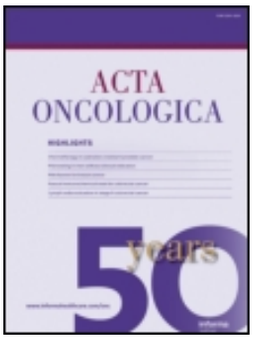

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ORIGINAL ARTICLE

Does a local bystander effect necessitate a revision of TCP models that are based on observed clinical data?

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Abstract

It is shown that in order to derive a general model for tumor control probability (TCP) the two assumptions that on the microscopic level (1) clonogens are non-interacting and (2) clonogen killings are uncorrelated events are not necessary. In fact, these two assumptions can be replaced with two weaker ones that only ask that (a) therapy fractions are independent and non-overlapping and (b) the probability of an event only depends on the number of incidents happening during a time interval and the length of this time interval but not on time itself. This change in assumptions implies that TCP models based on clinical data are flexible enough to include interaction of clonogens on the microscopic level and therefore also a possible bystander effect in cell killing. Based on this new set of assumptions the equation for TCP is derived, first for the homogenous case and then for the general case of a heterogeneous ensemble of tumors irradiated inhomogeneously.

Several investigators have shown that cytoxic effects can be induced in cells that are not directly traversed by high or low LET ionizing radiation [cf. 1–5]. This has been termed the radiation-induced bystander effect. On the one hand, Mothersill and colleagues [6] have stated that the existence of a bystander effect following both alpha and gamma irradiation of many cell lines is indisputable. While on the other hand, they call attention to the fact that relevance of this effect for radiation therapy requires its demonstration in-vivo [6]. Recently, Belyakov and colleagues [7] have described the bystander effect in a three-dimensional, normal human tissue system and have found that in this system unirradiated cells up to 1 mm away from irradiated cells showed an average increase in effect for micronuclei formation of 1.7 times and for apoptosis of 2.8 times over background. Nonetheless, in vitro experiments suggest that bystander effects saturate above a threshold dose of 0.05 Gy [8], i.e. doses of ionizing radiation above this threshold dose do not induce a greater bystander response. Consequently, the contribution of the bystander effect to cell kill diminishes as the dose increases [8]. Therefore, the contribution of the bystander effect to cell kill after doses used in fractionated radiation therapy is probably negligible. For this reason, the radiation induced bystander effect is usually emphasized in radiation protection since it can potentially affect the shape of the dose response curve in the low dose region (cf. Ref. [7] and references therein).

While, the contribution of the radiation induced bystander effect to cell kill in radiation therapy remains to be determined its possible in vivo existence (cf. Ref. [9]) violates the standard assumptions made in the derivation of models for estimating TCP. In the derivations of models estimating TCP, the following two assumptions have been made: That clonogens are noninteracting and cell killings are uncorrelated events. This leads one to the following questions: Does the presence of a radiation induced bystander effect mean that we have to alter our current TCP models, since on the microscopic level clonogens seem to be interacting and cell killings seem to be correlated events? Or are these assumptions too strong, and can be relaxed or replaced by much weaker ones in which on the microscopic level clonogens can be interacting and cell killings can be correlated events? In the following sections we explore these two questions in detail and show that

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these two assumptions are not necessary in order to derive a general model for tumor control probability for an inhomogeneously irradiated tumor.

Modeling of Tumor Control Probability based on clinical data

Various authors have proposed models that allow one to estimate the tumor control probability (TCP) for a tumor that is inhomogeneously irradiated (cf. [10–19]). Model parameters are derived from clinically observed control data obtained for uniformly irradiated tumors. All of these models are implicitly based on the following set of intrinsic assumptions [cf. Ref. [20]]:

1. Each tumor consists of a number of non-interacting clonogens;
2. Clonogen killings are uncorrelated events;
3. A tumor is controlled if all its clonogens are inactivated (sterilized).

Clearly, if a bystander effect exists then on the microscopic level assumptions (1) and (2) above are in conflict with it, since this implies that clonogens can interact and that clonogen killings can be correlated events.

Since the bystander effect is in conflict with assumption (1) and (2) above it is of interest if one can find an expression for TCP using macroscopic observable quantities that does not make explicit use of these assumptions or at least only uses a set of weaker assumptions that do not conflict with its existence.

Following Lindley [21 p. 63–73], let us consider a sample space in which each elementary event consists of an infinite sequence of real numbers that is strictly monotonically increasing. An elementary event corresponds to the observation of a process that begins at time $t = 0$ during which any number of incidents can take place, where the nth incident happens at time t_n. Let t and h be such that $0 \leq t < t+h$. Let F_1 be the event that refers to the number of clonogens surviving in the half open time interval $(0, t]$ after a treatment fraction has been delivered. For any non-negative integer k, let F_2 be the event of k clonogens surviving in the half open time interval $(t, t+h]$ after another treatment fraction has been delivered. We now make the following two assumptions, first that the events F_1 and F_2 are always independent, i.e. we assume that our system is a purely random process and second that the conditional probability $p(F_2|F_1) = p(F_2)$ (since F_1 and F_2 are independent) only depends on h and k, but not on t. Hence, the process describing TCP is a purely random stationary process, or a Poisson process. Assumption (3) above, which is also referred to as the clonogen hypothesis, then implies that when describing TCP it is clearly the probability of zero clonogens surviving that is of interest. Therefore, if μ is the average number of clonogens expected to survive after all treatment fractions have been delivered to an ensemble of identical tumors then the probability of no clonogens surviving is given by (cf. Theorem 2.3.1; Lindley [21]):

$$TCP = \exp[-\mu]. \tag{1}$$

In arriving at this operational definition of TCP we have made no use of assumptions (1) and (2) but have instead made use of the following two weaker assumptions:

a. Therapy fractions are independent and non-overlapping.
b. The probability of an event only depends on the number of incidents happening during a time interval and the length of this time interval but not on time itself.

Clearly, these two assumptions are satisfied in the case of fractionated radiation therapy since treatment fractions are always separated by time intervals that are large compared to the repair half times of normal tissues to allow for almost complete repair of sublethal damage in these normal tissues. Let n be the number of fractions and d be the dose per fraction for a given course of radiation therapy then the average surviving number of clonogens including proliferation is given by:

$$\mu = N_c \prod_{i=1}^{n} SF_i(d) \exp[\lambda\, \mathbf{1}(T - T_k)(T - T_k)].$$

In the expression above it is assumed that cell proliferation behaves exponentially and that there is no mitotic delay. Furthermore, $SF_i(d)$ denotes the in-vivo surviving fraction of clonogens after the ith fraction of dose d has been delivered. The proliferation term in the above expression contains the two free parameters λ and T_k as well as the covariate T, which denotes the overall length of treatment in days including weekends. Moreover, λ denotes the proliferation rate, which is defined as $\lambda \equiv \ln(2)/T_{\text{eff}}$, where T_{eff} denotes the effective doubling time of the clonogenic cells in days, and T_k denotes the kick off time, which represents any delay in the start of rapid clonogenic cell repopulation in response to radiation treatment after the treatment has started. Therefore, rapid repopulation of clonogenic cells due to radiation treatment is assumed to start after a lag period of T_k treatment days has passed. Withers et al. [22] have observed that for Head and Neck tumors this lag period is of the order of weeks, and

therefore clearly exists for some tumor types (also cf. Ref. [23]). Finally, $\mathbf{1}(T-T_k)$ denotes the Heaviside function, which is equal to zero if $0 \leq T < T_k$ and equal to 1 if $T_k \leq T$. If there is no residual effect from the bystander effect at the time when the next fraction is delivered, i.e. if the cytoxins released by a damaged cell have been washed out of the tumor system then we can assume a constant effect per fraction and the above expression then becomes:

$$\mu = N_c[SF(d)]^n \exp[\lambda\, \mathbf{1}(T - T_k)(T - T_k)]. \tag{2}$$

One can think of a tumor as a macroscopic system in the sense of statistical mechanics, whose response to radiation can be described by measurable macroscopic quantities associated with the tumor, such as the in-vivo surviving fraction of clonogens after dose d, SF(d), the proliferation rate, λ, and the kick-off time T_k for rapid repopulation. Therefore, Equation 2 has to be understood as describing the *macroscopic observable effects* of irradiating a tumor. However, the actual underlying microscopic mechanism for cell killing may be far more complicated and not be describable by such a simple equation. In the standard Linear Quadratic model it is assumed that the macroscopically observable in-vivo surviving fraction of clonogens after a dose d can be described by:

$$SF(d) = \exp\left[-\alpha d\left(1 + \frac{d}{\alpha/\beta}\right)\right] \tag{3}$$

Equation 2 can be rewritten to yield:

$$\mu = N_c \exp\left[-\alpha n d\left(1 + \frac{d}{\alpha/\beta}\right) + \lambda \mathbf{1}(T - T_k) \times (T - T_k)\right]. \tag{4}$$

This, of course, may no longer hold up in case of bystander effects or low-dose hypersensitivities and therefore, for the rest of this section we choose to work with the more fundamental Equation 2. Still the α/β-ratio may be introduced as an *operational* way of adjusting for dose per fraction (cf. Refs. [24,25]). Using Equation 2 the most basic equation for tumor control probability, which applies to an ensemble of similar homogeneous tumors of a certain type that is irradiated homogeneously using n fractions of dose d, is given by the following expression:

$$TCP = \exp[-N_c[SF(d)]^n \exp[\lambda \mathbf{1}(T - T_k) \times (T - T_k)]] \tag{5}$$

In Equation 5 all tumors in the ensemble are assumed to be identical with respect to all parameters such as clonogen number, radiation sensitivity, and extent of hypoxia and are irradiated homogenously. Let us now summarize the set of assumptions we have used up to this point:

1. Therapy fractions are independent and non-overlapping;
2. The probability of an event only depends on the number of incidents happening during a time interval and the length of this time interval but not on time itself;
3. A tumor is controlled if all its clonogens are inactivated (sterilized);
4. Clonogens within the tumor have the same radiation sensitivity;
5. Tumors of patients in the population under consideration have the same clonogen sensitivity.

Clearly assumptions (4) and (5) are a gross over simplification, and we will show in the following section how one can dispense with the homogeneity assumptions made above and derive a TCP model for the general case of a heterogeneous ensemble of similar tumors of the same type that is irradiated using inhomogeneous dose distributions.

However, Equations 1–5 clearly show that in order to estimate the TCP one has to estimate the expected average number of clonogens that will *survive* a given course of radiation therapy.

Tumor Control Probability of a heterogeneous ensemble of similar tumors that is irradiated using inhomogeneous dose distributions

In what follows, the abbreviation BNDVH denotes a differential biologically normalized dose volume histogram with M dose bins. The differential BNDVH is obtained from a differential DVH by normalizing the physical dose-per-fraction in each bin to a reference dose-per-fraction (2 Gy here) using the standard BED formalism (see Equation 9 below).

It has been clear for some time that distributions of the macroscopic parameters defining resistance to radiation treatment are necessary in calculations of the probability of surviving cells in solid tumors, instead of single well defined values of these parameters [26,27]. Moreover, evidence is mounting that a major determinant of treatment outcome is the radiation sensitivity, α, and its associated variance, and therefore the surviving fraction of cells after a 2 Gy fraction, SF_2, and its associated variance [26–31]. Buffa et al. [31] have suggested by fitting laboratory-measured data from human tumor biopsies that SF_2 should be log-normally distributed. In what follows we assume that the in-vivo SF_2 is also log-normally distributed. Working with a log-normal distribution for the in-vivo SF_2 has the operational advantage that one is dealing with a positive-definite

probability distribution, which does not have to be truncated at zero.

Thus let us denote by $\ln(\langle SF_2^{pop}\rangle)$ and σ_{pop}^g the central value and geometric standard deviation of the log-normally distributed population in-vivo SF_2^{pop} of an ensemble of similar tumors of a certain type. Furthermore, we denote by $\ln(\langle SF_2^{ind}\rangle)$ and σ_{ind}^g the central value and geometric standard deviation of the log-normally distributed individual in-vivo SF_2^{ind} of an individual tumor within this ensemble of similar tumors. With this notation let us define the following two log-normal probability distributions:

$$f_{pop}(\langle SF_2^{ind}\rangle, \langle SF_2^{pop}\rangle, \sigma_{pop}^g) = \frac{1}{\sqrt{2\pi(\sigma_{pop}^g)^2}} \times \frac{1}{\langle SF_2^{ind}\rangle} \exp\left[-\frac{\ln^2(\langle SF_2^{ind}\rangle/\langle SF_2^{pop}\rangle)}{2(\sigma_{pop}^g)^2}\right], \quad (6)$$

$$f_{ind}(SF_2^{ind}, \langle SF_2^{ind}\rangle, \sigma_{ind}^g) = \frac{1}{\sqrt{2\pi(\sigma_{ind}^g)^2}} \times \frac{1}{SF_2^{ind}} \exp\left[-\frac{\ln^2(SF_2^{ind}/\langle SF_2^{ind}\rangle)}{2(\sigma_{ind}^g)^2}\right]. \quad (7)$$

Suit et al. [17] have observed that heterogeneity of radiation response of human tumors of the same type clearly exists and that major parameters include the histopathologic type, clonogen number, hemoglobin concentration, cell proliferation kinetics, extent of hypoxia, and immune rejection by the human host. Here, we regard SF_2 as the in-vivo net result of a single 2 Gy fraction and for this reason we assume that heterogeneity of response to radiation of tumors can be described using the single log-normally distributed parameter. Then the log-normal distribution f_{pop} in Equation 6 describes the variation of the surviving fraction of clonogens, $\langle SF_2^{ind}\rangle$, from patient to patient in a population of patients having similar tumors of a certain type. On the other hand the log-normal distribution f_{ind} in Equation 7 describes the variation of clonogen surviving fraction, SF_2^{ind} *within* an individual tumor. The expected *TCP* for an inhomogeneously irradiated tumor within an ensemble of similar tumors is given by averaging the individual tumor control probability, TCP_{ind}, over the *between-tumor* log-normal distribution f_{pop}:

$$TCP = \int d\langle SF_2^{ind}\rangle f_{pop}(\langle SF_2^{ind}\rangle, \langle SF_2^{pop}\rangle, \sigma_{pop}^g) \times TCP_{ind}(\langle SF_2^{ind}\rangle). \quad (8)$$

Therefore, we now only need to find an expression for TCP_{ind}. In what follows let us for a given differential BNDVH denote by ${}^{bn}d_i^j$ the biologically normalized dose (to 2 Gy per fraction) for the i-th dose bin at the j-th fraction, which is given by:

$${}^{bn}d_i^j = d_i^j \frac{\alpha/\beta + d_i^j}{\alpha/\beta + 2}. \quad (9)$$

To reiterate, in our modeling we regard the in-vivo SF_2 and the α/β-ratio as macroscopic variables in the sense of statistical mechanics that have been derived from clinical data describing the macroscopically measurable response of a tumor system to radiation.

TCP_{ind} in Equation 8 represents the tumor control probability of an *individual* tumor in the entire ensemble of similar tumors of a certain type that are inhomogeneously irradiated. Note that in order to estimate TCP_{ind} we only need to find an expression for the expected average number of *surviving* clonogens (cf. Equation 1) when an *individual* tumor in the entire ensemble of similar tumors of a certain type is inhomogeneously irradiated. For the ith dose bin the expected surviving fraction taking repopulation into account is given by:

$$SF(D_i) = \prod_{j=1}^{n} SF(d_i^j)\exp[\lambda \mathbf{1}(T - T_k)(T - T_k)],$$

Here, D_i, denotes the total dose in the ith dose bin, d_i^j denotes the dose per fraction in the ith dose bin, and n denotes the number of fractions in the treatment course. Now using Equations 3 and 9 above it is then straightforward to show that for the ith dose bin the expected surviving fraction of clonogens is given by (cf. [32]).

$$SF(D_i) = (SF_2^{ind})^{0.5\sum_{j=1}^{n}\left[{}^{bn}d_i^j - \lambda \mathbf{1}(T-T_k)(T-T_k)\Big/\left[n\alpha\left(1+{}^{2}/_{\alpha/\beta}\right)\right]\right]} \quad (10)$$

Therefore, the average number of surviving clonogens after the inhomogeneous dose distribution represented by the BNDVH has been delivered for a given fractionation schedule including proliferation is given by:

$$\mu = N_c \sum_{i=1}^{M}\left[v_i \int dSF_2^{ind} f_{ind}(SF_2^{ind}, \langle SF_2^{ind}\rangle, \sigma_{ind}^g) SF(D_i)\right], \quad (11)$$

The sum in Equation 11 is computed over the M dose bins in the differential BNDVH, N_c is number of initial clonogens, v_i is the fractional volume corresponding to the ith dose bin D_i. Therefore, inserting Equations 10 and 11 into 1 we find for TCP_{ind} the following expression:

$$TCP_{ind}(\langle SF_2^{ind}\rangle) = \exp\left\{-N_c \sum_{i=1}^{M}\left[v_i \int dSF_2^{ind} f_{ind} \times (SF_2^{ind}, \langle SF_2^{ind}\rangle, \sigma_{ind}^g) SF(D_i)\right]\right\}. \quad (12)$$

Equation 12 is the generalization of Equation 5 to the general case of an inhomogeneously irradiated heterogeneous ensemble of tumors of a certain type.

Once SF_2, TCD_{50}, and the relative slope $\gamma_{50} = D\, dTCP/dD|_{TCD_{50}}$ of the TCP-response curve are specified, the consequential variance of SF_2 and the number of clonogens, N_c, for the specified tumor system can be estimated, cf. [16,33]. Therefore, looking at Equations 10 and 12 one can see that in order to use this TCP model one only needs to know the macroscopic parameters SF_2, TCD_{50}, γ_{50}, T_k, T_{eff} which can be found from clinical data. Of course this clinical data will have the consequences on cell kill due to the bystander effect built in. Therefore, Equations 8 and 12 represent a model for the calculation of tumor control probability that is based on macroscopic variables, which applies to the general case when one is considering a heterogeneous ensemble of similar tumors of the same type inhomogeneously irradiated.

Conclusions

In this work we have shown that the two assumptions that a tumor on the microscopic level consists of non-interacting clonogens and that clonogen killings are uncorrelated events are not necessary in order to derive a general model for tumor control probability. In fact these two assumptions can be replaced with the following two weaker macroscopic assumptions, namely that (a) therapy fractions are independent and non-overlapping and (b) the probability of an event only depends on the number of incidents happening during a time interval and the length of this time interval but not on time itself. This implies that TCP models based on this new set of assumptions are flexible enough to include interactions of clonogens on the microscopic level, and therefore a bystander effect in cell kill.

Therefore, with the interpretation that clinically observed quantities describing tumor response to radiation are *macroscopic* variables in the sense of statistical mechanics and the use of the fact that the stochastic process describing clonogen survival on the *macroscopic* level is a purely random stationary process, the interaction of clonogens and the bystander effect on cell killing at the *microscopic* level is already taken into account in a TCP model based on clinical data. In other words, such TCP models describe the *macroscopic* observable response of tumor systems to a cytoxic agent such as radiation in terms of a limited number of *macroscopic* observable quantities such as SF_2, γ_{50}, TCD_{50}, λ, and T_k and that the simple phenomenological relationships between these variables may not model any of the *microscopic* biological processes involved in cell killing.

However, this does not mean that the radiation induced bystander effect is unimportant. On the contrary, the bystander effect may well be very important in the modeling of normal tissue complication probability, since it implies that a low dose of radiation to a large volume is probably far more toxic to a biological system in terms of late normal tissue damage and induction of secondary cancers than a high dose to a limited volume of normal tissue. This is especially important when one considers dose distributions obtained using intensity modulated radiotherapy, where the low dose contribution from a large number of coplanar beams placed isotropically around the patient is smeared out over a larger volume of normal tissue as compared to more conventional field arrangements. Possible ways out of this conundrum should it prove to be clinically relevant would be the use of non-coplanar field arrangements in which each beam has a unique exit and entrance pathway. Such field arrangements yield dose distributions that are highly conformal and have steep dose gradients [34,35].

References

[1] Prise KM, Belyakov OV, Folkard M, Micheal BD. Studies of bystander effect in human fibroblasts using a charged particle microbeam. Int J Radiat Biol 1998;74:793–8.
[2] Randers-Pehrson G, Geard CR, Johnson CD, Elliston CD, Brenner DJ. The Columbia University single-ion microbeam. Radiat Res 2001;156:210–4.
[3] Hall EJ. The bystander effect. Health Physics 2003;85:31–5.
[4] Hall EJ, Hei TK. Genomic instability and bystander effects induced by high-LET radiation. Oncogene 2003;22:7034–42.
[5] Schettino G, Folkard M, Prise KM, Vojnovic B, Held KD, Michael BD. Low-dose studies of bystander cell killing with targeted soft X-Rays. Radiat Res 2003;160:505–11.
[6] Mothersill C, Seymour CB. Radiation-induced bystander effects: Past history and future directions. Radiat Res 2001; 155:759–67.
[7] Belyakov OV, Mitchel SA, Parikh D, Randers-Pehrson, Marino S, Amundson SA, et al. Biological effects in unirradiated human tissue induced by radiation damage up to 1 mm away. Proc Natl Acad 2005;102:14203–8.
[8] Mothersill C, O'Malley K, Seymour CB. Characterization of a bystander effect induced in human tissue explant cultures by low LET radiation. Radiat Prot Dosimetry 2002;99:163–7.
[9] Prise KM, Schettino G, Folkard M, Held D. New insights on cell death from radiation exposure. Lancet Oncol 2005;6(7): 520–8.
[10] Brahme A. Dosimetric precision requirements in radiation therapy. Acta Radiol Oncol 1984;23:379–91.
[11] Bentzen SM, Thames HD. Tumor volume and local control probability: Clinical and radiobiological interpretations. Int J Radiat Oncol Biol Phys 1996;36:247–51.
[12] Goitein M. The probability of controlling an inhomogeneously irradiated tumor. In: Zink S, editor. Report of the

working group on the evaluation of treatment planning for particle beam radiotherapy. Bethesda, Maryland, USA: National Cancer Institute; 1987.

[13] Goitein M, Niemierko A, Okunieff P. In: Kaulner K, Carey B, Crellin A, Harrison RM, editors. Quantitative imaging in Oncology. Proceedings of the 19th LH Gray Conference. London: Br Inst Radiol; 1995. p. 25–32.

[14] Fenwick JD. Predicting the radiation control probability of heterogeneous tumor ensembles: Data analysis and parameter estimation using a closed-form expression. Phys Med Biol 1998;43:2159–78.

[15] Nahum AE, Tait DM. Maximizing local control by customized dose prescription for pelvic tumours. In: Breit A, editor. Adv. Radiation Therapy Response Monitoring and Treatment Planning. Berlin: Springer; 1992. p. 425–31.

[16] Niemierko A, Goitein M. Implementation of a model for estimating tumor control probability for an inhomogeneously irradiated tumor. Radiother Oncol 1993;29:140–7.

[17] Suit H, Skates S, Taghain A, Okunieff P, Efird JT. Clinical implications of heterogeneity of tumor response to radiation therapy. Radiother Oncol 1992;25:251–60.

[18] Webb S, Nahum AE. The biological effect of inhomogeneous tumor irradiation with inhomogeneous clonogenic cell density. Phys Med Biol 1993;38:653–66.

[19] Zagras GK, Shultheiss TE, Peters LJ. Inter-tumour heterogeneity and radiation dose control curves. Radiother Oncol 1987;8:353–62.

[20] Munro TR, Gilbert CW. The relation between tumour lethal doses and the radiosensitivity of tumour cells. Br J Radiol 1961;34:246–51.

[21] Lindley DV. Introduction to Probability and Statistics: From a Bayesian Viewpoint Part 1, Probability. London: Cambridge University Press; 1965.

[22] Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131–46.

[23] Roberts SA, Hendry JH. Time factors in larynx tumor radiotherapy: lag times and intertumor heterogeneity in clinical datasets from four centres. Int J Radiat Oncol Biol Phys 1999;45:1247–57.

[24] Withers HR, Thames HD, Peters LJ. A new isoeffect curve for change in dose per fraction. Radiother Oncol 1983;2: 187–91.

[25] Fowler JF. The first James Kirk memorial lecture. What is next in fractionated radiotherapy? Br J Cancer Supp 1984;6: 285–300.

[26] Bentzen SM. Steepness of the clinical dose-control curve and variation in the in-vitro radio-sensitivity of head and neck squamous cell carcinoma. Int J Radiat Biol 1992;62: 417–23.

[27] Brenner JD. Dose, volume and tumor-control predictions in radiotherapy. Int J Radiat Oncol Biol Phys 1993;26:171–9.

[28] Roberts SA, Hendry JH. A realistic closed-form radiobiological model of clinical tumor-control data incorporating inter-tumor heterogeneity. Int J Radiat Oncol Biol Phys 1998;41:689–99.

[29] Suwinski R, Taylor JMG, Withers HR. The effect of heterogeneity in tumor cell kinetics on radiation dose-response. An exploratory investigation of a plateau effect. Int J Radiat Oncol Biol Phys 1999;50:57–66.

[30] Bentzen SM, Thames HD, Overgaard J. Does variation in the in vitro cellular radiosensitivity explain the shallow clinical dose-control curve for maligmant melanoma. Int J Radiat Biol 1990;57:117–26.

[31] Buffa FM, Davidson SE, Hunter D, Nahum AE, West CML. Incorporating biological measurements (SF2, CFE) in a tumor control probability model increases their prognostic significance: A study in cervical carcinoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2001;50: 1113–22.

[32] Tomé WA, Fowler JF. On the inclusion of the proliferation term into tumour control probability calculations for inhomogeneously irradiated tumours. Phys Med Biol 2003;48: N261–8.

[33] Tomé WA, Fowler JF. On cold spots in tumor subvolumes. Med Phys 2002;29:1590–8.

[34] Tomé WA, Meeks SL, Buatti LM, Bova FJ, Friedman WA, Li Z. A high precision system for conformal intracranial radiotherapy. Int J Radiat Oncol Biol Phys 2000;47:1137–43.

[35] Tomé WA, Meeks SL, McNutt TR, Buatti JM, Bova FJ, Friedman WA, et al. Optically guided intensity modulated radiotherapy. Radiotherapy Oncol 2001;61:33–44.