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Fast Neutron Radiotherapy for the Treatment of Carcinoma of the Urinary Bladder

A Review of Clinical Trials

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The major clinical investigations employing fast neutrons in the treatment of invasive bladder cancer are reviewed. Although data suggest that preoperative radiation schedules employing neutrons may result in a greater degree of pathologic downstaging than conventional precystectomy photon regimens, this has not led to an improved survival rate for neutron-treated patients over photon-treated patients. Randomized clinical trials comparing primary neutron irradiation and primary photon irradiation do not disclose an advantage for neutrons over photons as measured by survival rate or freedom from local tumor recurrence. The late complications in normal pelvic tissues following neutron irradiation with low-energy beams exceed those experienced after photon irradiation and have led to an unexpectedly high rate of treatment-related morbidity and mortality. A partial explanation for the toxicity may be attributed to the use of neutron beams with poor depth dose characteristics for the treatment of what is a deep-seated malignancy. An additional explanation is the documented lack of a differential in radioresponsiveness to neutrons between the bladder primary tumor and adjacent normal pelvic tissues.

Key Words: Fast neutrons—Bladder neoplasms.

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Conventional management of invasive transitional cell carcinoma of the bladder involves a preoperative course of radiation followed by radical cystectomy or primary radiation therapy alone. Primary radiation management has the advantage of allowing bladder preservation, with a high degree of bladder functionality for those patients with tumor-free bladders (1). Unfortunately, tumor recurrence in the bladder following radiation has been reported to occur in as many as 50% of patients, requiring cystectomy for patient salvage (2).

Randomized clinical trials comparing radiation alone with combined modality treatment consisting of radiation followed by planned cystectomy have shown a survival advantage for the combined approach (3). Patients whose tumor shows regression, or "downstaging," following preoperative radiation, such that no residual tumor is discernible in the cystectomy specimen have been shown to have a favorable prognosis in the range of 70–80% 5-year survival. Patients with tumors unresponsive to preoperative radiation have a poor prognosis in the range of 17–20% 5-year survival (4,5).

Clinical trials employing fast neutrons in the treatment of bladder cancer evolved either to improve on the results obtainable with primary photon radiation or to increase the percentage of tumor downstaging seen in combined modality approaches. The high linear energy transfer (LET) properties of neutrons relative to photons result in major differences between neutrons and photons in the radiobiologic parameters of tumor sublethal damage, potentially lethal damage, oxygen enhancement ratio, and cell-cycle specific radioresponsiveness (6–8). Neutrons exhibit a relative biologic effectiveness (RBE), which is generally at least threefold

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greater than photons on a unit dose basis. However, the neutron RBE varies considerably from tissue to tissue and may have numerically different values when defined on the basis of either immediate or late tissue effects (9). The theoretical advantages of neutrons for tumor control were a sufficient impetus to encourage the opening of clinical trials. Whether the increased RBE of neutrons would have a greater effect on tumors than on normal tissues is a critical determinant of neutron therapeutic gain over conventional photon radiation.

Much of the early neutron data on dose–response relations for tumor control and normal tissue complications were collected in the Netherlands at the Antoni van Leeuwenhoek Hospital in Amsterdam. Between 1976–9, 66 patients received neutron irradiation for locally advanced bladder or rectal cancer. Local control and normal tissue tolerance data were compared with results obtained some years earlier treating 61 similar patients with photons produced by a cobalt 60 unit. Although the depth dose characteristics of the 14-MeV d + T (deuterium to tritium) neutron generator in use in that facility were more comparable to a 250-kV orthovoltage x-ray unit than to a megavoltage linear accelerator, many of the first patients were treated with two parallel–opposed anterior and posterior portals. Additionally, these patients treated with neutrons early in the trial inadvertently received an 8% overdose. The combination of these two factors resulted in a 25% severe complication rate for the neutron-treated patients as a result of exceeding the tolerance of both the large and the small bowel as well as the skin and subcutaneous tissues.

Dose–effect analysis of both tumor control and late morbidity allowed the derivation of neutron RBE values relative to cobalt 60 for either bladder tumor eradication or skin and intestinal tolerance. A neutron RBE of 3.19 (2.73–3.65) was obtained for bladder tumor control, versus 3.17 (2.92–3.42) for the development of late skin fibrosis or severe intestinal damage. The investigators concluded that an optimum balance could be achieved by delivering a dose of 19 neutron Gray (nGy) to the tumor, with a probable 50% tumor control rate and 10% severe late complications (10).

These expectations were tested in the same institution by a randomized trial, also involving patients with locally advanced and unresectable tumors of the bladder or rectum. Patients were randomly assigned to a treatment arm involving photons given as 50 Gy in 20 fractions over 4 weeks or to one of two neutron treatment arms involving either 17 or 19 nGy in the same fractionation pattern. The poor outcome resulting from the prior use of only two neutron fields for treatment led to the adoption of a six-field arrangement, which distributed doses more homogeneously to the normal tissues adjacent to the tumors. Overall, 92 patients were enrolled in the study. Within this group were 30 patients with bladder cancer, of whom 24 received neutrons (12 patients at each dose level) and six received photons. No differences in the survival rate between the three treatment arms were noted. In 10 of an evaluable 22 neutron cases there was local tumor control, and five of 22 patients survived 2 years. Complications leading to surgical intervention were seen in seven of 22; three of 7 surgeries involved colostomy (11). It was the conclusion of the investigators in this and subsequent reports that neutrons demonstrated no greater efficacy than photons in the 73 bladder cancer patients eventually treated with neutrons between 1975–81, and that "the differential effect between tumor and normal tissues (was) smaller with fast neutrons than with photons" (12,13).

In 1978, two major clinical trials were initiated in the United Kingdom, also randomly assigning bladder cancer patients to photon irradiation alone or neutron irradiation alone. One trial was carried out at Christie Hospital in Manchester and the other at Western General Hospital in Edinburgh. Both institutions employed neutrons produced from a 15-MeV deuteron on beryllium reaction, and both institutions used a six-field arrangement for the neutron treatments.

In the Christie Hospital trial, 99 evaluable cases of T_2- or T_3-staged bladder carcinomas were randomized, with an equal distribution of patients with T_2 and T_3 tumors between treatment arms. Photon treatments were given by 8-MeV photons via 280° lateral arcs. Treatments were given in 16 fractions over 21 days to a total dose determined by the size of the field required to encompass the primary tumor. Patients requiring smaller fields to adequately encompass the primary tumor received a tumor dose of 55 Gy, and those requiring larger fields received a tumor dose of 52.5 Gy. Neutron treatments were given in the same fractionation and time schedule, to total doses of 16.5, 17.0, 18.0, or 18.5 nGy, also as an inverse function of field size. Patients receiving either 16.5 or 17.0 nGy were combined for data analysis into a "low-dose" group (20 total), and the remaining neutron patients (20) were aggregated into a "high-dose" group. Fifty-nine patients received photons.

The 3-year survival rate overall for all groups was 43%, with no difference in survival observable between the photon group and either the low-dose or high-dose neutron group. When subgroup analysis was applied to patients with T_2 versus T_3 tumors, the 3-year survival rate for patients with T_2 tumors was 62%, versus 31%

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for those with T_3 tumors. Non-statistically significant differences were seen between those receiving neutrons and photons, although it appeared that patients with T_2 tumors had a better survival rate with photons, and patients with T_3 tumors had a better survival rate with neutrons. Seventy-eight patients had follow-up cystoscopy at least once. A total of 22 of 41 (54%) patients in the photon group, four of 14 (29%) in the low-dose neutron group, and seven of 15 (47%) in the high-dose neutron group had locally recurrent tumor. These differences were not significant.

Major complications, defined as resulting in surgical intervention or patient death, were seen in five/15/10% of photon/low-dose neutron/high-dose neutron patients, respectively, and minor complications of treatment were recorded in three/30/15%. No conclusive evidence for a therapeutic gain for neutron therapy was documented in this study (14).

In the Edinburgh study, 113 patients were stratified by tumor stage and randomized in a similar fashion to the Manchester trial, with 53 patients receiving neutrons and 60 receiving 4–6 MeV megavoltage photons via a three-field arrangement. Both neutron and photon field sizes varied with the tumor stage of the patient. Patients with earlier lesions staged as T_1 or T_2 generally received small fields covering only the bladder, and patients with more advanced T_3 tumors received large pelvic fields for the initial portion of treatment, followed by smaller boost fields limited to the bladder.

When treated with photons, the bladder received between 52.5–55.0 Gy in 20 fractions over 4 weeks, with pelvic fields contributing 35.0 Gy of this total for those patients receiving pelvic irradiation. Patients randomized to neutron treatment were also treated with 20 fractions over 4 weeks and received doses to the bladder of 16.0–16.5 nGy (with an estimated 9.7% additional contribution from photons contaminating the neutron beam), with pelvic fields contributing 12.8 nGy in those patients receiving pelvic irradiation. In both photon and neutron cohorts, the higher bladder doses were given to patients receiving only small-field irradiation. Patients with T_4 tumors received only large-field pelvic irradiation, amounting to 47.5 Gy for those receiving photons, and 15.0 nGy for the neutron-treated patients.

Complete tumor regression was achieved in 64% of the neutron cohort and 62% of the photon cohort. Local tumor recurrences were observed in 31% of the patients in both arms. No differences in tumor control by treatment were observed in a stage-for-stage analysis.

Later morbidity was assessed in both cohorts and judged to be substantially greater in the patients who received neutrons. Where 38% of patients receiving photons had normal tissue complications, 78% of those receiving neutrons had serious late morbidity in at least one tissue. Twenty-four of the 53 neutron-treated patients had severe late reactions in the bowel, as opposed to six of 60 in the photon group. Twenty and 15 patients receiving neutrons and photons, respectively, had late bladder contracture below 150 ml of capacity. Where patients receiving photons were found to have morbidity generally limited to one tissue, 24 patients receiving neutrons had involvement of multiple organs.

As a result of the neutron-associated morbidity, more treatment-related deaths (19) were attributed to neutrons than photons (2), statistically significant at a level of $p < 0.01$. The overall survival rates reflected these treatment-related deaths as well as the inability to surgically salvage local tumor recurrences in neutron-treated patients because of accompanying pelvic fibrosis. The 5-year survival rate for the photon-treated group was 45.3 ± 11%, versus 12.0 ± 6% for patients receiving neutrons (15).

In a separate report, the Edinburgh investigators analyzed the morbidity vis-a-vis early and late effects of treatment. Acute bladder reactions were in fact more pronounced in patients receiving photons (45.7 versus 10.6%, $p < 0.001$), as were severe acute bowel reactions (8.5 versus 3.4%, $p < 0.05$). Late reactions showed the opposite results, as previously reported. Determinations of neutron RBE relative to megavoltage photons (given in large fraction sizes of 2.75 Gy or less) were made for both immediate and late effects. It was estimated that for bladder toxicity, the RBE for early and late effects was <3.3 and 3.4 respectively, and 3.4 and 3.8 for early and late effects on the bowel (9).

The major U.S. trial investigating fast neutrons for bladder cancer was carried out as a nonrandomized phase I–II study under the auspices of the Radiation Therapy Oncology Group. Patients with muscle-invading tumors (Jewett–Strong–Marshall clinical stages B_1, B_2, C, and D_1) received either precystectomy radiation or definitive radiation, with surgery reserved for the salvage of local recurrences. Except for four patients who were treated with neutrons alone, neutrons were given as a component of "mixed-beam" therapy in which the patient received alternating treatment with neutrons or photons such that the percentage of the biologically effective total dose contributed by neutrons was 40%. This mixed-beam approach was employed out of concerns about late tissue morbidity that might occur with neutron treatment alone, although at the time this study was initiated (June 1977), these potential complications were as yet undocumented.

Thirteen patients received mixed-beam treatment in a preoperative context followed by planned cystectomy

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4–6 weeks following completion of therapy, and 26 patients received definitive mixed-beam treatment alone. Patients treated preoperatively received a 50-Gy "photon equivalent" (photon dose plus neutron dose × RBE) given to pelvic fields encompassing regional lymphatic glands over a 5–6-week period, followed by an optional 10-Gy boost to positive nodal areas. Patients receiving definitive radiation received a 15–20-Gy photon-equivalent boost to the bladder following the pelvic radiation. Both four-field arrangements and two-field arrangements were employed.

Of those 13 patients treated preoperatively, 12 underwent cystectomy as planned, with seven of 12 (58%) patients having no evidence of tumor in the cystectomy specimen. This appeared to be a substantially higher percentage of complete preoperative downstaging than reported from series using conventional photon irradiation, where 25–35% rates of complete downstaging have been reported (16).

Of the 26 patients treated with definitive mixed-beam radiation, 18 (69%) achieved tumor clearance at some time during their follow-up observation, with a projected survival rate of 34% at 30 months following treatment. At the time of the first analysis (December 1984), eight of 18 (44%) who had initially achieved a complete response had exhibited local relapse. Those patients with clinical stage B or C disease had a projected survival rate at 30 months of 60%. Accepting that this was not a randomized trial, there was no difference in survival rate between patients treated in the combined modality approach and patients receiving mixed-beam treatment alone, although the pelvic control rate with planned surgery was considerably higher (90% of those having successful surgery) than with mixed-beam treatment alone (56% were complete responders to radiation) (16).

These data have been updated more recently (July 1987) without substantial changes in the results. There continues to be no statistically significant difference in survival rate as a function of treatment employed, although only 12% (three of 26) of the mixed-beam patients are alive at 5 years, as opposed to 31% (four of 13) of the patients who underwent planned cystectomy. Locoregional pelvic tumor control at 5 years in the mixed-beam group is 23% (six of 26) and is 61% (eight of 13) in the combined-modality group ($p < 0.02$). Of the stage B and C patients, 30% (three of 10) are alive at 5 years. Of the initial group of 16 patients with stage D_1 disease, including eight patients with tumors fixed within the pelvis, 63% (10 of 16) of their tumors initially cleared, but all patients had died by 4 years following treatment (J. M. Krall, unpublished data).

The late effects of treatment in patients receiving mixed-beam treatment in either of the two treatment options appear to have been less severe than in the trials using neutrons alone. Two patients incurred complications that were life threatening, and five had complications categorized as severe. These complications were confined to the large or the small bowel. Of the patients receiving mixed-beam treatment (26), eight had moderate late bladder complications of decreased capacity or cystitis, and six had only mild sequelae (J. M. Krall, unpublished data). As in the European experience, salvage cystectomy was complicated by the greater degree of pelvic fibrosis found in mixed-beam irradiated patients than was customarily found in patients treated with pelvic photon irradiation.

Preoperative neutron therapy has also been investigated in Japan, with a study population of 22 patients having high-grade invasive bladder cancer. Patients received either 9.1 nGy or 30 Gy of photons in 2 weeks' time, followed by planned cystectomy. Tumor downstaging was documented in 38% of all of the patients, with the impression that "better effect seemed to be obtained in fast neutron treated (patients) than in x-ray (patients)" (17).

A summary of the clinical results achieved in the European, U.S., and Japanese trials is tabulated in Table 1.

CONCLUSIONS

There is little in the available clinical trials to encourage further investigations into the use of fast neutrons for the treatment of bladder carcinoma. Fast neutrons have shown no definitive superiority with regard to tumor clearance rates, have been associated with an unexpectedly high rate of late complications, and have even compromised conventional surgical salvage options that have historically cured a certain percentage of local tumor recurrences in patients treated with photon irradiation.

Nonetheless, it must be noted that these clinical trials placed in direct comparison two treatment modalities of widely differing capabilities to treat deep-seated tissues. The limited penetration of neutrons obtained from the first-generation neutron treatment facilities can likely account for a significant component of the late morbidity encountered in these trials, even despite the sophistication of the multiple field arrangements used in the later efforts. The Edinburgh investigators themselves comment in their first report that the dose variation given to patients with neutrons was ±5.5%, as opposed to ±1.5% for photons, and that "It is clear that the dose received by pelvic tissues outside the target volume was substantially greater in patients treated by neutrons" (15). Given the steep slope of the dose–response curves for neutron complications of normal pelvic tissues reported by the [illegible]

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TABLE 1. *Trials of fast neutrons for bladder cancer*

Trial	No. of patients	Stage	Treatment	Bladder dose, Gy or cGy	Survival, % (yr)	Local tumor recurrence, resistance, %	Severe complications %
Amsterdam (11–13)	22	T_3, T_4	Neutrons	17–19	23 (2)	55	14
	6	T_3, T_4	Photons	50	—	—	0
Manchester (14)	20	T_2, T_3	Neutrons	16.5–17.0	43 (3)	29	15
	20	T_2, T_3	Neutrons	18.0–18.5	43 (3)	47	10
	59	T_2, T_3	Photons	52.5–55.0	43 (3)	54	5
Edinbergh (9, 15)	53	T_1, T_2, T_3	Neutrons	15.0–16.5	12 (5)	31	78
	60	T_1, T_2, T_3	Photons	52.5–55.0	45 (5)	31	38
RTOG[a] (16)[c]	26	B_1, B_2, C, D_1	Mixed beam	65–70[b]	12 (5)	77	55
	13	B_1, B_2, C, D_1	Mixed beam plus cystectomy	50	31 (5)	39	23
Japan (18)	22	T_3, T_4	Photons or neutrons	30.0 9.1	38 (Downstaging, at surgery)	—	—

[a] RTOG, Radiation Therapy Oncology Group.
[b] Photon gray equivalent.
[c] With updated statistics with permission of J. M. Krall, American College of Radiology (unpublished).

the neutron dose variation is a parameter of some significance (10).

Other neutron investigators have criticized the Manchester trial for the same disparity, remarking that ". . . the dose distributions with 15 MeV neutrons were markedly inferior to those obtained with 8 MV X-rays which were used in the control arm" (18). This same editorial pointed out that a more appropriate control arm for that trial would have used orthovoltage x-ray equipment, noting that this would hardly have been an ethically acceptable alternative given the inherent superiority of megavoltage to orthovoltage x-rays in precisely those areas of dose distribution and late tissue effects.

Despite these criticisms, there are few data to suggest that the neutron control rate of bladder tumors is any better than photon control, independent of late tissue effects. One might look to see neutron superiority in clinical situations where the RBE with respect to tumor control exceeded the RBE for normal tissue late morbidity. The existing data show little differential in this regard (9,10).

With the arrival of second-generation hospital-based cyclotrons, which can deliver high-energy fast neutrons having depth–dose characteristics comparable to photons produced from megavoltage linear accelerators, the opportunity exists to design randomized trials comparing more evenly matched technologies. Such phase III trials are already under way in the treatment of salivary cancers, head and neck tumors, prostate carcinomas, and soft-tissue sarcomas, all areas where prior experiences, albeit with suboptimal neutron generators, have suggested a benefit for high LET radiation. Given the disappointments of the recent past in using neutrons for bladder cancer, it is unlikely that much enthusiasm will be generated for rekindling investigations for this site.

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