Physica Medica xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

Risk of secondary cancers: Bridging epidemiology and modeling

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ARTICLE INFO

Article history:
Received 29 December 2016
Received in Revised form 8 March 2017
Accepted 19 March 2017
Available online xxxx

Keywords:
Radiotherapy
Second primary cancer
Epidemiology
Modeling

ABSTRACT

Epidemiological studies of long term radiotherapy survivors provide useful insights into dose-response relationships for secondary cancer induction risk at high doses. There are uncertainties involved in estimating the dose to the location of the second malignancy, because the dose distributions in radiotherapy patients can be spatially highly heterogeneous and the size of the diagnosed tumor is on the order of a few cm. Therefor it is nearly impossible to obtain the exact dose corresponding to the exact tumor induction location and so organ specific dose-response relationships have large errors not only in the reported risk, but also in the estimated dose.

In this work two alternative methods are proposed for future applications involving investigations into dose response relationships for second cancer induction risk, the method of organ sub-division and the method of risk equivalent dose. The method of organ sub-division takes the inevitable inhomogeneous dose distribution into account by applying epidemiological methods to organ sub-divisions which have a nearly homogenous dose. The method of risk equivalent dose combines risk modeling and epidemiological data analysis. Risk models can be optimized by using an iterative procedure assuming a variation of organ specific dose-responses.

The advantage of the alternative methods is that the inhomogeneity of the dose in the organs at risk is taken into account. The second method has the additional advantage that the dose to the location of the tumor site must not be known and that epidemiologically obtained risks that were not stratified by organ specific risk can be used.

1. Introduction

In developed countries, more than half of all cancer patients receive radiotherapy (RT) at some stage in the management of their disease. However, a radiation-induced secondary malignancy can be a long-term side-effect of the success of curing, or at least controlling, the primary cancer. Therefore, there is increasing concern regarding radiation-related second cancer risks in long-term RT survivors and a corresponding need to be able to predict cancer risks at high radiation doses. Of particular interest are second cancer risk estimates for new radiation treatment modalities such as intensity modulated RT, intensity modulated arc-therapy and proton and heavy ion RT. The long term risks from such modern RT treatment techniques are unlikely to become manifest for many years, due to the long latency time for solid tumor induction and have therefore not yet been fully quantified.

Most information on the dose-response of radiation-induced cancer is derived from data on the Japanese A-bomb survivors who were exposed to gamma-rays and neutrons. In radiation protection, the dose span of main interest is between zero and one Gy, and since the analysis of the A-bomb survivors covers this range, this cohort is of particular relevance here.

With increasing RT cure rates for primary cancers, estimates of secondary cancer risk for tissues receiving doses larger than one Gy are becoming more relevant. Thus epidemiological studies of RT patients have been performed to determine the risk of second cancers. Unfortunately it is generally not possible to reliably distinguish cancers which were caused by radiation from those occurring spontaneously because the field of research into biomarkers for radiation induced cancers has to date only produced a few candidate biomarkers [1,2]. Thus, usually large cohort sizes are necessary to get statistically significant risk estimates. In epidemiological studies risk is often stratified by dose, which is necessary to obtain the dose response relationship. However a consequence of dose stratification is a reduction of statistical power.

One major difference between the A-bomb survivors and RT-patients is that the A-bomb survivors were irradiated with more

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http://dx.doi.org/10.1016/j.ejmp.2017.03.011
1120-1797/

uniform dose distributions in contrast to RT patients who are irradiated with highly non-uniform dose distributions, in particular in organs and tissues adjacent to the treated volume. The quantification of the correlation between dose and risk is affected by the uncertainties involved in relating a tumor which was induced decades after the treatment of the primary disease to the actual dose at the tumor site. A major reason for this is that the dose outside of the treated volume cannot be predicted by clinically used treatment planning systems [3–5]. Even if the dose is calculated by Monte Carlo methods or by empirical models based on measurements, the remaining uncertainty is of the order of 40% [5]. Additionally a dose prediction is problematic in regions of large dose gradients as illustrated in Fig. 1 where a dose profile through the breast for a typical treatment of Hodgkin's disease is shown with a hypothetical 2 cm diameter tumor location. However, a large number of second primary cancers, if not the majority, are located at the field borders of the original treatment fields [6–9]. In the regions of large dose gradients, it is difficult to estimate the dose at secondary tumor origin as the size of a diagnosed tumor is already of the order of a few cm and thus it is nearly impossible to pin-point the correct dose at the location of origin. Other dosimetric uncertainties include patient movement, the impact of fractionation on the dose distribution, anatomical changes and simplified dose reconstructions. Organ specific dose-response relationships are therefore subject to large uncertainties, not only for the obtained risk, but also for the estimated dose.

In this work two alternative methods are proposed for future applications involving investigations into dose-risk relationships for second cancer induction considering the unavoidable heterogeneity in the dose distribution. The first method incorporates the inhomogeneous dose distribution, by organ sub-division into sections where the dose is more or less constant, into the classical epidemiological approach. The other method is a combination of risk modeling and epidemiological data analysis. Risk models can be optimized in an iterative procedure by starting from a linear dose-response relationship for each organ. The risk model is convoluted with the dose-volume histogram of the whole organ at risk which yields a risk proportional quantity for the specific organ and the assumed dose-response relationship. The results are combined with the A-bomb survivor data and the dose-response relationship is modified until agreement between observation and model prediction is reached. The advantage of this method is that observed cancer risk used for modeling must not be dose stratified and is thus subject to smaller uncertainties. In addition the exact dose to the second tumor must not be known as the optimization of the dose-response model is performed by predicting a whole organ risk based on dose volume histograms.

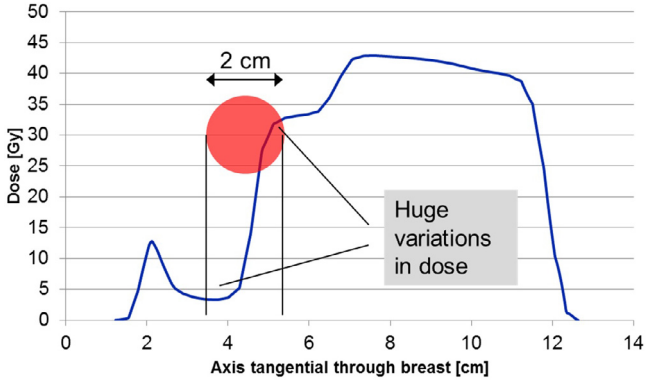

Fig. 1. Typical dose profile through the female breast for a radiotherapy treatment of Hodgkin's disease. The hypothetical secondary cancer site is marked with a red circle of 2 cm diameter. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Methods

2.1. Method of organ sub-division

When organs or tissues of interest are irradiated inhomogeneously the main question is: Which dose should be assigned to the organs in the people who did not get cancer, i.e., to the organs contributing person-years at risk, relevant to the determination of the baseline cancer rates? What is proposed here is some sort of organ sub-division into sections where the dose is precisely known for those persons with and without cancer – so instead of considering a particular organ as an entity for comparison – predefined organ sections can be considered as entities and the risks in these "organ sections" should be obtained first, before combining these to get the total organ risks. This would mean that each of those persons without cancer would provide "multiple comparisons", one for each cancer free organ section. A similar method was already proposed and applied to the Japanese A-bomb data by Walsh et al. [10,11] to obtain risks for all solid cancer per unit organ specific dose from the publicly available data that only gave colon doses. In past analyses of the A-bomb data all solid cancer risks had been based on colon dose and [12] had noted that "It is impossible to use more specific organ doses for solid cancers as a class, since there is no designated organ for those not dying of cancer." However this difficulty was resolved [10] by formally treating each person as a set of 13 sub-units at risk, each belonging to one organ category. In practical terms, this meant creating a new organ category at the lowest level of the data structure groups (for combinations of city, gender, age attained, age at exposure and colon dose category), each group containing the number of cases of death from different types of solid cancer. For each of these original data records, new organ-specific records were created to contain the numbers of deaths for each cancer type and the relevant organ-specific doses. So instead of having persons forming cancer-free comparison groups, one has a collection of organs forming comparison groups.

Of great importance here would be that a precise "organ section" dosimetry for those subjects with and those without cancer is available. Then it is possible to calculate the ERR and EAR from the number of secondary cancers, person-years at risk and the doses in these organ sections and then combine these sub-unit risks to obtain the overall risks to the organ.

2.2. Method of risk equivalent dose

Another, completely different method, to obtain the organ-specific second cancer risk after radiotherapy is based on the use of dose-volume histograms (DVH) which are frequency distributions of dose in a specific organ of interest. The main idea behind this is to avoid the difficult procedure of dose determination at the position where the tumor was initiated and to search for DVHs which are characteristic for tumor initiation. The concept is similar to equivalent uniform dose (EUD) as proposed by Niemierko [13] which provides a single metric for reporting non-uniform dose distributions. It is defined as the uniform dose that, if delivered over the same number of fractions as the non-uniform dose distribution of interest, yields the same radiobiological effect. A similar approach method was already proposed by Schneider and Walsh [14]. It is proposed here to apply a risk equivalent dose which is defined as a dose metric which is proportional to risk including fractionation and, if averaged over the whole organ, yields an organ equivalent dose (OED). Organ equivalent dose is then, by

Please cite this article in press as: Schneider U, Walsh L. Risk of secondary cancers: Bridging epidemiology and modeling. Phys. Med. (2017), http://dx.doi.org/10.1016/j.ejmp.2017.03.011