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The Frank Ellis Lecture

The Inaugural Frank Ellis Lecture — Iatrogenic Cancer: The Impact of Intensity-modulated Radiotherapy☆

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ABSTRACT:
It is an honour and personal pleasure to give the inaugural Frank Ellis Lecture to celebrate his 100th birthday, and to acknowledge his enormous contributions to radiation oncology.
Intensity-modulated radiotherapy (IMRT) allows dose to be concentrated in the tumour volume while sparing normal tissues. However, the downside to IMRT is the potential to increase the number of radiation-induced second cancers because more fields are used which involves a bigger volume of normal tissue exposed to lower doses.
It has been estimated that IMRT may double the incidence of solid cancers in long-term survivors. This may be acceptable in older patients if balanced by an improvement in local tumour control and redced toxicity. On the other hand, the incidence of second cancers is higher in children, so that doubling it may not be acceptable. IMRT represents a special case for children. First, they are more sensitive to radiation-induced cancer than adults. Second, radiation scattered from the treatment volume is more important in the small body of the child. Third, there is the question of genetic susceptibility, as many childhood cancers involve a germline mutation.
The levels of leakage radiation in current Linacs can be reduced, but the cost would be substantial. An alternative strategy is to replace X-rays with protons. This is an advantage only if the proton machine uses a pencil scanning beam, as passive modulation of a scattering foil produces neutrons, which results in an effective dose to the patient higher than that characteristic of IMRT. Hall, E. J. (2006). *Clinical Oncology* 18, 277–282
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Key words: IMRT, leakage radiation, passive modulation, pencil beams, protons, second cancers

Introduction

It is an honour, and at the same time a great personal pleasure, to give the inaugural Frank Ellis Lecture. Establishing this lecture was a birthday present, given jointly by The Royal College of Radiology and The British Institute of Radiology, to celebrate Professor Ellis' 100th birthday and to recognise his enormous contributions to radiation oncology (Fig. 1).

For me, personally, it is almost exactly 50 years to the day that I started my first job in Oxford, with FE (as I always called him) as my Chief. I owe him an enormous debt of gratitude for his influence on my life and my career. I learned several lessons from him that have stayed with me for all the years that I have been in New York. He taught me:

- Honesty and integrity; if you make a mistake, admit it.
- If something can be done, it probably can be done better. Innovate.

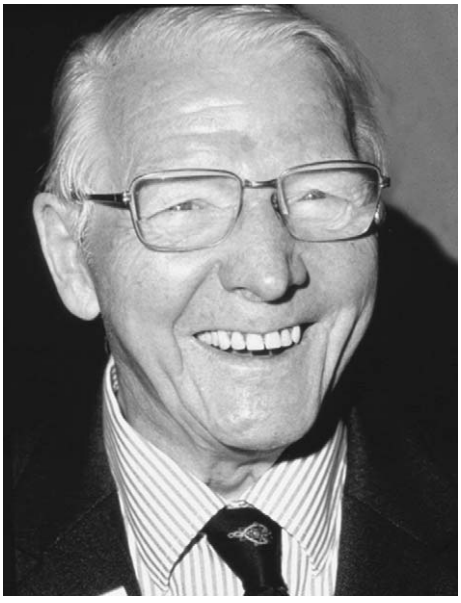

Fig. 1 — Frank Ellis, MD, OBE.

☆ Professor Frank Ellis, OBE, derived much pleasure from the numerous celebrations of his 100th birthday during 2005, including being present at the Inagural Frank Ellis Lecture on 14 September. With much regret, we must record that he died on 3 February 2006.

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- Don't be afraid to have ideas, and relentlessly pursue those that work.
- Every day work a little, every day play a little. No work day is so long that there is no time for a game of squash and a pint of beer.

Perhaps the most important lesson involves ideas, because Professor Ellis was an endless source of ideas, from wedge filters to tissue compensators to the concept of 'nominal standard dose' (NSD). I was impressed by a quote about the importance of ideas that I came across recently from Charles Townes, the inventor of the laser. He ended his acceptance speech on the day he received The Nobel Prize with the words:

Its like the beaver told the rabbit
as they stared at the Hoover Dam…
No I didn't build it myself,
But it's based on an idea of mine

As a subject for this first Frank Ellis lecture, I have chosen to examine the effect of new technology in radiotherapy, epitomised by Intensity-modulated Radiotherapy (IMRT), on the potential incidence of second-radiation-induced malignancies.

IMRT allows dose to be concentrated in the tumour volume while sparing normal tissues [1]. This is a major step forward. However, the downside to IMRT is the potential to increase the number of radiation-induced second cancers [2—5]. There can be few worse things for a patient than to survive the initial treatment, live with the long-term morbidity of treatment, only to find that they have developed a radiation-induced second cancer, which may have a worse prognosis than their original tumour.

Quantitative Data of Radiation-induced Cancer

Knowledge of radiation-induced cancer comes from the A-bomb survivors, from radiation accidents, and from individuals medically exposed to radiotherapy. This includes people who have developed second cancers after radiation therapy. Figure 2 shows data for mortality from radiation-induced solid cancers in the atom-bomb survivors [6]. There is a linear relation 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 in tumours in tissues hormonally controlled, such as the breast. Table 1, taken from NCRP report 116, shows the relative probabilities of developing second malignancies by organ site, and it is at once apparent that the colon, lung and stomach are prime sites [7].

In most cases it is difficult to assess the risk of second cancers in patients who have undergone radiotherapy, because an appropriate control group does not exist, that is, a group of individuals who have the same initial malignancy but are treated without radiation. The major

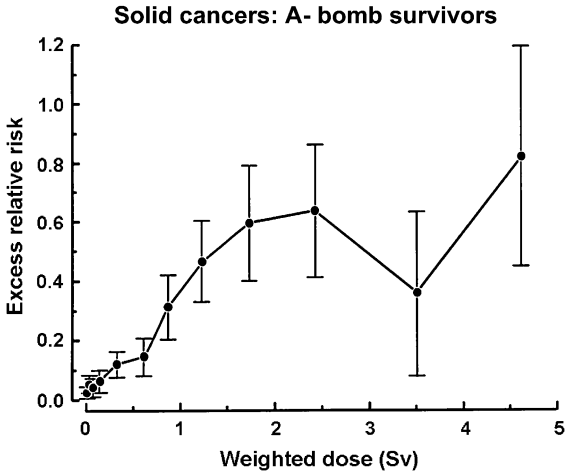

Fig. 2 — Data for fatal solid cancer in atomic-bomb survivors, 1950—1990, shown in terms of the excess relative risk (ERR) as a function of dose. The ERR seems to be quite linear for doses below 3 Sv but flattens off significantly at higher doses, probably because of cell killing (adapted from ref. [6]).

exceptions are cancer of the prostate and cancer of the cervix, where 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 disease. Here, the risk of breast cancer in young women is so obvious that it cannot be missed [10]. In patients who have undergone radiotherapy, the induced tumours include carcinomas, as in the Japanese survivors. These may appear in sites adjacent to or remote from the treated area [9]. The number of tumours is relatively large, but the relative risk is small. In addition, sarcomas may appear in heavily irradiated tissues, either within the treatment field or close by; this is in contradistinction to the A-bomb survivors who were not at increased risk of sarcomas because the doses were never sufficiently high. In patients who have received

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
Oesophagus	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

Table 2 — Prostate cancer treated with radiotherapy or surgery (SEER Program) 1973—1993

	Radiotherapy	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
% of 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

radiotherapy, sarcomas are small in number but are characterised by a large relative risk. Radiation-induced tumours in patients who have received radiotherapy will become increasingly important as younger patients are treated and improved cure rates obtained.

Table 2 summarises the largest published study of second cancers induced in patients treated for prostate cancer by radiotherapy, compared with similar patients who received surgery [9]. This is a large study based on the SEER database of the National Cancer Institute in the USA. The results of this study are summarised in Fig. 3. Ten years after treatment, the incidence of an induced malignancy is about one in 70. The principal sites for radiation-induced tumours include the rectum, bladder, colon and lung (i.e. some sites close to and some remote from the treatment area). In addition, sarcomas appear in, or close to, the treatment field, in heavily irradiated tissue.

The Effect of Intensity-modulated Radiotherapy

Two factors must be considered when a conventional treatment is replaced by IMRT. First, there will be more monitor units and therefore a larger total body dose resulting from leakage radiation from the head and collimator [11]. Second, because, in general, more fields are used, a larger volume of normal tissue will be exposed to lower doses [4,5]. These two factors will be considered in turn.

First, the increase in monitor units: delivery of a specified dose to the iso-centre from a modulated field delivered by IMRT would require the accelerator to be energised for a longer time, and hence there will be more monitor units. It, therefore, follows that the total body dose due to leakage radiation will be increased. Second, as an IMRT treatment usually involves more treatment fields, a bigger volume of normal tissue will be exposed to lower radiation doses. The importance of this depends on the shape of the dose—response relationship for radiation-induced carcinogenesis [12]. From 0.1 to 2.5 Sv, there is a linear

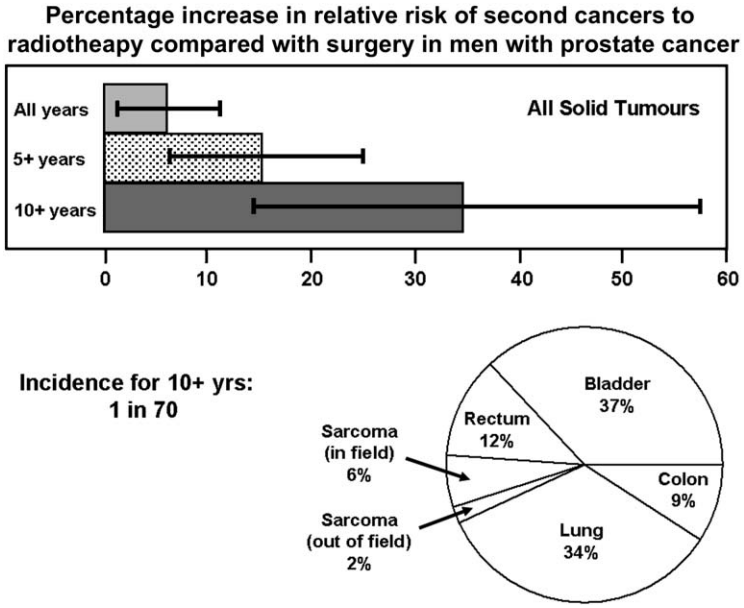

Fig. 3 — The upper panel shows the percentage increase in relative risk for all solid tumours as a function of time after radiotherapy. The error bars represent 95% confidence limits. 'All years': refers to all years after treatment; the standard error is smaller in this case because of the larger number 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 (data from ref. [9]) (figure courtesy of Dr. David Brenner).

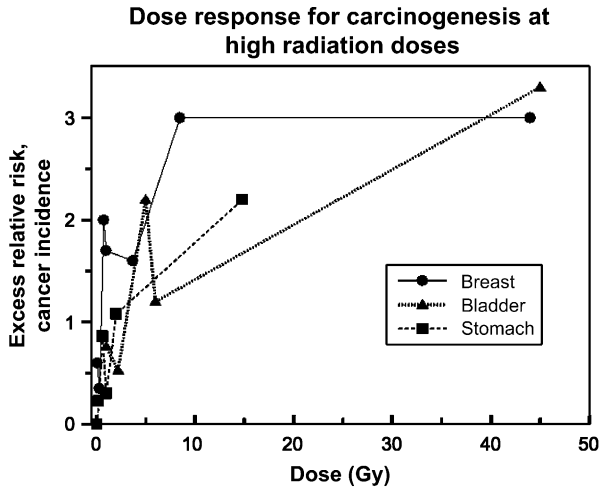

Fig. 4 — The dose—response relationship for radiation-induced carcinogenesis for three types of cancer, for which data are available over a wide range of doses. The low-dose data dome from the A-bomb survivors, the high-dose data from radiotherapy patients (figure compiled by Dr. Elaine Ron, NCI).

relationship based on the A-bomb survivor data, but, at higher doses, the shape of the dose response to relationship is in doubt, and the shape in this dose range is important for the induction of second cancers after radiation therapy. Figure 4 shows data compiled by Dr. Elaine Ron at the National Cancer Institute in Washington, DC. For three tissues, namely breast, bladder and stomach, the cancer incidence as a function of dose rises rapidly at low doses and then plateaus; it does not fall rapidly at high doses because of cell killing (Ron E, personal communication, 2005). In the case of these three tissues, low-dose data are available from the A-bomb survivors, whereas high-dose data came from patients receiving radiotherapy.

Table 3 summarises several attempts that have been made to date to estimate the risk of fatal radiation-induced malignancies after IMRT compared with conventional treatment. First, there is the estimate of Hall and Wuu in 2003 [4]. They estimated that the percentage of radiation-induced malignancies after IMRT would be about double compared with conventional treatment. In a later paper, 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]. The various investigators used different methodologies and made different assumptions. However, the overall conclusion is similar, namely, that IMRT may approximately double the induced cancer rate compared with conventional treatment.

Table 3 — Risk of fatal radiation-induced malignancy after radiotherapy for prostate cancer (%/Sv)

Hall and Wu [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

IMRT, intensity-modulated radiotherapy.

The Special Case of Children

Children represent a special case when IMRT is concerned. There are three reasons for this. First, children are more sensitive to radiation-induced cancer than adults by a factor of at least 10 [13]. Second, radiation scattered from the treatment volume is more important and more significant in the small body of a child than in the larger body of an adult. Put another way, nearby radiogenic organs are closer in a child than in an adult. Third, there is the question of genetic susceptibility. Many types of childhood cancer involve a germline mutation, which may confer susceptibility to radiation-induced cancer. These factors need to be discussed in turn.

First, the question of sensitivity of children. As the Japanese A-bomb data have matured, it has become evident that the lifetime risk of induced cancer as a function of age dramatically varies [13]. The usually quoted figure of 5%/Sv for the risk of radiation-induced cancer is an average for all ages; in fact, the risk is closer to 15%/Sv for a young female and drops to about 1%/Sv for mature individuals in their 60s. There are a number of examples of a high incidence of radiation-induced malignancies after radiotherapy of children, notably the incidence of breast cancer in children treated for Hodgkin's lymphoma [14]. The second factor involving children is doses are greater, and therefore the risk is greater, to radiogenic organs close to the treatment site in children than in adults. This is a direct result of the smaller size of the body of a child compared with an adult.

The third special factor involving children is the possibility of genetic susceptibility. Within the past few years, it has clearly been shown that haploinsufficiency for a number of genes such as *ATM*, *BRCA1* or *RAD9* results in increased radiosensitivity to oncogenic transformation in mouse embryo fibroblasts [15,16]. Many types of childhood cancer involve a germline mutation, and it is possible that this may include an increased sensitivity to induced cancer. For example, one study showed that patients with Hodgkin's lymphoma treated with radiation resulted in an incidence of breast cancer. It was suggested that they were more sensitive to the induction of breast cancer than the children with other malignancies, such as Wilm's tumour or neuroblastoma [14].

Source of Radiation Leakage from Linacs

The maximum allowable leakage from a Linac 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 iso-centre, whereas leakage from a multi-leaf collimator (MLF) is about 1 to 3%. This was considered to be adequate when MLFs replaced Cerebend blocks, which were characterised by a leakage of about 5%. The consequence of this leakage radiation is that a patient treated with radiation therapy for a localised tumour is, in fact, exposed to a total body dose of radiation. In addition, when IMRT is used and only part of the field is open at any given time, there is also leakage through the MLF, which is much greater than from the head. This leakage through the MLC results in radiation that can be scattered to organs distant from the treatment field [17].

Protons

At this point, it might be tempting to suggest that X-rays should be replaced by protons, as particle irradiation results in a reduced volume of normal tissue being exposed, and one would assume that this would reduce the incidence of second cancers. However, this is only the case if the proton machine uses a pencil scanning beam [18]. Many proton facilities in use today use passive modulation in order to produce a field of sufficient size (i.e. the pencil beam of protons emerging from the cyclotron or synchrotron is made simply to impinge on a scattering foil in order to produce a field of useful size). If this is done, the scattering foil becomes a source of neutrons, which result in a total body dose to the patient. It should be noted that neutrons are highly effective at cancer induction [19]. In fact, passive modulation results in effective doses distant from the field edge that are much higher than those characteristic of IMRT with X-rays. The full benefit of protons is only achieved if a scanning beam is used.

Conclusions

Induced cancers increase with time after radiotherapy. In elderly patients, induced cancers increase to about 1.5% at 10 years after treatment. This figure may be doubled by new techniques, such as IMRT. In patients in their 60s or 70s, doubling the second cancer incidence from 1.5 to 3% may be acceptable if it is balanced by an improvement in local tumour control and reduced acute toxicity. Although these improvements have not yet been documented in controlled clinical trials, there seems every prospect that they will materialise in due course. On the other hand, children are a special case. Second cancer incidence is much higher in children, so that doubling it may not be acceptable.

However, present levels of leakage radiation are not inevitable. Manufacturers play by the rules and rules can be altered. In the case of X-rays, three steps can be taken to mitigate the problem of leakage radiation: (1) the shielding in the treatment head can be increased. For example, the addition of 20 cm of tungsten would reduce leakage by 90%. (2) Secondary beam blocking can be introduced, allowing secondary jaws to track the MLC. This would substantially reduce the leakage through the MLC. (3) A flattening filter is not needed in a Linac devoted to IMRT. Removing the flattening filter removes a source of scattered radiation as well as increasing the dose rate at the centre of the field.

These steps could greatly reduce the leakage radiation from an X-ray linear accelerator. The alternative, which may be of special importance in the case of children, is to replace X-rays with protons, but only if a scanning beam is available.

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