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Fast Neutron Radiotherapy in the Treatment of Locally Advanced Adenocarcinoma of the Prostate

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Clinical Experience and Future Directions

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The major clinical experiences using fast neutrons for the treatment of locally advanced prostatic carcinomas are reviewed. In all trials to date, there is evidence that treatment regimens employing a component of fast neutrons achieve results that equal or surpass those obtainable with conventional megavoltage external beam irradiation for comparable groups of patients. Late complications of neutron treatment have not exceeded the complication rate expected by photon irradiation. The structure of the current Radiation Therapy Oncology Group phase III randomized trial comparing neutron and photon treatment of patients with stages B_2, C, and D_1 disease is discussed.

Key Words: Fast neutrons—Prostate neoplasms.

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The management of locally advanced prostatic cancer with conventional photon irradiation remains far from ideal. Reported control of large stage C primary tumors has been as low as 71.7% when clinical methods have been used to assess tumor control (1). In trials employing posttreatment biopsies for the determination of tumor clearance, persistent disease has been documented in as many as 61% of those who underwent biopsy, even in the face of a continued clinical remission (2). As there is evidence to suggest that patients with abnormal biopsy results following primary radiation have a worse prognosis than those with normal biopsy results (3), concern exists that photon irradiation of these large primary tumors may be suboptimal in controlling the gross tumor and its subsequent metastatic potential.

Similar controversy surrounds the treatment of patients with prostate cancer that has already involved regional pelvic lymph nodes. While there are data to suggest that a percentage of patients with surgically documented pelvic nodal metastases may achieve long-term disease-free survival following pelvic irradiation (4–7), there are equally compelling data to suggest that this conventional photon treatment does not alter the natural history of this advanced clinical appearance nor its tendency for early systemic dissemination (8,9).

Trials employing neutron radiation for prostate cancer have evolved in the setting of these two issues. As high LET (linear energy transfer) radiation, neutrons deposit from 20 to 100 times more energy per centimeter of tissue traversed than do photons (10). The biological consequences of this are many and include a diminished dependence of neutrons on tumor oxy-

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genation for effective cell kill and enhanced neutron effectiveness in limiting tumor sublethal and lethal damage repair of radiation injury (11,12). Additionally, the wide variations in tumor cell radiosensitivity to photons, which depend on the position of a cell within the cell cycle, are much less pronounced when neutron irradiation is employed (13).

Altogether, these documented radiobiological advantages of neutrons suggest a theoretical clinical superiority for neutrons in the treatment of tumors such as prostate cancer, which has a small growth fraction and a relatively large population of quiescent (G_0) cells. What remained a relatively unexplored question prior to the initiation of clinical trials was whether neutrons would have a differential effect on tumors and normal tissues or whether any enhanced neutron effects on tumors would be accompanied by parallel effects on adjacent normal tissues. The lack of any differential effect would be manifested as pronounced late complications of neutron treatment in normal tissues, which would negate any therapeutic gains in the treatment of the primary tumor.

REVIEW OF PAST CLINICAL TRIALS

Clinical investigations have been reported from the United States (14,15), Europe (17–20), and Japan (21). The largest group of patients has been treated in the United States under the auspices of the Radiation Therapy Oncology Group (RTOG). This trial, RTOG 77-04, is also the only randomized prospective trial that has been carried out comparing neutron therapy directly with conventional megavoltage photon therapy. Details of the study design and execution have been fully reported (14,15), but are reviewed as follows.

In this study, patients with clinical C- and D_1-stage initial appearances were randomly assigned to treatment employing either photon radiation or a combination of neutrons and photons, so-called "mixed-beam" treatment. At the initiation of the study, a number of the participating facilities had neutron beams similar to orthovoltage radiation in their penetrating properties. A major reservation in using the lower-energy neutron beams stemmed from the lack of skin sparing with such units relative to that achievable with higher-energy cyclotron beams or megavoltage photon irradiation. This lack of skin sparing and the poor penetration of these beams raised the possibility of producing unacceptably high rates of normal tissue complications, similar to that one might expect from orthovoltage-era photon units, if neutrons alone were used for the large treatment volumes required to incorporate pelvic lymph node chains.

and three times-weekly treatment with photons. As the relative biological effectiveness of neutrons (RBE) is approximately threefold that of photons, the daily neutron dose was adjusted (the neutron dose plus the percentage of cyclotron output containing photon contamination times the individual institutional RBE), so that equivalent biological doses of neutrons or photons were given on each day.

Between 1977–83, 91 patients were enrolled in the study, with a purposely skewed randomization leading to 55 patients assigned to the mixed-beam arm and 36 to the conventional photon arm. Seventy-four cases were staged as C, and 17 were staged as D_1. Prior hormonal treatment had been given in 25% of the patients randomly chosen to receive photons and in 11% of patients randomly chosen to receive mixed-beam therapy. The majority of cases had been staged by clinical and radiographic criteria (involving physical examination, serum acid phosphatase determination, pelvic computed tomography scanning, lymphography, and radionuclide bone scans) alone, with only three (8%) photon-arm patients and five (9%) mixed-beam patients having undergone surgical sampling of pelvic lymph nodes. Using chi-squared analysis, the two groups were found to be balanced relative to all major prognostic factors.

Patients randomly chosen to receive photons received 5,000 cGy in 180–200 cGy fractions with treatment portals encompassing the prostate and regional pelvic lymph nodes. A subsequent boost of 2,000 cGy was given to the prostate and areas of tumor extension beyond the prostate. Patients treated with mixed-beam irradiation received a dose of 5,000 cGy "photon equivalent," followed by a similar 2,000-cGy photon-equivalent boost, using the alternating schedule of neutrons and photons outlined earlier.

At the time of the last data analysis in November 1986, the median follow-up time of all patients was 6.7 years. The actuarial survival rate at 8 years for the patients receiving mixed-beam treatment was 63%, versus 13% for the patients receiving photons alone. This difference in outcomes achieved a statistical level of significance of $p = 0.01$. Corresponding survival rates adjusted to exclude intercurrent non–cancer-related deaths were 82 and 54%, respectively ($p = 0.02$). Freedom from local tumor recurrence, as determined by clinical and radiographic criteria, was 81% for mixed-beam patients and 61% for the cohort receiving photons alone ($p < 0.01$). As posttreatment biopsies were performed only on an ad hoc basis, no meaningful conclusions could be drawn about the relative rates of histologic clearance of the two treatments.

Comparisons of the short- and long-term effects of

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beam-irradiated patients. Mixed-beam patients tended to have more pronounced acute and self-limited skin reactions, a greater tendency to have mild localized edema, and more frequent complaints of tenesmus and proctitis. Severe side effects of treatment were seen in eight of 36 patients in the photon cohort and 10/55 patients in the mixed-beam cohort.

Criticisms raised regarding this study and its conclusions revolved around the issues of the small number of patients randomly chosen to receive photons only and the poor survival outcome of this cohort relative to other institutions' results with similarly staged cases. When the subset of patients in the photon treatment arm with stage D_1 tumors was excluded from analysis and the relevant statistics recalculated, the adjusted 5-year survival of 58% for the remaining patients with stage C tumors compared more favorably with other series in the literature as well as with the results for photon-treated patients in a prior RTOG prostate protocol, where a 5-year survival rate of 65% had been achieved (16).

In Europe, prostate clinical trials involving fast neutron irradiation have been carried out primarily in the cyclotron facilities at Louvain-la-Neuve, Belgium, and at Hamburg, Germany.

In the Belgian experience, a neutron regimen similar to the RTOG mixed-beam approach was used, but photons were combined with high-energy p(65)+Be neutrons that have a better delivery of the neutron dose to greater tissue depths. Accordingly, three treatments per week, or 60% of the total treatment, was composed of neutrons, as opposed to the 40% neutron contribution in the mixed-beam treatment used in the RTOG trial. Treatment to the pelvis was carried to a total dose of 5,000-cGy photon equivalent, and the prostate received an additional 1,600-cGy photon-equivalent boost. Patients were treated in a phase II setting without any intended randomization. As of December 1984, the number of treated patients numbered 50, with a distribution of 14 with stage A tumors, 30 with stage C, and 6 with stage D_2. Twenty-eight of the stage C patients had been observed a minimum of 1 year.

Tumor local control rates of 93 and 90% were reported at 1 and 3 years in the stage C patients, with 28 and 10 patients available for analysis at these time points. Seven of the 10 patients observed for 3 years are alive and without evidence of disease. Complications in this group of patients have been minimal, with only one patient having a urethral stricture requiring surgical attention (17,18).

The group in Hamburg has reported similarly encouraging results. Originally, a mixed-beam schedule was employed, combining 14-MeV (deuterium–tritium) neutrons and megavoltage photons. Pelvic nodes were treated with photons alone, to a total of 3,000–4,500 cGy over 3–4.5 weeks at conventional 200-cGy/day fractions. The boost dose to the prostate was carried out with neutrons alone, treating eight isocentrically centered fields per day, three treatments per week, for a total boost of 390–840 neutron cGy (an approximately 1,200–2,600 photon cGy equivalent). The treatment of 13 stage C (UICC stage T_3, NX-2, MX-0 and T_4, Nx-2, Mx-0) tumors was well tolerated, with all patients having obtained complete tumor regression and no patient having suffered adverse long-term reactions (19). A recent update of this experience reported 5-year survival figures for the 12 evaluable cases, with 85% (seven) of the patients with T_3 tumors alive, and 20% (five) of the patients with T_4 tumors alive. No adverse sequelae of neutron treatment were observed in these patients with regard to bowel, bladder, or intestinal complications.

At Chiba University in Japan, 26 patients received primary radiotherapy consisting of either fast neutrons alone (15 patients) or mixed-beam radiation (11 patients). Treatment fields either encompassed the pelvic nodes, with a subsequent boost to the prostate (16 patients) or were limited to the prostate alone. A number of radiation doses were employed, reported as (time–dose–fractionation) values (22) in the range of 98–124. For the 14 patients with stage C tumors, a 77% 3-year survival rate was reported (21).

The results of the U.S., European, and Japanese trials are summarized in Table 1. Survival results are tabulated for the patient groups with locally advanced tumors, who constitute the majority of the patients treated to date and for whom there are the most complete published data available.

FUTURE DIRECTIONS

The great majority of patients treated with fast neutrons for prostate cancer have been treated with mixed-beam schedules, for the reasons cited earlier. With the arrival and implementation of a new generation of high-energy hospital-based cyclotrons, capable of delivering neutrons to deep-seated tumors with dose distributions comparable to those obtained from megavoltage linear accelerators, an opportunity has been presented to advance clinical research efforts beyond what has been achieved to date with mixed-beam schedules and to treat patients with neutrons alone.

In April 1986, the successor study to RTOG 77-04 was initiated. Eligible patients for RTOG 85-23 include those with stages B_2 (Gleason pattern score > 6), C, and D_1 adenocarcinomas of the prostate. Surgical staging of pelvic lymph nodes is encouraged, and patients will be subjected to routine posttreatment biopsies 2 years following treatment. The patient randomization is between photon and neutron irradiation. Patients randomly chosen to receive neutrons receive treatments

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TABLE 1. *Fast neutron irradiation for locally advanced prostate cancer*

Trial	No. of patients	Treatment (no. of patients)	Stage (no. of patients)	Survival, % (yr)
RTOG[a] (14,15)	55	Mixed beam	C/D_1	63 (8)
RTOG	36	Photons	C/D_1	13 (8)
RTOG	55	Mixed beam	C/D_1	82[b] (8)
RTOG	36	Photons	C/D_1	54[b] (8)
Louvain-la-neuve (18)	50	Mixed beam	A (14)	
			C (30)	90, local control[c] (3)
			D (6)	
Hamburg (20)	13 (12 cases evaluable)	Mixed beam	T_3 (7)	85 (5)
			T_4 (5)	20 (5)
Chiba University (21)	25	Mixed beam (11) Neutrons only (15)	C (14)	77 (3)

[a] RTOG, Radiation Therapy Oncology Group.
[b] Adjusted to exclude intercurrent noncancer deaths.
[c] Seven of 10 patients observed for 3 years have no evidence of disease.

three times weekly, 170 neutron cGy per fraction, for a total of 1,360 neutron cGy to the pelvis and 2,040 neutron cGy to the prostate. These neutron doses were chosen as the maximal safe doses tolerated based on data previously collected in an RTOG phase I dose-searching protocol investigating the tolerance of pelvic tissues to fast neutrons. Neutron treatments are therefore completed in 12 fractions over 4 weeks, compared with the 35 fractions and 7 weeks required to complete photon irradiation.

As of February 1988, 102 patients have been entered into this collaborative trial. To date, acute reactions among the patients treated with the high-energy neutrons have been reasonable, and patient acceptance of the rapid-treatment course has been high. It is expected that this study will provide the definitive data to assess whether fast neutron irradiation of prostatic carcinoma will provide the incremental improvement over photon irradiation that the earlier experiences suggest.

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