

COMMENTARY

Feasibility of Assessing the Carcinogenicity of Neutrons among Neutron Therapy Patients

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Nuclear workers, oil well loggers, astronauts, air flight crews, and frequent fliers can be exposed to low doses of neutrons, but the long-term human health consequences of neutron exposure are unknown. While few of these exposed populations are suitable for studying the effects of neutron exposure, patients treated with neutron-beam therapy might be a source of information. To assess the feasibility of conducting a multi-center international study of the late effects of neutron therapy, we surveyed 23 cancer centers that had used neutron beam therapy. For the 17 responding institutions, only 25% of the patients treated with neutrons (2,855 of 11,191) were alive more than 2 years after treatment. In a two-center U.S. pilot study of 484 neutron-treated cancer patients, we assessed the feasibility of obtaining radiotherapy records, cancer incidence and other follow-up data, and of estimating patient organ doses. Patients were treated with 42 MeV neutrons between 1972 and 1989. Applying a clinical equivalence factor of 3.2 for neutrons, total average organ doses outside the treatment beam ranged from 0.14 to 0.29 Gy for thyroid, 0.40 to 2.50 Gy for breast, 0.63 to 2.35 Gy for kidney, and 1.12 to 1.76 Gy for active bone marrow depending upon the primary cancer treatment site. We successfully traced 97% of the patients, but we found that patient survival was poor and that chemotherapy was not confirmable in a quarter of the patients. Based on our findings from the international survey and the feasibility study, we conclude that a large investigation could detect a fivefold or higher leukemia risk, but would be inadequate to evaluate the risk of solid cancers with long latent periods and therefore would likely not be informative with respect to neutron-related cancer risk in humans. © 2002 by Radiation Research Society

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INTRODUCTION

Although the carcinogenic effects of X and γ radiation have been studied extensively (1, 2), the risk of cancer associated with neutron exposures in humans is not known (3). In the U.S., certain workers (oil well loggers, some nuclear workers, astronauts, air flight personnel), the public (frequent fliers), and patients treated with high-energy linear accelerators (4) can be exposed to low doses of neutrons each year. Recently, concern has increased over the adequacy of standards and guidelines regarding the occupational exposure of military and domestic flight crews to cosmic radiation (5–9), of which up to 60% is due to neutron exposure (2). Because these workers typically are exposed to very low doses of neutrons, an extremely large sample size would be required to study the carcinogenic effects of neutrons in an occupational setting (10, 11). Persistent residual stable chromosomal aberrations have been detected among six workers exposed to neutrons during criticality accidents, among whom a dose–response relationship was seen 16 to 17 years after exposure (12). Although the frequency of unstable aberrations usually declines over a few years, dicentrics and rings have been observed in two of four persons 19 years after an experimental reactor accident in which over 50% of the dose was from neutrons (13). The significance of the persistence of unstable aberrations after neutron exposure is not known, but following such a small number of exposed workers is unlikely to be informative.

Many early animal experiments showed that neutrons are 5 to 20 times more effective than X or γ rays in inducing malignancies (14–19; reviewed in 20), including leukemias (14, 18). The most recent compilation of animal data on leukemia, however, suggested that the relative biological effectiveness (RBE) for neutrons was lower than previously estimated and was consistent with a value of 1.0 (3). Furthermore, neutron energy, dose rate, total dose, number of

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fractions, and site of irradiation also had considerable influence on RBE values. In humans, the comparative risk estimates associated with exposure from detonation of the atomic bombs over Hiroshima and Nagasaki were thought to be informative in regard to neutrons, but when the dosimetry was reassessed in the 1980s (DS86), the estimated neutron dose in Hiroshima was reduced markedly, making it more difficult to determine the effects of neutrons (21, 22). The DS86 dosimetry system is currently being re-evaluated (23, 24), but since the neutron component may comprise only about 1–2% of the total dose, the atomic bomb survivor studies still may not be adequate for estimating the cancer risks from neutron exposure in humans (3, 25).

The rationale for neutron therapy has evolved over time. After World War II, neutrons were thought to provide a curative advantage in hypoxic tumors compared with X-ray therapy because the lower oxygen enhancement ratio of neutrons was expected to increase tumor cell killing (26). Over the last 25 years, high-dose neutron therapy has been used to treat a variety of cancers, including brain, uterine cervix, prostate and head and neck tumors. Unfortunately, neutron therapy did not confer the anticipated therapeutic benefit, and late tissue complications were common, resulting in decreased clinical use. Because of a larger RBE for late tissue effects, neutron therapy may be efficacious in some slowly growing tumors, and it is presently being used for salivary gland tumors, soft tissue sarcomas, and prostate cancer (26–29).

Despite the complex dosimetry, the cell killing at high doses, and the γ -ray component, survivors of neutron-beam therapy could provide information on the carcinogenic effects of neutrons in humans. A strength of such a study is that adequate statistical power might be achieved because doses are high. Furthermore, radiotherapy records provide extensive information with regard to neutron dose and treatment site, allowing for reconstruction of neutron exposures to other organ sites.

To evaluate the feasibility of conducting an epidemiology study of patients treated with neutrons, we first identified all institutions that used neutron-beam radiotherapy and surveyed these institutions to assess their willingness to collaborate. We determined the total number of neutron-treated patients who would be available for study and the prevalence of the use of alkylating agents and other chemotherapy. We then conducted a pilot study of patients at two U.S. institutions. Our aims were to (1) determine whether the quality of the radiotherapy records would be adequate for estimating individual patient and organ doses; (2) evaluate completeness of covariate information (other radiotherapy treatment, chemotherapy, previous primary malignancy) in medical records; (3) assess the data available for conducting follow-up; and (4) identify subsequent cancers to ascertain whether excess cancers might be observed. Our ultimate goal was to decide whether a large international multi-center study should be conducted based on the information collected during the survey and the feasibility study.

INTERNATIONAL CANCER TREATMENT INSTITUTION SURVEY

We mailed surveys to 23 institutions worldwide with neutron-beam treatment facilities. The questionnaires elicited information on the number of patients treated with neutron therapy who survived for 2 years or longer after therapy, years of neutron-beam therapy, the type of radiation treatment used (neutrons only or mixed photons and neutrons), and the willingness of each institution to participate. Seventeen of the 23 potential collaborating institutions using neutron-beam therapy, including two institutions that used californium-252 and one that used heavy ions, responded to our survey. Of the 14 centers that used a neutron beam for cancer treatment, 11 institutions predominantly treated patients with mixed photon and neutron beams. Alkylating agents were used in chemotherapy regimens in 2 centers (12 centers responded to this question). Averaging across the reports from all the responding centers, 25% (2,855/11,191) of patients survived for 2 or more years.

FEASIBILITY STUDY IN TWO U.S. CANCER TREATMENT INSTITUTIONS

For the feasibility study, we chose the University of Texas M. D. Anderson Cancer Center and the Cleveland Clinic Foundation because of their relatively large number of patients, willingness to participate, and the interest of a clinical collaborator. We obtained institutional review board approval at both centers before initiation of the study. Radiotherapy records from M. D. Anderson Cancer Center and Cleveland Clinic were screened to identify all neutron-treated patients. The records were of high quality, in that all necessary parameters to estimate dose were available, including field size and location (accompanied by diagrams and photographs), tumor dose from neutron and photon beams, the beam energies, and the dates of treatment. Information related to patient demographics and follow-up, clinical status of first cancer, radiotherapy, chemotherapy, and development of subsequent cancers was abstracted from the hospital records. The radiotherapy records from both institutions were photocopied and provided to the Radiation Physics Department at M. D. Anderson Cancer Center where specially trained abstracters coded the information needed for dose reconstruction. All patients who received neutron therapy between 1972 and 1987 and survived at least 2 years after treatment were eligible for inclusion.

Various tracing resources, including hospital medical records, the M. D. Anderson Cancer Center Registry, patient or relative telephone contact (by special permission for Cleveland Clinic Foundation patients only through 1990), and the National Death Index (through 1993) were searched to identify and confirm cancer outcomes and vital status. Of the 484 study subjects, 97% were traced successfully. Death certificates were obtained for 298 out of 301 dece-

dents. The mean and median follow-up times were 5.5 and 4.1 years, respectively, (range, 2–17 years). Follow-up time was calculated from treatment date to death or date last known alive; however, we excluded the person-years associated with the 2-year survival requirement for study entry in any person-time calculations performed. We found that 59% were deceased and only 5% were still alive and were able to be followed beyond 10 years.

Patients were treated with a neutron beam alone or in combination with photon beams (cobalt-60, 25 MV betatron, or 10 MV Linac) depending upon the tumor site. Approximately 15% of the patients received radiotherapy that consisted of neutrons only, but most received mixed neutron and photon radiotherapy with or without chemotherapy. About 40% of the patients underwent chemotherapy, and of these 66% received alkylating agents. Because many patients underwent their radiation treatment at the cyclotron site and then returned home to their treating physicians/oncologists for their prescribed chemotherapy, we were unable to definitely determine whether chemotherapy was administered in conjunction with neutron radiotherapy for about 25% of these patients. Subsequent treatment (at least 6 months after primary treatment), excluding therapy for second primaries, was reported in 20% of patients. Additional neutron-beam therapy was used in a small fraction (1.6%) of the patients.

A variety of tumor types were treated with neutrons at both hospitals, using many different treatment protocols. Because nearly 50% of the study patients were treated for cancers of the uterine cervix, prostate, or head and neck, and because these treatments varied less in their anatomical location (than bone or soft tissue tumors), doses were estimated only for patients treated for any of these three cancers. Radiation doses for selected organ sites and tissues, inside and outside the radiation field, were estimated based on measurements using paired lithium and calcium fluoride dosimeters in a water phantom. The total active bone marrow (ABM), breast and thyroid were selected for study because they are known to be radiosensitive organs. The kidneys were also selected because of their semi-central location in the trunk and to illustrate dose fall-off outside the irradiated fields. For the purpose of estimating radiation doses, the ABM was divided into 16 compartments (weighted by the proportion of active marrow in each compartment) and the estimated doses were averaged over all of the compartments to calculate one dose for the total ABM (both including and excluding the treatment field). To take into account the likely RBE for treatment effects of neutrons, we multiplied the neutron absorbed dose by a factor of 3.2 to obtain a clinically equivalent photon absorbed dose. This “clinical equivalence factor” is consistent with that used at the time of treatment and represents an absorbed dose (so we report dose in gray).

Combined neutron- and photon-beam treatment parameters are described in Table 1 for uterine cervix, prostate, and head and neck cancer at both institutions. Generally the

typical neutron doses were higher at M. D. Anderson than at the Cleveland Clinic for cervical cancer; however, the Cleveland Clinic used higher neutron doses (and a larger field size) for head and neck and prostate cancer than did M. D. Anderson. The photon doses did not differ greatly between the two institutions except that M. D. Anderson typically treated head and neck patients with higher photon doses than the Cleveland Clinic.

Dose estimates to selected organs from typical treatments at each institution are presented in Table 2. The neutron and photon organ dose differences between institutions reflect the variation in clinical treatment parameters for uterine cervix, prostate, and head and neck cancers, shown in Table 1. The neutron dose to the ABM ranged from 0.33 to 6.28 Gy, with the highest average bone marrow dose occurring with pelvic irradiation. The average ABM photon-beam doses always exceeded the average ABM neutron doses, irrespective of the treatment site. The neutron dose to the ABM outside the beam was also estimated and ranged from 0.19 to 1.10 Gy. The average neutron dose to the thyroid from treatment to the uterine cervix or prostate ranged from 0.10 to 0.19 Gy. For treatment of head and neck cancer, the thyroid neutron dose ranged from 0.73 Gy at M. D. Anderson to 19.3 Gy at the Cleveland Clinic, reflecting both the larger field sizes and higher neutron doses used by the Cleveland Clinic. For the breast, neutron doses ranged from 0.23 to 0.57 Gy for all three initial cancer treatment sites. For the kidneys, the dose varied by the tumor site treated, and the neutron doses were either equal to or less than the photon-beam doses.

CONCLUSIONS

There is interest in evaluating the cancer risk from low-level exposures to neutrons, principally because this exposure occurs in certain occupational settings. Since little is known about cancer risks, evaluation of neutron-treated patients would be a unique source of information on neutron effects in humans. Upon initial consideration of this idea, the disadvantages of small numbers of treated patients, their serious illness, and the very high exposure doses did not outweigh the primary advantages of relatively precise dose data and the good follow-up information, which were confirmed to be available in the pilot study. In addition, the decline in neutron therapy use increases the appeal of retrospectively assembled patient cohorts.

Cytogenetic evaluation of a subset of these patients ($n = 33$) detected persistent reciprocal translocations in lymphocytes of patients up to 17 years after treatment with neutrons (30). As expected, the asymmetric chromosomal aberrations (dicentric and rings) had declined sharply within 4 years after neutron therapy, but stable aberrations (balanced translocations, inversions) persisted at similar levels, within individual patients, for many years. However, differences between patients were substantial and the number of stable aberrations was not strongly associated with av-

TABLE 1
Typical Combined Neutron Beam and Photon Beam Radiation Treatment Parameters
at the University of Texas M. D. Anderson Cancer Center (MDACC) and Cleveland
Clinic Foundation (CCF)

Cancer site and treatment center	Treatment parameters	
	42 MeV neutrons	Photons
Cervical cancer MDACC	A & P ^a Pelvis 16 × 16 cm FS ^b , 5.40 Gy GD ^c Reduced to 12 × 15 cm FS, 1.1 Gy GD	Betatron 25 MV A & P Pelvis 15 × 15 cm FS, 14.3 Gy GD R & L Lat ^d Pelvis 10 × 15 cm FS, 12.9 Gy GD
		10 MV A & P Pelvis 16 × 16 cm FS, 10.7 Gy GD R & L Lat Pelvis 10 × 16 cm FS, 15.9 Gy GD
CCF	A & P Pelvis 15 × 15 cm FS, 3.94 Gy GD	Betatron 25 MV A & P Pelvis 12 × 12 cm FS, 15.6 Gy GD R & L Lat Pelvis 8 × 12 cm FS, 13.1 Gy GD 8 × 10 cm FS, 1.6 Gy GD
Prostate cancer MDACC	A & P Pelvis 12.7 × 12.4 cm FS, 3.92 Gy GD 12.1 × 10.5 cm FS, 1.71 Gy GD	10 MV A & P Pelvis 16.5 × 16.5 cm FS, 15.6 Gy GD Reduced to 10.9 × 10.9 cm FS, 4.2 Gy GD
		R & L Lat Pelvis 11 × 16.5 cm FS, 14.9 Gy GD Reduced to 10.9 × 10.9 cm FS, 6.0 Gy GD
CCF	A & P Pelvis 15 × 15 cm FS, 7.60 Gy GD 10 × 10 cm FS, 1.43 Gy GD	⁶⁰ Co R & L Lat Face 7.5 × 8 cm FS, 33.8 Gy GD R & L Ant Supraclav ^e 10 × 9 cm FS, 50.0 Gy GD
Head and neck cancer MDAC	R & L Lat Face 6 × 6 cm FS, 4.31 Gy GD	R & L Lat Head/Neck 12 × 17 cm FS, 18.8 Gy GD 8 × 17 cm FS, 7.2 Gy GD R & L Ant Supraclav 22 × 17 cm FS, 50.0 Gy GD
CCF	R & L Lat Head/Neck 12 × 15 cm FS, 3.26 Gy GD 8 × 15 cm FS, 1.79 Gy GD	

Note. Typical combined treatments at the University of Texas M. D. Anderson Cancer Center delivered neutrons on Monday and Thursday and photons the remaining days of the week.

^a A & P: Anterior and Posterior.

^b FS = field size. Comment: During the course of therapy, field sizes were reduced to deliver a higher dose to the tumor bed.

^c GD: dose to d_{max} (given dose).

^d R & L Lat: Right and Left Lateral.

^e R & L Ant Supraclav: right and left anterior supraclavicular.

erage bone marrow dose. [The correlation between number of translocations per 100 metaphases and average bone marrow dose in gray was 0.25, $P = 0.17$, calculated from Table 4 in ref. (30)].

In our patient series from the University of Texas M. D. Anderson Cancer Center and the Cleveland Clinic Foundation, we found that the median follow-up time of 4.1 years might be sufficient for incident leukemias to occur (31), but we did not observe any, contrary to our expect-

tations. This could be due to the small sample size, chance or cell killing. A further difficulty was that we could not confirm chemotherapy treatment in 25% of the patients. Chemotherapy was administered at the same time as neutron-beam treatment in 40% of patients. Overall about 26% of patients were treated with alkylating agents. Alkylating and other agents (such as epipodophyllotoxins), which are known to increase subsequent cancer risk, would make it difficult to determine the risk associated with neutron ex-

TABLE 2
Average Organ Dose Estimates in Gray for Thyroid, Breast, Kidney and Active Bone Marrow Treated with Radiation by Cancer Site and Institution

Cancer site treated institution ^a	Organs	Dose in Gy			Total dose in Gy ^b	
		Neutron beam		Photon beam Betatron		
		Neutron ^b component	Photon ^c component			
Cervical cancer						
MDACC	Total ABM ^d	5.83	0.18	7.55	13.56	
	ABM excluding high-dose regions ^e (≥ 10 Gy)	0.99	0.07	0.60	1.66	
	Thyroid	0.15	0.02	0.11	0.29	
	Breasts	0.33	0.04	0.23	0.60	
CCF	Kidneys	1.55	0.11	0.68	2.34	
	Total ABM	3.42	0.11	7.91	11.44	
	ABM excluding high-dose regions ^e (≥ 10 Gy)	0.56	0.04	0.52	1.12	
	Thyroid	0.10	0.01	0.03	0.14	
	Breasts	0.26	0.03	0.11	0.40	
Kidneys		1.03	0.07	0.84	1.94	
	Prostate cancer					
	Betatron					
	MDACC	Total ABM	3.17	0.12	5.81	9.10
ABM excluding high-dose regions ^e (≥ 10 Gy)		0.67	0.06	0.49	1.22	
Thyroid		0.12	0.02	0.11	0.25	
Breasts		0.28	0.03	0.23	0.54	
CCF	Kidneys	0.77	0.07	0.44	1.29	
	Total ABM	6.28	0.22	7.92	14.42	
	ABM excluding high-dose regions ^f (≥ 10 Gy)	1.10	0.09	0.58	1.76	
	Thyroid	0.19	0.03	0.04	0.26	
	Breasts	0.47	0.05	0.11	0.63	
Kidneys		1.60	0.13	0.63	2.35	
	Head and neck cancer					
	Co-60					
	MDACC	Total ABM	0.33	0.04	4.23	4.60
ABM excluding high-dose regions ^f (≥ 10 Gy)		0.19	0.03	1.17	1.39	
Thyroid		0.73	0.06	40.70	41.50	
Breasts		0.23	0.03	2.24	2.50	
Kidneys		0.10	0.02	0.51	0.63	
CCF	Total ABM	1.09	0.06	3.46	4.60	
	ABM excluding high-dose regions ^g (≥ 10 Gy)	0.43	0.04	0.95	1.42	
	Thyroid	19.30	0.44	39.70	59.40	
	Breasts	0.57	0.06	1.87	2.50	
	Kidneys	0.19	0.03	0.45	0.67	

^a MDACC: University of Texas M. D. Anderson Cancer Center; CCF: Cleveland Clinic Foundation.

^b Neutron physical dose, multiplied by 3.2 (clinical equivalence factor), to sum absorbed doses from neutrons and photons. Total dose may not always sum perfectly due to rounding.

^c Photon component of the neutron beam.

^d ABM: active bone marrow.

^e ABM regions with dose ≥ 10 Gy make up 28.8% of the total ABM and include lumbar spine 5, sacrum, upper femurs and most of the pelvic bones.

^f ABM regions with dose ≥ 10 Gy make up 31.8% of the total ABM and include lumbar spine 5, sacrum, upper femurs and most of the pelvic bones.

^g ABM regions with dose ≥ 10 Gy make up 22.0% of the total ABM and include sacrum, upper femurs and most of the pelvic bones.

^h ABM regions with dose ≥ 10 Gy make up 28.8% of the total ABM and include lumbar spine 5, sacrum, upper femurs and most of the pelvic bones.

ⁱ ABM regions with dose ≥ 10 Gy make up 12.1% of the total ABM and include facial bones, mandible, cervical spine 4–7, thoracic spine 1–3, clavicle, scapula, ribs 1–2, and top of sternum.

^j ABM regions with dose ≥ 10 Gy make up 14.0% of the total ABM and include facial bones, mandible, cervical spine 1–7, thoracic spine 1–3, clavicle, scapula, ribs 1–2, and top of sternum.

posure dose. Obtaining follow-up information was not problematic, but poor patient survival shortened the follow-up time (59% were censored at death), and only 5% were followed beyond 10 years. The short patient survival di-

minishes significantly the chance for radiogenic solid cancers to develop. This problem cannot be corrected even in a study with substantially more patients.

We determined the power of a large multi-center study

to detect neutron-related excess risk of leukemia based on information gathered from the pilot study. For the 14 centers that used neutrons or neutrons in combination with photons, approximately 2205 patients (25%) were alive after 2 years. If we assume the mean survival time found in the feasibility study, i.e. 3.5 years (excluding the first 2 years of survival required for study entry), then the total person-time would be ~ 7700 years. Using the leukemia rate in the external referent as 14.0 per 100,000 (based on U.S. age-adjusted rates of leukemia above the age of 40 years in both sexes and all races, excluding chronic lymphocytic leukemia), approximately 1.1 leukemias would be expected. Assuming 80% power, a one-sided test, and $\alpha = 0.05$, then only relative risks of 5.1 or more would be detectable. Assuming an average approximate ABM dose of 1.5 Gy outside the treatment field (from Table 2), the number of excess leukemias can be calculated using gender-specific excess absolute risk equations in Preston *et al.* derived from the atomic bomb survivors (32). For men and women, assuming the sex distribution in the feasibility study, about 9.6 and 1.4 excess leukemias would be expected, respectively (or about 11.0 total), indicating that relative risks of 10 are plausible. It should be kept in mind that these calculations fail to take into account the non-uniformity of doses, the cell killing at higher doses, and the variability of ABM doses outside the beam from different cancer treatments. Regardless, given that no leukemias were observed in the pilot study, it may be unlikely that 10-fold risks would be observed.

In conclusion, even a large international study could not detect lower than fivefold leukemia risk, nor would such a study be adequate to evaluate solid tumors with long latent periods. In addition, because of the added complexity of alkylating agent and other chemotherapy regimens received by neutron-treated patients, a large study probably would not be informative with respect to neutron-related cancer risk in humans.

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