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Out-of-field doses in radiotherapy: Input to epidemiological studies and dose-risk models

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ABSTRACT

Out-of-field doses in radiotherapy have been increasingly studied in recent years because of the generally improved survival of patients who have received radiotherapy as part of their treatment for cancer and their subsequent risk of a second malignancy. This short article attempts to identify some current problems, challenges and opportunities for dosimetry developments in this field. Out-of-field doses and derived risk estimates contribute to general knowledge about radiation effects on humans as well as contributing to risk-benefit considerations for the individual patient. It is suggested that for input into epidemiological studies, the complete dose description (i.e. the synthesis of therapy and imaging doses from all the treatment and imaging modalities) is ideally required, although there is currently no common dosimetry framework which easily covers all modalities. A general strategy for out-of-field dose estimation requires development and improvement in several areas including (i) dosimetry in regions of steep dose gradient close to the field edge (ii) experimentally verified analytical and Monte Carlo models for out-of-field doses (iii) the validity of treatment planning system algorithms outside the field edge (iv) dosimetry of critical sub-structures in organs at risk (v) mixed field (including neutron) dosimetry in proton and ion radiotherapy and photoneutron production in high energy photon beams (vi) the most appropriate quantities to use in neutron dosimetry in a radiotherapy context and (vii) simplification of measurement methods in regions distant from the target volume.

1. Introduction

It has been well-known for many years that the inevitable doses delivered to non-target organs and tissues (out-of-field doses) in radiotherapy has the potential to induce second malignancies, but in the past, the long latent periods of 10–15 years coupled with poor prognoses made this an issue of relatively low priority. Radiotherapy, a key component of cancer therapy, has seen an impressive technological expansion in recent years, with the introduction of intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), proton and ion beam facilities. In parallel, the prognosis for many patients is more favourable and longer term survival is possible. This is particularly relevant for paediatric patients where 80% may be expected to survive for longer than 5 years [1,2]. The issue of radiotherapy-induced second cancers is now more prominent [3] with increasing efforts to quantify dose and risk to critical organs and tissues so that comparisons between treatment modalities can be explored and risks minimised.

Accordingly, epidemiological studies and mathematical models of out-of-field doses demand increasingly comprehensive dosimetry throughout the body, although uncertainties in the dose-risk relationships make it difficult to estimate the accuracy required. It is also clear that the risk models used to underpin legislation relating to the exposure of radiation workers [4,5] may not necessarily be appropriate for the medical exposures of individuals. New models may be necessary in radiotherapy and diagnostic imaging, where critical sub-structures and dose heterogeneities within organs may make the use of mean organ dose of questionable validity. Whichever dose-risk models become prominent, it is nevertheless assumed that the starting point for risk estimation is the absorbed dose in critical organs and tissues.

In photon radiotherapy, doses outside the target volume are caused by (i) scatter from the main beams within the patient (ii) scatter from the collimators and (iii) leakage radiation from the accelerator treatment head. At effective accelerating potentials of >8 MV, fast neutrons are also produced in the treatment head and enhance out-of-field doses. Numerous studies of out-of-field dose measurements are now available, although they are inevitably specific to the experimental conditions used and generalisation is difficult. A comprehensive review has been given by Xu et al. [6].

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2. Input of out-of-field doses to epidemiological studies

The requirements of epidemiological studies vary, and this will influence the type and number of required dose measurements. For example, a comparison of second cancers in two groups of prostate cancer patients, one receiving radiotherapy and the other receiving surgery (with no radiotherapy) can be carried out without detailed whole body dosimetry, provided that radiotherapy protocols are similar and that the patient populations are matched. Conversely, and particularly if absolute risks need to be estimated, the doses to multiple organs may need to be measured, so that the organ risks can be summed to give a total risk. Doses and risks to single organs may also be required, for example in assessing the risk to the heart, or the contralateral breast, from breast radiotherapy. Finally, the organ at risk may not be conveniently compact and easily identifiable by imaging, but be extended or disseminated throughout the body, e.g. bone marrow, skin.

In addition to providing benefits to patients by optimising treatments to minimize second cancers, the study of radiotherapy patient cohorts is an important field generally in the study of radiation effects on humans. Simon and Linet [7] identified four main attributes in the design of epidemiological studies of radiation-exposed populations:

1. *Population size must be adequate to meet statistical power considerations.* There are approximately 14 million new cancer cases per year worldwide [8] and over half of all cancer treatments will involve radiotherapy (in the developed world) [9], Very large radiotherapy patient cohorts are potentially available, even if sub-sets (e.g. paediatric patients) are chosen.
2. *There should be a large enough average dose and a wide enough dose range to derive a dose-response relationship*; In radical radiotherapy, treatment doses vary from tens of Gy (at the target) to tens of mGy (at the extremities). This range covers most of the dose-risk curve from high doses where non-linearity may be evident to low doses (where the linear no-threshold (LNT) relationship is often assumed).
3. *There should be an understanding and capability to determine or reliably estimate individual doses usually required for specific organs.* Radiotherapy target doses are accurately calculated, controlled and delivered with rigorous supporting QA and are well documented. However, out-of-field doses are not so extensively measured or calculated.
4. *The study should have potential value as determined by public health, clinical, or societal concerns.* In radiotherapy, there is a clear clinical need and basic radiation protection requirement for risk/benefit judgements to be made, either to provide an estimate of absolute risk of second cancer induction, or to compare radiotherapy treatment options, or indeed to compare radiotherapy risks with those from alternative treatments which do not involve the administration of ionising radiation.

3. The complete dose description and the need for a common dosimetry framework

For input to epidemiological studies of the effects of a given radiotherapy treatment, the total dose to the critical organs is ideally required and is referred to here as the complete dose description. This is the synthesis of therapy and imaging doses from all the treatment and imaging modalities employed. Radiotherapy modalities include those based on the linear accelerator, tomotherapy, GammaKnife, brachytherapy, robotic arm systems, proton and ion beams. Diagnostic systems are associated with radiotherapy planning (primarily CT, but also SPECT and PET) and also on-board kV or MV imaging which are used for frequent verification during the treatment period. For any particular treatment, usually not more than two therapy modalities will be used, but several imaging techniques may be required.

The complete dose description is particularly valuable in regions close to the radiotherapy field. Diallo [10] and Dörr and Herrman [11] have shown that the frequency of second cancers as a function of distance from the field edge is significantly peaked about the edge, i.e. most second cancers are seen within ±5 cm from the field edge. This is a region of steep dose gradient, with the highest doses in the region of the dose-risk curve which may be non-linear. Measurements in this region require small dosemeters if adequate spatial dose resolution is to be achieved. It has been shown that dose models in this region (for example those used by treatment planning systems) are not always accurate [12,13]. For a critical organ in this region, an estimate of the mean dose may not be sufficient; doses to sub-volumes (which may have differing radiation sensitivity, e.g. the coronary arteries of the heart) may also be required. A dosimetry methodology for organs close to, or overlapping, the target volume has been given by Howell [14].

Radiotherapy out-of-field doses have been commonly measured by simulating the treatment using an anthropomorphic phantom [15], or by applying measured water tank data. The latter technique has been extensively developed by Stovall et al. [16] and applied to numerous studies and thousands of patients. Matrices of out-of-field dose data were acquired for a comprehensive range of single beams, from orthovoltage X-ray energies to 25 MV photons for various field sizes and distances from the field. A 3-D mathematical model of patients covering a wide range of ages and shapes was generated by synthesizing each patient from a combination of regular geometrical shapes. The dose to a point in an organ of interest is calculated by positioning each radiation beam onto the mathematical model of the patient and calculating the distance to the point from the field edge and the surface. The dose at this point is then calculated from a mathematical fit to the measured 3-D dose matrix.

In contrast, organ doses in CT have been acquired by measurement of the Computed Tomography Dose Index (CTDI) [17] which is related to organ dose by prior Monte Carlo calculations using a mathematical phantom. Recent advances in the development of mathematical phantoms e.g. the National Cancer Institute dosimetry system for CT (NCICT), [18] have led to families of reference adult and paediatric phantoms which have been used in epidemiological studies. These phantoms represent increased realism compared with previous stylized mathematical phantoms based on simple mathematical shapes. Dabin [19], in a comparison of organ doses to a 5 year anthropomorphic phantom with corresponding calculations based on the NCICT system for five different scanners from four manufacturers, concluded that the difference between measured and simulated mean organ doses was generally within ±20%. Although this agreement is encouraging, current CT dosimetry methodologies do not address the issue of organ sub-volume dosimetry and mean organ doses are commonly quoted. When considering the combination of radiotherapy and CT imaging doses, this may be acceptable for organs far from the radiotherapy field edge, but the combined dose from radiotherapy and imaging is more relevant in regions near the field edge, as noted above. In this region, critical organs may overlap the field edges of both radiotherapy and imaging fields. Some authors have argued that the links between CTDI and organ dose, for the purpose of risk assessment, are too tenuous and have suggested that CT dose measurements in anthropomorphic phantoms should be adopted [20]. Dose distributions from a combination of therapy and imaging fields have been explored by Harrison et al. [21] and Hälg et al. [22]. The latter concluded that image-guided radiation therapy (IGRT) can be administered without increasing the dose outside

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