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CRITICAL REVIEW

INTENSITY-MODULATED RADIATION THERAPY, PROTONS, AND THE RISK OF SECOND CANCERS

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Intensity-modulated radiation therapy (IMRT) allows dose to be concentrated in the tumor volume while sparing normal tissues. However, the downside to IMRT is the potential to increase the number of radiation-induced second cancers. The reasons for this potential are more monitor units and, therefore, a larger total-body dose because of leakage radiation and, because IMRT involves more fields, a bigger volume of normal tissue is exposed to lower radiation doses. Intensity-modulated radiation therapy may double the incidence of solid cancers in long-term survivors. This outcome may be acceptable in older patients if balanced by an improvement in local tumor control and reduced acute toxicity. On the other hand, the incidence of second cancers is much higher in children, so that doubling it may not be acceptable. IMRT represents a special case for children for three reasons. First, children are more sensitive to radiation-induced cancer than are adults. Second, radiation scattered from the treatment volume is more important in the small body of the child. Third, the question of genetic susceptibility arises because many childhood cancers involve a germline mutation. The levels of leakage radiation in current Linacs are not inevitable. Leakage can be reduced but at substantial cost. An alternative strategy is to replace X-rays with protons. However, this change is only an advantage if the proton machine employs a pencil scanning beam. Many proton facilities use passive modulation to produce a field of sufficient size, but the use of a scattering foil produces neutrons, which results in an effective dose to the patient higher than that characteristic of IMRT. The benefit of protons is only achieved if a scanning beam is used in which the doses are 10 times lower than with IMRT.

Intensity-modulated radiation therapy, Passive modulation, Pencil beams, Protons, Second cancers.

INTRODUCTION

Many of the most important advances in radiation therapy have resulted from innovations in technology and engineering; for example, the introduction of megavolt machines, such as cobalt units and linear accelerators, both spinoffs from World War II technology, followed by the computer revolution applied to treatment planning. These advances have culminated in the sophisticated technique of intensity-modulated radiation therapy (IMRT) (1).

Intensity-modulated radiation therapy allows dose to be concentrated in the tumor volume while sparing normal tissues. This property is a major step forward, especially for children, in whom sparing normal tissues to avoid a subsequent growth detriment is critically important. However, the downside to IMRT is the potential to increase the number of radiation-induced second cancers (2–5). Few things are worse for a patient than to survive the initial treatment, live with the long-term morbidity of therapy, only to find that they have developed a radiation-induced second cancer with a worse prognosis than the original tumor.

At the present time, approximately 10% of patients who present at major cancer centers in the United States have a second malignancy. Causes may be related to lifestyle, genetic predisposition, or treatment of a previous malignancy. This last category is of concern here.

Quantitative data of radiation-induced cancer

Knowledge of radiation-induced cancer comes from the atomic-bomb survivors, from radiation accidents, and from individuals medically exposed, which includes patients who have developed second cancers after radiation therapy. Figure 1 shows the data for radiation-induced solid cancers in the atomic-bomb survivors (6). A linear relation exists between cancer and dose from about 0.1 Sv up to about 2.5 Sv. These data represent the gold standard for our knowledge concerning radiation-induced cancer. The cancers consist principally of carcinomas in the lining cells of the body, such as the digestive tract or lung, or tumors in tissues

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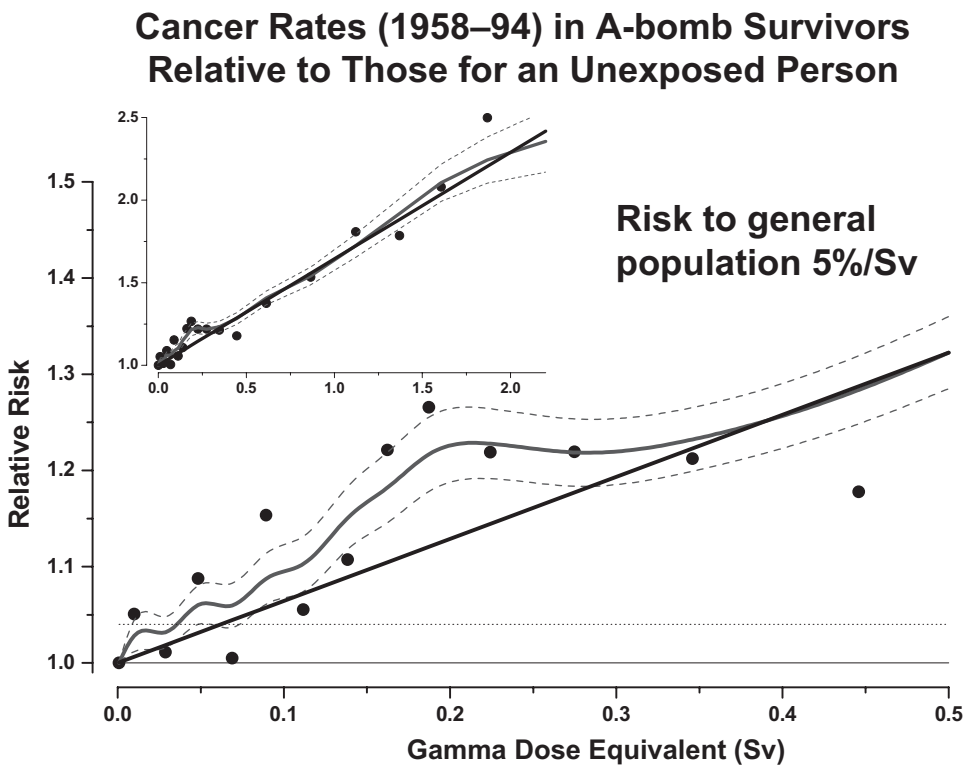

Fig. 1. Cancer rates (1958–1994) in atomic-bomb survivors relative to those for the unexposed control group. (Top) The dose–response curve approximates a linear function of dose up to about 2 Sv. (Bottom) The low-dose region is expanded to show that some low-dose points tend to be above the linear extrapolation from higher doses. (Redrawn from Pierce and Preston (6).)

hormonally controlled, such as the breast. Table 1, taken from National Council on Radiation Protection and Measurements (NCRP) report 116, shows the relative probabilities of developing second malignancies by organ site and the colon, lung, and stomach are seen to be prime sites (7).

In most cases, assessment of the risk of second cancers in radiotherapy patients is difficult because no appropriate control group exists; that is, a group of individuals who have the same initial malignancy but were treated without radiation. The major exceptions are cancer of the prostate and cancer of the cervix, in which surgery is a viable alternative to radiotherapy (8–9). Another instance in which the risk of a second cancer can be studied is in Hodgkin's lymphoma, where the risk of breast cancer in young women is so obvious that it cannot be missed (10). In radiotherapy patients, the induced tumors include carcinomas, as in the Japanese atomic-bomb survivors, that may appear in sites adjacent to or remote from the treated area (9). The number of carcinomas is relatively large, but the relative risk is small. In addition, sarcomas may appear in heavily irradiated tissues, either within or close by the treatment field; this finding is in contradistinction to the atomic-bomb survivors, who have no increased risk of sarcomas because the doses were never sufficiently high. In radiotherapy patients, sarcomas are small in number but are characterized by a large relative risk. Radiation-induced tumors in radiotherapy patients will become increasingly important as younger patients are treated and improved cure rates obtained.

Table 1. Lifetime probabilities of developing fatal secondary malignancies by organ site

Organ	Probability of fatal cancer (%/Sv)
Bladder	0.30
Bone marrow	0.50
Bone surface	0.05
Breast	0.20
Esophagus	0.30
Colon	0.85*
Liver	0.15
Lung	0.85*
Ovary	0.10
Skin	0.02
Stomach	1.10*
Thyroid	0.08
Remainder of body	0.50
Total	5.00

* Prime site for developing a second malignancy.

Table 2 summarizes the largest study in the literature of second cancers induced in patients treated for prostate cancer by radiotherapy, compared with similar patients who received surgery (9). This study is a very large study based on the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute in the United States. The results of this study are summarized in Fig. 2.

Table 2. Prostate cancer treated with radiotherapy or surgery (SEER program), 1973–1993

	RT	Surgery
Persons at risk	51,584	70,539
Person-years at risk	218,341	312,499
Average follow-up after diagnosis (years)	4.2	4.4
Average age at diagnosis (years)	70.3	71.4
Average age at second cancer diagnosis (years)	75.3	77.0
Person-years at risk (%)		
0–1 years after primary diagnosis	18.2	17.4
1–5 years after primary diagnosis	52.1	51.5
5–10 years after primary diagnosis	22.7	23.4
10+ years after primary diagnosis	6.9	7.7

Abbreviations: RT = radiation therapy; SEER = Surveillance Epidemiology and End Results.

By 10 years after treatment, the incidence of an induced malignancy is about 1 in 70. The principal sites for radiation-induced tumors include the rectum, bladder, colon, and lung; that is, some sites close and some remote from the treatment area. In addition, sarcomas appear in or close to the treatment field in heavily irradiated tissue.

The impact of IMRT

When we consider IMRT as a replacement for conventional treatment, two factors must be taken into account: (*1*) more monitor units are used, which results in a larger total-body radiation dose (11), and (*2*) more fields are used,

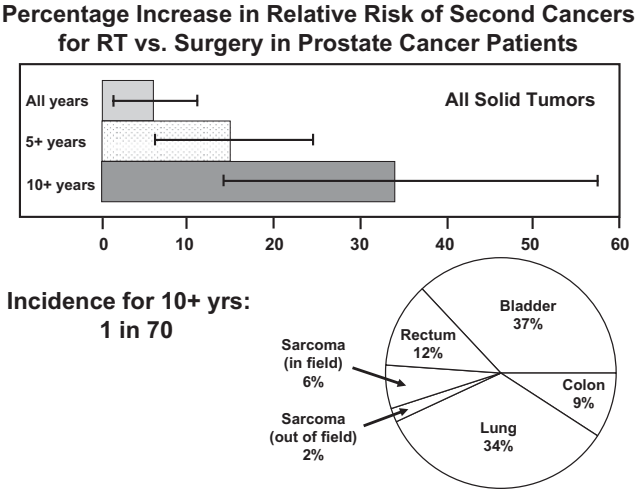

Fig. 2. The upper panel shows the percentage increase in relative risk for all solid tumors as a function of time in patients who received radiotherapy for prostate cancer. The error bars represent 95% confidence limits. "All years" refers to all years after treatment. The standard error is smaller in this case because of the larger number of patients; most did not survive to 5 or 10 years. The lower panel shows the distribution of the principal radiation-induced cancers, namely bladder, lung, rectum, and colon. A small number of sarcomas also appear in heavily irradiated areas. The figure is courtesy of Dr. David Brenner. Data are from Brenner *et al* (9).

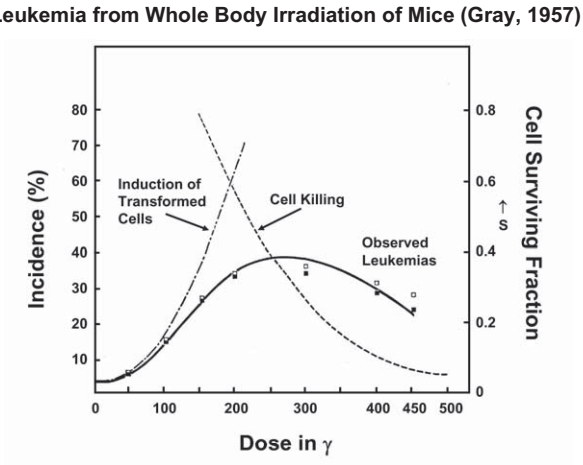

Fig. 3. Illustration of the concept, introduced by Gray, that the incidence of radiation-induced cancer follows a "bell" shape because of the balance between the induction of transformed cells and cell killing. The figure is adapted from Gray (12).

which results in a larger volume of normal tissue exposed to lower radiation doses (4–5).

Increase in monitor units. Delivery of a specified dose to the isocenter from a modulated field delivered by IMRT would require the accelerator to be energized for a longer time, and, hence, more monitor units will be needed. Thus, the total-body dose will be increased because of leakage radiation.

Lower radiation-dose exposure in normal tissue. The importance of a larger volume of normal tissue exposed to lower radiation doses depends on the shape of the dose–response relationship for radiation-induced carcinogenesis. Figure 3, taken from the classic paper by Gray (12) at the 1957 M.D. Anderson symposium, shows the incidence of leukemia in mice after total-body irradiation with various doses of X-rays. Gray explained the shape of the observed curve for leukemias in terms of a balance between the induction of transformed cells, which increased with dose, and the killing of cells as the doses were increased. The balance between these 2 factors results in a curve that rises rapidly at low doses, plateaus, and fall steeply of high doses. Although this model fits leukemia from total-body radiation in animals, we will see that it does not apply to solid tumors in humans.

Figure 4 shows the shape of the dose–response relationship for induced cancer over a wide range of doses. From 0.1 to 2.5 Sv we see a linear relationship based on the atomic-bomb survivor data. At low doses, risks may be slightly higher, but they are not statistically significant. At low doses, the shape of the dose–response curve is uncertain. At doses above 2.5 Sv, the shape of the dose–response curve is also in doubt, and the shape in this dose range is a vital factor in assessing the incidence of second cancers after radiation therapy. If the Gray model for leukemia were to apply, then high doses of radiation would not be important for the induction of cancer. However, that outcome is not in accord with clinical experience, in which the majority of sec-

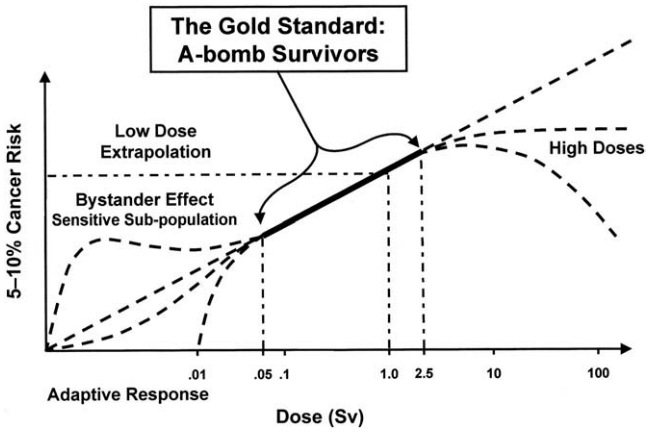

Fig. 4. Illustration of the dose–response relationship for radiation-induced carcinogenesis in humans. The atomic-bomb data represents the "gold standard," that is, the best quantitative data over a dose range from about 0.1 to 2.5 Gy. Considerable uncertainty exists above and below this dose range. At doses below this range, standards organizations, such as International Commission on Radiological Protection or National Council on Radiation Protection and Measurements, recommend a linear extrapolation from the high-dose data; however, the bystander effect and the existence of radiosensitive subpopulations would suggest that this procedure would underestimate risks, whereas phenomena such as adaptive response suggests that a linear extrapolation would overestimate risks at low doses. Equal uncertainty exists concerning the dose–response relationship at high doses characteristic of radiation therapy. Does the risk continue to rise as a linear function of dose, does it plateau, or does the risk fall at higher doses because of cell killing?

ond induced tumors occur in or close to the high-dose treatment volume. Figure 5 shows data compiled by Dr. Elaine Ron (13) at the National Cancer Institute in Washington D.C., which shows that for 3 tissues, namely breast, bladder, and stomach, the cancer incidence as a function of dose rises

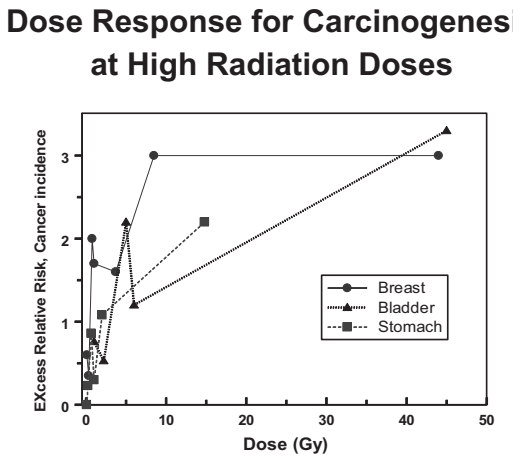

Fig. 5. The dose–response relationship for radiation-induced carcinogenesis for 3 types of cancer, for which data are available over a wide range of doses. The low-dose data are from the atomic-bomb survivors, and the high-dose data are from radiotherapy patients. The figure was compiled by Dr. Elaine Ron, National Cancer Institute (13).

Table 3. Estimated risk of fatal radiation-induced malignancies after RT for prostate cancer (%/Sv)

Hall and Wuu (4)	
Conventional 6 MV	1.5
IMRT 6 MV	3.0
Kry *et al.* (5)	
Conventional 18-MV Varian	1.7
IMRT 6-MV Varian	2.9
Siemens	3.7
IMRT 10-MV Varian	2.1
IMRT 15-MV Varian	3.4
Siemens	4.0
IMRT 18-MV Varian	5.1

Abbreviations: IMRT = intensity-modulated radiation therapy; MV = megavoltage; RT = radiation therapy.

rapidly at low doses and then plateaus; it does not fall rapidly at high doses, because of cell killing.

Table 3 summarizes the attempts that have been made to date to estimate the risk of fatal radiation-induced malignancies after IMRT compared with conventional treatment. Hall and Wuu (4) estimated that the percentage of radiation-induced malignancies after IMRT would be about doubled compared with conventional treatment. Kry *et al.* (5) studied a number of different linear accelerators at several different energies and came up with estimates that are not very different from those by Hall and Wuu (4). Some machines leak a little more than others, but the overall conclusion is that IMRT may approximately double the induced-cancer rate compared with conventional treatment. Compared with three dimensional conformal RT (3D-CRT), IMRT may double the incidence of solid cancers in long-term survivors because of a combination of the increase in monitor units and the changed dose distribution.

The special case of children

The use of IMRT with children represents a special case for 3 reasons. First, children are more sensitive to radiation-induced cancer than are adults by a factor of at least 10 (14). Second, radiation scattered from the treatment volume is more significant in the small body of the child than in the larger body of an adult. Third is the question of genetic susceptibility. Many of the cases of childhood cancer involve a germline mutation that may confer susceptibility to radiation-induced cancer. These factors need to be discussed in turn.

Sensitivity in children. As the Japanese atomic-bomb data have matured, it has revealed a dramatic variation in the lifetime risk of radiation-induced cancer as a function of age (14). The data are shown in Fig. 6. The usually quoted figure of 5% per Sv for the risk of radiation-induced fatal cancer is an average for all ages; the risk is closer to 15% per Sv for a young female and drops to about 1% per Sv for mature individuals 60 years of age and older. A number of examples have been seen of a high incidence of radiation-induced malignancies after radiotherapy of children, notably the

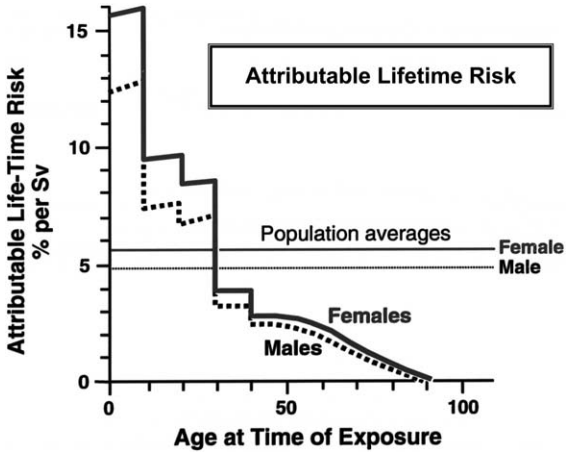

Fig. 6. The attributable lifetime risk from a single small dose of radiation at various ages at the time of exposure. Note the dramatic decrease in radiosensitivity with age. The higher risk for the younger age groups is not expressed until late in life. These estimates are based on a multiplicative model and on a dose and dose-rate effectiveness factor (DDREF) of 2. The figure was adapted from International Commission on Radiological Protection (ICRP) Publication 60 (14).

incidence of breast cancer in children treated for Hodgkin's lymphoma (15).

Radiation scatter from the treatment volume. The relatively bigger radiation dose in children presents a greater risk to radiogenic organs close to the treatment site. This risk is a direct result of the smaller size of the body of a child compared with an adult. Put another way, nearby radiogenic organs are closer in a child than in an adult. This factor is illustrated in Fig. 7.

Genetic susceptibility. Within the past few years, haploinsufficiency for a number of genes such as ATM, BRCA1, and rad9 has clearly been shown to result in increased radiosensitivity to oncogenic transformation in mouse embryo fibroblasts (16, 17). Many cases of childhood cancer involve a germline mutation, and the distinct possibility exists that this mutation may include an increased sensitivity to radiation-induced cancer. The study of Hodgkin's patients treated with radiation, which resulted in an incidence of breast cancer, included the suggestion that the patients were more sensitive to the induction of breast cancer than were children with other malignancies, such as Wilm's tumor or neuroblastoma (15).

Source of radiation leakage from linear accelerators

The maximum allowable leakage from a typical linear accelerator is governed by an international agreement (International Electrotechnical Commission). The leakage from the head is limited to 0.1% of the dose rate at the isocenter, and leakage from a multileaf collimator (MLC) is of the order of 1% to 3%. This leakage was considered acceptable when MLCs replaced cerrobend blocks, which were characterized by a leakage of about 5%. The consequence of this leakage radiation is that a patient treated with radiation therapy for a localized tumor in fact receives a total-body dose of radiation. In addition, when IMRT is

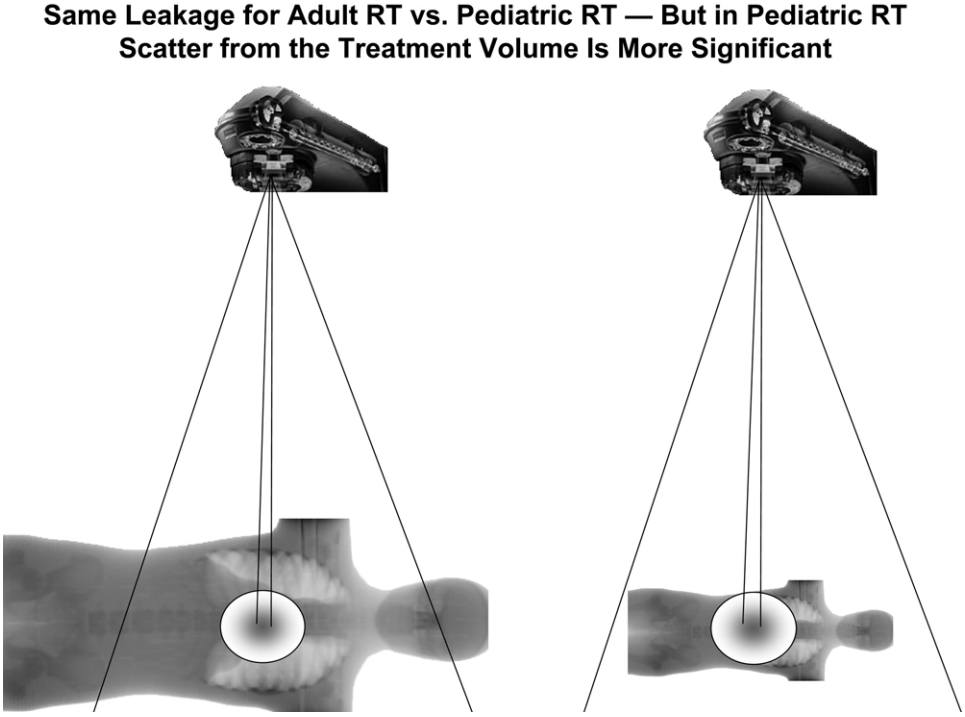

Fig. 7. When a primary tumor is treated with radiotherapy (RT) in a small child, nearby potentially radiogenic organs inevitably receive larger doses of radiation than when a comparable treatment is delivered to an adult, simply because of the closer proximity of organs in a child.

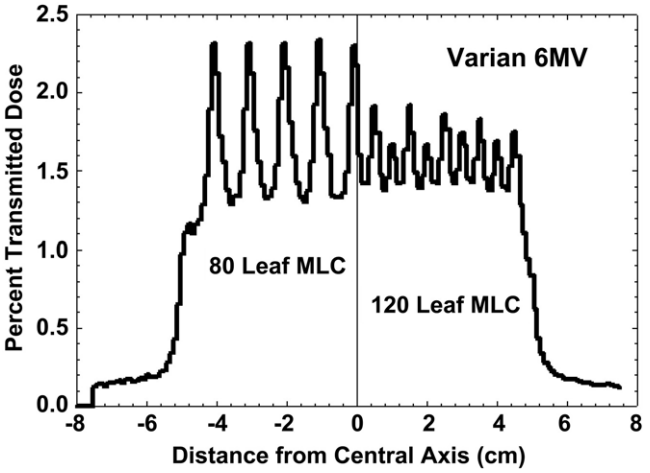

Fig. 8. Leakage radiation through multileaf collimators (MLCs) for a 6-MV linear accelerator. The figure is courtesy of Dr. Paul Keall and based on data from Kim *et al*. (21).

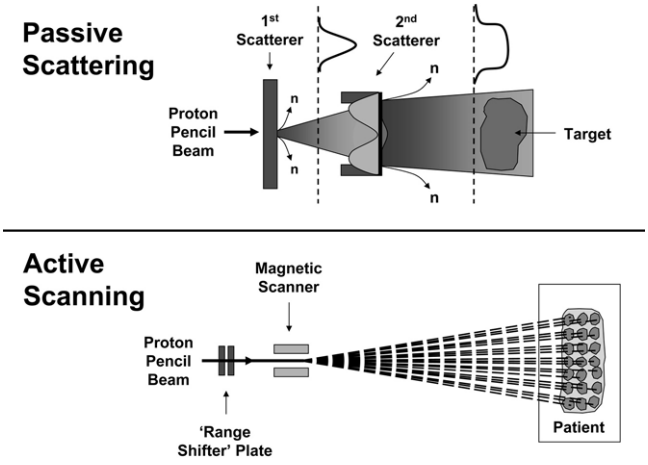

Fig. 9. The protons emerging from a cyclotron or synchrotron form a narrow pencil beam. To cover a treatment field of practical size, the pencil beam must be either scattered by a foil or scanned. Passive scattering is by far the simplest technique but suffers the disadvantage of increased total-body effective dose to the patient.

used, and only part of the field is open at any given time, leakage occurs through the MLC that is much greater than leakage from the head. Figure 8 shows Monte Carlo calculations of the leakage through a 60-leaf or 120-leaf MLC from the work of Dr. Paul Keall of the Medical College of Virginia. This leakage through the MLC results in radiation that can be scattered to distant parts of the body.

Protons

At this point, we might be tempted to suggest that X-rays should be replaced by protons, because this type of particle irradiation results in a reduced volume of normal-tissue exposure, with a consequent reduction in the incidence of second cancers. However, this outcome is only the case if the proton machine employs a pencil scanning beam (18). Many proton facilities use passive modulation to produce a field of sufficient size; that is, the pencil beam of protons that emerges from the cyclotron or synchrotron is made simply to impinge on a scattering foil to produce a field of useful size (Fig. 9). However, the scattering foil becomes a source of neutrons, which results in a total-body dose to the patient (19). The consequences of this exposure are shown dramatically in Fig. 10. Passive modulation results in doses distance from the field edge that are 10 times higher than those characteristic of IMRT with X-rays. The full benefit of protons is achieved only if a scanning beam is used in which doses are 10 times lower than the doses from X-rays.

In the case of X-rays, secondary photon radiation consists of scatter, which predominates near the treatment field, and leakage, which predominates away from the treatment field. Just outside the treatment field, doses are lower for IMRT than for 3D-CRT (20). On the hand, away from the treatment field doses, are higher with IMRT because of the increased number of monitor units, with correspondingly more leakage radiation. The curves for IMRT and 3D-CRT cross, as can be seen in Fig. 10.

CONCLUSIONS

Induced cancers increase with time after radiotherapy and in elderly patients amount to approximately 1.5% by 10 years after treatment. This figure may be doubled by new techniques, such as intensity-modulated radiotherapy. In older patients, for example patients with carcinoma of the prostate, doubling the second cancer inci-

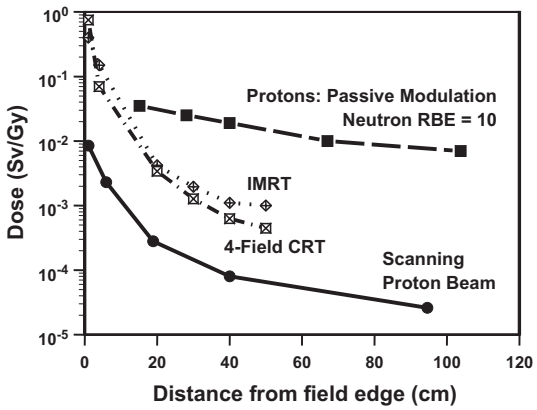

Fig. 10. The equivalent dose outside the edge of the treatment field as a fraction of the dose at the isocenter for protons with passive modulation, for a scanning proton beam, and for 6-MV X-rays, either 4-field conformal radiation therapy (CRT), or intensity-modulated radiation therapy (IMRT). The doses are rough estimates and are likely to be highly facility dependent. The passive-modulation: proton data are from Yan *et al*. (19), renormalized to a 10-cm × 10-cm field and to a neutron relative biologic effectiveness (RBE) or quality factor of 10. The pencil-beam scanning proton data are from Schneider *et al*. (18), renormalized to a 10-cm × 10-cm field and an RBE or quality factor of 10. Both proton curves were produced by Dr. Harald Paganetti, Massachusetts General Hospital and Harvard Medical School. X-ray data are 4-field CRT and IMRT. Unpublished data for a 6-MV linear accelerator were provided by Dr. C. W. Wuu, Columbia University Medical Center, New York.

dence from 1.5% to 3% may be acceptable *if* it is balanced by a substantial improvement in local tumor controlled and reduced acute toxicity. These improvements have not yet been documented in control clinical trials. On the other hand, children are a special case. Second cancer incidence is much higher in children, so doubling it may not be acceptable.

An important point is that the present levels of leakage radiation are not inevitable. Manufacturers play by the rules, and rules can be altered. In the case of X-rays, 3 steps can be taken to mitigate the problem of leakage radiation:

1. The shielding in the treatment head can be increased. For example, the additions of 20 cm of tungsten would reduce leakage by 90%.
2. Secondary beam blocking can be introduced, which would allow secondary jaws to track the MLC. This modification would substantially reduce the leakage through the MLC.
3. A flattening filter is not needed in a linear accelerator dedicated to IMRT. Removal of the flattening filter would remove a source of scattered radiation as well as increase the dose rate at the center of the field.

These steps could greatly reduce the leakage radiation from an X-ray linear accelerator. The alternative, that may be important in the case of children, is to replace X-rays with protons. However, an inherent problem with the present generation of proton therapy installations in the United States is that a scattering foil is used to produce fields large enough for therapy. This process inevitably produces neutrons that deliver a total-body equivalent dose that is even larger than the leakage radiation from conventional linear accelerators. A scanning beam avoids the production of neutrons and, consequently, reduces the total-body dose. Scanning beams are available on a few facilities in Europe but, to date, not on US facilities. The use of a scanning beam will allow the full potential of protons to be realized.

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