Pergamon

Int. J. Radiation Oncology Biol. Phys., Vol. 33, No. 1, pp. 225–230, 1995

0360-3016/95 $9.50 + .00

0360-3016(95)00092-5

● *Special Feature*

PHOTONEUTRONS FROM MEDICAL LINEAR ACCELERATORS—RADIOBIOLOGICAL MEASUREMENTS AND RISK ESTIMATES

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Purpose: To assess the oncogenic potential of the photoneutrons produced by high energy medical linear accelerators.
Methods and Materials: An established line of cells of rodent origin (C_3H 10T1/2) was used to assess the oncogenic potential of the radiation dose received in the breast of an anthropomorphic "randoman" phanton, while the cervix received a dose of 70 Gy. Experiments were performed at 6 MV, below the threshold for the production of photoneutrons, and at 20 MV where the dose includes about 0.01 Gy of photoneutrons as well as scattered x-rays.
Results: A significantly higher transformation incidence was observed for the 20-MV machine, consistent with the measured neutron dose of about 0.01 Gy and a quality factor of 20.
Conclusion: An estimate can be made of the additional deaths from second malignancies that might result from the photoneutrons generated by higher energy linear accelerators (Linacs), which must be offset against the possible improvements in survival that might result from the higher tumor doses made possible by the increased percentage depth doses.

Photoneutrons, Second malignancies, Linear accelerators.

INTRODUCTION

The production of photoneutrons in high energy medical linear accelerators is a subject of considerable topical interest, and represents a real challenge to the neutron dosimetrist, as discussed in a previous paper (10). More and more high energy machines of around 20 MV have come into routine clinical use for radiation therapy, particularly in treatment plans designed with curative intent, because of the greater percentage depth doses that result in improved dose distributions for deep-seated tumors.

Photoneutrons are generated, primarily, in the high-Z material of the target and collimators, with a threshold of about 6 to 8 MeV for lead, tungsten, or uranium (12). There is a giant resonance (i.e., a peak) in the photoneutron production cross-section in these heavy materials at a photon energy around 14 MeV. Neutrons with a broad energy range are generated, the mean being around 1–3 MeV. Because the principal source of photoneutrons is in the collimator of the machine, the patient lying on a couch beneath the machine receives essentially a total-body neutron dose.

Many attempts have been made to measure both the quantity and quality of these photoneutrons, as described in a previous paper (10). However, essentially all of these involve physical measurements and therefore, still do not allow an estimate to be made of the biological hazard involved because a quality factor or radiation weighting factor must be assumed.

The present paper describes experiments designed to make a direct measurement of the biological effectiveness of the photoneutrons from a medical linear accelerator, using an established *in vitro* assay for oncogenic transformation. It also offers possible risk estimates based on published data.

METHODS AND MATERIALS

Irradiation techniques and dosimetry

An anthropomorphic "Randoman" phantom was irradiated to a total dose of 70.2 Gy using 6- or 20-MV photon linear accelerators with a geometry that simulated a typical external beam treatment of the uterine cervix.[1]

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Acknowledgement—This research was supported by Grant No. CA12536 awarded by the National Institutes of Health.

Accepted for publication 24 February 1995.

[1] The 6-MV photon beam was generated by a Theratronics Therac-6 accelerator and the 20-MV beam by a Siemens Mevatron-77.

For both irradiations, the phantom was placed on the treatment couch in the supine position, and irradiated isocentrically (100 cm source-to-axis distance on both accelerators) using a standard four-field box technique. First, 45 Gy were delivered (simulating 1.8 Gy/day × 25 fractions) using equally weighted anterior, posterior, left, and right lateral fields, 18-cm wide by 14 cm in length. This was immediately followed by a 25.2 Gy four-field "cone down" dose (simulating a typical 1.8 Gy/day × 14 fractions regimen) with field sizes of 10-cm wide by 12 cm in length. The dose rate on both accelerators was nominally 2.5 Gy/min and the total treatment time (including field changes) was approximately 50 min.

The plan was to measure the incidence of oncogenic transformation in cells located in the breasts of the Randoman phantom while the cervix was irradiated. The centers of the breasts (containing the tissue culture flasks) were 30 cm from the center of the treatment volume, and approximately 20 cm from the superior edge of the anterior treatment field. Thus, for both accelerators, the dose to the tissue culture flasks was entirely due to leakage and scattered radiation.

Capsules of lithium fluoride thermo luminescence dosimeters (TLD-100) were placed inside the phantom breast adjacent to the tissue culture flasks during exposures to determine the total dose to the cells. Additional dosimetric measurements were performed with a diode detector to independently determine this dose. All dosimeters were calibrated in a 10 × 10 cm^2 x-ray field at the appropriate energy (i.e., 6 or 20 MV). Diode leakage current was corrected for, but variations in diode or TLD sensitivity to scattered vs. primary photon beam energies were not. Both of these detectors, however, have a fairly flat response (< 5%) for photon energies between 500 keV and 20 MeV, as determined from a concurrent calibration with cobalt-60 gamma-rays. The diode detector and TLDs yielded results *within 10% of each other,* with average readings (to the tissue culture flasks) of 0.25 Gy for the 6-MV photon beam, and 0.55 Gy for the 20-MV photon beam (per 70.2 Gy total dose to the pelvis).

Neither of these detectors, however, are capable of differentiating between neutrons and photons. The neutron dose on the 6-MV accelerator is nominally zero, as all relevant photoneutron reactions have energy thresholds of at least 6–8 MeV. The 20-MV photon beam, however, does produce neutrons, principally in the high-Z materials comprising the flattening filter, collimators, and head shielding.

The manufacturer's specifications for the 20-MV accelerator note a maximum neutron production rate at the x-ray target of approximately 3×10^{12} neutrons for each x-ray Gy delivered at the isocenter. Kerma varies rapidly with neutron energy, being approximately 0.2×10^{-11} Gy per neutron/cm^2 at thermal energies, but rising to nearly a value of 3×10^{-9} at 2 MeV. Assuming an average kerma of approximately of 1×10^{-11} Gy per neutron/cm^2 (2), and an isotropic distribution of neutrons (around the x-ray production target), the expected *maximum* neutron dose to the randophantom breast would be approximately 0.015 Gy for a 70.2 Gy treatment to the pelvis. Some degree of neutron absorption occurs in the high-Z shielding in the accelerator head, so 0.015 Gy should be regarded as an upper limit for the neutron dose. (This dose is quoted in Gy, and does not include the quality factor for neutrons of approximately 20). In the absence of exact knowledge of the neutron energy spectrum, kerma can only be estimated as above. However, our measurements of neutron dose using bubble detectors and microdosimetry (10) are independent of kerma and provide an independent, complementary method for determining neutron dose.

As discussed in a previous paper (10), accurate dosimetric measurements of low level neutron beams are extremely difficult, and any attempt to accurately determine this dose would be well beyond the intended scope of these experiments. Nonetheless, an attempt was made to independently verify the neutron doses to the tissue culture samples using neutron bubble detectors. The use of these detectors has been described in the literature, and is also discussed in an accompanying paper (10). Our bubble detector measurements indicated an approximate neutron dose of 0.005 Gy to the tissue culture flasks. This value is consistent with the upper limit from the above kerma calculation as well as the results of microdosimetric measurements reported earlier (10) (i.e., 0.007 Gy neutrons per 70.2 Gy at isocenter as measured with the ultraminiature proportional counter).

Thus, three independent, albeit crude, determinations of the neutron dose all yield values between 0.005 and 0.015 Gy. This is also consistent with (although slightly higher than) neutron doses quoted by Nath *et al.* (11) of 0.0006–0.001 Gy neutron/10 Gy dose at the isocenter. Our doses were measured in a breast phanton whose neutron attenuation would be low (i.e., at shallow depth). This fact, plus the uncertainty in measuring photoneutrons, make our doses slightly higher than those estimated by Nath *et al.* (11).

Cell culture; C_3H 10*T*1/2 *cells*

C_3H 10T1/2 cells are an established fibroblast cell line, originating from a mouse embryo, that have been used for many years as an *in vitro* assay for oncogenic transformation (3, 5, 13). These cells stop growing when they form a confluent monolayer (i.e., they are contact inhibited) unless treated with a carcinogen, such as radiation, in which case foci composed of densely stained piled-up cells with a criss-cross pattern at the edges develop. Cells isolated from these foci grow in soft agar and form fibrosarcomas when injected into immunosuppressed animals.

For these experiments, cells between passages 8 and 14 were grown in Eagles basal medium with 10% heat inactivated bovine calf serum supplemented with trans-

Table 1. Data for C_3H 10T1/2 cells

Group	X-ray dose (Gy)	No. of cells plated	S.F.*	No. of dishes	Total cells at risk × 10^4	No. II	Foci III	Fraction of dishes with foci	Transformation frequency/dish
6 MV	0.25	1.5×10^3	0.93	67	0.39	1	1	2/67	
			0.90	68	2.70	1	0	1/67	
			0.90	150	5.33	8	5	13/150	
	Total					16			0.0563‡
20 MV	0.55	1.5×10^3	1.00	68	0.59	4	10	14/68	
			0.89	121	4.82	6	6	12/121	
			0.92	139	5.04	16	13	29/139	
	Total					55			0.168‡
Control	0	1.5×10^3	0.05†	53	0.33	0	0	0/53	
			0.299†	135	6.05	5	3	8/135	
			0.262†	95	3.73	2	2	4/95	
	Total					12			0.0424‡

* Surviving fraction; †Plating efficiency; ‡Pooled transformation frequency per dish.

ferin and 25 μg/ml Gentamycin. Cells were maintained in humidified incubators at 37.5°C in a 5% CO_2–95% air environment.

Two days prior to each experiment, exponentially growing cells were trypsinized and replated into T-25 tissue culture flasks. Shortly before treatment, the flasks were filled brimful with tissue culture medium and transported to the appropriate radiation therapy unit for irradiation. Immediately following all radiation procedures, the cells were trypsinized, counted, and replated for both survival and transformation studies. For the transformation assay, cells numbers were plated to yield an estimated 300 ~ 400 viable clones per 100 mm diameter petri dish and incubated for 6 weeks, with medium changes every 10 days. The cultures were then fixed with formaldehyde, stained with Giemsa, and scored for both Type II and III transformants as described previously (8, 13). Transformation frequencies were expressed as either transformants per surviving cell or fractions of dishes with foci. Three separate experiments involving a total of 900 dishes were included in these studies. For cell survival, correspondingly treated cells were plated at a lower density and colonies were counted after 10–12 days.

RESULTS

The data from three separate experiments are summarized in Table 1. Based on the measurement of the TLD dosimeters, the phantom "breast" and subsequently the flask cultures received an x-ray dose of 0.25 Gy from the 6-MV linear accelerator, and a dose of 0.55 Gy from the 20-MV machine. Neither of these doses induced a significant cytotoxic effect in C_3H 10T1/2 cells as shown in Table 1, where the mean survival fractions are 0.91 and 0.94, respectively, for the 6- and 20-MV linear accelerators. In contrast, transformation data pooled from three independent experiments indicated that there was a significantly higher number of transformants induced with the 20-MV than with the 6-MV linear accelerator (Table 1). At a dose of 0.25 Gy of x-rays, the transformation incidence induced by the 6 MV machine was only slightly higher than the spontaneous frequency; that is, 16 as opposed to 12 foci. By contrast, based on an equivalent number of dishes used, the estimated rate of induced transformants (absolute minus background) due to the higher energy linear accelerator was about nine times higher than that for the 6-MV machine, with transformation frequencies/dish of 0.13 (95% confidence limits 0.07 → 0.19) compared with 0.014 (95% confidence limits 0 → 0.06). This factor of 9 is, of course, quite uncertain but is certainly large, implying an important role for neutrons in the production of transformed foci. Because the scattered x-ray dose delivered by the 20-MV machine was roughly twice that of the 6-MV, and assuming that the transformation incidence was proportional to the dose, the contribution by the photoneutrons appears to be substantial.

DISCUSSION

The experiments reported here suggest that it is possible to detect the biological effect of the photoneutrons produced by a high energy medical linear accelerator. For C_3H 10T1/2 cells, the total number of transformants induced by 0.25 Gy from the 6-MV linear accelerator was 16 against a control value of 12. The frequency expressed as the fraction of dishes with transformed foci was not significantly different from the background. For the 20-MV linear accelerator, the induced frequency was roughly 9 times higher than that of the low energy machine. The total dose involved was 0.55 Gy, of which 0.005 to 0.015 Gy was due to photoneutrons.

Table 2. Estimated relative biological effectiveness (RBE) for the 20-MV ($\gamma + n$) beams relative to the 6-MV (γ)

	20-MV ($\gamma + n$) beam relative to 6-MV (γ) beam	Neutrons from 20-MV beam relative to 6-MV (γ) beam
C^3H 10T1/2	4.8 ± 2.8	215 ± 124

Note: (a) RBE estimates correspond to one standard deviation, based on random errors only. Other systematic uncertainties in deriving these estimates are discussed in the text. (b) These estimates assume a linear dose–effect relation, a neutron dose from the 20-MV accelerator of 0.01 Gy, and that the biological effectiveness of 20 MV and 6 MV photons is comparable.

Given the fact that only single doses of the two different modalities were used, estimations of their relative effectiveness involve considerable uncertainties. Specifically, it is necessary to assume dose–effect relations to estimate equi-effect doses. For neutrons, at the doses of interest here (0.005 to 0.01 Gy), a linear dose–effect relation is reasonable in that the number of tracks passing through each cell will be either 0 or 1. For the γ-ray doses of interest here (0.25 to 0.55 Gy) each cell will be exposed to multiple tracks, and thus the dose–effect relation is less certain. However, several independent reports on radiation-induced oncogenic transformation in C_3H 10T1/2 cells (4, 7) suggest a linear dose–effect relationship at doses below 0.75 Gy.

We therefore assume a linear dose–effect relation in the estimates of relative effectiveness given in Table 2, but caution that the values obtained must be considered as little more than "guesstimates." In addition to the assumptions about linearity, we also assume that the neutron dose delivered in the 20-MV irradiation was about 0.01 Gy, and that the biological effectiveness of 6-MV photons is comparable to that of 20-MV photons.

From Table 2, it can be seen that (a) the 20-MV beam appears to be significantly more effective than the 6-MV beam and (b) if this difference is attributed solely to 0.01 Gy (±0.005 Gy) of neutrons, then the relative biological effectiveness (RBE) of these neutrons appears large. Again it is stressed that the uncertainties quoted in Table 2 are based only on random errors from counting statistics. Systematic errors are primarily due to the assumption of linearity and of a neutron dose of 0.01 Gy.

It is further possible to estimate the number of additional malignancies that might result from the use of high energy linear accelerators, and the inevitable presence of photoneutrons based on estimates of the photoneutron dose and cancer risk estimates available from the literature. Three numbers are necessary for this estimate to be made:

1. The total body dose of photo neutrons as a function of γ-ray dose applied, and its value for a prescribed target dose of 70 Gy. This is shown in Table 3 from the published work of Nath *et al.* (11) and also from the bubble detector measurements and fluence calculations presented above.
2. The estimate of the detriment, largely cancer, that results from total body irradiation. This is given by the International Commission on Radiological Protection (ICRP) as 4×10^{-2} per Sv (9).
3. The estimated number of patients treated with high energy linear accelerators who are cured of their first malignancy and live sufficiently long to be at risk of a radiation-induced second malignancy. This estimate is about 42,000 patients per year, arrived at by considering one million new cases of cancer per year in the United States; about one half of these are treated by radiotherapy and one half of these are treated with intent to cure, of which one half are cured. Finally about one third of these are treated with high energy machines.

These data can be combined to estimate the number of second malignancies induced by photoneutrons as a consequence of 1 year of practice of radiation therapy in the United States. The figures are shown in Table 3. The number of second malignancies is 140–232, based on the neutron dose estimates of Nath *et al.* (11), and 163–490 based on the neutron dose estimates from this investigation. It should be made clear that these numerical estimates are based on ICRP figures and are not based on the transformation experiments reported in this paper. What the transformation data add is the experimental corroboration that a biological effect of these low energy neutrons can be detected.

In summary, it seems clear that, when high energy linear accelerators are used for the treatment of deep-seated tumors, such as carcinoma of the uterine cervix or carcinoma of the prostate, the patients may receive a larger total body dose of scattered x-rays (depending in part on accelerator design, shielding, and treatment geometry), and also a small but significant dose of photoneutrons. The photoneutrons have an extremely high RBE; that is, they are in the energy range that is maximally effective at inducing second malignancies. It should be expected, therefore, that patients treated with high energy linear accelerators might show a higher incidence of second malignancies. Indeed, if the present measurements are taken at face value, the photoneutron component at least doubles the risk of second tumors. Attempting to confirm this prediction from clinical observations is likely to be a difficult task in view of the massive studies that were needed to show a significant incidence of second malignancies in patients treated conventionally for carcinoma of the cervix (1).

If one accepts the data presented in Table 3, then the increased risk of treating curative cancer patients with

Table 3. Estimated number of second malignancies induced by radiotherapy with high energy linear accelerators

Source	Whole body neutron dose (Gy) per Gy of γ-rays delivered	Equivalent neutron dose (Sv) for 70 Gy of γ-rays (Q = 20)	Number of second malignancies per 42,000 patients treated
Nath *et al.*, 1984	6×10^{-5} to 1 $\times 10^{-4}$	$(8.4-14.0) \times 10^{-2}$	140–232
Kliauga and Amols, 1984	7×10^{-5} to 2.1×10^{-4}	$(9.8-29) \times 10^{-2}$	163–490

high energy photon beams due to photoneutron contamination is approximately 140–490 induced cancers in the 42,000 patients per year treated on these machines (i.e, 0.3–1.2%).

Nath *et al.* (11) point out that this risk is negligible when compared to a background cancer rate of 15% to 20%. However, this is not the relevant comparison. This risk of inducing cancer must be compared to the improved cure rates resulting from high energy beams. For definitive treatment of cancers with high energy x-rays, the use of computed tomography (CT) and magnetic resonance imaging (MR) enhanced treatment planning, and multiple highly conformal treatment fields is rapidly becoming the standard of care. At many institutions, for example, six-field conformal beam treatments are routinely given for definitive treatment of the prostate.

We have compared two otherwise identical treatment plans of this type using both 6-MV and 20-MV x-rays. Dose–volume histograms (DVHs) were calculated for target volume (tumor plus margin), rectum, and bladder. These are displayed in Fig. 1, and clearly demonstrate that for equal target doses, 20-MV x-rays yield a dose sparing of approximately 5% to the bladder and rectum (the two critical normal tissues which limit dose prescriptions for these treatments) as compared to 6-MV x-rays. Table 4 gives the average organ doses, as determined from the DVHs.

Figure 1 and Table 4 demonstrate that for the same

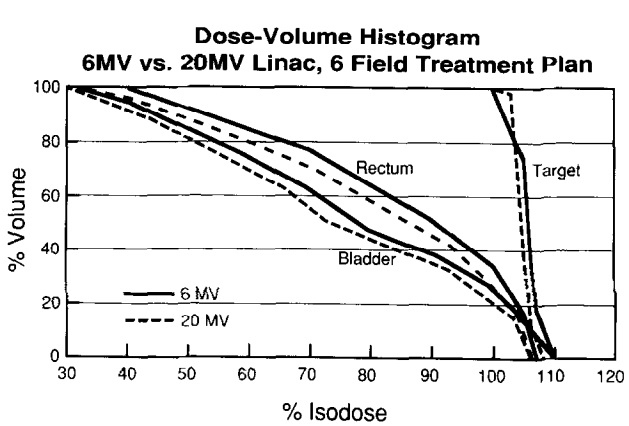

Fig. 1. Dose–volume histograms for six-field treatment of Ca prostate using 6- and 20-MV photon beams. Both treatment plans were normalized to 100% minimum target dose. Field sizes, gantry angles, blocking, and wedges were identical for both plans. Comparison of the solid (6-MV) and dashed (20-MV) lines show normal tissue sparing of approximately 5% for the higher energy beam.

level of patient morbidity (i.e., dose to bladder and rectum), one can deliver approximately 5% additional dose to the target volume with the higher energy beam. This in turn could increase tumor control probabilities by approximately $3\frac{1}{2}$% assuming a 1% per Gy increase in local control and a total dose of 70 Gy. Some data suggest this for the prostate when escalating doses beyond 70 Gy (5, 6).

If the 20-MV beam does in fact improve control rates by $3\frac{1}{2}$%, it would result in approximately 1470 additional cures per year among the 42,000 patients treated with high energy beams (Table 3). This is to be compared to 140–490 induced cancers among that same group of patients. The net result is that the benefits of high energy photons outweigh the risks by a factor of 3 to 10. The large uncertainties in some of the numbers used for this comparison, however, render the conclusion less than certain.

It should be noted that we chose 6 and 20 MV for comparison because the former energy represents the threshold for photoneutron production (there are virtually no photoneutrons in the 6-MV beam), and the latter energy represents the approximate midrange of clinical high energy linear accelerators (i.e., 10–25 MV). A 10-MV x-ray beam, however, would yield normal tissue sparing intermediate between that of 6 and 20 MV, but with far fewer photoneutrons than 20 MV. This is because depth dose increases approximately linearly with energy, while photoneutron production increases exponentially.

A 10-MV beam treatment would, therefore, yield a very favorable DVH but with negligible photoneutron risk, making it perhaps the ideal energy for treatment. The question, therefore, of whether or not the benefits of high energy beams outweigh the risk, is one that requires further study.

Table 4. Comparison of six-field wedged treatment plans for 6- and 20-MV x-rays

	Average dose* (%)		Range of doses (minimum–maximum)	
Structure	6 MV	20 MV	6 MV	20 MV
Target	106	105	100–109	100–107
Rectum	86	81	43–108	38–106
Bladder	78	75	15–109	17–107

The average dose is defined to be a volume weighted integral of the doses taken from fig. 1, i.e., $\frac{\int \text{dose } xdV}{\int dV}$.

REFERENCES

1. Boice, J. D.; Engholm, G.; Kleinerman, R. A.; *et al.* Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat. Res. 116:3–35; 1988.
2. Caswell, R. S.; Coyne, J. J.; Randolph, M. L. Kerma factors for neutron energies below 30 MeV. Radiat. Res. 83:217–225; 1980.
3. Hall, E. J.; Hei, T. K. Modulating factors in the expression of radiation induced oncogenic transformation. Environ. Health Perspect. 88:149–155; 1990.
4. Hall, E. J.; Miller, R. C. The how and why of in vitro oncogenic transformation. Radiat. Res. 87:208–223; 1981.
5. Hanks, G. E.; Leibel, S. A.; Krall, J. M.; Kramer, S. Patterns of Care Studies: Dose-response of observations for local control of adenocarcinoma of the prostate. Int. J. Radiat. Oncol. Biol. Phys. 11:153; 1985.
6. Hanks, G. E.; Martz, J. H.; Diamond, J. J. The effect of dose on local control of prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. 15:1299–1305; 1988.
7. Hei, T. K.; Komatsu, K.; Hall, E. J.; Zaider, M. J. Oncogenic transformation by charged particles of defined LET. Carcinogenesis 9:747–750; 1988.
8. IARC/NCI/EPA Working Group. Cellular and molecular mechanisms of cell transformation and standardization of transformation assays of established cell lines for the prediction of carcinogenic chemicals: Overview and recommended protocols. Cancer Res. 45:2395–2399; 1985.
9. International Commission on Radiological Protection. Recommendations. Report No. 60. New York: Pergamon Press; 1991.
10. Kliauga, P.; Amols, H. Photoneutrons from high energy medical linear accelerators: Measurement of the spectrum and dose using a miniature proportional counter. Int. J. Radiat. Oncol. Biol. Phys. 31:629–633; 1995.
11. Nath, R.; Epp, E. R.; Laughlin, J. S.; Swanson, W. P.; Bond, V. P. Neutrons from high-energy x-ray medical accelerators: An estimate of risk to the radiotherapy patient. Med. Phys. 11:231–241; 1984.
12. National Council on Radiological Protection and Measurements. Neutron contamination from medical electron accelerators. Report #79. Bethesda, MD; 1984.
13. Reznikoff, C. A.; Bertram, J. S.; Brankow, D. W.; Heidelberger, C. Quantitative and qualitative studies on chemical transformation of cloned C_3H mouse embryo cells sensitive to post confluence inhibition of cell division. Cancer Res. 33:3239–3249; 1973.