CONF-760982--17

A MODEL FOR THE INDUCTION OF BONE CANCER BY ^{224}Ra

Peter G. Groer and John H. Marshall

Biological Effects of Ra-224 Commission of
the European Communities
Munchen, West Germany
September 20-21, 1976

UofC AUA-USERDA

ARGONNE NATIONAL LABORATORY, ARGONNE, ILLINOIS

operated under contract W-31-109-Eng-38 for the
U. S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

The facilities of Argonne National Laboratory are owned by the United States Government. Under the terms of a contract (W-31-109-Eng-38) between the U. S. Energy Research and Development Administration, Argonne Universities Association and The University of Chicago, the University employs the staff and operates the Laboratory in accordance with policies and programs formulated, approved and reviewed by the Association.

MEMBERS OF ARGONNE UNIVERSITIES ASSOCIATION

The University of Arizona	Kansas State University	The Ohio State University
Carnegie-Mellon University	The University of Kansas	Ohio University
Case Western Reserve University	Loyola University	The Pennsylvania State University
The University of Chicago	Marquette University	Purdue University
University of Cincinnati	Michigan State University	Saint Louis University
Illinois Institute of Technology	The University of Michigan	Southern Illinois University
University of Illinois	University of Minnesota	The University of Texas at Austin
Indiana University	University of Missouri	Washington University
Iowa State University	Northwestern University	Wayne State University
The University of Iowa	University of Notre Dame	The University of Wisconsin

A MODEL FOR THE INDUCTION OF BONE CANCER BY ^{224}Ra *

Peter G. Groer and John H. Marshall

Radiological and Environmental
Research Division

Argonne National Laboratory
9700 South Cass Avenue
Argonne, Illinois 60439

Abstract:

A mathematical model for the transformation of normal endosteal cells into malignant tumor cells by α irradiation is applied to ^{224}Ra. The model postulates that a normal endosteal cell near the bone surface is transformed into a malignant cell by three consecutive events. The first two events are the initiation events. The probability of their occurrence is proportional to the absorbed endosteal dose and they generate dormant tumor cells. These dormant tumor cells are promoted by the third event, the promotion event. The probability of this last event is proportional to the rate of bone remodeling but independent of the radiation dose. In competition with these transforming events is the killing of any endosteal cell by α irradiation. Killing is balanced by replacement of killed endosteal cells by normal stem cells. This model provides the following interesting predictions for the human ^{224}Ra cases. 1) After the decay of ^{224}Ra the tumor rate decreases exponentially at a rate proportional to the bone turnover rate. 2) For exposure to the same dose the model predicts an increased number of tumors for protracted exposure (i.e. exposure at a lower dose rate).

Implications of this model for the therapy of ankylosing spondylitis are discussed. Statistical procedures are suggested for comparison of this theoretical model with the existing data on the induction of osteosarcomas by ^{224}Ra in man.

---

* Work performed under the auspices of the United States Energy Research and Development Administration.

Introduction:

Many investigators have attempted to model carcinogenesis in general and radiation carcinogenesis in particular. A thorough review of these attempts has been given by Armitage and Doll (1951). Advances in the understanding of the metabolism of radium isotopes (Marshall et al. 1972) and the determination of the cells at risk (Lattit et al. 1967) made it possible to formulate at the cellular level a new mathematical model for osteosarcoma induction in man by α-irradiation (Marshall and Groer 1976). This model was applied successfully to the human ^{226}Ra cases. In this paper we will give a set of equations of the model adapted to ^{224}Ra. We will derive predictions which follow from these equations and will point out possible implications for the treatment of ankylosing spondylitis by ^{224}Ra injections. We will also present a method of statistical analysis of the data on tumor induction by ^{224}Ra in man with specific consideration of competing risks; such an analysis is necessary for a correct comparison of the model with the data.

The mathematical model:

The complete set of equations given earlier (Marshall and Groer 1976) is:

$$\begin{aligned}
\dot{M}_o &= \rho\,(f_3 - \sum_{i=o}^{3} M_i) - F_K M_o - F\sigma M_o \\
\dot{M}_1 &= F\sigma M_o - F_K M_1 - F\sigma M_1 \\
\dot{M}_2 &= F\sigma M_1 - F_K M_2 - \lambda M_2 \\
\dot{M}_3 &= \lambda M_2
\end{aligned} \qquad (1)$$

where M_o = number of normal endosteal cells ($\sim 10^{11}$),

M_1 = number of endosteal cells initiated once ($\sim 10^5$),

M_2 = number of endosteal cells initiated twice (dormant tumor cells) (0—10),

M_3 = number of promoted tumor cells (0—1),

s = initial number of normal endosteal cells (i.e. $M_o(t = 0) = s$)

κ = killing probability per cell (10^{-2} rad^{-1}),

ρ = rate at which killed cells are replaced by M_o cells (about 0.1 day^{-1}),

σ = initiation probability per cell ($\sim 10^{-8}$ rad^{-1}),

λ = promotion rate (10^{-2} year^{-1}),

F = endosteal dose rate (about 3.2 to about 63 rad day^{-1})

Figure 1 illustrates the process of tumor induction as described by Eqs. (1). Normal endosteal cells (M_o cells) can be killed (κ term) or initiated (σ term). If initiated once they become M_1 cells. These cells can be initiated again (M_1 cells become M_2 cells) or some of these cells can be killed. M_2 cells can again be killed, or promoted at a rate λ. We postulate that λ is proportional to the bone turnover rate. The loss of endosteal cells (M_o, M_1, and M_2) through killing is compensated by the first term in the first equation. This term describes the replacement of killed cells by normal stem cells. Killing of M_3 cells has been neglected for two reasons. First, new malignant cells will probably be produced so quickly that only a small proportion could be killed, and second, the tumor cells will soon grow out into the marrow space so that most of the

malignant tumor cells will be beyond the range of α particles emitted from the bone. An estimate for the endosteal dose in the human ^{224}Ra cases can be obtained by multiplying the average skeletal dose by a factor of 9 (Spiess and Mays 1973). This agrees with the endosteal dose derived by Marshall et al. (1974) despite some differences in the derivation of this factor. If one divides this endosteal dose by the injection span one obtains the average endosteal dose rate (Spiess and Mays (1973)). For a constant dose rate F, the equations (1) can be solved successively and explicitly. We skip the solutions for M_o and M_1 and give only the solution for the tumor rate P:

$$P(t+g) = \lambda M_2(t)$$

$$P(t+g) \cong [\rho/(\rho+\kappa F)]\ (\sigma^2 \lambda s/\kappa^2)\ [1 - \exp(-\kappa F t) - \kappa F t \exp(-\kappa F t)], \quad (2)$$

where g = tumor growth period (about 5.4 yrs in man (Groer and Marshall 1976)). Equation (2) is valid for $t \leq t_d$ (the duration of the injections) and for $\kappa F \gg \lambda$ which is certainly the case for the ^{224}Ra cases. The order of magnitude of λ is a few percent per year and κF for the lowest dose rate in the adult subgroup of the ^{224}Ra cases is about 3% per day. For times larger than the injection period t_d one obtains:

$$P(t+g) \cong [\rho/(\rho+\kappa F)]\ (\sigma^2 \lambda s/\kappa^2)\ [1 - \exp(-\kappa F t_d) - \kappa F t_d \exp(-\kappa F t_d)] \quad (3)$$
$$\times \exp[-\lambda\ (t - t_d)]$$

Predictions of the model and methods of comparison with the data:

Equation (3) shows that after a build up of M_2 cells during t_d, the number of M_2 cells decreases exponentially. This means that the model predicts a tumor rate $P = \dot{M}_3 \sim \exp(-\lambda t)$. It is clear that λ can not be much larger than

0.05 (yr^{-1}) since tumors are still appearing 20 years after the injections. Formula (3) also shows that for the same endosteal dose, lower dose rates will cause more tumors. The ratio R of the number of tumors induced at the lower dose rate, Γ_L to the number of tumors induced at the higher dose rate Γ_H is approximately given by:

$$R \cong (\rho + \kappa\Gamma_H) / (\rho + \kappa\Gamma_L) \cong M_o^L / M_o^H \qquad (4)$$

where M_o^L and M_o^H are the number of normal endosteal cells for the two dose rates at the same and otherwise arbitrary time. There are as yet no measurements of the replacement rate ρ available. However, as a first approximation R can be taken to be equal to the observed incidences for the adult long and short span cases (Table 4 in Spiess and Mays (1973)). This yields $\rho \cong 0.175$ (day^{-1}). This implies that on the average every killed cell (M_0, M_1, or M_2) is replaced by a normal cell after approximately 6 days.

If comparative medical follow up studies should show that the benefits of ^{224}Ra treatment for ankylosing spondylitis outweigh the risks of such a treatment, the following suggestions for ^{224}Ra therapy would follow from the model:

1) The injection spans should be kept as short as feasible. The radiation dose would then be delivered at a higher dose rate and the tumor rate would be lowered as shown by equations (3) and (4).

2) The promotion rate should be kept as small as possible. Since in the model λ is proportional to the bone turnover rate, any treatment in in addition to the ^{224}Ra injections which would increase the metabolic activity of bone should be avoided.

These suggestions are a logical consequence of the model considered here and should not be understood as an endorsement of ^{224}Ra therapy. However, these suggestions should be useful for the therapist, if a careful analysis of the data on tumor induction by ^{224}Ra should verify these predictions of the model and if medical follow up studies should demonstrate the advantages of ^{224}Ra therapy.

The data on tumor induction by ^{224}Ra in adults and children as published in the literature so far does not permit us to make a statistically rigorous comparison of model and data. The reason is the notorious problem of competing risks. The subjects in every medical follow up study die from many different causes; some are lost from the study and sometimes the study is terminated at an early time when many of the individuals are still alive and well. For this reason the times of death from causes other than osteosarcomas, the times when some individuals were lost from the study and the truncation point of the follow-up are necessary for a rigorous comparison. These times will subsequently be called censoring times as is conventional in statistical analysis. Such an analysis has to be based on the "model of potential survival times" (see e.g. David (1974)) until approaches for inter dependent risks have been developed. This model assumes that the different risks (i.e. causes of death) act independently of each other. One cause of death does not influence the potential time of death due to another cause. This assumption of independent risks makes the following analysis of the complete ^{224}Ra data possible.

The tumor rate as given by Eq. (3) defines a time dependent Poisson process. The likelihood of a set of tumor appearance times and censoring

times corresponding to a certain cohort of people can therefore be calculated. Simplifying Eq. (3) for the moment we write:

$$P(t) = \lambda B \exp(-\lambda t), \tag{5}$$

where B is the λ independent factor in equation (3). Time is now measured from the end of the injection period and the tumor growth period g (5.4 years) has been subtracted from all tumor appearance times t_i (i = 1, 2...r) and the censoring times T_i (i = 1, 2...n-r). Equation (5) gives the following cumulative probability distribution:

$$W(t) = 1 - \exp\left[-\int_0^t P(t')\,dt'\right] \tag{6}$$

W(t) is the probability of a tumor appearance at a time smaller or equal to t. The derivative of W(t) is the probability density function w(t). It gives the probability of a tumor appearing in the infinitesimal interval (t, t + dt). The likelihood L of observing a particular set of tumor appearance times t_i and censoring times T_i is given by the following product of probabilities:

$$L = w(t_1)\, w(t_2)\ldots w(t_r)\,[1 - W(T_1)]\,[1 - W(T_2)]\ldots[1 - W(T_{n-r})]$$

Using expressions (5) and (6) the explicit form of the likelihood L can be calculated. One finds for the logarithm of L:

$$\log L = r \log \lambda + r \log B - \lambda \sum_{i=1}^{r} t_i - nB + \tag{7}$$

$$+ B\left(\sum_{i=1}^{r} \exp(-\lambda t_i) + \sum_{i=1}^{n-r} \exp(-\lambda T_i)\right)$$

Taking the derivative of (7) with respect to λ and setting it equal to zero gives an equation for λ, whose solution is a maximum likelihood estimate for this parameter. ρ can be estimated by comparing the tumor rates soon after the end

of the injection period for different dose rates. Knowing these two parameters the expected number of tumors and observed number of tumors can be compared with statistical tests or with a hazard plot (Groer and Marshall 1976).

With the estimated values of λ and ρ inserted into Eq. (3), one can then calculate the net risk (see e.g. Chiang (1968)) for tumor induction by ^{224}Ra in a given population. This is the risk of an osteosarcoma in a certain time interval after a given injection of ^{224}Ra, if this is the only risk in effect in this population. This net risk can then be used to calculate the number of tumors in an actual population with the appropriate life table. As a corollary of this method of data analysis we would also like to point out, that the net risks should be used when comparing toxicities of different radio nuclides. A simple comparison of cumulative incidences in populations with widely varying survival characteristics is misleading since it does not separate the different risks competing for the life of an individual.

References:

Armitage P. and Doll R., 1961, Stochastic Models for Carcinogenesis. Proc. of the 4th Berkeley Symp. on Math. Statistics and Probability. Vol. 4, p. 19—38.

Chiang, Ch. L., 1968, Introduction to Stochastic Processes in Biostatistics, John Wiley & Sons, Inc. New York.

David H. A., 1974, Parametric Approaches to the Theory of Competing Risks. Reliability and Biometry, Statistical Analysis of Life Length. F. Proschan and R. J. Serfling eds., SIAM, Philadelphia. p. 275—290.

Groer P. G. and Marshall J. H., 1976, Hazard Plotting and Estimates for the Tumor Rate and the Tumor Growth Time for Radiogenic Osteosarcomas in Man. Radiological and Environmental Research Division Annual Report, Part II July 1975—June 1976, ANL 76-88, Part II, Argonne National Lab., Argonne, Illinois.

Loutit J. et al., 1967, A Review of the Radiosensitivity of the Tissues in Bone, ICRP Publication 11, Pergamon Press, London.

Marshall J. H. et al., 1972, Alkaline Earth Metabolism in Adult Man. ICRP Publication 20, Pergamon Press, New York.

Marshall J. H. et al., 1974, Dose to Endosteal Cells and Relative Distribution Factors for ^{224}Ra and ^{239}Pu Compared to ^{226}Ra. Symposium of Biological Effects of ThX, Alta, Utah, July 22—24.

Marshall J. H. and Groer P. G., 1976, Theory of the Induction of Bone Cancer by Alpha Radiation. Submitted to Radiation Research.

Spiess H. and Mays C. W., 1970, Bone Cancers Induced by ^{224}Ra (ThX) in Children and Adults. Health Physics 19, p. 713.

Spiess H. and Mays C. W., 1973, Protraction Effect on Bone Sarcoma Induction of ^{224}Ra in Children and Adults. Radionuclide Carcinogenesis G. L. Sanders et al. eds. p. 437.

FIGURE CAPTIONS

FIG. 1. Summary of the Model. The different events in the tumor induction process as described by Eq. (1) are shown. The numbers indicate the cell type M_o, M_1, M_2, and M_3.

INDUCTION OF OSTEOSARCOMA BY ALPHA PARTICLE RADIATION