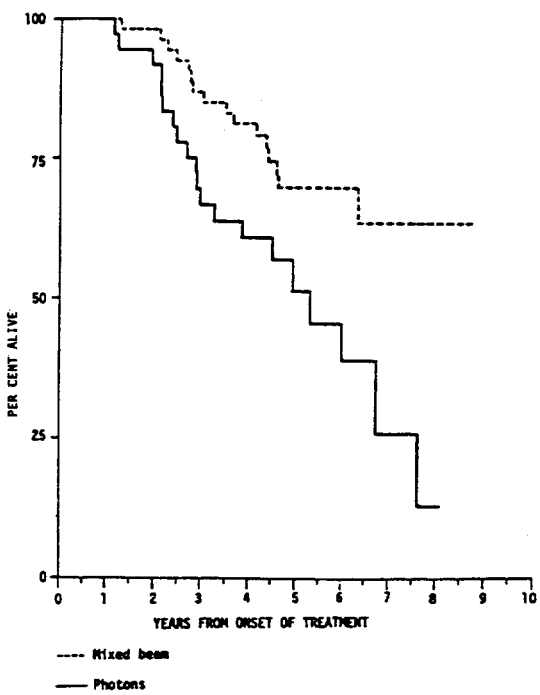

Fig 3. Patient survival as a function of treatment. The two curves are different at the $P = 0.01$ level.

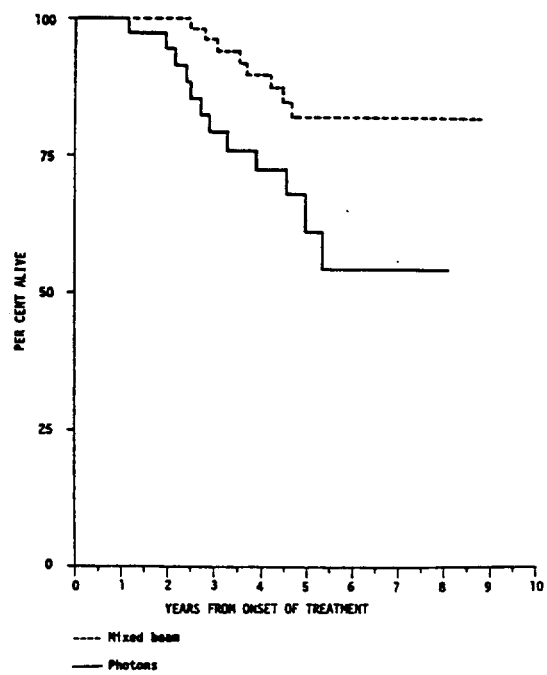

Fig 4. Patient survival as a function of treatment using active cancer (local or distant) at the time of death as the endpoint. Deaths due to intercurrent disease with no evidence of cancer present are treated as censored observations. The two curves are different at the $P = 0.02$ level.

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Table 1. Cox Step-Wise Analysis of Prognostic Variables

Independent Variable	P Value	Rank
Treatment (mixed beam v photons)	$P < 0.01$	1st
Age	$P < 0.05$	2nd
Stage (C v D1)	$P < 0.05$	3rd
Elevated serum acid phosphatase	$P = 0.06$	4th

this study as shown in Table 1. Age, stage of lesion, and whether serum acid phosphatase levels were initially elevated were important parameters associated with survival. However, these parameters proved to be less important predictors of survival than form of treatment. The most important predictor of survival was whether or not patients were treated with neutrons ($P < 0.01$).

Complications associated with the two treatments are comparable, and have been previously reported. Acute skin reactions were more severe in the neutron treated patients due to the poor skin sparing qualities of the lower energy neutron beams.

DISCUSSION

Neutrons and photons differ significantly in their interactions with tissues, with a far greater intensity (linear energy transfer or LET) of energy deposition by neutrons. As a result of this intense deposition of energy, or at least associated with it, there are a number of discreet biologic differences between neutrons and photons that would suggest a superiority of neutrons in the treatment of malignant tumors.

First, there is the decreased ability of tumors to repair neutron induced damage, assayed in laboratory systems as diminished sublethal damage repair, and diminished potentially lethal damage repair (PLDR).[16,17] PLDR is a form of repair of radiation damage which occurs in slowly proliferating tissues with a low growth fraction and a large quiescent (G_0) population, and might be expected to be particularly relevant in prostate cancer.

Additionally, neutrons are less dependent than photons on the presence of cellular oxygen to achieve cell killing. Whereas there is a factor of 3 difference in the photon radiosensitivity of sensitive oxygenated tumors *v* resistant hypoxic tumors, this ratio of sensitivities is 1.6 for neutron radiation.[18] This decreased oxygen enhancement ratio (OER) would be expected to prove advantageous in larger tumors with significant viable hypoxic cell populations.

Lastly, there is less variation across the cell cycle in radiosensitivity to neutrons than to photons, and there is evidence that neutrons and photons cause DNA damage by different mechanisms. Photons are thought to cause DNA strand breaks primarily by indirect mechanisms involving the generation of free radicals. Neutron damage appears to occur by primarily direct action on the DNA.[19]

Overall, these properties of neutrons result in a greater relative biologic effectiveness (RBE) than for photons (measured as the inverse of the ratio of neutron dose to photon dose required to achieve a given biologic endpoint). Whether this increased RBE is selective for tumors, or applies equally to normal tissues, is not fully known. In certain tissues and histologies (salivary gland adenoid cystic tumors, for example) the RBE for the tumor is 8.0, whereas the RBE for the surrounding normal tissues is 3.0.[9] Comparable data for prostate adenocarcinoma and the adjacent normal prostate, bladder, and rectum, is not as clearly known, and the tolerance of these organs to neutron irradiation has only been determined by Phases I and II clinical trials. Nonetheless, the overall differences in biologic effects between neutron and photon irradiation are compelling enough to suggest a theoretical superiority for neutrons over photons, particularly in the treatment of slow growing, low growth fraction tumors typified by adenocarcinoma of the prostate. As the photon irradiation of locally advanced prostate cancer has been far from uniformly successful, the use of neutrons as a part of the treatment tests whether a theoretically more effective local modality can impact on overall survival of these patients.

Considerable controversy is evident in the oncologic literature regarding the most efficacious management of locally advanced prostate cancer. It is contested whether a local modality can have substantial impact at all in a clinical situation that is felt by many to imply systemic dissemination of tumors. A number of investigators have reported long-term survival data supporting the use of external beam megavoltage photon irradiation in Stage C presentations.[2-6]

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Other investigators have presented survival data to suggest that external beam photon radiotherapy in Stage C patients does not alter the natural course of the disease any more effectively than delayed androgen deprivation.[8]

Similar debate surrounds the treatment of patients with histologically proven pelvic lymph node metastases. While pelvic irradiation has been advocated by some with long-term survivals reported in patients with surgically documented lymph node involvement, the efficacy of this treatment is discounted by others, who find equivalent survivals in groups treated without pelvic irradiation, by palliative surgery, or by hormonal deprivation.[7,20,21]

This study cannot provide data to either prove or disprove the efficacy of photon irradiation in these clinical settings. However, it appears with a median follow-up of 6.7 years, there is evidence to suggest that treatment involving neutrons is superior to treatment employing solely photons, both by criteria of survival and local control. A stepwise Cox analysis, applied to identify patient parameters determining overall survival, yielded the finding that treatment modality (mixed beam *v* photons) was the most important predictor of outcome ($P < 0.01$), even over stage (C *v* D), elevation of serum acid phosphatase, and age.[13]

Differences in frequency of follow-up, diagnostic evaluation at follow-up, criteria for local tumor control, and routine posttreatment biopsy make comparisons among reported series difficult. However, there are several articles that report photon results which appear to be superior to the photon (control) results reported in this study. Perez et al have described a tumor free 5 year actuarial survival of 56% for a similar cohort of patients, with a local failure rate of 12% for patients receiving at least 7000 rad to the prostate.[3] The results of Rangala et al are a 5 year actuarial disease free survival of 69% in Stage C patients, with a local recurrence free survival of 76%.[5] Bagshaw has reported a 5 year actuarial survival of 61% in 219 patients with extracapsular extension of tumor outside the prostatic capsule.[1] Neglia et al found a 5 year survival of 58.5% for their patients with advanced Stage C disease (invading bladder or rectum, or fixed to pelvic sidewalls), and a local control rate of 71.7% for these patients, who are similar in their advanced stage to those in this study.[3] Less advanced Stage C patients had a local control rate of 93.8% and 5 year survival of 72.2%. As these investigators correlated photon control rates and survival outcomes with tumor size, and as there is a similar correlation found in the postirradiation biopsies performed in the Stanford series, this may account for some of the differences in outcome, as most of our patients had locally extensive tumors.[22] Additionally, the inclusion of Stage D1 patients in our results may bias the outcomes unfavorably.

In an effort to better understand these results, freedom from local/regional tumor recurrence and survival analysis from this study were compared with results from the National Patterns of Care Study reported by Hanks et al.[23,24] Fig 5 illustrates the results in terms of clinical freedom from local/regional tumor recurrence, and Fig 6 illustrates the results in terms of survival. In both

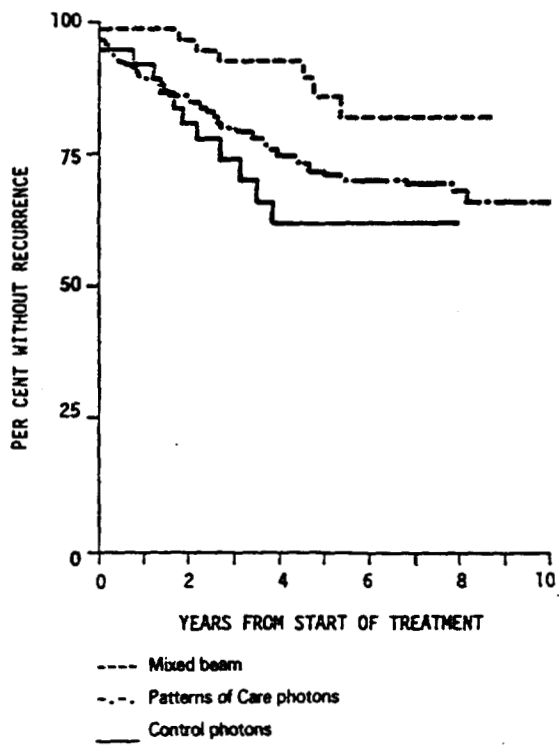

Fig 5. Comparison of neutron study results with results from the National Patterns of Care Prostate Study with freedom from local/regional tumor recurrence as the endpoint.

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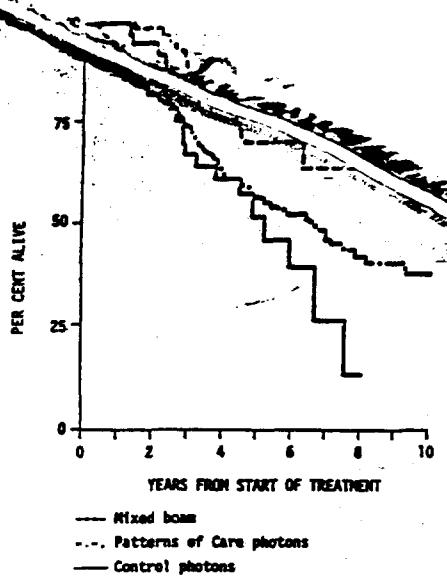

Fig 6. Comparision of neutron study results with results from the National Patterns of Care Prostate Study with survival as the endpoint.

instances, the neutron treated group exhibits a superior result when compared with the photon only treated groups. This is in spite of the fact that D1 tumors were included in this study, but were not included in the Patterns of Care Study.

One issue as yet unresolved is whether neutron treatment is superior to photons in achieving complete histologic clearance of tumor. Posttreatment biopsy was not mandatory in this study, and as only 11 patients have been biopsied (on a somewhat ad hoc basis), no definitive conclusions can be drawn from the study in this regard. Whereas published data suggest either no prognostic significance for this finding or, conversely, a significantly adverse outcome, much disagreement surrounds the significance of a posttreatment biopsy uncovered in the clinical context of a normal prostate exam. As the majority of conventially irradiated Stage C patients will probably have a positive biopsy 18 months or more following treatment, this is another parameter by which the efficacy of neutron treatment will need to be judged.[23]

The results of this trial suggest that a local modality (neutrons + photons) can have a favorable survival impact on locally advanced prostate cancer. As this is the only study of its kind, these results will need to be confirmed.

With the advent of a new generation of hospital based, high-energy cyclotrons designed solely for medical applications and capable of delivering doses at depths comparable with the dose distributions of a megavoltage linear accelerator, the opportunity has emerged to use neutrons alone in the treatment of prostate cancer. Currently the efficacy of neutrons used alone is being tested in a national cooperative study. It is hoped that the development of these new treatment machines will result in a further improvement in the results of treatment of this disease.

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