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Research Article

Dose assessment by quantification of chromosome aberrations and micronuclei in peripheral blood lymphocytes from patients exposed to gamma radiation

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Abstract

Scoring of unstable chromosome aberrations (dicentrics, rings and fragments) and micronuclei in circulating lymphocytes are the most extensively studied biological means for estimating individual exposure to ionizing radiation (IR), which can be used as complementary methods to physical dosimetry or when the latter cannot be performed. In this work, the quantification of the frequencies of chromosome aberrations and micronuclei were carried out based on cytogenetic analyses of peripheral blood samples from 5 patients with cervical uterine cancer following radiotherapy in order to evaluate the absorbed dose as a result of partial-body exposure to ^{60}Co source. Blood samples were collected from each patient in three phases of the treatment: before irradiation, 24 h after receiving 0.08 Gy and 1.8 Gy, respectively. The results presented in this report emphasize biological dosimetry, employing the quantification of chromosome aberrations and micronuclei in lymphocytes from peripheral blood, as an important methodology of dose assessment for either whole or partial-body exposure to IR.

Key words: chromosome aberrations, micronuclei, biodosimetry, partial-body irradiation, lymphocyte.

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Introduction

Absorbed dose is the most important physical quantity for evaluating potential biological response as a result of exposure to ionizing radiation (IR). Physical dosimetry is commonly performed by instruments that are sensitive to the physical effects of IR. However, in most cases involving real or suspected accidental exposure, people are not wearing a dosimeter and, as a result, physical dosimetry is not straightforward. For such situations, the study of early biological effects induced by an exposure to IR has been proposed as either a complementary or an alternative method for dose assessment (Downing, 2000; Amaral, 2002; Bonassi and Au, 2002; Ramalho and Nascimento, 1991; Ramalho *et al.*, 1995; Voisin *et al.*, 2001).

Biological dosimetry (biodosimetry) is based on the investigation of radioinduced biological effects (bioindicators) in order to correlate them with the radiation dose. Among the bioindicators employed in biodosimetry, the scoring of chromosome aberrations (CA) is the most reliable method for evaluating individual exposure (Du Frain *et al.*, 1980; Bender *et al.*, 1988; Voisin, 1997; Albertini *et al.*, 2000). Scoring of radio-induced CA from peripheral blood lymphocytes has been developed into a valuable dosimetric tool in radiological protection (IAEA, 2001). In particular, unstable CA (dicentrics, rings and fragments) are generally considered as specific to radiation exposure, and these types of aberrations are referred to as unstable CA because of their persistence in the body decline with cell division cycles (Amaral, 2002).

On the other hand, micronuclei (MN), a kind of unstable CA byproduct, are cytoplasm chromatin masses that arise from centric or acentric products of damaged chromosomes. They have the appearance of small nuclei, in addition to the cell's nucleus (Köksal *et al.*, 1996; Uma Devi *et al.*, 1998; IAEA, 2001), and they are identified during the division of mitogen-activated human lymphocytes by blocking cytokinesis (Uma Devi *et al.*, 1998). As the scoring of MN is more sensitive and faster than the scoring of CA, improvements in MN methodology for biodosimetry have been tested (IAEA, 2001).

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For dose assessment purposes, the choice of the circulating lymphocytes in human blood is adequate because samples are easily obtained from the peripheral blood and the vast majority of peripheral lymphocytes reside in the G_0 phase of the cell cycle, representing a cell population which is predominantly in a DNA presynthetic stage. When mitogen stimulation converts these resting lymphocytes into cycling cells, DNA lesions can be visualized in the metaphase chromosome (Lindholm, 2000).

Biological dosimetry using the analysis of unstable chromosomal aberrations in human lymphocytes from peripheral blood is well established and accurate, especially in the case of acute exposure, and when the blood samples are obtained within few days after the real or suspected radiation exposure (Lucas, 1997; IAEA, 2001; Camparoto *et al.*, 2003).

As in most cases of accidents involving exposure to ionizing radiation concern partial-body irradiation, the goal of this work was to evaluate the scoring of the frequency of CA and MN, in circulating lymphocytes, for dose evaluation in such situations. Thus, this study was carried out based on cytogenetic analyses of peripheral blood samples from patients with cervical uterine cancer following treatment based on partial-body irradiation with ^{60}Co.

Material and Methods

Patients

The studied group was composed of five women under treatment for cervical uterine cancer at the Radiotherapy Department of the *Hospital do Câncer* (Recife, Brazil). All patients (ages varying between 40 and 59) provided written informed consent before the beginning of this study, for approval from the ethical practices committee of that Hospital. None of the studied individuals had been exposed to IR in the two years before the radiotherapy.

Radiotherapy and dosimetry

No changes in the hospital's protocol for patient treatment were made because of this research. Details such as dose and dose-rate delivered to the patients were provided by the physician responsible for the treatment in that hospital. The same protocol for radiotherapy was employed for all patients included in this study. Primarily, 0.08 Gy was delivered to the patient's irradiated volume during the phase of tumor localization. Henceforth, for each radiotherapy session, a mean dose of 1.8 Gy was delivered to the irradiated volume of the patient, using a source of ^{60}Co (dose-rate: 0.33 cGy.min^{-1}).

Lymphocyte sampling

The patient's blood samples were obtained in sterile heparinized tubes. 5 mL of peripheral blood were collected prior to any medical radiation exposure. Similarly, equal volumes of blood samples were collected 24 h after tumor localization and the first radiotherapy session, respectively. From each patient, blood samples were obtained in three different situations, corresponding to the absorbed doses of 0.0 (background radiation), 0.08 and 1.8 Gy. The samples were transported to the cytogenetic laboratory (HEMOPE - Recife, Brazil), in an ice bath, according to IAEA recommendations (2001). Although the protocol included additional radiotherapy sessions, in the present work only the three cited phases of the treatment were taken into account.

Culture set up for CA analyses

For the chromosome aberration studies, 0.3 mL of the blood samples were cultured for 48 h, in a humidified atmosphere containing 5% CO_2, at 37 °C. The culture medium consisted of 4 mL of RPMI-1640 (Sigma-Aldrich, Irvine, UK) supplemented with 20% fetal bovine serum. Besides this, 0.1 mL of phytohemagglutinin (PHA-Gibco BRL, Grand Island, NY) was added to stimulate cell division. To block the mitotic process of the cells at the metaphase stage, Colcemid (Gibco BRL) was added for the last 2 h of culture at a final concentration of 0.1 μg/mL. The cells were harvested, given hypotonic shock treatment with 75 mM KCl and fixation with methanol-acetic acid (ratio 1:4 v/v). Slides were prepared for each sample and stained with 10% Giemsa (Merk) and mounted. The number of aberrations was observed under an Olympus microscope, using the 100x objective, and a cell was considered as aberrant if it had one or more unstable CA (dicentric, rings and chromosome fragments).

Culture set up for MN analyses

The presence of MN in a binucleated cell was assayed by blocking the cell at the cytokinesis stage as described by Fenech and Morely (1985). Peripheral blood lymphocytes were cultured for 72 h, in a humidified atmosphere containing 5% CO_2, at 37 °C; to this, a blood sample of 0.3 mL was added to the culture medium, which consisted of 4 mL of RPMI-1640 (Sigma-Aldrich, Irvine, UK) supplemented with 20% fetal bovine serum. Besides this, 0.1 mL phytohemagglutinin (PHA-Gibco BRL, Grand Island, NY) was added to stimulate cell division. To block the cells at the telophase stage, citocalasine-B was added for the last 24 h of culture at a final concentration of 5 μg/mL. Harvesting involved isotonic shock with NaCl (0.9%) and fixation with acetic acid (ratio 1:4 v/v), slides were prepared for each sample and stained with 10% Giemsa (Merk). The investigation into the number of MN was observed under an Olympus microscope using the 100x objective.

Results and Discussion

Chromosome aberrations

Table 1 presents the number of unstable CA (dicentrics and fragments) in lymphocytes, as well as their

Table 1 - Distribution of unstable CA (dicentrics and fragments) for absorbed doses of 0 Gy (background), 0.08 Gy and 1.8 Gy.

Dose (Gy)	Patient (age)	CS	NCA	ND	NF	FD	FCA
0	A (40)	1000	1	1	0	0.0010	0.0010
	B (42)	1000	1	1	0	0.0010	0.0010
	C (44)	1150	2	1	1	0.0009	0.0017
	D (53)	1000	1	1	0	0.0010	0.0010
	E (59)	1200	2	2	0	0.0017	0.0017
	Mean ± SD					0.0011 ± 0.0003	0.0013 ± 0.0004
0.08	A (40)	450	1	1	0	0.0022	0.0022
	B (42)	610	1	1	0	0.0016	0.0016
	C (44)	550	1	1	0	0.0018	0.0018
	D (53)	501	1	1	0	0.0020	0.0020
	E (59)	820	2	1	1	0.0012	0.0024
	Mean ± SD					0.0018 ± 0.0004	0.0020 ± 0.0003
1.8	A (40)	280	11	4	7	0.0143	0.0393
	B (42)	282	11	5	6	0.0177	0.0390
	C (44)	214	8	3	5	0.0140	0.0374
	D (53)	200	9	4	5	0.0200	0.0450
	E (59)	260	10	4	6	0.0154	0.0385
	Mean ± SD					0.0163 ± 0.0025	0.0398 ± 0.0030

CS - cell scored; NCA - number of unstable chromosome aberrations; ND - number of dicentrics; NF - number of fragments; FD - frequency of dicentrics; FCA - frequency of unstable aberrations.

frequencies for all patients, before radiation exposure, and after receiving doses of 0.08 and 1.8 Gy, respectively.

In the case of the 0 and 0.08 Gy, the number of fragments was negligible, and the results concerning the frequency of dicentrics and the frequency of total unstable CA were obviously the same. Fragments were observed as a result of the exposure to the dose of the 1.8 Gy, which justified the difference between dicentric and total CA frequency.

For evaluating the mean absorbed dose in the irradiated volume based on these results, Eq. (1) was employed, which was experimentally obtained by Lloyd *et al.* (1986), by following *in vitro* irradiation of blood samples and using the protocol suggested by the International Atomic Energy Agency (IAEA, 1986). In this study the authors investigated whole-body exposures through the scoring of the frequency of unstable CA (dicentrics, rings and chromosome fragments) by *in vitro* blood irradiation with ^{60}Co (dose-rate 0.5 Gy.min^{-1}) of fresh human blood from a panel of healthy volunteers, obtaining the following calibration curve:

$$Y = 0.001 + 0.0164D + 0.0493D^2 \quad (1)$$

In the above equation Y represents the frequency of unstable CA (dicentrics and fragments) scored after irradiation as a function of the dose D in grays (Gy).

To relate the frequency of CA obtained experimentally with those predicted by Eq. (1), one must considerer that 24 h after partial-body exposure to ^{60}Co, the irradiated lymphocytes will be redistributed in peripheral blood, since the organ-circulating blood turnover takes about 30 min (IAEA, 2001). Next, taking into account a homogeneous distribution of blood in the human body (Milnor, 1974), it can be inferred that 24 h after irradiation the frequency of unstable chromosome aberrations in peripheral blood will be proportional to the percentage of the patient's irradiated volume. According to the data from the planning of dose distributions, the irradiated volume of each patient corresponded to about 1/5 of the total volume of their bodies.

Based on the above remarks, one can compare the frequencies of CA obtained experimentally and those predicted directly by substituting the dose value in Eq. (1). However, as the frequency of CA obtained from blood samples is a result of a partial-body exposure, the values shown in Table 1 for the frequency of CA (FCA) must be multiplied by 5 to correlate it with a whole-body exposure for it to be in agreement with the frequency of CA predicted by Eq. (1). Obviously, this reasoning is not applied to spontaneous aberrations (background) that depend only on natural radiation. Table 2 summarizes this comparison.

For the dose of 0.08 Gy, there is a great difference between the frequencies experimentally obtained and those predicted by Eq. (1). The relationship between the accuracy of this method is strongly dependent on the number of metaphases scored. For example, a detection limit of about

Table 2 - Comparison between estimated and experimental frequencies of unstable CA.

Dose (Gy)	$\overline{Y}$ (predicted by Eq. (1))	Y (this work*)
Background	0.0010	0.0013
0.08	0.0026	0.0100
1.8	0.1900	0.1990

*After considering the irradiated volume of the body.

0.2 Gy is related to the analysis of 500 metaphases (Voisin, 1997), which is the case here.

Micronuclei

Table 3 shows the scored binucleated cells (SBC) and micronuclei (SMN), as well as the frequency of MN (FMN) in lymphocytes for the same blood samples. FMN is expressed as a percentage ratio of the total number of MN to the observed binucleated cells.

To investigate whole body exposures, Voisin *et al.* (2001) studied the frequency of MN by *in vitro* blood irradiation with ^{60}Co (dose-rate 0.5 Gy.min^{-1}) of peripheral blood samples from 47 healthy individuals (ages varying from 25 and 30), obtaining the following calibration curve:

$$Y = 0.012 + 0.071D + 0.028D^2 \quad (2)$$

Here, Y represents the frequency of MN noted after irradiation as a function of the dose D, in grays (Gy).

Table 3 - Distribution of the frequencies of micronuclei for the absorbed doses of 0 Gy (background), 0.08 Gy and 1.8 Gy.

Dose (Gy)	Patient (age)	SBC*	SMN*	FMN*
0	A (40)	1200	01	0.0008
	B (42)	1140	01	0.0009
	C (44)	1500	02	0.0013
	D (53)	1000	01	0.0010
	E (59)	1820	03	0.0016
	Mean ± SD			0.0011 ± 0.0003
0.08	A (40)	1415	03	0.0021
	B (42)	1000	02	0.0020
	C (44)	1500	03	0.0020
	D (53)	1400	03	0.0021
	E (59)	1640	04	0.0024
	Mean ± SD			0.0021 ± 0.0002
1.8	A (40)	1000	41	0.0410
	B (42)	1000	52	0.0520
	C (44)	450	21	0.0477
	D (53)	1000	55	0.0550
	E (59)	1200	79	0.0658
	Mean ± SD			0.0523 ± 0.0092

*SBC - Scored Binucleated Cells; SMN - Scored Micronuclei; FMN - Frequency of Micronuclei.

Using Eq. (2) to predict the frequency of MN, one obtains 0.018 and 0.230 respectively for the absorbed doses of 0.08 and 1.8 Gy (Table 4). In order to compare the predicted frequencies with the ones shown in Table 3, one must remember that all patients were partially exposed to IR. As for chromosome aberrations, 24 h after irradiation the exposed lymphocytes are expected to be homogenously distributed in the patient's body. As a result, the frequency of MN is therefore about 1/5 of the value predicted by Eq. (2). Thus, to compare the frequency of MN experimentally obtained with those predicted from Eq. (2), one should multiply the experimental values by 5, following the same reasoning as for chromosome aberrations. The results to dose of the 1.8 Gy are in good agreement with each other as summarized in Table 4.

Observing the background level (0.012) in Eq. (2), one may infer that in the group used to determine the equation the spontaneous frequency of MN is higher than the similar frequency obtained from the group investigated is this work (0.0011). This may justify the great difference observed between the values presented for the expected frequencies of MN and those obtained in this work. On the other hand, disregarding the background level in this equation to predict the frequency of MN, for dose of 0.08 Gy, yields a result of 0.006, which is in better agreement with the experimental value of 0.010 (Table 4) than the analyses by chromosomal aberration. Indeed, several works have shown that the detection limit of the methodology based on scoring of MN is lower than that of chromosome aberrations (Voisin, 1997; Voisin *et al.*, 1999; IAEA, 2001).

This work was designed to investigate the use of both methodologies (scoring of CA and MN) for dose evaluation from a simulation of a partial-body exposure to IR. This was possible due to the characteristics of treatment and health conditions of each subject. Although all patients presented a diagnosis of cervical cancer, the reason for choosing them was judicious because their general health aspects were appropriate for the objective of this research. The normal leucogram test was the basic parameter for inclusion of each of the 5 patients. For all patients, the results obtained for spontaneous chromosome aberrations and micronuclei (Tables 1 and 3), corresponding to an individual exposure to background radiation, are in good agreement with those presented in literature. This contributes to the fact that those

Table 4 - Comparison between the values expected by Eq. (2) and the frequency of micronuclei obtained in this research, considering partial-body exposure.

Dose (Gy)	$\overline{Y}$ (predicted by Eq. (2))	Y (this work*)
Background	0.012	0.0011
0.08	0.018	0.010
1.8	0.230	0.262

*After considering the irradiated volume of the body.

patients can be considered healthy individuals that were partially exposed to ionizing radiation.

To interpret the scoring of either CA or MN in terms of radiation dose, a calibration curve (frequency of CA or MN *versus* dose) is necessary. For this interpretation, calibration curves obtained in vivo and in vitro were employed. In fact, since the radiosensitivity of lymphocytes *in vitro* and *in vivo* are the same, the dose-effect relationship obtained after *in vitro* irradiation of blood (as in the case of Eq. (1)) can therefore be used to estimate effects from an irradiation *in vitro* (IAEA, 2001).

Comparing the two methods in terms of material, similar material is employed in both, differing only in the time of cell culture and in the application of the citocalasine-B. Therefore, the requirements to implement one or the other are almost identical. In terms of workload, the MN method is faster than chromosome aberrations. For example, in conducting this work, the average number of metaphases observed per day was about 150 compared to 800 binucleated cells.

In this context, scoring of CA and MN can be extremely useful in the immediate response to accidents, where initial information is often confusing or scarce. For example, Lloyd and co-workers suggest an approach in which only 20 and 50 cells need to be scored initially, for medical triage of whole body and partial-body irradiation, respectively (Lloyd *et al.*, 2000). Based on this approach one can reduce the counting workload.

Both methods reported in the present work can be improved with the employment of the Fluorescent *In situ* Hybridization (FISH) technique, which allows marked nucleic acid probes to be visualized on target tissues, cells, nuclei, and chromosomes so accurately that specific nuclei acid sequences can be located in the biological structure observed. On the basis of the FISH technique, using a pan-centromeric probe, the observation of dicentrics is an indisputable advantage in terms of speed and simplicity compared to the drawbacks of the conventional "G banding" technique. However, FISH methodology remains an expensive technique and it is not essential in terms of medical-legal evaluation, where the length of time spent for scoring of either CA or MN does not represent a crucial parameter, as in the case of expertise in radiation protection.

Conclusion

In response to radiation accidents, dose estimates are crucial for risk assessment, as well as for clinical planning of treatment of highly exposed victims. In many accidents initial information generally becomes available only after detailed, and ambiguous, dose reconstruction. The results presented in this work point out that the scoring of either chromosome aberration or micronuclei are reliable methodologies for investigating exposure to ionizing irradiation, such as partial-body ones. However, according to the methodology presented and discussed here, more knowledge about the irradiated part of the individual is necessary. Apart from precise dose reconstructions, biodosimetry can also be used in the immediate response to accidents, where few cells need to be scored initially, and for medical triage of whole body and partial-body irradiation, respectively. In this case, this would play an important role in national emergency responses to a large-scale accident where many persons may have been exposed.

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