Physical examination revealed cachexia, bradyphrenia, right-sided homonymous hemianopia, a slight motoric aphasia and ptosis of the left eye due to oedema of the eyelid. The mass in the neck was 3 cm in diameter. Computer tomography (CT) of the brain showed multiple cerebral and cerebellar metastases, including a large mass in the left occipital area (Figure 1(a)). Chest X-ray showed no new lesions, but a CT scan of the abdomen showed four suspected peritoneal lesions, while the liver was uninvolved. Treatment consisted of dexamethasone 4 mg four times daily and ranitidine 150 mg twice daily, and tamoxifen was restarted at a dose of 20 mg daily. However, the patient refused radiotherapy to the brain. The treatment resulted in a good symptomatic response until he developed progressive fatigue in July 1996. At that time he was found to have a severe normocytic anaemia (haemoglobin 4.7 mmol/l, prior value in May 8.7 mmol/l), tentatively due to gastrointestinal haemorrhage. Despite the fact that the patient had stopped taking dexamethasone after approximately 10 days, he had no headache, diplopia or other neurological complaints. Six months after the diagnosis of brain metastases, a CT scan of the brain was repeated showing complete resolution of the brain metastases (Figure 1(b)). Also the cervical mass disappeared. The only medication he is currently using consists of tamoxifen 20 mg daily.

Tamoxifen is considered to be the first-line hormonal treatment for male patients with breast cancer [5, 6]. The drug is lipophilic and high concentrations, up to 46-fold higher than the serum concentration, of the parent compound and its main metabolites have been found in brain metastases [7]. Anecdotal reports exist of female breast cancer patients whose brain metastases responded to tamoxifen, but we are unaware of previous reports showing a similar response in male breast cancer patients.

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Co-segregation of *BRCA1* 185delAG Mutation and *BRCA2* 6174delT in One Single Family

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BRCA1 185delAG mutation and *BRCA2* 6174delT mutation constitute the two most frequent mutation alleles predisposing to hereditary breast cancer in the Ashkenazi Jewish population with reported carrier frequencies of 1.09% and 1.52%, respectively [1]. Yet, the calculated contribution of the *BRCA1* 185delAG mutation and the *BRCA2* 6174delT mutation to breast cancer cases diagnosed before the age of 50 years in Ashkenazi Jewish women is approximately 20% and 8%, respectively [2, 3]. *BRCA1* 5382insC is another mutation over-represented in the Ashkenazi Jewish population with a reported carrier frequency of 0.13% [1]. These numbers taken together indicate that the penetrance of *BRCA1* 185delAG mutation is approximately four times that of *BRCA2* 6174delT mutation. The relative risk of developing breast cancer by the age of 42 years is estimated to be 9.3 for 6174delT compared to 31 for 185delAG [4].

Two sisters with breast cancer were referred to us for genetic testing. The younger sister, currently 52 years old, had bilateral breast cancer and underwent right mastectomy at the age of 41 years and left lumpectomy at the age of 50 years. She was found to carry *BRCA1* 185delAG. Her elder sister, currently 56 years old, who at the age of 54 underwent left lumpectomy for breast cancer, tested negative for the 185delAG mutation and was rather considered to have sporadic breast cancer, until further testing showed her to carry the *BRCA2* 6174delT mutation.

Noteworthy is the occurrence of monolateral breast cancer at the age of 54 years in one sister carrying the *BRCA2* 6174delT mutation as opposed to the occurrence of bilateral breast cancer at ages 41 and 50 years, respectively, in the younger sister, carrying the *BRCA1* 185delAG mutation. This case, although single, might serve to underline the observation that the *BRCA2* 6174delT mutation has a lower penetrance compared to *BRCA1* 185delAG. Differences in the cumulative lifetime penetrance for the common Ashkenazi mutations has been noted and it remains to be determined how much of the low penetrance attributed to the *BRCA2* 6174delT mutation is due to a late onset effect.

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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.

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

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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

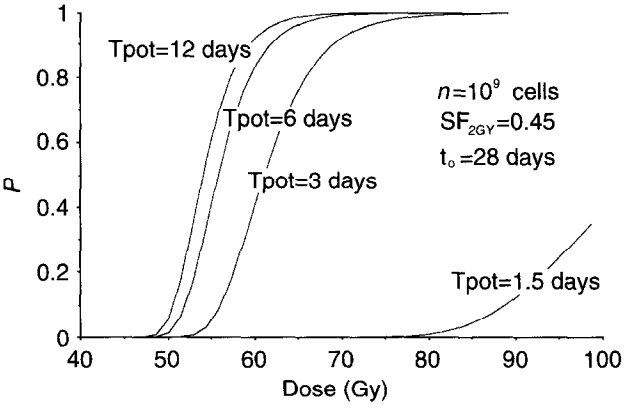

Figure 1. Model of a tumour dose-response relationship, assuming that 2 Gy was given per day (10 Gy per week), that the accelerated repopulation started after 28 days of radiation treatment and that $SF_{2Gy} = 0.45$. There is an excessive decrease in the probability of tumour control if T_{pot} is less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

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