Since both *BRCA1* 185delAG and *BRCA2* 6174delT mutations are common in the Ashkenazi Jewish population, the chance occurrence of two separate mutations in one single family should always be considered in any family member at risk seeking carrier testing for a specific mutation known to be segregating in a particular family. The occurrence of both the *BRCA1* 185delAG and *BRCA2* 6174delT mutations in a single family of both paternal and maternal Ashkenazi descent is expected to occur at a frequency of approximately 0.00015% (1 in 6666 families).

Recently, Ramus and associates [5] reported on a Hungarian patient diagnosed with breast and ovarian cancer at 48 and 50 years of age, respectively. These observations strengthen the importance of analysing the Jewish population for specific mutations in both *BRCA1* (185del AG and 5382ins C) and *BRCA2* (6174delT) in order to exclude the inheritance of more than one mutation in one single individual or family.

1. Roa BB, Boyd AA, Volcik K, Richards SC. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996, **14**, 185–187.
2. Fitzgerald MG, Deborah JM, Krainer M, *et al.* Germline BRCA1 mutation in Jewish and non Jewish women with early onset breast cancer. *N Engl J Med* 1996, **334**, 143–149.
3. Neuhausen S, Gilewski T, Norton L, *et al.* Recurrent BRCA2 6174del in the Ashkenazi Jewish women affected by breast cancer. *Nat Genet* 1996, **13**, 126–128.
4. Oddoux C, Struewing JP, Clayton CM, *et al.* The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet* 1996, **14**, 188–190.
5. Ramus JS, Friedman LS, Gayther AS, Ponder BAJ, Bobrow LG. A breast/ovarian cancer patient with germline mutations in both BRCA1 and BRCA2. *Nat Genet* 1997, **15**, 14–15.

European Journal of Cancer, Vol. 33, No. 13, pp. 2284–2285, 1997
© 1997 Elsevier Science Ltd. All rights reserved
Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00230-X

Is it Reasonable to Select the Median Value of T_{Pot} As a Cut-off Level in Prediction of the Radiation Treatment Outcome?

R. Suwinski[1] and H.R. Withers[2]

[1]Centre of Oncology, M. Sklodowska-Curie Memorial Institute, 44-100 Gliwice, Wybrzeze Armii Krajowej 15, Poland; and [2]Department of Radiation Oncology, UCLA Medical Center, Los Angeles, California 90095, U.S.A.

SEVERAL CLINICAL studies have demonstrated that tumour cell proliferation should be recognised as one of the most important factors determining radiation treatment outcome [1, 2]. Acceleration of tumour growth could become a serious clinical problem for patients with squamous cell head and neck cancer if treatment is extended beyond 3–4 weeks [1]. The effective volume doubling time of a tumour (T_d) after 4 weeks of radiation treatment may approach the value of the potential doubling time (T_{pot}), thus becoming many times shorter than T_d of an untperturbed tumour [3]. It has been consequently suggested that flow cytometric measurements of pretreatment T_{pot} in individual patients may disclose a predictive capacity in radiation therapy for head and neck cancer [4].

In spite of high expectations, the research results on the predictive value of T_{pot} appear to be rather confusing so far. While some studies have implied the predictive value of T_{pot} [5, 6], others have failed to find any significant correlation between T_{pot} and the clinical outcome [7, 8]. The median value of T_{pot} (ranging from 4.6 to 5 days) is commonly used as a value separating tumours whose growth rate is potentially fast or slow.

The remarkable discrepancies in assessment of the predictive value of T_{pot} prompted us to perform a series of exploratory calculations. If the exponential model of tumour cell survival after fractionated radiotherapy is accepted, the surviving fraction of cells (SF) would be found from the equation: $SF = e^{-\alpha D}$ where D is the total radiation dose and α is the slope of a multifraction dose survival curve. Assume that 10 Gy is given per week (e.g. 2 Gy/fraction except for Saturdays and Sundays), the accumulated total dose after t days of radiation treatment may be estimated as $D = 1.43\ \text{Gy} \times t$. If we disregard the tumour cell repopulation up to t_0 days, and assume that the growth rate (T_d) of a tumour after t_0 days is equal to T_{pot}, the surviving fraction after t days of irradiation can be determined from the equation $SF = e^{-\alpha D + \gamma(t-t_0)}$; the γ factor is equal to $\ln 2/T_{pot}$ [9]. The probability (P) of tumour control can be determined using the formula $P = e^{-N \times SF}$, if n represented the number of tumour cells.

The graphical illustration of the results of calculations in which it was assumed that the α value was 0.40 (corresponding to $SF_{2Gy} = 0.45$), $n = 10^9$ and T_{pot} values were 1.5, 3.0, 6.0 and 12.0 days is demonstrated (Figure 1). A striking effect can be observed: a linear change in T_{pot} will bring about a non-linear change in the probability of tumour control. The variants of the model (assuming distribution of cell number in individual tumours from 10^9 to 10^{10}, assuming

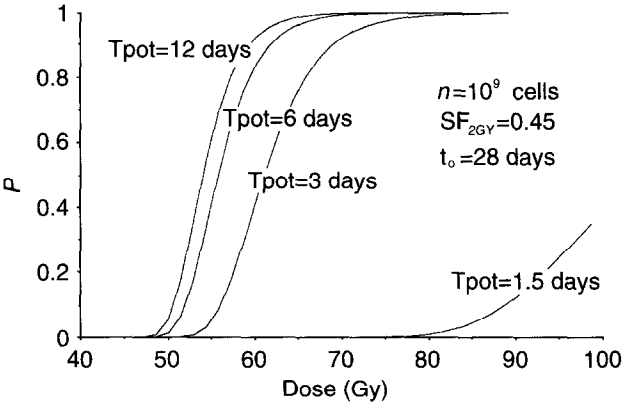

Figure 1. Model of a tumour dose-response relationship, assuming that 2 Gy was given per day (10 Gy per week), that the accelerated repopulation started after 28 days of radiation treatment and that $SF_{2Gy} = 0.45$. There is an excessive decrease in the probability of tumour control if T_{pot} is less than 3 days.

Correspondence to R. Suwinski, UCLA School of Medicine, Department of Radiation Oncology, 10833 LeConte Ave, Los Angeles, CA 90024-1714, U.S.A.
Received 18 Mar. 1997; accepted 28 Apr. 1997.

values for α higher or lower than 0.4, or assuming $t_0 = 0$ days) will not change this conclusion (except for a theoretical consideration of a negative correlation between T_{pot} and radiosensitivity, when shortening of T_{pot} could not affect or even increase tumour control). The model suggests: (a) if T_{pot} is considered as a prognostic factor for the probability of tumour control, a lower than median value of T_{pot} is likely to ascertain the prognostic cut-off level; and (b) stratification of patient treatments could be suboptimal if candidates for accelerated treatment were chosen on the basis of values less than the median T_{pot}.

1. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 1988, **27**, 131–146.
2. Skladowski K, Law MG, Maciejewski B, Steel GG. Planned and unplanned gaps in radiotherapy: the importance of gap position and gap duration. *Radiother Oncol* 1994, **30**, 109–120.
3. Fowler JF. Rapid repopulation in radiotherapy: debate on mechanism. The phantom of tumor treatment–continually rapid repopulation unmasked. *Radiother Oncol* 1991, **22**, 156–158.
4. Begg AC, McNally NJ, Shrieve DC, Karcher H. A method to measure the duration of DNA synthesis and the potential doubling time from a single sample. *Cytometry* 1985, **6**, 620–623.
5. Corvo R, Giaretti W, Sanguineti G, *et al. In vivo* cell kinetics in head and neck squamous cell carcinomas predicts local control and helps guide radiotherapy regimen. *J Clin Oncol* 1995, **13**, 1843–1850.
6. Begg AC, Hofland L, Moonen L, *et al.* The predictive value of cell kinetic measurement in a European trial of accelerated fractionation in advanced head and neck tumor: an interim report. *Int J Radiat Oncol Biol Phys* 1990, **19**, 1449–1453.
7. Nylander K, Anneroth G, Gustafsson H, Roos G, Stenling R, Zackrisson B. Cell kinetics of head and neck squamous cell carcinomas. *Acta Oncol* 1994, **33**, 23–28.
8. Bourhis J, Dendale R, Hill C, *et al.* Potential doubling time and clinical outcome in head and neck squamous cell carcinoma treated with 70 Gy in 7 weeks. *Int J Radiat Oncol Biol Phys* 1996, **35**, 471–476.
9. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Cancer* 1989, **62**, 679–694.