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The Frank Ellis Lecture

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

E. J. Hall

Center for Radiological Research, Columbia University Medical Center, College of Physicians and Surgeons, New York, NY, USA

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

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.

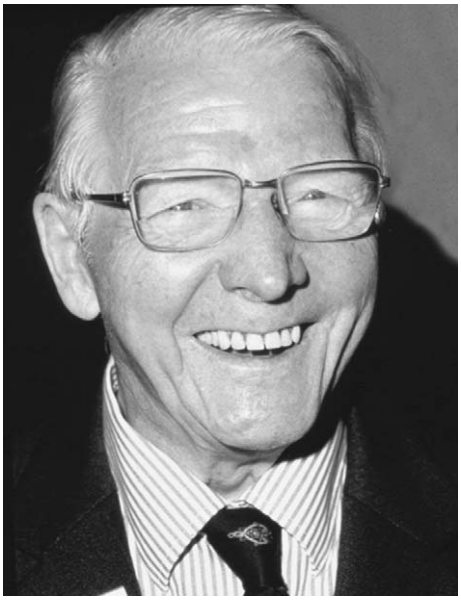

Fig. 1 — Frank Ellis, MD, OBE.

☆ 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

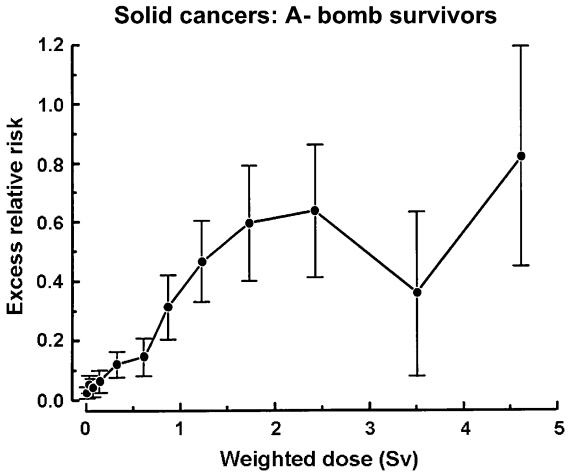

Fig. 2 — Data for fatal solid cancer in atomic-bomb survivors, 1950—1990, shown in terms of the excess relative risk (ERR) as a function of dose. The ERR seems to be quite linear for doses below 3 Sv but flattens off significantly at higher doses, probably because of cell killing (adapted from ref. [6]).

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