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Point of View

Radiotherapy-induced Second Cancers: Are We Doing Enough to Protect Young Patients?

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INTRODUCTION

LITTLE PUBLICITY greeted last year's centenary of the discovery of ionising radiation, perhaps indicating a degree of public ambivalence about this technology. Such ambivalence might have surprised Wilhelm Roentgen, who would surely have been gratified to know that his findings were destined to yield a major anticancer treatment. Progress in radiobiology has resulted in other applications which Roentgen could not have imagined, of course; but in recent times it has been the problems linked to these applications which have received most attention.

As was true for Roentgen, our own ability to foresee long-term problems is limited by fragmentary and immature data. These limitations do not eliminate the responsibility for anticipating and avoiding such problems—although it is equally important to avoid inflaming public anxiety by uninformed speculation. Like hormones and cytotoxic drugs, radiation is now recognised to be a trigger as well as a treatment for cancer. Here we describe some evolving concerns about radiation-inducible carcinogenesis, and discuss the cautionary implications of this knowledge for the future practice of radiation oncology.

WHY WORRIES OVER RADIATION RISKS ARE RISING

Along with cigarettes and viruses, radiation is an established exogenous (hence avoidable) carcinogen. Although less transforming than many chemicals, radiation engenders particular anxiety on account of its ubiquity and invisibility. Indeed, the scale of international disapprobation following recent nuclear tests in the Pacific undoubtedly derives in part from such fears about environmental induction of human cancer.

To what extent are these fears justified? Most studies of human radiation carcinogenesis have focused on a handful of cohorts, notably the Hiroshima/Nagasaki survivors, irradiated ankylosing spondylitis patients, and women undergoing irradiation for gynaecological disorders [1]. These studies have supplied much detail about the relationship between radiation and tumorigenesis. Radiogenic lung cancers, for example, are generally characterised by a minimum age of 35 years, latency of at least 5 years, predilection for the upper lung fields and synergistic induction by smoking [1, 2]. Defining a 'safe' lower limit for exposure on the basis of such data has proven difficult, with generalisations about safety often losing credibility in the face of isolated counterexamples: one instance of the latter is Madame Curie's recent exhumation which confirmed her level of radium contamination to have been well below that officially deemed leukaemogenic [3].

Among new developments to be factored into public perceptions of radiation, few are likely to prove more potent than the cloning of the ataxia telangiectasia (*AT*) gene [4], a 'radiosensitivity gene' encoding a DNA-binding protein kinase implicated in cell-cycle control and chromosomal maintenance [5]. Heterozygous *AT* mutations affect approximately 0.5% of the population and are associated with both radiosensitivity and cancer predilection [6]—a combination of factors which seems certain to generate major public health implications. For example, with respect to mammography (which delivers 2–10 mGy per two-view examination [7, 8]), some estimates have suggested that a maximum of 1000 new breast cancers may be induced per million screened using older techniques [8]. While newer technology may be associated with a far lower risk than this for normal subjects, the risk for *AT* heterozygotes could plausibly be an order of magnitude higher [6].

HOW LOW-DOSE RADIATION MAY POSE GREATER LONG-TERM HAZARDS THAN HIGHER DOSES

The toxicity of high-dose irradiation is mainly acute: malaise, tissue inflammation and cell necrosis. However, the carcinogenic effects of radiation are not restricted to those tissues manifesting clinical toxicity; as detailed below, the opposite may in fact be more accurate, since high-dose radiation may 'sterilise' the carcinogenetic potential of a tissue

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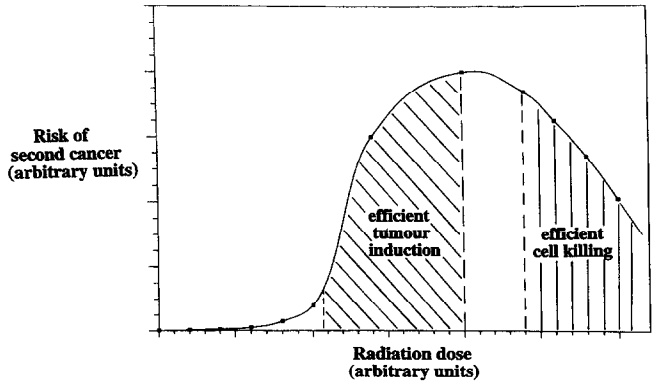

Figure 1. Radiation carcinogenesis. Schematic representation of the biphasic relationship between second cancer risk and radiation dose. The sigmoid shape of the curve at low radiation exposures, followed by a rapid linear escalation of tumour risk, is consistent with a wide spectrum of animal and human data.

by killing cells in proportion to DNA double-strand break induction. Such doses are used therapeutically, but destroy only a proportion of tumour cells with each treatment fraction. Cells which are not killed delay growth to repair damage, and it is in this cell subset that DNA repair errors may lead to the integration of transforming mutations. In this model, the efficiency of tumour induction varies inversely with repair capacity which in turn depends on the integrity of cell-cycle checkpoints such as are controlled by the *AT* gene product [5]. Interestingly, although homozygosity for the *AT* mutation causes marked radiosensitivity and cancer-proneness, homozygotes (unlike heterozygotes [6]) are not clearly predisposed to radiogenic second cancers [9]—consistent with enhanced cell killing at the expense of mutant cell survival in this cohort, and corresponding to a 'left-shift' of the curve represented in Figure 1.

Clinical evidence corroborates this biphasic relationship between dose and tumour induction. Papillary thyroid cancer is inducible by low-dose radiation, whereas higher doses (>2000 cGy) abolish the malignant potential of the thyroid [1]. Similarly, patients prescribed high-dose radiotherapy for cervix cancer or spondylitis exhibit sizeable 'leukaemia deficits' compared with those receiving lower exposures [1]. Breast exposures of 20–50 cGy can likewise induce tumours [10, 11], whereas doses exceeding 10 Gy are less carcinogenic than lower doses [1, 10, 12].

WHY BAD LUCK CAN SOMETIMES BE DOSE-DEPENDENT

The preferential tumorigenicity of low-dose irradiation represents an intuitive paradox. Traditionally, this paradox has been resolved by characterising radiation carcinogenesis as a stochastic, and thus unavoidable, phenomenon which bears no direct relationship to dose. In the sense that radiogenic transformation is, for practical purposes, an irreducibly complex phenomenon, the stochastic model is reasonable. However, given that the efficiency of radiogenic tumour induction might normally be expected to vary with cell repair capacity—to be restricted, in other words, to the range of net sublethal damage (Figure 1)—no simple dose–response relationship is expected. Wide differences in radiosensitivity between cell types further complicate the derivation of dose-dependent algorithms for tumorigenicity, while difficulties in accurately measuring target exposures (even in the therapeutic context [13]) could underlie historical discrepancies between dose and effect.

Radiation tumorigenesis therefore represents a 'yin-and-yang' balance between radiogenic transforming events and cell death (apoptosis)—a balance now known to involve a number of specific molecular intermediaries, with the best-known being the tumour-suppressor p53 phosphoprotein. Like the *AT* kinase, by which it could conceivably be regulated, p53 controls a cell-cycle checkpoint which is activated by DNA damage; put conversely, dysfunctional aberrations of AT or p53 permit uncontrolled cell-cycle progression in the presence of DNA damage. Confusingly, the usual clinical contexts of these aberrations are distinct, with *AT* mutations inducing a 'radiosensitive' phenotype in normal tissues while *TP53* mutations allow treated tumour cells to evade apoptosis ('radioresistance'). An endpoint of both (heritable) *AT* and (acquired) *TP53* mutations is chromosomal instability, manifesting respectively as 'spontaneous' carcinogenesis or tumour progression due to microevolution of radioresistance [14]. What, however, is the radiocarcinogenetic significance of heterozygous *AT* or *TP53* mutations in phenotypically normal tissues? *De novo* transformation can certainly be p53-dependent [15, 16], consistent with experimental models of carcinogenesis in which *TP53* mutations constitute a classical initiating event [17]. Indeed, the long latency of many radiation-induced solid tumours fits well with the time-frame of tumorigenesis in families with germline *TP53* mutations [18].

Variations in radiation dose can thus be expected to modulate a variety of interdependent short- and long-term cellular outcomes dictated by the balance between growth, apoptosis, mutation, repair and genetic instability. The complexity of this balance in no way implies a lack of dose-dependency—on the contrary, a general conclusion about radiation carcinogenesis has been that tumours are induced in a supralinear relationship with (sublethal) dose [1, 19]. For example, breast irradiation within the range 50–400 cGy increases relative (not absolute) cancer risk by approximately 40% per Gy [12]. Fractionation does not reduce risk, further implicating cumulative dose as the key variable [10]. Hence, notwithstanding that tumorigenic exposures tend to be subclinical, tumour-preventive initiatives would seem best framed around substantive reductions of radiation doses—an objective especially relevant to therapeutic exposures.

HOW YOUNG PATIENTS WITH GOOD-PROGNOSIS TUMOURS FIND THEMSELVES AT GREATEST RISK OF RADIOTHERAPY-INDUCED SECOND CANCERS

Radiotherapy is a time-honoured component of both the curative (radical) and palliative (symptomatic) management of many human cancers. Prophylactic (adjuvant) irradiation has lately become fashionable, and randomised studies confirm enhanced relapse-free survival following adjuvant treatment of tumours affecting the breast, rectum, limbs, head and neck, and lymph nodes. While these benefits currently outweigh any doubts over short-term hazards, adjuvant irradiation also causes several delayed toxicities of which second malignancies are the best-known. Concerns over the long-term incidence of this complication in young 'good-prognosis' irradiated patients—such as those with

Hodgkin's disease or early premenopausal breast cancer—have deepened in recent years due to a number of related developments.

One of these has been the growth of screening programmes to detect radiosensitive tumours at an earlier stage and, hence, in younger patients with a better disease-specific prognosis. Screen-detected breast tumours, for example, tend to be not only smaller but also biologically less aggressive than their symptomatic counterparts [20]—good news in terms of disease natural history, but worrying for therapists who audit long-term treatment sequelae. Moreover, expansion of screening has coincided with increased prescription of adjuvant irradiation, particularly for younger patients desiring less extensive primary surgery. Indeed, this approach has become all but standard for breast cancer in many parts of North America and Western Europe, with only the exceptional lumpectomy patient foregoing 'top-up' radiotherapy. Another key factor provoking 'radiation anxiety' has been the recognition that lifelong increases in second cancers (e.g. lung [2]) are mainly associated with irradiation of younger patients [1]. Young age (<45 years) at exposure is a particular risk factor for radiogenic breast cancer [11, 21, 22], with up to 6-fold increases in younger patients receiving 1–4 Gy breast exposure; postmenopausal women, in contrast, incur less than half this increased risk [11, 19]. Latency of radiogenic breast tumours usually exceeds 10 years [1] and, unlike leukaemias, increased risk does not reach maximum until 25 years and persists for at least a further 20 years [10, 21] and probably lifelong [23]. Longevity after radiotherapy thus constitutes a paradoxical risk factor for second cancers.

WHY THE CONTRIBUTION OF RADIOTHERAPY TO SECOND BREAST CANCERS REMAINS A CONUNDRUM

Unlike cytotoxic drugs which mainly predispose to leukaemia [24], ionising radiation induces neoplasia in virtually any tissue [1, 23], causing not only leukaemias but also sarcomas [26], and carcinomas of the lung [3], thyroid [1], stomach [27] and breast [6, 10–12, 21]. With respect to the latter, the evidence implicating a radiocarcinogenic effect is indisputable, with increased breast cancers having been particularly well documented following mantle irradiation [1, 28]. Viewed in the light of these data, the failure of some studies to confirm a carcinogenic effect of breast irradiation seems anomalous, and may in some cases be traced to confounders such as insufficient follow-up, small numbers, selection bias in non-randomised studies and competing causes of death in older cohorts. Despite this, the extent to which patients undergoing adjuvant breast irradiation sustain long-term increases in metachronous (ipsilateral or contralateral) cancer continues to be debated, with some well-conducted studies failing to confirm increased risk [22, 29, 30]. Disturbingly, however, the tumorigenic dose range closely approximates the radiation dose to the contralateral breast [22, 29–32]. Why has this hazard proven so difficult to clarify? First, tumours supervening within the irradiated breast are conventionally ascribed to recurrence of the primary tumour—even though 40% of postradiation tumours represent new primaries [33]. Second, contralateral primaries occur with increased frequency even in unirradiated patients with a past history of breast cancer [34]. Hence, although the added absolute risk of contralateral cancer for a 'cured' 40-year old receiving a dose to that side of 3 Gy [22] has been estimated as 6% after 30 years [10], the 'background' incidence of contralateral cancer over this period (15% in one postmastectomy series [34]) makes the additional radiogenic risk unlikely to be detectable [35]. Far from providing reassurance, this poses an ethical dilemma: does our inability to confirm a highly plausible, mathematically predictable yet potentially preventable incidence of second malignancies excuse complacency? Only an extended multicentre study is capable of resolving such uncertainties. In the meantime, data as to the tumorigenic effects of radiotherapy in long-lived survivors remain scarce [24].

HOW THE FUTURE INCIDENCE OF RADIOTHERAPY-INDUCED CANCERS MIGHT BE REDUCED

Luckily, the practical implications of these uncertainties are less daunting than their outright elimination. We and others [36] have noted that postradiotherapy second cancers tend to cluster around the outside edge of the radiation field (Epstein and Hanham, unpublished data), consistent with a critical subtherapeutic ('scatter') radiation dose predisposing to tumorigenesis. The magnitude of such adventitious irradiation (Figure 2) varies inversely with distance from the field edge but persists as a long 'tail' (approximately 0.5% total dose) at distances up to 50 cm [32, 37]. During breast radiotherapy, for example, shielding of collimator scatter from medial fields significantly reduces the contralateral dose, although shielding of the lateral field achieves little [37]. Fraass and colleagues have shown that differences in technique produce wide variations in contralateral breast dose (averaging 50–200 cGy) and that the use of portal imaging adds an extra 50 cGy; they conclude that good technique should reduce the contralateral dose to 50 cGy in total [32]. While the relevance of such measures is immediately applicable to premenopausal women undergoing adjuvant breast irradiation, there seems little reason why similar precautions should not become part of everyday radiotherapy practice for all patients with reasonable life expectancies. Indeed, such procedures are routinely implemented during gonadal protection and pregnancy, and already represent standard practice in many centres.

Contemporary radiotherapy planning seeks to minimise acute toxicity to normal tissues while including all tumour within the treatment volume. Given the safety concerns detailed here, it would seem wise to factor in longer-term iatrogenic morbidity when assessing treatment desirability in young patients with good outlooks—increasing numbers of whom may live three decades or more after radiotherapy. The extent to which some degree of local tumour prophylaxis can reasonably be sacrificed to offset carcinogenic risks is thus a central issue, although by no means a simple one. Notwithstanding that effective anticancer management rightly remains the therapeutic priority, we submit that the importance of strategies for minimising radiation scatter should not be underestimated. Systematic regional reviews of techniques used in such patients might be a useful first step towards this end, while further development of conformal radiotherapy—in which three-dimensional imaging allows the treatment volume to 'conform' more closely to the target, thus potentially reducing the dose of radiation scattered to normal tissues [38]—also seems sensible [13].

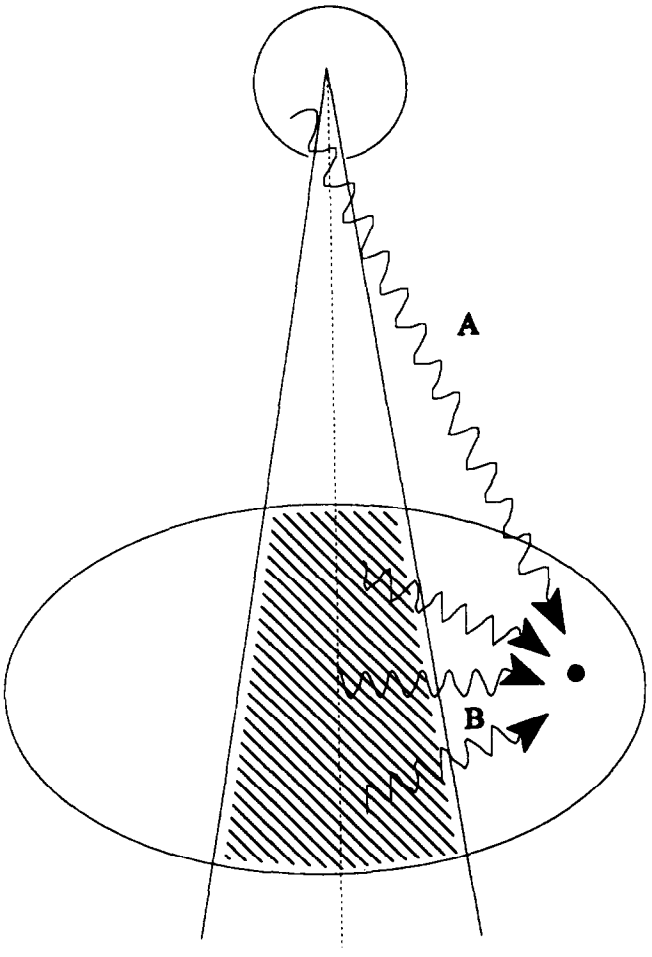

Figure 2. Origins of radiation scatter. Two radiation components contribute to the dose received by tissues outside the treated volume. Component A represents direct radiation originating from the treatment machine itself, and which may be due to leakage and scatter from collimators or wedges. The magnitude of such components may sometimes be reduced by direct shielding. Component B is made up of scattered radiation arising from the treated volume within the patient. The magnitude of this component, which falls rapidly with distance from the field edge, is dependent on the volume irradiated.

To recapitulate, the consequences of cell damage induced by ionising radiation depend upon a dynamic interplay between molecular and cellular variables currently being elucidated. No tissue is immune to radiocarcinogenesis, and increased incidence of many solid tumours is detectable 5–50 years after irradiation. High-dose (cell-killing) radiotherapy of target tissues appears less carcinogenic than subtherapeutic (scatter) radiation received by 'non-treated' tissues peripheral to the target field; however, tumour incidence within the latter tissues remains dose-dependent and scatter doses in many routine clinical settings reach the tumorigenic range. Hence, the long-term risk of radiation-induced second malignancies may well be reduced by minimising the dose to bystander tissues using measures such as optimal beam alignment, field size reduction and/or conformal techniques and (in some cases) shielding of non-treated regions. While empirical evidence confirming the benefit of this approach seems likely to remain elusive for the foreseeable future, implementation of such measures may now prove prudent in younger patients undergoing radiotherapy for potentially curable tumours. In this respect, the medical profession must not only be vigilant, but also be seen to be vigilant: reasoned acknowledgement that some degree of morbidity from 'friendly fire' is inevitable [39] should not be equated, however inadvertently, with passive endorsement of the 'killing fields'.

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