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Correspondence

DETERMINATION OF PARAMETERS FOR THE LINEAR-QUADRATIC MODEL FOR RADIATION-INDUCED LUNG DAMAGE

To the Editor: The problems of deriving α/β ratios from data in which overall time varies was demonstrated recently in an excellent paper by van der Kogel *et al.* (7). This paper contained interesting results comparing the effects of fractionation for x-rays and pions on mouse lung. Since they recognized that time was a potential problem, they used four different procedures to derive α/β ratios. The resulting α/β ratios and time factors as derived in the paper of van der Kogel *et al.* (7) are summarized in Table 1, lines 1–5.

One problem with the use of the equation of Travis and Tucker (5) is that the derivation of the time factor requires an assumed α/β ratio and the derivation of an α/β ratio using this formalism requires an assumed time factor. We have recently modified the Travis and Tucker approach such that an α/β ratio and a γ/β time factor can be determined simultaneously from one set of data (8). The description of the methodology can be found, in detail, in reference 8. The resultant equation comparing two isoeffect doses is given by

$$\frac{D_2}{D_1} = \frac{\frac{1}{D_1}\frac{\gamma}{\beta}(t_2 - t_1) + (\alpha/\beta + d_1)}{(\alpha/\beta + d_2)}, \qquad (1)$$

where D_2, D_1, d_2, and d_1 are two isoeffective total doses and doses per fraction, t_2 and t_1 are the times for the two different fractionation schemes, and γ/β is the factor for the effect of time.

By rearranging Eq (1), we obtained the following

$$D_m - D_n = \beta/\alpha(d_n D_n - d_m D_m) + \gamma/\alpha(t_m - t_n) \qquad (2)$$

In this formula n and m represent any two different fractionation schemes with the same biological effect. By performing a least squares fit to a function of the form

$$y = a_1 + a_2 x_1 + a_3 x_2, \qquad (3)$$

best fit values for a_1, a_2, and a_3 can be obtained where $a_2 = \beta/\alpha$, $a_3 = \gamma/\alpha$, $y = D_m - D_n$, $x_1 = d_n D_n - d_m D_m$, and $x_2 = t_m - t_n$. With these equations, α/β and γ/β ratios can be determined using a multiple linear regression procedure found in the statistical software package (1). The resultant α/β ratios and γ/β time factors for the x-rays and pion data of van der Kogel *et al.* (7) are shown in line 6 of Table 1. Our α/β ratio for x-rays is clearly different from the α/β ratios determined without the inclusion of time but consistent with that reported by others. Our γ/β time factor is similar to that derived by the Travis and Tucker procedure as well as the average value of 2.7 ± 1.4 Gy^2/day that we derived (8) based on data from a number of published reports. For pions, our derived α/β ratio is 5.6 ± 0.9 Gy while our γ/β time factor is 1.0 ± 0.5 Gy^2/day. The latter value is different from 2.6 Gy^2/day assumed by van der Kogel *et al.* (7). The apparent reduced effect of time for pions demonstrates a trend which is consistent with the observation by Field and Hornsey (3) that higher LET radiations, in their case neutrons, exhibit a smaller change in biological effect as a result of changing the overall treatment time.

Table 1. Linear quadratic parameters for lung damage data from van der Kogel *et al.* (7)

	α/β (Gy) x-rays	γ/β (Gy^2/day) x-rays	α/β (Gy) pion	γ/β (Gy^2/day) pions
1. F_e plot (2)	0.6	—	4.0	—
2. Tucker equation (6)	0.7	—	3.9	—
3. Direct analysis (Thames *et al.* (4))	0.6	—	4.1	—
4. Travis and Tucker equation (5) (x-rays)	3.0 (assumed)	2.6 (derived)	—	—
5. Travis and Tucker equation (5) (pions)	—	—	6–10 (derived)	2.6 (assumed)
6. Van Dyk *et al.* (8)	3.0 ± 1.4	2.3 ± 1.3	5.6 ± 0.9	1.0 ± 0.5

While van der Kogel *et al.* (7) recognized the time problem in deriving α/β ratios for lung, others have not. In reviewing the literature (8), we found that several authors had derived α/β ratios from the lung response data of Wara *et al.* (9). The derived ratios from the same experimental data ranged between 1.8 and 5.5 Gy, that is, a variation of a factor of 3 depending on the method of determination and whether or not time was considered. In summary, the neglect of time in derivation of α/β ratios could yield substantially different values. We believe that overall treatment time, when relevant, is an important consideration in the future development and potential clinical application of this formalism.

J. VAN DYK, M.SC., F.C.C.P.M.
T. J. KEANE, M.B., M.R.C.P.I., F.R.C.P.(C)
Ontario Cancer Institute
500 Sherbourne Street
Toronto, Ontario
M4X 1K9 Canada

1. Dixon, W. J., ed. BMDP statistical software. LA: University of California Press; 1983.
2. Douglas, B. G.; Fowler, J. F. The effect of multiple small doses of x-rays on skin reactions in the mouse and a basic interpretation. Radiat. Res. 66:401–426; 1976.
3. Field, S. B.; Hornsey, S. Slow repair after x-rays and fast neutrons. Brit. J. Radiol. 50:600–601; 1977.
4. Thames, H. D.; Rozell, M. E.; Tucker, S. L.; Ang, K. K.; Fisher, D. R.; Travis, E. L. Direct analysis of quantal radiation response data. Int. J. Radiat. Biol. 49:999–1009; 1986.
5. Travis, E. L.; Tucker, S. L. Isoeffect models and fractionated radiation therapy. Int. J. Rad. Oncol. Biol. Phys. 13:283–287; 1987.
6. Tucker, S. L. Tests for the fit of the linear-quadratic model to radiation isoeffect data. Int. J. Radiat. Oncol. Biol. Phys. 10:1933–1939; 1984.
7. van der Kogel, A. J.; Martin, J. C.; Smith, A. R.; Raju, M. R. Late effects of fractionated pi-mesons compared to x-rays on mouse lung. Int. J. Radiat. Oncol. Biol. Phys. 14:1175–1184, 1988.
8. Van Dyk, J.; Mah, K.; Keane, T. J. Radiation-induced lung damage: Dose-time-fractionation considerations. Radioth. Oncol. 14:55–69; 1989.
9. Wara, W. M.; Phillips, T. L.; Margolis, L. W.; Smith, V. radiation pneumonitis: a new approach to the derivation of time-dose factors. Cancer 32:547–552; 1973.

AN ALTERNATIVE EXPLANATION FOR THE RADIOSENSITIZATION OF AIDS PATIENTS

To the Editor: We would like to offer several comments regarding the interesting article by Watkins *et al* (18) on the increased radiosensitivity of AIDS patients with Kaposi's sarcoma. Kaposi's sarcoma (KS) has apparently existed from ancient times but was first described by Kaposi in 1872. A second malignancy, usually malignant lymphoma, supervenes or precedes KS in up to one-third of cases (1). It is more common in

men than women and more common in older persons, mean age early sixties (range 22–94) (8, 9). It is also more common in individuals of Jewish and Mediterranean descent (1, 6). The occasional appearance of the disease in brothers and male twins, as well as in other members of the same family, has led others to suggest that there may be genetic or environmental factors that contribute to the predisposition to the disease (4). According to a report published by the Center for Disease Control in the United States in 1981, there are only two previously noted exceptions to the above epidemiological pattern. The first occurs in an endemic belt across equatorial Africa where Kaposi's sarcoma commonly affects children and young adults and accounts for up to 9% of all cancers. Secondly, the disease appears to have a higher incidence in renal transplant recipients and in others receiving immunosuppressive therapy (8). In the latter group the disease appears 3–58 months after the commencement of treatment and tends to be of a more generalized and aggressive form. The tumor is relatively sensitive to radiation therapy. This therapy is successfully used in the treatment of "classical" KS, with minimal complications.

The results are not as good in transplant patients and individuals, with diseases such as lupus erythematosus, who are receiving prednisone, azothioprine or other immunosuppressive drugs. However, when the immunosuppressive drugs are discontinued or reduced the tumor in some of these patients may regress completely or partially and is successfully treated with very small doses of radiation (10 Gy) (4, 6).

Since 1981, a third exception to the common epidemiological patterns of KS has been recognized. The disease also appears with high frequency in AIDS patients. Unlike the case of "classical" KS where minimal toxicity is associated with radiotherapy, the treatment of this tumor in AIDS patients is associated with very high morbidity, necessitating discontinuation of treatment, which results from radiosensitization of the non-malignant tissue (13, 18).

Some authors attribute the radiosensitization to interferon with which their patients were treated concurrently (13). However, Watkins *et al.* have shown that this is an unlikely cause. They have also shown that the status of the patient's immune system at the time of irradiation does not appear to impact upon the development of radiation toxicity (18).

It is well known that electron affinity is the dominant property affecting the ability of a compound to act as a sensitizer; the higher the oxidative power of the compound the more effective it is as a sensitizer. This realization has considerably aided the search for new sensitizers (1, 16). One of the factors most directly related to cellular radiotoxicity is the oxidation of cellular sulphydryl groups (SH groups) by oxidizing agents. Once the cellular SH groups are oxidized, unless subsequently reduced, the cell remains radiosensitive even in the absence of the agent which induced their oxidation (17). Nitroso compounds, including nitrites, are some of the best known radiosensitizers (12, 16, 20).

In America, nitrites have been used, sporadically, as recreational drugs by both heterosexuals and homosexuals since the 1960's. However, in about 1978 there was an enormous increase of such use by homosexual individuals which was reported in "every corner of gay life" (10). At about the same time a very high increase in homosexual promiscuity was also observed. This practice leads to very high amounts of sperm being deposited in the rectum of some homosexuals (passive partner), from where it is absorbed in the general circulation. Ejaculated sperm is also known to be a powerful oxidant (11). Thus, nitrites and sperm, alone or in combination, could induce a high oxidative stress in homosexuals with KS causing radiosensitization and increased toxicity. It may also be of interest that difficulties are also encountered in the treatment of P. carinii pneumonia of the AIDS patients due to a conversion of hemoglobin to methemoglobin, a process known to be induced by all oxidizing agents, including nitrites and some of the drugs used to treat P. carinii pneumonia (10, 14).

Presently, it is generally accepted that AIDS is caused by Human Immunodeficiency Virus (HIV) and that KS is the main clinical characteristic of AIDS. Gallo put forward the retrovirus hypothesis of AIDS in 1982, but the theory does not explain why KS is present mainly, if not exclusively, in homosexuals rather than other AIDS risk groups. This, as well as other factors, leads to the emerging consensus that HIV is not the causative agent of KS in AIDS patients (2, 3, 11, 19). Gallo himself admits that ". . . the precise role HTLV-III in the predisposition of the disease is unclear" (21). Nitrites and sperm are not only radiosensitizing agents but also immunosuppressive, mutagenic, mitogenic and carcinogenic. For this and other reasons nitrites and sperm, acting either alone or synergistically have been postulated as the causative agents of KS in AIDS patients (11). The above data would suggest, as one of us has proposed elsewhere (11), the following combination therapy for KS in AIDS patients:

1. Cessation of nitrites intake and anally deposited sperm. The presently observed longer survival of AIDS patients with KS may be due to change in lifestyle.
2. Localized radiotherapy or hyperthermia.
3. Administration of antioxidants and in particular sulphydryl compounds which are known to correct immune deficiencies (7), to inhibit the toxic effects induced by radiation in normal tissue thus permitting a more radical local irradiation (12), and also to augment the effects of hyperthermia (15).

ELENI PAPADOPULOS-ELEOPULOS
BRUCE HEDLAND-THOMAS
DAVID A. CAUSER
ALUN P. DUFTY
Department of Medical Physics
Royal Perth Hospital
Wellington Street
Perth, Western Australia 6000

1. Adams, G. E.; Flockhart, I. R.; Smitten, C. E.; Stratford, I. J.; Wardman, P.; Watts, M. E. Electron-Affinic Sensitization. VII. A correlation between structures, one-electron reduction potentials, and efficiencies of nitroimidazoles as hypoxic cell radiosensitizers. Radiat. Res. 67:9–20; 1976.
2. Afrasiabi, R.; Mitsuyasu, R. T.; Nishanian, P.; Schwartz, K.; Fahey, J. L. Characterization of a distinct subgroup of high-risk persons with Karposi's sarcoma and good prognosis who present with normal T4 cell number and T4:T8 ratio and negative HTLV III/LAV serologic tests results. Am. J. Med. 81:969–973; 1986.
3. Duesberg, P. H. Retroviruses as carcinogens and pathogens: expectations and reality. Cancer Res. 47:1199–1220; 1987.
4. Friedman-Kien, A. E.; Laubenstein, L. J. AIDS: The epidemic of Kaposi's sarcoma and opportunistic infections. New York: Masson Publishing USA Inc; 1984.
5. Gottlieb, G. J.; Ackerman, A. B. Kaposi's sarcoma: an extensively dissemmated form in young homosexual men. Hum. Pathol. 13: 882–892; 1982.
6. Harwood, A. R.; Osoba, D.; Hofstader, S. L.; Goldstem, M. B.; Cardella, C. J.; Holecek, M. J.; Kungaetz, R.; Giammarco, R. A. Kaposi's sarcoma in recipients of renal transplants. Am. J. Med. 67: 759–765; 1979.
7. Heidrick, M. L.; Albright, J. W.; Makinodan, T. Restoration of impaired immune functions in aging animals. IV. Action of 2-mercaptoethanol in enhancing age-reduced immune responsiveness. Mech. Ageing Dev. 13:367; 1980.
8. Holecek, M. J.; Harwood, A. R. Radiotherapy of Kaposi's sarcoma. Cancer 41:1733–1738; 1978.
9. Morbidity and Mortality Weekly Report. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California, Vol. 30. No. 25. U.S. Dept. of Health and Human Services/Public Health Service. July 3, 1981.
10. Newell, G. R.; Mansell, P. W. A.; Spitz, M. R.; Reuben, J. M.; Hersh, E. M. Volatile nitrites: use and adverse effects related to the current epidemic of the acquired immune deficiency syndrome. Am. J. Med. 78:811–816; 1985.
11. Papadopulos-Eleopulos, E. Reappraisal of AIDS—is the oxidation induced by the risk factors the primary cause? Med. Hypotheses 25: 3, 151–1623; 1988.
12. Proceedings of the Fifth International Congress of Radiation Research. Nygaard, O. F., Adler, H. I., Sinclair, W. K., eds. New York: Academic Press; 1975.
13. Real, F. X.; Krown, S. E.; Nisce, L. Z.; Oettgen, H. F. Unexpected toxicity from radiation therapy in two patients with Kaposi's sarcoma receiving interferon. J. Biol. Resp. Modif. 4:141–146; 1985.
14. Reiter, W. M.; Cimoch, P. J. Dapsone-induced methemoglobinemia in a patient with P. carinii pneumonia and AIDS. N. Engl. J. Med. 317:27, 1740–1741; 1987.
15. Schrek, R.; Stefani, S. Toxicity of sodium ascorbate, lactate and other reagents to heated lymphocytes (Abstr.). The Third International Symposium: Cancer Therapy by Hyperthermia, Drugs and Radiation; 1980:42.
16. Simic, M.; Powers, E. L. Correlation of the efficiencies of some radiation sensitizers and their redox potentials. Int. J. Radiat. Biol. 26:87–90; 1974.

17. Sinclair, W. K. Cell cycle dependence of the lethal radiation response in mammalian cells. Curr. Top. Radiat. Res. Quart. 7:264–285; 1972.
18. Watkins, E. B.; Findlay, P.; Gelmann, E.; Lane, H. C.; Zabell, A. Enhanced mucosal reactions in AIDS patients receiving oropharyngeal irradiation. Int. J. Radiat. Oncol. Biol. Phys. 13:1403–1408; 1987.
19. Weiss, R. A. Retroviruses and human disease. J. Clin. Pathol. 40: 1064–1069; 1987.
20. Whillans, D. W.; Adams, G. E. Electron transfer oxidation of DNA radicals by paranitroacetophenone. Int. J. Radiat. Biol. 28:501–510; 1975.
21. Wong-Staal, F.; Gallo, R. C. Human T-lymphotropic retroviruses. Nature 317:395–403; 1985.

THE EFFECT OF DOSE ON LOCAL CONTROL OF PROSTATE CANCER

To the Editor: I read with considerable interest "The effect of dose on local control of prostate cancer" by Dr. Hanks and colleagues (4). This communication is, obviously, of considerable interest since it contains such a unique, large data base of prostate cancer patients treated with a variety of doses. However, despite the large number of patients who are reported, the patterns of care outcome surveys are still fundamentally retrospective reviews and are subjective to the myriad biases that frustrate interpretation of all retrospective reviews. Indeed, the authors have carefully looked at some of these biases by assessing the effect of histologic grade, hormonal therapy, photon energy, and field size on in-field recurrence rates. Although the authors have been appropriately cautious in their interpretation of this information, I believe the following issues should be addressed:

1. How were patients declared eligible for this analysis: Prior patterns of care papers have analyzed only 574 of an original 682 patients reviewed (37 with positive nodes, 14 without doses, and 57 with unknown stage were excluded) (1, 3, 5). This analysis discussed 667 patients, 14 of whom had unknown stage and were excluded. Presumably, the patients with positive nodes are now included within the analysis. If this is the case, in what sense are they considered Stage A–C, and why are they not considered at least D1? Likewise, the second national survey (1978) originally reviewed 685 patients (372 Stage B, 228 Stage C). There is again some discrepancy in the numbers with the present report, and the reader is left without a clear understanding of the precise eligibility criteria or the number of patients excluded as ineligible from the original number of patients reviewed.

2. What is the follow-up of patients in this study? This data is not given in the present paper, and all recurrence rates are actuarially computed. Although prior patterns of care communications (2) have documented that some of these patients have 10-year actual follow-up, presumably the number of patients actually followed at 10 years is quite small. What percent of the originally reviewed as well as the eligible patients had actual follow-up at 3, 5, and 10 years without being censored due to ineligibility or lack of follow-up? This issue is extremely important because of the propensity of prostate cancer to manifest local failure at periods exceeding 5 and 10 years of follow-up. If the current data set is immature, that is, if an insufficient number of patients have actual 5- and 10-year follow-up, then it may be premature to assume that there is no relationship of dose to in-field recurrence in Stage B patients between 60 and 70+ Gy, since with further follow-up, one may, indeed, see significant differences in local control. Likewise, more mature follow-up might negate the apparent relationship of dose to in-field recurrence in Stage C patients, since patients treated with more aggressive doses may exhibit increasing in-field recurrence rates and thus eliminate the apparent improvement in local control.

3. Was the apparent improvement in local control for Stage C patients treated with 70+ Gy due to dose or other factors? The authors have demonstrated that more poorly differentiated tumors have a profoundly adverse effect on local control. Since the effect of grade appeared to be of greater magnitude than the effect of dose, it is important to know whether the apparent dose effect persists after adjustment for the effect of stage.

This already important paper would be further strengthened if these issues were addressed.

STEPHEN R. SMALLEY, M.D.
Department of Radiation Oncology
University of Kansas Medical Center
Kansas City, KS 66207

1. Hanks, G. E. Optimizing the radiation treatment and outcome of prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. 11:1235–1245; 1985.
2. Hanks, G. E.; Diamond, J. J.; Krall, J. M.; Martz, K. L.; Kramer, S. A ten year follow-up of 682 patients treated for prostate cancer with radiation therapy in the United States. Int. J. Radiat. Oncol. Biol. Phys. 13:499–505; 1987.
3. Hanks, G. E.; Leibel, S. A.; Krall, J. M.; Kramer, S. Patterns of care studies: Dose-response observations for local control of adenocarcinoma of the prostate. Int. J. Radiat. Oncol. Biol. Phys. 11:153–157; 1985.
4. Hanks, G. E.; Martz, K. L.; Diamond, J. J. The effect of dose on local control of prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. 15:1299–1305; 1988.
5. Leibel, S. A.; Hanks, G. E.; Kramer, S. Patterns of care outcome studies: Results of the national practice in adenocarcinoma of the prostate. Int. J. Radiat. Oncol. Biol. Phys. 10:401–409; 1984.

RESPONSE TO STEPHEN R. SMALLEY, M.D.

To the Editor: I appreciate Dr. Smalley's communication and will respond as possible or pertinent.

First, please don't confuse the Patterns of Care retrospective study technology with any other retrospective study reported. Many of the potential biases in a retrospective study were eliminated by the sampling design developed in coordination with Dr. Sedransk. These studies were a brief window in time, 2 years for the 1973–1974 patients and 1 year for those treated in 1978. This eliminates the influence of stage migration and of changes in adjuvant therapy and treatment technology that have plagued the usual retrospective studies which require 10–20 years to accumulate a few hundred patients in a single institution. As previously explained in detail, all facilities in the United States were identified, characterized and then each strata randomly sampled in proportion to its national presence so that the data obtained are true national averages. In addition, individual cases selected for review at a given institution were randomly selected from the total seen during the time interval, thus providing a second level of random sampling designed to further reduce bias. This two-level random sampling is not present in any single institution retrospective study.

The dose response tabulation based on A, B, C staging does not show a dose response effect between 6000 and 7000 rads. That does not mean dose is not important between those brackets, rather one could not be seen. A previous analysis of the 1973–1974 data by the UICC T, N, M system was, in fact, more discriminating, suggesting effects between 6000 and 7000 rads. Unfortunately, no one uses that system any longer and the A, B, C system remains preferred over the most recent but inadequate AJC system. The lack of fine detail in these clinical dose response observations is true, but the clear observation of a dose effect is nearly unique in radiation therapy. It is particularly important when you consider the data base is the best control study outside of a prospective clinical trial. Obviously, a prospective trial could not treat patients with the lose doses (<6000 rads) necessary to show that higher doses are good.

Regarding patient numbers, the 1973 national survey contains 682 patients, the 1973 large facility survey 190 patients, and the 1978 national survey 770 patients. Deducted from these 1642 cases were 57 implants and 52 patients with unknown stage yielding 1533 patients. For the subgroup analysis questioning dose, deduct 17 patients with unknown dose. For the subgroup concerning grade, deduct 246 patients where grade could not be identified, and for the adjuvant hormone question, deduct 17 patients for which this was unknown. The analysis of energy of treating machine was known for all 1533 patients. Patients with N+ status were left in this analysis where the endpoint was local control.

Regarding follow-up, the 1533 patients with known stage ranged in follow-up from 1 month to 10 years 2 months: 1244 patients at risk for 3 years, 577 at risk for 5 years, and 315 at risk for 7 years. In the figures presented, the curves were continued to the end of the data as they were flat. The tables present the detailed analysis used in determining the statistics for comparison of the entire curves. In this analysis the tabular data was not considered when group size fell below ten patients as indicated by an asterisk in the tables.

Regarding the question of effect of grade on dose response for Stage C, an analysis was done for Stage C patients in which dose was related to infield recurrences while stratifying for grade. The stratified by grade