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To cite this article: K E Ekstrand and R L Dixon 1982 Phys. Med. Biol. 27 407

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Lymphocyte chromosome aberrations in partial-body fractionated radiation therapy

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Received 22 July 1981, in final form 30 October 1981

Abstract. A relationship between lymphocyte chromosome aberration yields which occur in partial-body fractionated radiation therapy and those yields measured in vitro is derived. These calculations are applied to the case of patients undergoing radiation therapy for mammary carcinoma.

1. Introduction

In conjunction with a series of measurements being carried out at our institution on radiation induced lymphocytopenia in cancer patients, a method has been developed for estimating the dose received by recirculating lymphocytes during a course of fractionated external beam radiotherapy (Ekstrand et al. 1981). After the publication of this work we received a suggestion from Dr Helen Q Woodward of the Memorial Sloan–Kettering Cancer Center that our procedure might be used to calculate the production of chromosome aberrations appearing in peripheral blood lymphocytes of cancer patients who have undergone a course of radiation therapy. The determination of the relationship between the yield of chromosome aberrations during partial body irradiation and that observed in vitro would be helpful in establishing lymphocyte chromosome aberration counting as a form of biological dosimetry (Lloyd 1978). The purpose of this work is the demonstration of the applicability of our calculation procedure to this problem.

2. The calculation of the surviving fraction of lymphocytes

During any single treatment in a course of localised radiation therapy only a fraction of the lymphocytes will lie within the radiation field. Lymphocytes are distributed throughout the body principally in the lymph nodes, spleen, bone marrow, thymus, and the lymphoid tissue of the gut. Trepel (1974) has estimated the distribution of lymphocytes within these compartments and other tissue in the normal adult human. Changes in the physiological state of an individual can alter this distribution, but at present these alterations are known only qualitatively.

Aside from those that are circulating in the blood, the lymphocytes remain stationary during a single radiation treatment and therefore, if the distribution of dose throughout the treatment volume is uniform, all the lymphocytes which are exposed will receive the same dose. Typically the time between treatment fractions is at least 24 hours. This is sufficient for the lymphocytes to redistribute themselves, either within or
outside the radiation field. Lymphocytes within the blood do not receive a uniform dose during a treatment since they move in and out of the field. Since so few lymphocytes are in the blood at any one time (2.2% of the total number), and since these cells receive only a small portion of the daily dose, for the sake of simplicity we shall consider these cells outside the radiation field.

Let $F(N, I)$ be the fraction of lymphocytes which have been in the radiation field $N$ times and have survived interphase death after the patient has received $I$ treatments. These fractions can be expressed in terms of their values after $I-1$ treatments according to the equation

$$F(N, I) = (1-r) F(N, I-1) + r \cdot q \cdot F(N-1, I-1)$$

where $r$ is the fraction of cells within the field in any one treatment and $q$ is the fraction of cells surviving interphase death after having been exposed. In making use of the above equation we are assuming that for each cell $q$ is independent of previous exposure. The survival curve for lymphocytes is well represented by a simple exponentially decreasing function (Lloyd et al 1973). We may therefore express the surviving fraction by

$$q = \exp(-D_1/D_0)$$

where $D_1$ is the daily dose and $D_0$ is the dose for which the surviving fraction is $1/e$. This representation of $q$ is not necessary for our general formalism however. Survival curves with a shoulder, indicating the repair of radiation damage, are equally applicable in equation (1) as long as the shape of the single-exposure survival curve is not altered by previous exposures. It has been shown, however, that fractionation has no effect on the radiation induced interphase death of lymphocytes (Virsik et al 1980). For this reason, and for the sake of simplicity, we will use equation (2) to evaluate $q$ in this work.

The technique for solving equation (1) has been described in our earlier paper. The solution is

$$F(N, I) = 1 - (1-r) \sum_{N=0}^{I} \frac{I!}{N!(I-N)!} (1-r)^N r^N.$$ 

The total fraction of lymphocytes which have survived $I$ treatments is

$$F = \sum_{N=0}^{I} F(N, I) = (1-r+qr)^I.$$ 

3. The calculation of chromosome aberration yield

The yield of chromosome aberrations per lymphocyte for in vitro irradiation has been successfully fitted to the relation $Y = \alpha D + \beta D^2$ (Leonard and Gerber 1977). For dicentric plus ring aberrations $\alpha = 0.0521 \pm 0.03$ and $\beta = 0.0707 \pm 0.0081$ if the dose, $D$, is expressed in grays. For those cells which have been exposed $N$ times and survived, the yield of aberrations will be

$$Y(N) = \alpha N D_1 + \beta N^2 D_1^2.$$ 

Equation (4) does not account for the effect of the repair of chromosome damage between fractions. Sasaki (1978) has indicated that repair does not take place except in the case of activated lymphocytes or lymphocytes exposed in an artificial medium. Other researchers have disputed this (Virsik and Harder 1980). They found, however, that when repair does occur it is virtually complete within two hours of the irradiation.
The values for \( \alpha \) and \( \beta \) cited above were measured up to two hours after irradiation (Leonard and Gerber 1977), and it would therefore seem that, by the use of these values, repair has been incorporated into the model. It is clear, however, that further work is needed with respect to this point.

After \( I \) treatments the average yield of aberrations will be

\[
\bar{Y} = \alpha D_1 \bar{N} + \beta D_1^2 \bar{N}^2
\]

(5)

where

\[
\bar{N} = \frac{\sum_{N=0}^{T} N^K F(N, I)}{\sum_{N=0}^{T} F(N, I)}.
\]

(6)

For \( K = 1 \) or \( K = 2 \) we can evaluate equation (6) as

\[
\bar{N} = \frac{qrI}{(1-r+qr)}
\]

\[
\bar{N}^2 = \frac{q^2 r^2 I^2 + qr(1-r)I}{(1-r+qr)^2}.
\]

Equation (5) can then be rewritten as

\[
\bar{Y} = \alpha'(D_1 I) + \beta'(D_1 I)^2
\]

(7)

where

\[
\alpha' = \frac{\alpha qr(1-r+qr) + \beta D_1 qr(1-r)}{(1-r+qr)^2}
\]

(8)

and

\[
\beta' = \frac{\beta qr^2 r^2}{(1-r+qr)^2}.
\]

(9)

Thus we see that if the yield of aberrations is expressed in terms of total local dose received by the patient, the proportionality factors for the linear and quadratic terms are modified. It should be noted that \( \alpha' \) has terms arising from both \( \alpha \) and \( \beta \). Thus, even if in vitro \( \alpha = 0 \), there can still be a significant linear term in equation (7). It should also be noted that if \( r \) is small the linear term will predominate over the quadratic term. This point will be demonstrated in the next section.

4. Comparison with observations

To compare our calculations with observations in patients we require that the irradiated volume (and therefore the fraction of lymphocytes within the irradiated field) be constant over the course of treatments and that the dose be uniform throughout the irradiated volume. The data of Antoine et al (1981) on lymphocyte chromosome aberrations in patients irradiated for mammary carcinoma fit these criteria well. To apply equations (8) and (9) we must determine the parameters \( r \) and \( q \). There are two approaches which one can take to evaluate \( r \), the fraction of lymphocytes within the field. One is to estimate the amount of lymphocyte-bearing tissues within the field and then use the data of Trepel (1974) on the distribution of lymphocytes within each lymphoid compartment. We will instead take an alternative approach and use the observations of Idestrom et al (1979) on the lymphocytopenia produced in post-mastectomy patients who were irradiated in a manner similar to that of Antoine et al
We first determine $q$ for these patients. The daily dose was 1.8 Gy. The data of Trowell (1952) indicate a $D_0$ for interphase death in lymphocytes of 2.16 Gy. From these values we calculate a $q$ of 0.435. After 25 treatments the surviving fraction of lymphocytes was 0.35. Therefore from equation (3) we have $(1 - r + 0.435r)^{25} = 0.35$. From this we obtain $r = 0.073$.

The patients of Antoine et al (1981) received a daily dose of 2.0 Gy. For these patients $q = 0.40$. Using these values and the in vitro values for $\alpha$ and $\beta$ in equations (8) and (9) we calculate $\alpha' = 0.568 \times 10^{-2}$ and $\beta' = 0.013 \times 10^{-2}$. Thus according to our calculations fractionated partial body irradiation results in the linear term predominating over the quadratic in the yield versus dose equation. The good agreement between our calculations and the observed yields can be seen in table 1 comparing the observed yields at three dose levels with values determined using our calculated $\alpha'$ and $\beta'$. The errors in the calculated values were obtained by applying the errors given in Leonard and Gerber (1977) to equation (5).

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Observed dicentrics $\dagger$</th>
<th>Calculated yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>$0.031 \pm 0.005$</td>
<td>$0.036 \pm 0.006$</td>
</tr>
<tr>
<td>16</td>
<td>$0.105 \pm 0.014$</td>
<td>$0.107 \pm 0.017$</td>
</tr>
<tr>
<td>22</td>
<td>$0.167 \pm 0.013$</td>
<td>$0.156 \pm 0.025$</td>
</tr>
</tbody>
</table>

$\dagger$ Data from Antoine et al (1981)

Another source of comparison with our calculations is the series of measurements from patients receiving radiation treatments for ankylosing spondylitis (Buckton et al 1967). These patients were treated with posteriorly applied fields using 2.7 mm Cu HVL x-rays, which results in a non-uniform dose distribution throughout the treated volume. We have calculated the effective $\alpha'$ and $\beta'$ for these patients using a representative dose distribution and using the data of Cristy (1981) and Trepel (1974) to estimate the fraction of lymphocytes within the field. The calculated yields are approximately half the observed values. This discrepancy is not unexpected however. The nature of the disease is such that the treated area is infiltrated with lymphocytes. Thus the fraction of lymphocytes which were exposed in the treatments is likely to have been greater than we have calculated using data applicable to normal individuals.

5. Conclusion

We have developed a method for calculating chromosome aberration yields in partial body fractionated irradiation. The technique has been applied to patients receiving irradiation for mammary carcinoma and the results are in good agreement with observations. Since the average dose to the recirculating lymphocytes is much less than the local dose delivered to the patient, the observed yields expressed as a function of the delivered dose are less by more than an order of magnitude from the in vitro yields. In addition, fractionated partial-body irradiation increases the ratio of the coefficient of the linear term to that of the quadratic in the equation relating yield to the dose to the patient. These results should prove useful in the interpretation of chromosome aberration yields as a form of in vivo dosimetry.
Acknowledgment

We gratefully acknowledge the suggestions of Dr Helen Q Woodard concerning this work.

Résumé

Aberrations des chromosomes lymphocytaires au cours des radiotherapies fractionnées localisées.

Nous déduisons une relation entre les lésions des chromosomes lymphocytaires apparaissant au cours des radiothérapies fractionnées localisées et celles mesurées in vitro. Ces calculs sont appliqués à surveillance des malades radiothééapés pour un carcinoma mammaire.

Zusammenfassung

Lymphozyten-Chromosomen aberrationen in der fraktionierten Teilkörper-Stahlentherapie.


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