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Models for the risk of secondary cancers from radiation therapy

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ABSTRACT

The interest in the induction of secondary tumours following radiotherapy has greatly increased as developments in detecting and treating the primary tumours have improved the life expectancy of cancer patients. However, most of the knowledge on the current levels of risk comes from patients treated many decades ago. As developments of irradiation techniques take place at a much faster pace than the progression of the carcinogenesis process, the earlier results could not be easily extrapolated to modern treatments. Indeed, the patterns of irradiation from historically-used orthovoltage radiotherapy and from contemporary techniques like conformal radiotherapy with megavoltage radiation, intensity modulated radiation therapy with photons or with particles are quite different. Furthermore, the increased interest in individualised treatment options raises the question of evaluating and ranking the different treatment plan options from the point of view of the risk for cancer induction, in parallel with the quantification of other long-term effects. It is therefore inevitable that models for risk assessment will have to be used to complement the knowledge from epidemiological studies and to make predictions for newer forms of treatment for which clinical evidence is not yet available. This work reviews the mathematical models that could be used to predict the risk of secondary cancers from radiotherapy-relevant dose levels, as well as the approaches and factors that have to be taken into account when including these models in the clinical evaluation process. These include the effects of heterogeneous irradiation, secondary particles production, imaging techniques, interpatient variability and other confounding factors.

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1. Introduction

Better detection of cancerous lesions in earlier stages and developments of more effective treatment methods have increased the life expectancy for many cancer patients. This allowed a longer temporal window for the expression of late effects, including the induction of second cancers following radiation therapy [1]. Indeed, the risk for the induction of second cancers due to the irradiation of tissues has been a concern since the first decades of radiation therapy, with one of the first attempts to characterise and quantify the radiation induced tumours dating from 1948 [2]. Epidemiological studies on the patients treated in subsequent years [3–8] have shown that radiotherapy leads to a small but significant risk of inducing cancers which is often referred to as ‘the price of success’ for this treatment modality [9]. Consequently radiation is often described as a two-edged sword in relation to cancer, being capable of both sterilising tumour cells and inducing them through

the mutations they create [10]. Given this dual nature of radiation therapy, patients and clinicians alike are interested both in the success rates and the risks for the induction of secondary cancers that could be associated with their treatments. Thus, faced with several treatment options (treatment techniques, plans, radiation modalities etc.) that would lead to the same success rate, the natural approach would be to rank them and choose the one with the smallest risk. This is however not an easy task as most of the knowledge on the current levels of risk comes from patients treated many decades ago with radiotherapy techniques that are no longer in use. Indeed, irradiation patterns from historically-used radiotherapy and from contemporary techniques are quite different. Furthermore, the long latency time of carcinogenesis and the rapid developments in radiation therapy make it practically impossible to determine risks in clinical cohorts for each treatment modality. Therefore one would have to resort to modelling to extrapolate the existing knowledge to new treatment methods and techniques. This work aims to present a critical review of models, methods and approaches that could be used to predict the risk for secondary cancers from radiation therapy.

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2. Radiation carcinogenesis

Radiation induced cancers originate in viable mutations in genes that regulate cell growth, induced by the damage inflicted by radiation at the level of the DNA. Carcinogenesis is however a multistage process in which cells acquire specific capabilities that are considered the hallmarks of cancer [11,12]. The induction of the initial mutation is only the initiation stage of the carcinogenesis process, being followed by promotion in which the mutations are expressed and the malignant progression in which cells acquire other capabilities. The progression is a very slow process taking several years and this translates into a long latency between the initiation phase and the clinical manifestation of the disease. Not surprising, the first models for cancer induction have focused on the multistage character of carcinogenesis [13,14]. However, as it is thought that there is no predefined sequence for the acquisition of the genetic hallmarks and particular mutations may simultaneously confer several malignant capabilities [11], the length of the latency period may vary between individuals. Furthermore, other factors that have to do with hormonal activity or lifestyle may influence the rates of mutations and would therefore impact upon the carcinogenesis process. These aspects illustrate the difficulties faced both by epidemiologists and by modellers when trying to account for the factors that influence the appearance of cancers in both unirradiated and in irradiated individuals.

3. Modelling approaches for cancer induction following irradiation

In general modelling could be performed with several approaches. Thus, mechanistic modelling starts from the ground principles and processes that describe the operation and evolution of a system, while empirical modelling is based on observations of the evolution of the system. In between these two extremes of the modelling spectrum one could have combinations of basic processes and observations that would be described as either semi-empirical or semi-mechanistic modelling approaches. In particular to risk modelling, quantification could be performed either in terms of the excess absolute risk (EAR), the additional risk above the background absolute risk, or in terms of excess relative risk (ERR), the proportional increase in risk over the background absolute risk. Both approaches are used in radioprotection, but using the EAR has been preferred for risk reporting in radiotherapy as it avoids the dangers of overrepresentation of changes for very small absolute risks. This preference will be maintained in this review as well.

A purely mechanistic modelling of carcinogenesis would imply that each of the intracellular signalling processes and networks in the cell are mathematically described and the evolution of the system is the simultaneous solution of all the resultant equations. However, the large number of processes and parameters needed, including their modification by internal and external factors which is often not known, make this approach quite impractical for modelling carcinogenesis. Furthermore, some processes are probabilistic and may not be amenable to a deterministic description as implied by the mechanistic modelling.

Empirical modelling of radiation induced second cancers correlates epidemiological observations with dose determinations. The approach has been used for the analysis of cancer induction in the survivors of the atomic bombings of Hiroshima and Nagasaki. This group includes 90,000 persons of both sexes with a wide distribution of ages that received significant doses of radiation and were carefully followed throughout the years leading to several reports [15,16]. The atomic bomb survivors generally received a short-term exposure to a mixture of photons and neutrons.

Although uncertainties exist with respect to the precise doses to the survivors [17], the follow-up of the cohort has led to important conclusions regarding the carcinogenic potential of radiation and has created the foundations for the radiation protection practice. Thus, it has been concluded that irradiation leads to an excess of cancers in the irradiated population compared to an unirradiated one and that cancer induction is linearly correlated with radiation dose up to about 1–2 Gy. Furthermore, different tissues have different sensitivities and radiation protection reports list relevant coefficients for site-specific cancer incidence determinations [18–20].

Although very much used for radiation protection, the linear risk model is recommended to be applied only to populations of patients, not to individuals. The use of the effective dose, common in radioprotection, should also be avoided for risk assessment in individuals after medical exposures since these are often characterised by heterogeneous dose distributions [20]. Furthermore, extrapolations of the linear risk model outside the dose range from which it was derived are also subject to limitations. Currently, there is a debate regarding the relevance of the linear risk model for very low doses of radiation [21]. Similarly, the extrapolation of the linear risk model to dose levels relevant for radiotherapy also has some limitations. Thus, the use of a linear risk model implies a dose above which the risk probability is greater than 1 and this mathematical dilemma suggests that risk models deviate from linearity at high doses. Nevertheless, the linear approach from radioprotection has been used in some risk evaluations in radiotherapy [22]. These either separated the primary and scatter contributions and applied the linear model only to the latter [23,24] or applied the linear risk model to all but therapeutic doses [25,26]. The former approach underestimates the risk as the contribution of primary radiation is neglected and could lead to bias against treatment techniques characterised by a higher proportion of scatter radiation, as is for example the case of intensity modulated radiation therapy (IMRT) versus three-dimensional conformal radiation therapy (3D-CRT). The latter approach could also lead to erroneous risk estimations due to overrepresentation of the contribution of large doses and also falsely identifies the average or the integral doses as indicators of the risk for second cancer. Indeed, a nonlinear relationship between dose and risk would preclude the use of linear combinations of heterogeneous irradiation compartments for risk estimations. Nevertheless, it is important to mention that risk evaluations using the linear approach usually modify the risk factors from radioprotection with a dose and dose-rate effectiveness factor (DDREF) that accounts for the non-protracted delivery of radiation in radiotherapy [18].

Derivations of the shape of the dose-risk relationship for doses relevant for radiotherapy are quite difficult with empirical approaches because of the many confounding factors that have to be accounted for. Thus, data from radiation treatment patients is thought to provide the best estimates of the risk models for second cancers following radiotherapy [1], but there are significant uncertainties especially in dose gradient regions or caused by a number of other aspects like the inter-patient variations or the irradiation technique used, the fractionated delivery of the treatment that may favour repair of lesions and cell proliferation, the impact of adjuvant treatments and last, but certainly not least, the age distribution of the patients. Indeed, there is a scarcity of clinical data to set up epidemiological studies to account for all these factors and the rapid evolution of treatment techniques during the latency time of carcinogenesis would anyhow require the extrapolation of the findings to new treatment methods. In these conditions it appears that combinations of mechanistic and empirical approaches are the most promising for the development of risk models together with the incorporation of effects from factors that have been identified to influence the risk for second cancers in radiotherapy. Such an approach typically implies a reduction of

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