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3D-CRT

RADIATION-INDUCED SECOND CANCERS: THE IMPACT OF 3D-CRT AND IMRT

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Information concerning radiation-induced malignancies comes from the A-bomb survivors and from medically exposed individuals, including second cancers in radiation therapy patients. The A-bomb survivors show an excess incidence of carcinomas in tissues such as the gastrointestinal tract, breast, thyroid, and bladder, which is linear with dose up to about 2.5 Sv. There is great uncertainty concerning the dose-response relationship for radiation-induced carcinogenesis at higher doses. Some animal and human data suggest a decrease at higher doses, usually attributed to cell killing; other data suggest a plateau in dose. Radiotherapy patients also show an excess incidence of carcinomas, often in sites remote from the treatment fields; in addition there is an excess incidence of sarcomas in the heavily irradiated in-field tissues. The transition from conventional radiotherapy to three-dimensional conformal radiation therapy (3D-CRT) involves a reduction in the volume of normal tissues receiving a high dose, with an increase in dose to the target volume that includes the tumor and a limited amount of normal tissue. One might expect a decrease in the number of sarcomas induced and also (less certain) a small decrease in the number of carcinomas. All around, a good thing. By contrast, the move from 3D-CRT to intensity-modulated radiation therapy (IMRT) involves more fields, and the dose-volume histograms show that, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2 to 3, increasing the total body exposure, due to leakage radiation. Both factors will tend to increase the risk of second cancers. Altogether, IMRT is likely to almost double the incidence of second malignancies compared with conventional radiotherapy from about 1% to 1.75% for patients surviving 10 years. The numbers may be larger for longer survival (or for younger patients), but the ratio should remain the same. © 2003 Elsevier Inc.

Second cancers, Carcinogenesis, IMRT, 3D-CRT, Total body irradiation.

INTRODUCTION

There is an abundance of data to indicate that radiation can induce cancer in the human. Indeed, radiation has been described as a "two-edged sword" because, while it is a major modality for the treatment of cancer, it can also be the cause of cancer.

Our knowledge of radiation-induced cancer comes from survivors of the A-bomb attacks on Japan; from radiation accidents; and from individuals medically exposed—and these include second cancers in patients receiving radiation therapy.

There are a number of interesting conclusions that emerge from the study of the A-bomb survivors. First, the malignancies observed are leukemias and carcinomas of the cells that line the body. Second, there is no excess of sarcomas. Third, the overall risk of fatal cancers is estimated to be 8%/Gy, i.e., if 100 individuals were exposed to 1 Gy, 8 would develop a fatal cancer due to the radiation, over and above the spontaneous incidence. Fourth, there is a very large variation of risk, with young children being about 15 times as sensitive as middle-aged adults.

There is an interesting difference in the second malignancies induced in patients by radiation therapy. First, carcinomas are observed in the lining cells of the body (much like the A-bomb survivors) and often in tissues and organs that received lower doses because they were remote from the treatment site. Second, sarcomas are induced in heavily irradiated tissues in or close to the radiation fields. This class of tumors was not seen in the A-bomb survivors who received doses of a few Gray.

SECOND MALIGNANCIES IN RADIOTHERAPY PATIENTS

The risk of second malignancies after radiotherapy is a subject not without controversy. One of the reasons for the

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uncertainty is that patients undergoing radiotherapy are often at high risk of a second cancer because of their lifestyles or genetic predisposition, which could be more dominant than the radiation risk.

There are many single-institution studies in the literature involving radiotherapy for a variety of sites that conclude that there was no increase in second malignancies, although a more accurate assessment would have been that the studies had limited statistical power to detect a relatively small increased incidence of second malignancies induced by the treatment (1).

Whenever large studies have been performed, radiotherapy has been shown to be associated with a statistically significant, though very small, enhancement in the risk of second malignancies, particularly in long-term survivors. In particular, there are two studies of special interest which had a suitable surgical control group:

 Second cancers after radiotherapy for prostate cancer. Brenner and colleagues described a study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (2). The risk of a second solid tumor of any type and at any time postdiagnosis was significantly greater after radiotherapy than after surgery, by about 6%. The increased relative risk (RR) became greater with time and reached 34% after 10 years or more. (Relative risk is an epidemiologic term in which the risk of a disease resulting from irradiation is expressed as some percentage increase of the normal rate of occurrence of that disease.) The most dramatic increases were for the bladder (77%) and the rectum (105%) for 10 years or more after diagnosis.

For sarcomas produced in the heavily irradiated tissues within the field, a RR of 145% (compared with surgical patients) was observed at 5 years and longer times.

2. Radiation therapy for carcinoma of the cervix. In the largest study of its kind, Boice and colleagues studied the risk of second malignancies in a wide range of organs and tissues as a consequence of the treatment by radiation of carcinoma of the uterine cervix (3). This study is strengthened enormously by the fact that an ideal control group is available for comparison; this malignancy is equally well treated by radiation surgery, so that the incidence of radiation-induced second tumors can be assessed by comparing patients receiving radiation therapy with those for whom surgery was the initial treatment chosen. They reported that very high doses, on the order of several hundred Gray, increased the risk of cancer of the bladder, rectum, vagina, possibly bone, uterine corpus, and cecum and of non-Hodgkin's lymphoma, whereas doses of several Gray increased the risk of stomach cancer and leukemia. The RR are summarized in Table 1.

Table 1. Second cancer risk in patients treated with radiation therapy for Ca cervix

	Relative risk
Tissues receiving several hundred Gy	
Ca bladder	4.5
Rectum	1.8
Vagina	2.7
?Bone	1.3
?Uterine corpus	1.3
?Cecum	1.5
Non-Hodgkin's lymphoma	2.5
Tissues receiving several Gy	
Ca stomach	2.1
Leukemia	2.0

From Boice et al. (3).

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THE IMPACT OF THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) AND INTENSITY-MODULATED RADIATION THERAPY (IMRT)

Now to a consideration of the potential impact of the new technologies, such as 3D-CRT and IMRT, on the induction of second malignancies. There are two reasons why the change from 3D-CRT to IMRT may result in an increase in second malignancies. First, the change from 3D-CRT to IMRT involves the use of more fields, and as a consequence, a bigger volume of normal tissue is exposed to lower doses. Second, delivery of a specified dose to the isocenter from a modulated field, delivered by IMRT, will require the accelerator to be energized for longer (hence more monitor units are needed) compared with delivering the same dose from an unmodulated field. It therefore follows that the total body dose due to leakage radiation will be increased. These will be discussed in turn, but first we must arrive at a dose-response relationship for radiation-induced cancer.

Dose–response relationship for radiation-induced carcinomas

For single whole-body exposures, the relationship between mortality from solid tumors among the atomic bomb survivors is consistent with linearity up to about 2.5 Sv with a risk of about 10%/Sv (4). At doses of a few Gy, it would seem prudent and appropriate to use the data from the Japanese A-bomb survivors, except that some allowance must be made for fractionation. This allowance for fractionation must of necessity be crude, because accurate and detailed information is simply not available.

A dose-rate effectiveness factor (DREF) is defined to be the factor by which cancer risks should be reduced when radiation is delivered at low doses and low dose-rates, or in a fractionated schedule, compared with a single high-doserate exposure. The National Council on Radiological Protection suggested a range of 2–10, based on animal studies (5). Both the United Nations Scientific Committee on the Effects of Atomic Radiations (UNSCEAR 88) and Biological Effects of Ionizing Radiations (BEIR V) committees adopted the same range. A recent report summarizing cancer risks to radiologists exposed for 40 years or more suggested that their risk, for a given dose, was 2 to 7 times lower than that of the A-bomb survivors, due presumably to the fact that the radiation was spread out over a long period of time (6). For protection purposes, the International Commission on Radiological Protection (ICRP) recommends a DREF of 2 for exposures at low dose and low dose-rate, a very conservative assumption in the light of the range suggested from the aforementioned studies (7).

In the absence of specific data for the DREF for a typical radiotherapy schedule, which is not as protracted as exposures in a radiation protection environment, we propose to use a value of 2.

There is considerable uncertainty concerning the shape of the dose–response relationship for higher doses in the context of radiotherapy, where limited volumes of tissue receive doses of 70 Gy or more, whereas a much larger volume receives a lower dose because it is exposed to only some of the treatment fields.

Three possibilities can be entertained. First, it might be expected that the risk of inducing cancer would fall off at higher doses due to cell killing, on the grounds that dead cells cannot give rise to a malignancy. This effect has been observed in animal studies (8). The effective slope of a cell survival curve for multifraction irradiation, after allowing the full repair of sublethal injury between fractions, becomes progressively shallower as the dose per fraction decreases. It has been estimated by Withers and Peters (9) that the effective D_o for mammalian cells is about 3.17 Gy when the radiation is delivered in 2 Gy fractions. D_0 is the reciprocal of the slope; i.e., the dose required to reduce cell survival to 37% on the linear portion of the survival curve. This is one possibility based on radiobiologic considerations, and is illustrated in Fig. 1.

However, none of the dose-response curves from humans have this shape. It must be regarded, therefore, as an extreme possibility. The other extreme possibility, suggested by the data from some human studies, is that the risk of solid tumors shows a leveling off at 4 to 8 Gy but does not decline thereafter. (This would include women irradiated for endometrial cancer in whom the risk for leukemia reaches a plateau [10] and children given radiotherapy for cancer in whom the risk for thyroid cancer levels off [11, 12].) An intermediate case is represented by women who have been treated with radiation for cervical cancer and have an increased risk of developing leukemia, but the dose-response relationship is complex: the risk increases with doses up to about 4 Gy and decreases at higher doses but much more slowly than the D_0 of 3.17 Gy assumed above (13–15). To the extent that the data can be represented in this way at all, the D_0 would be closer to 10 Gy (see Fig. 1).

We thus have three possible dose–response relationship for radiation-induced carcinogenesis. All three are virtually identical at doses up to about 4 Gy in a fractionated protocol, because this represents the solid data from the Japanese



Fig. 1. Data from the Japanese A-bomb survivors provide good estimates of the risk of solid tumors for total body irradiation; up to about 2 Gy, risk is linear with dose reaching about 8%; assuming a DREF of 2, for a fractionated schedule this maximum value would occur at about 4 Gy. The shape of the dose–response relationship at higher doses is very uncertain. Some data in humans and animals indicate a reduction in risk at higher doses, usually attributed to cell killing. Curve A shows what might be expected with cell killing after a D_o of 3.17 Gy, that observed for a fractionated regime of 2 Gy/day. This might be described as the predictions of a naïve cell biologist. No *in vivo* data support this. Curve B shows a slower fall-off, as observed, for example, with leukemia in women receiving radiotherapy for cervical carcinoma; the fall-off corresponds to a D_o closer to 10 Gy. Curve C shows no reduction of risk as the dose increases.

A-bomb survivors, corrected for fractionation. The three dose–response relationships differ widely at high dose because they depend on the assumptions made concerning cell killing. In Fig. 1, curve A represents the dose–response for radiation-induced cancer where cell killing is characterized by a D_o of 3.17 Gy. Curve B is characterized by a much slower fall-off due to cell killing, the D_o being 10 Gy. Curve C shows essentially a plateau after a dose of about 5 Gy.

It is difficult to choose the most realistic dose–response relationship for carcinogenesis in general. However, in the case of the induction of carcinoma of the bladder by radiation, an interesting conclusion can be arrived at more easily, which strongly favors curve C. Good data on the incidence of this particular malignancy are available from the A-bomb survivors as well as from patients receiving radiotherapy for prostate cancer and for carcinoma of the cervix. In the radiotherapy situations, all of the bladder received quite a large dose of radiation.

The data from the A-bomb survivors indicate a RR for bladder of about 4 at a dose of 2 Gy (4). Patients who survive 10 years or more after radiotherapy for prostate cancer show a RR of 1.8 for bladder cancer (2). (If the



Fig. 2. Illustration of the dependence on dose of the relative risk (RR) of developing a radiation-induced bladder cancer. In the Japanese survivors, the RR was 4 at a dose of 2 Gy. Patients who lived 10 years or more after radiotherapy for prostate cancer show a RR of developing a bladder cancer of 1.8 when the bladder received a dose of 48 to 67 Gy. In the case of patients receiving radiotherapy for carcinoma of the cervix, the dose received was 30 to 80 Gy and the RR of developing bladder cancer was 5. These data imply that the RR of developing bladder cancer varies little with dose over this enormous range; there appears to be little, if any, fall-off attributable to cell killing.

patients had lived longer, or been younger at the time of irradiation, this RR would certainly be higher.) Dose–volume histograms (DVHs for prostate cancer treatments indicate a range of doses to the bladder of 48 to 67 Gy. In the case of patients receiving radiotherapy for carcinoma of the cervix, the RR for bladder cancer was reported to be 5 for an organ dose of 30–80 Gy (3). This is illustrated in Fig. 2. A comparison of these data imply comparatively little differences in the RR over the dose range from 2 to 80 Gy, thus strongly favoring the flat relationship with little if any fall-off attributable to cell killing.

A comparison of the incidence of second malignancies from 3D-CRT and IMRT for the treatment of prostate cancer

A simple way to compare 3D-CRT and IMRT is to assume, as a first approximation, that the cancer risk associated with irradiating part of the trunk is directly proportional to the volume irradiated. This is not, of course, strictly true because the ICRP tissue weighting factors for organs in the trunk vary from 0.12 to 0.05 (7). More importantly, not all organs are radiogenic. However, it can be used as a first approximation. Comparing 3D-CRT and IMRT (from their respective DVHs shown in Fig. 3) and using the three dose– response relationships illustrated in Fig. 1, the results shown in Table 2 can be derived. For dose–response relationship A, with the steep fall-off due to cell killing, there is little difference between the risk of a second malignancy between 3D-CRT and IMRT. However, this conclusion is questionable because when this dose–response relationship is used, essentially all of the cancer risk results from tissue exposed to low doses of a few Gy. Scattered and leakage radiation will be major contributing factors, and the DVHs are currently not reliable.

In the case of a dose–response relationship where the fall-off due to cell killing is either modest or nonexistent, small but larger risks are implied for IMRT, which is intuitive.

What is important here is the difference between 3D-CRT and IMRT. The absolute values for the risks are too high because they were calculated using a risk estimate of 5%/Gy, which applies to a general population of all ages, whereas radiotherapy patients tend to be older, with the risk estimate closer to 2%/Gy. It might be estimated, therefore, that IMRT might increase the risk of radiation-induced carcinomas by perhaps 0.5%.

The effect of an increase in monitor units

Delivery of a specified dose to the isocenter from a modulated field, delivered by either dynamic IMRT or the step-and-shoot method of IMRT, will, in general, require the accelerator to be energized for longer (hence more monitor units are needed) compared with delivering the same dose from an unmodulated field (16). It therefore



Fig. 3. Dose–volume histograms for two typical treatment plans for prostate cancer; a four-field conformal plan and a nine-field plan using intensity modulation.

follows that patient dose due to leakage radiation will be increased, although its spatial distribution and magnitude will depend on many interrelated factors, including the design and operation of the multileaf collimator and associated backup diaphragms, the patterns of modulation specified by the treatment planning process, and the algorithms used to convert the patterns of modulation into a series of leaf sequences by which the beams are delivered. An IMRT treatment plan will then result in an increase in monitor units by a factor of 2 to 3, increasing the dose outside the boundary of the primary collimator due to both leakage and scattered radiation.

The situation is complicated by two factors: (1) IMRT will reduce the use of physical wedges and physical compensators, and hence the increased beam on-time will not be as great as initially predicted. (16). (2) Multileaf collimators allow more leakage than conventional collimators, but on the other hand, conformal therapy and IMRT will generally result in smaller volumes being treated, which will impact on the scattered radiation dose. This is relevant because Lillicrap *et al.* (17) have shown that scattered radiation is the dominant source of radiation outside the beam up to 14 cm from the beam edge.

 Table 2. Effect of cell killing on the percentage of patients who developed a second malignancy

D _o of cell killing component (Gy)	Estimated % patients with second malignancy	
	3D-CRT	IMRT
3.17	1.9	1.8
10	3.1	3.8
1,000	7.2	9.5

Some years ago, we made measurements of scattered and leakage radiation using an anthropomorphic "Randoman" phantom (18). We used ionization chambers to measure the dose to a breast, whereas a four-field technique was used to deliver a dose of 70 Gy to the cervix. Using a 6-MV linear accelerator (linac), the breast dose was 0.25 Gy, whereas with a 20-MV linac the dose consisted of 0.5 Gy of X-rays plus a photoneutron component of about 1 cGy. We need only consider the data for the 6-MV linac, because higher energies are not usually used for IMRT. The breast dose of 0.25 Gy translates into a risk of radiation-induced cancer of about 0.25%, using a risk estimate of 2%/Gy, appropriate for older patients.

CONCLUSIONS

A number of general conclusions can be drawn from the above discussion. First, concerning radiation-induced sarcomas, because these tumors occur only in heavily irradiated tissues, it is unlikely that a difference will be detected between 3D-CRT and IMRT, since the high dose volume is not much changed. Their absolute number is small if follow-up is short, but the number may increase dramatically for long life expectancy.

Second, concerning radiation-induced carcinomas, there is likely to be an increased incidence for IMRT compared with 3D-CRT due to the dose distribution, i.e., a larger volume irradiated to lower doses. It is estimated that an additional 0.5% of surviving patients will develop a second malignancy as a result of this factor. There will also be an increased incidence for IMRT due to an increase in monitor units. It is estimated that an additional 0.25% of surviving patients will develop a radiation-induced malignancy because of this factor. This adds up to a total of about 0.75% of surviving patients who would be expected to develop a second malignancy as a consequence of the change to IMRT, which is approximately a doubling of incidence observed for more conventional radiation therapy.

Some years ago, Followill and colleagues at the M. D. Anderson Hospital made estimates of whole-body dose equivalent resulting from IMRT (19). They concluded that, compared with conventional radiotherapy, IMRT may approximately double the risk of secondary cancers from 0.4% to 1%. These figures apply to a 6-MV accelerator; estimates were much higher for 18 MV and for tomotherapy, but 18 MV is not often used for IMRT, and tomotherapy is not a widely utilized technique. This possible doubling of the second cancer risk is similar to our conclusion above, but their *absolute* levels are much lower. There are two reasons for this. First, they considered only the increase in monitor units and did not address the question of a bigger volume of normal tissue being exposed to lower doses. Second, as an estimate of the average whole-body dose equivalent they computed the dose at 50 cm from the center of a 20×20 cm field. Using an average dose leads to a substantial underestimate of the carcinogenic potential of a radiotherapy protocol. For example, in the treatment of carcinoma of the prostate or of the cervix, the most radiogenic organs, which account for most second cancers, are much closer than 50 cm from the center of the field, and therefore receive much higher doses than the average whole-body dose. Organs and tissues at greater distances from the treatment field include the head and extremities, which are less radiogenic.

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