[CANCER RESEARCH 54, 5021, September 15, 1994]

Letter to the Editor

Correspondence re: D. G. Brachman *et al.*, Mutation Does Not Correlate with Radiosensitivity in 24 Head and Neck Cancer Cell Lines. Cancer Res., *53:* 3667-3669, 1993.[1]

The recent article "*p53* Mutation does not correlate with radiosensitivity in 24 head and neck cancer cell lines" by Brachman *et al.* (1) investigated the relationship between *p53* gene status and tumor radiosensitivity. In this regard, the authors list the *in vitro* surviving fractions at 2 Gy (SF_2) for 24 cell lines derived from patients with head and neck cancer. This dose was chosen because it is a typical dose used in conventional fractionated radiotherapy. The conclusion was that there was no relationship between radiosensitivity and *p53* gene mutations using the SF_2 end point. In this paper, however, the authors also comment that "the data...support the conclusion that...*p53* alterations may instead predispose to increased radioresistance." This is an important speculation, but the justification for the statement is not clear.

For example, in their discussion of "Materials and Methods," the authors state that, for certain cell lines, SF_2 values were calculated by a least-squares linear regression analysis of all data points lying on the exponential portion of the curve obtained after irradiation with 1, 3, 5, or 7 Gy. Some of the cell lines referred to have surviving fractions at 2 Gy ranging from 0.658 to 0.804 (*e.g.*, HNSCC 135, HNSCC 29, HNSCC 42, and HNSCC 143), which implies nonlinear "shouldered" survival curves. How then can the SF_2 be calculated from the data lying on the exponential portion of the curve? Back extrapolation of the linear part of the curve to the 2-Gy level would overestimate the actual survival at 2 Gy. Or is this meant to indicate calculation of a quasi-threshold (*Dq*) value, which is not the same as the SF_2 value?

Some of the data presented in the paper of Brachman *et al.* (1) were published previously in 1989 (2). In the 1989 paper, additional data were given that allow more complete characterization of the shape of the survival curve. In particular, values for the one- and two-hit inactivation parameters for some of these cell lines were listed, using the linear-quadratic formalism of cell killing in which survival was calculated as $(S) = \exp - (\alpha D + \beta D^2)$ where *S* is survival and *D* is dose. In radiobiological terms, the α and β constants incorporate aspects of the number and types of lesions produced in a cell per given dose, as well as the capability of the cell to biochemically repair such lesions (3). In Table 1, we list these α and β parameters for 10 cell lines cross-listed in both the 1989 and the current paper. The average α value for the cell lines that possess a *p53* mutation is only about 0.67 that of the cell lines that lack a *p53* mutation (0.28 *versus* 0.43). This lower α value would lead to a higher survival after a dose of 2 Gy and is consistent with the observation of the authors that the presence of a *p53* mutation might lead to increased radioresistance. Such a finding is also consistent with the recent observations of Lee and Bernstein (4), which when analyzed according to the linear-quadratic formalism, also show that the effect of the *p53* mutation is via a change in the α coefficient in the linear quadratic equation.[2] Due to the small samples numbers (6 and 4, respectively, for the $+p53$ and $-p53$ mutation classes) however, calculation of the 95% confidene limits using the appropriate two-tailed *t* values (2.78 and 4.30 at $P = 0.05$ for N-2 degrees of freedom) (Ref. 5) shows that no statement of statistical difference can be made. In this regard, it is disappointing that sufficient information was not supplied in the 1993 paper to allow a more definite statistical analysis to be carried out, although apparently complete survival curves were performed on six additional cell lines (HNSCC 135, JSQ 13, HNSCC 42, HNSCC 80, HNSCC 143, and HNSCC 58). If α and β values were available for these six lines, it would increase the respective N values to 10 and 6, reduce the *t* values to 2.31 and 2.78, and provide additional statistical power. Obviously, additional information might simply serve to strengthen the observation that *p53* mutations do not modify radiosensitivity but given the recent observation of Lee and Bernstein (4), as well as the observations that other oncogenes may also modify radiosensitivity (6), this would appear to be an important area for clarification.

Table 1 *Linear-quadratic descriptors of radiation survival of head and neck cancers*

Cell line	*p53* mutation	α ($\times 10^1$ Gy^{-1})	β ($\times 10^2$ Gy^{-2})
SCC-25	+	4.52	3.0
SQ-9G	+	4.78	2.3
SQ-20B	+	2.50	1.6
HNSSC-29	+	0.68	3.4
JSQ-3	+	1.54	2.2
HN-SCC-131	+	2.50	1.1
		2.84[a]	2.3
		0.60[b]	0.3
		0.17[c]	0.9
SCC-35	−	3.57	1.1
SQ-31	−	3.21	0.8
HN-SCC-28	−	4.54	0.8
SCC-61	−	5.71	4.4
		4.26[a]	1.8
		0.48[b]	0.8
		2.06[c]	3.3

[a] Mean.
[b] SEM.
[c] CL, confidence limits.

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Received 10/21/93; accepted 7/15/94.
[1] No reply received.
[2] J. Leith, unpublished data.