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Difficult cases for chromosomal dosimetry: Statistical considerations

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ABSTRACT

Several examples are selected from the literature in order to illustrate combinations of complicating factors, which may occur in real-life radiation exposure scenarios that affect the accuracy of cytogenetic dose estimates. An analysis of limitations in the current statistical methods used in biodosimetry was carried out. Possible directions for further improvement of the statistical basis of chromosomal dosimetry by specific mathematical procedures are outlined.

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1. Introduction

Dose estimates obtained by cytogenetics sometimes disagree with physical doses (calculated or directly measured) or, more importantly, with clinical symptoms in irradiated persons. The reasons can be either methodological or statistical in nature. Methodological problems are those that occur due to either incorrect implementation of the laboratory procedures or lack of data concerning cytogenetic mechanisms. Statistical problems can be defined as those requiring mathematical solutions.

Obviously, the initial step in resolving these difficulties must be clear recognition of the problems and their causes. The objectives of the present work were to classify combinations of complicating factors, which occurred in real-life scenarios of radiation exposure, and to examine how these affect the accuracy of biological dose assessment.

2. Methods

In an extensive literature review (Vinnikov et al., 2010) about 600 papers were selected detailing biodosimetry investigations following accidents, occupational exposure, radiotherapy, *in vitro* experiments for generating calibration curves, inter-laboratory comparisons and exercises involving accident simulations. When a discrepancy was found between reported cytogenetically derived doses and doses that were either measured physically or inferred from clinical symptoms, its cause was categorized as being due to methodological or statistical limitations. The problems of a statistical nature were then analyzed in order to identify their origins. Also for the present work several radiation exposure scenarios were specifically chosen from the literature in order to illustrate which combinations of complicating factors may occur in real-life situations and how these combinations affect the statistical aspects of data treatment for chromosomal dosimetry.

3. Results

3.1. Scenarios of radiation exposure and complicating factors

There are three main types of radiation exposure scenarios:

1. Normal occupational;
2. Medical: diagnostic or therapeutic;
3. Unplanned events: accidents and incidents of varying scale.

The magnitude and qualitative characteristics of radiation-induced cytogenetic effects in human cells differ drastically between these broad categories. Normal occupational and medical exposure scenarios provide an opportunity to establish a correlation between accumulated radiation doses and chromosome aberration yields directly from *in vivo* data. These results can be

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used for comparing genotoxicity or making dose-effect extrapolations for other similar groups/individuals, if needed. Obviously, no such predictive dose–responses can be generated empirically for accidental exposures.

Cytogenetic dosimetry in accident cases has been developed around an “ideal” exposure scenario – acute, homogeneous, whole body irradiation, which reflects the criteria normally used in setting up calibration curves *in vitro* (Table 1). The Poisson distribution has been traditionally used for modelling aberration data. This classic, frequentist approach considers the aberration yield as something fixed and thus provides a deterministic estimate of radiation dose and associated confidence limits (Szłuińska et al., 2007).

However, the ideal radiation exposure scenario occurs rarely in real life; instead a wide range of situations exists. For each of the factors listed in Table 1, a deviation from the “ideal” influences the results of biodosimetry through its own biophysical or cellular mechanism. Eventually, these different mechanisms lead to one of two general *statistical* problems: either (i) low numbers of aberrations, or (ii) deviations in aberration-per-cell distributions leading to over- or under-dispersion from the Poisson model (Table 2).

3.2. Main limitations of existing solutions

The classical formalism of cytogenetic dose–response curve fitting and subsequent converting aberration yields into dose estimates has remained essentially unchanged for a long time (Merkle, 1983). The most advanced version of this statistical approach for dose calculation and presentation of the confidence limits was reported by Szłuińska et al. (2007). The dicentric yield can usually be satisfactorily modelled with the Poisson distribution and thus can be converted into a Gaussian dose–probability profile, which by definition has normal confidence limits. The recorded physical dose can then be compared with this dose profile. However, the reverse calculation, i.e. modelling the aberration-per-cell distribution from a Gaussian probability profile of mean dicentric yield expected at a given dose, cannot be executed.

Classic dose–response models (LQ for low LET and linear for high LET) are inadequate when saturation begins to appear above 4 Gy.

The resolution power of cytogenetic dosimetry (the accuracy of discriminating between two doses) depends significantly on the dose range. For acute γ-rays one can distinguish between 0 and 250 mGy, or 250 and 500 mGy. However, the same magnitude of difference, i.e. 250 mGy, cannot be detected if the lower and higher dose values are, for example, 3.00 Gy and 3.25 Gy, respectively.

For mixed (low plus high-LET radiation) exposures a method exists to distinguish doses from γ-rays and neutrons in criticality accidents. However, no such methods exist for other scenarios, e.g. γ-rays plus heavy ions.

Aberrant lymphocyte elimination varies with time after irradiation. Amongst several suggested mathematical models, a bi-exponential model appears to be most biologically relevant. However, the speed of removal of aberrant cells from the lymphocyte pool positively depends on their initial frequency as well as the absorbed dose. Therefore, after exposure to clinically significant doses, any elimination model constructed from *in vivo* data can be considered as descriptive only, and aberration frequency measured in delayed samples cannot be directly converted into the ‘initially induced’ yield for retrospective dose assessment.

Table 1
The ideal exposure scenario for cytogenetic biodosimetry.

Factor	The ideal scenario
Time delay for blood sampling	1–5 days
Protraction of exposure	Acute irradiation
Homogeneity of exposure	Total body, homogeneous
RBE	Low LET
Source	External
Dose range	0.2–4.0 Gy
Number of potentially irradiated individuals and workload conditions	Up to 5 persons; 500–1000 metaphases per sample scored in one accredited laboratory

Dolphin’s Contaminated Poisson Method (CPM) and Sasaki’s Qdr technique are based on aberration-per-aberrant-cell yield and provide estimates of the mean dose to the irradiated fraction of lymphocytes (IAEA, 2001). That is too simplistic for graded doses (i.e. gradient dose distributions), which are very frequent in real-life situations. Also, CPM and Qdr both require a sufficient number of cells with $\geq$2 dicentrics and centric rings to be present.

When radiation exposure is protracted *and* inhomogeneous, biological doses are frequently underestimated due to:

- using CPM or Qdr methods in acute irradiation mode (i.e. ignoring protraction of exposure);
- using the G-function correction in total body irradiation mode (i.e. not considering partial-body nature of exposure).

In trying to overcome the limitations of CPM and Qdr in the situation when a dose gradient from high to low occurs, it was suggested to use an approach of unfolding mixed Poisson distribution (Nugis, 2003; Sasaki, 2003). This approximates the entire lymphocyte population to a mixture of fractions, each homogeneously irradiated to a particular dose with its own Poisson distribution of aberrations. Sources of statistical uncertainty arising in such cases are: (i) the number of co-existing lymphocyte fractions must be arbitrarily assigned; (ii) the most appropriate approach of stratifying the lymphocyte population (into equal dose intervals or graded) must be chosen; (iii) each lymphocyte fraction must be corrected for interphase survival and mitotic delay.

Moreover, a dose-related DNA damage-induced G2/M checkpoint arrest in cells irradiated to higher doses is combined with an aberration burden-related mitotic delay in cells irradiated to lower doses. Technical solution to this problem can be proposed as a laborious process of multiple fixation regimes. However, to date, no algorithm has been suggested for dealing with uncertainties associated with these two reasons for mitotic delay, if aberration data from two or more fixation points are combined.

3.3. Examples of “nightmares of chromosomal biodosimetry”

Usually in real-life events both categories of statistical limitations occur simultaneously, because several complicating factors act together. Examples are as follows.

3.3.1. Radiation workers with a long history of chronic external exposure to low doses of γ-rays and additional irradiation from internally deposited α-emitting ^{241}Am (Bauchinger et al., 1997)

Complicating factors: chronic exposure, presence of high-LET component; internal emitter with inhomogenous distribution in the body; irradiation within low dose range.

Statistical problems: high uncertainty of individual dose estimates due to low number of aberrations and inability to discriminate the high-LET component because the aberration distribution was Poisson.

3.3.2. Chernobyl clean-up workers (Maznyk et al., 2003)

Complicating factors: protracted and fractionated exposure to low doses; very high number (thousands) of irradiated individuals; very high workload requiring triage style analysis.

Statistical problems: very large uncertainty of individual dose estimates due to low number of aberrations. This prevented accurate

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