Specific Growth Rate versus Doubling Time for Quantitative Characterization of Tumor Growth Rate

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Abstract

Doubling time (DT) is widely used for quantification of tumor growth rate. DT is usually determined from two volume estimations with measurement time intervals comparable with or shorter than DT. Clinical data show that the frequency distribution of DT in patients is positively skewed, with some very long DT values compared with the average DT. Growth rate can also be quantified using specific growth rate (SGR; %/d), equal to ln2/DT. The aim of this work was to compare DT and SGR as growth rate variables. Growth rate calculations were computer simulated for a tumor with DT of 100 days, measurement time interval of 1 to 200 days, and volume estimation uncertainty of 5% to 20%. Growth rate variables were determined and compared for previously published clinical data. The study showed that DT is not a suitable variable for tumor growth rate because (*a*) for short measurement time intervals, or high volume uncertainties, mean DT can either overestimate or underestimate the average growth rate; (*b*) DT is not defined if the consecutively estimated volumes are equal; and (*c*) the asymmetrical frequency distribution of DT makes it unsuitable for common statistical testing. In contrast, mean SGR and its equivalent DT give the correct values for average growth rate, SGR is defined for all tumor volume changes, and it has a symmetrical frequency distribution. SGR is also more accurate to use when discussing, for example, growth fraction, cell loss rate, and growth rate heterogeneities within the tumor. SGR should thus be used, instead of DT, to quantify tumor growth rate. [Cancer Res 2007;67(8):3970–5]

Introduction

Tumor growth rate is widely used for prognostic purposes and can quantify therapeutic effects of different treatment modalities (1–9). Tumor cells duplicate during cell cycle, which theoretically causes an exponential growth. When a tumor becomes larger, its growth rate might decrease and change to nonexponential growth model (e.g., the Gompertzian model; refs. 10–12). To observe growth retardation during volume increase, the tumor must be followed for a long period with several volume measurements. However, in clinical studies, volume estimations of nontreated tumors are usually available only for short measurement time intervals and tumor growth may well be described by an exponential model.

Tumor growth rate is usually characterized by the tumor volume doubling time (DT). The term DT was introduced 50 years ago and a graphical method was proposed for its estimation (13). For an exponentially growing tumor, the growth rate is proportional to its volume (V):

$$\mathrm{dV/dt} = \mathrm{SGR} \cdot \mathrm{V} \qquad \text{(A)}$$

or

$$\mathrm{SGR} = (1/\mathrm{V}) \cdot (\mathrm{dV/dt}) \qquad \text{(B)}$$

where SGR and t are the specific growth rate and time, respectively. The solution of Eq. B gives the well-known exponential growth equation:

$$\mathrm{V_2} = \mathrm{V_1} \cdot \exp\{\mathrm{SGR} \cdot (\mathrm{t_2} - \mathrm{t_1})\} \qquad \text{(C)}$$

and

$$\mathrm{SGR} = \ln(\mathrm{V_2}/\mathrm{V_1})/(\mathrm{t_2} - \mathrm{t_1}) \qquad \text{(D)}$$

DT is the time period when $V_2 = 2V_1$, then

$$\mathrm{DT} = \ln 2/\mathrm{SGR} = (t_2 - t_1)\ln 2/\ln(V_2/V_1) \qquad \text{(E)}$$

The right side of Eq. E is equal to the formula, which was introduced by Schwartz (14) to estimate the growth rate of tumors.

To estimate DT of a tumor, its volume should be measured at least on two different occasions (Eq. E). The average growth rate for several tumors in one patient, or for the same tumor type in many patients, may be estimated by the arithmetic mean value of DT, DT_m (15, 16). Clinical studies have shown that the frequency distribution of tumor DT for the same tumor type is usually asymmetrical in relation to the mean value (i.e., there are tumors with very long DT values compared with the mean value; positively skewed; ref. 17). Therefore, DT_m does not indicate the average growth rate and DT is not suitable for common statistical testing. Some researchers have tried to obtain a symmetrical distribution by assuming a log-normal distribution of DT (4–6, 8, 17, 18). The average growth rate is then estimated by DT_{log}, calculated as the antilog to the arithmetic mean of the logarithms of DTs (17, 19, 20). The logarithm of DT, log(DT), is also proposed to be more suitable for statistical testing (17). DT_{log} is mathematically equal to geometric mean DT, DT_{gm}, which is also used to estimate the average growth rate (4, 8, 21). In this article, we propose the equivalent DT, DT_e, which is the value of DT calculated from Eq. E for the mean SGR. To our knowledge, the reason for the asymmetry in the frequency distribution of DT and the correctness of mean DT as an average growth rate estimator were not studied.

Some degree of uncertainty is included in all tumor volume measurements, which depends on several factors related to measurement technique/investigator (21–25). The uncertainty of the volume measurement propagates to the estimated DT and SGR values. If the tumor volume at the first measurement is underestimated, or overestimated at the second measurement, then the

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tumor growth rate will be overestimated, and vice versa. If the estimated volume at the second measurement is smaller than the first measurement, then the DT and the SGR of tumor will be negative. Both DT and SGR can be used to quantify the growth rate of a tumor, but the relationship between these variables is not linear (Eq. E). If the growth rates of a set of tumors are quantified using DT and the frequency distribution of DT and the mean DT are determined, then the results will not necessarily be similar to the frequency distribution of SGR and the mean SGR of the same set of tumors.

The aim of this study was to compare the frequency distribution and the mean value of different growth rate variables in relation to the true growth rate of tumor, based on computer simulations and evaluation of previously published clinical data. The final goal was to propose a better way to quantify tumor growth rates.

Materials and Methods

Monte Carlo simulations. To compare different methods of expressing tumor growth rate, DT, log(DT), and SGR, the frequency distribution of these variables and variation of their means, DT_m, DT_{log}, and DT_e, were analyzed by computer simulations for an exponentially growing tumor (constant SGR). Computer simulations were done using a Monte Carlo code, written in visual basic 6.0 (Microsoft), with the following assumptions: (*a*) The estimated volume of the tumor at the first measurement, V_1, was a normally distributed random variable with the mean value V_{1true} and the SD σ_{v1}. V_{1true} was supposed to represent one unit of volume. (*b*) The true volume of the tumor at the second measurement, V_{2true}, was calculated using Eq. C. The measured volume, V_2, was a normally distributed random variable with the mean value V_{2true} and the SD σ_{v2}. (*c*) The relative uncertainties of V_1 and V_2 were equal: $(\sigma_{v1} / V_1) = (\sigma_{v2} / V_2)$. (*d*) Because V_1 and V_2 cannot be negative, the symmetry of each distribution was kept undisturbed by symmetrical truncation in the positive range. (*e*) DT_{true} was assumed to be 100 days (SGR = 0.7%/d), which is a typical value of the growth rate of tumors in a clinical setting (26). Simulations were done for different measurement time intervals varying from 1 to 200 days. Each step was 1 day and the relative uncertainty of the volume estimation was 5%, 10%, or 20%.

For each time interval, 10^5 simulations were done. In each simulation, V_1 and V_2 were generated and SGR_i and DT_i were estimated for the range of i indices 1 to 10^5. For each time interval, DT_m, DT_{log}, mean SGR (SGR), and DT_e were calculated, where

$$\overline{SGR} = (SGR_1 + SGR_2 + \ldots + SGR_{100000})/100000 \quad (F)$$

and

$$DT_e = \ln(2)/\overline{SGR} \quad (G)$$

The relative uncertainty of SGR ($\sigma_{SGR}/\overline{SGR}$) was calculated and compared with the expected uncertainty calculated from Eq. D, which can be rewritten as $SGR = [\ln(V_2) - \ln(V_1)]/(t_2 - t_1)$, giving

$$\sigma_{SGR} = \sqrt{\sigma_{\ln(V1)}{}^2 + \sigma_{\ln(V2)}{}^2}/(t_2 - t_1) = \quad (H)$$

$$\sqrt{(\sigma_{V1}/V_1)^2 + (\sigma_{V2}/V_2)^2}/(t_2 - t_1)$$

If both sides of the above equation are divided by SGR and SGR on the right side is replaced from Eq. E, then

$$\sigma_{SGR}/SGR = (1/\ln 2) \cdot \{DT/(t_2 - t_1)\} \cdot \quad (I)$$

$$\sqrt{(\sigma_{V1}/V_1)^2 + (\sigma_{V2}/V_2)^2}$$

Because DT is inversely proportional to SGR, the simulation will generate unstable results for SGR close to zero. Therefore, SGR values between −0.0000693 and +0.0000693, corresponding to DT_i with absolute values >10,000 days, were excluded from the calculations.

Because the logarithm of negative and zero values are undefined, the following method was used in the calculation of DT_{log} in the presence of negative DT_i values: the absolute value of the minimum possible DT (−10,000) plus one (i.e., 10,001) was added to all DT values, and the mean of their logarithms was calculated. Thereafter, DT_{log} was derived by subtracting 10,001 from the obtained mean value. To investigate how the exclusion of negative growth rate values can influence the average growth rate estimators, DT_m, DT_{log}, and DT_e, the simulation was then repeated excluding SGR values less than +0.0000693.

Evaluation of clinical data. DT_m, DT_{log}, and DT_e were calculated for several types of tumors using quantitative data from previously published clinical studies (Table 1; refs. 2, 3, 9, 21, 27–30). The results were then compared with computer simulations.

Table 1. Growth rate of different types of tumors observed in clinical evaluations

Study	Tumor	Measurement time interval (d)	DT range (d)	No. tumors	Reference
1	Pancreatic carcinoma	Not published	18–232	12	Nishida et al. (28)
2	Pancreatic carcinoma	99–751	64–255	9	Furukawa et al. (3)
3	Adenocarcinoma (lung)	159–396	72–131	8	Wang et al. (9)
4	Adenocarcinoma (lung)	25–1,212	(−1,350)–964	15	Winer-Muram et al. (30)
5	Bronchioalveolar (lung)	39–973	36–1,092	9	Winer-Muram et al. (30)
6	Squamous cell lung carcinoma	43–536	(−1,214)–225	16	Winer-Muram et al. (30)
7	Non–small cell lung carcinoma	82–948	48–698	6	Winer-Muram et al. (30)
8	Non–small cell lung cancer	16–99	8–171	18	Sharouni et al. (2)
9	Small cell lung cancer	299–386	54–132	4	Wang et al. (9)
10	Sarcoma (lung metastases)	14–819	7–1,172	21	Blomqvist et al. (21)
11	Hepatocellular carcinoma (W)	43–252	38–274	19	Nakajima et al. (27)
12	Hepatocellular carcinoma (W)	63–763	76–720	15	Saito et al. (29)
13	Hepatocellular carcinoma (M)	13–224	17–91	9	Nakajima et al. (27)
14	Hepatocellular carcinoma (M)	91–210	94–380	6	Saito et al. (29)
15	Hepatocellular carcinoma (P)	20–182	20–78	6	Nakajima et al. (27)

Abbreviations: W, well differentiated; M, moderately differentiated; P, poorly differentiated.

Results

Figure 1 shows the simulated frequency distributions of DT (Fig. 1*A*), log(DT) (Fig. 1*B*), and SGR (Fig. 1*C*) for different time intervals (1, 5, 10, 50, 100, and 200 days), when the relative uncertainty of the volume measurement was 10%. For a time interval of 200 days (2 DT_{true}), all DT values were positive and the frequency distribution of DT was symmetrical and centered at DT of 100 days (Fig. 1*A*). When the time interval was 100 days (1 DT_{true}), the frequency distribution of DT was positively skewed and the peak shifted toward lower DT values. When the time interval was 50 days (0.5 DT_{true}), the peak shifted more toward lower DT values and negative DT values appeared in the data as a very small peak in the negative range. The peak in the negative range increased further with decreasing time interval. With a 1-day time interval, the two peaks were very close and symmetrical in relation to zero and appeared as a single peak centered at zero (Fig. 1*A*). Therefore, mean DT was close to zero for very short time intervals (Fig. 2*A*). Theoretically, when the time interval approaches zero, the position of two peaks asymptotically approaches zero with a height of infinity. If negative values of DT were excluded, the peaks on the negative side of the frequency distribution of DT disappeared. Variations in the frequency distribution of log(DT) (Fig. 1*B*) were comparable with that of DT. For the time intervals of 200 and 100 days, all DT values were positive and only one peak appeared in the frequency distribution of log(DT) centered at 4.6 (=log 100) for 200 days and slightly shifted to the left for 100 days. For shorter time intervals, where negative DT values appeared in data, the peak shifted more to lower values in relation to 4.6, when negative DT values were excluded (Fig. 1*B*). When negative DT values were included for 50-, 10-, 5-, and 1-day time intervals, the symmetry point was shifted to 9.21 (=log 10,001; see Materials and Methods) comparable with zero in the frequency distribution of DT (Fig. 1*B, inset*). For a 1-day time interval, the two peaks looked like a single peak centered at 9.21. Therefore, also DT_{log} was close to zero for very short time intervals (Fig. 2). The frequency distribution of SGR was symmetrical for all time intervals studied. The mean SGR was equal to the true SGR (0.7%/d) and its uncertainty increased with decreased time interval. The expected uncertainty of SGR from Eq. I and the calculated uncertainty of SGR from the simulations were well correlated ($R^2 > 0.999$).

The results of the computer simulations of DT_m, DT_{log}, and DT_e are shown in Fig. 2. When the time interval was very long compared with DT_{true}, all DT estimators were equal to DT_{true} of the tumor (Fig. 2*A*). When the time interval decreased, DT_m overestimated DT_{true} with a maximum deviation of ~30%. For very short time intervals compared with DT_{true}, DT_m underestimated DT_{true} and approached zero for time intervals down to a few days. DT_{log} showed a similar variation as DT_m, with a maximum overestimation of ~20% but a larger underestimation than DT_m for short time intervals. Neglecting small fluctuations at very short time intervals, DT_e was equal to DT_{true} for all time intervals studied (Fig. 2*A*). When the negative growth rate values were excluded, DT_m and DT_{log} followed a similar shape as when the negative values were included (i.e., overestimation up to a maximum and then decreasing with decreasing time interval; Fig. 2*B*). However, the ranges of deviation from DT_{true} were different. When negative values were excluded, DT_m was much higher, whereas DT_{log} was closer to the results when negative values were included. Furthermore, DT_e decreased with decreasing time interval and

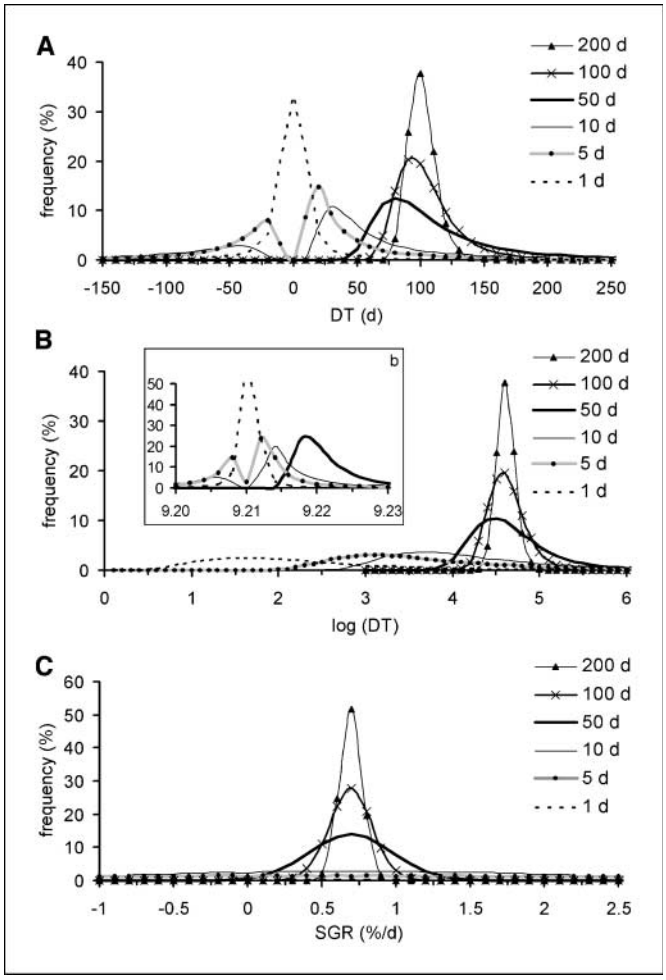

Figure 1. Simulated frequency distributions of DT (*A*), log(DT) (*B*), and SGR (*C*) at measurement time intervals from 1 to 200 d. The relative uncertainty of volume estimation was 10% and the true DT was 100 d. For 50-, 10-, 5-, and 1-d measurement time intervals, negative DT values were excluded for (*B*) whereas included for (*B, inset*) and (*A* and *C*). Note the different scales of the Y-axes of all panels and the different scales of the X-axes of (*B*).

was lower than DT_{log}, which in turn was lower than DT_{true} when negative values were excluded. Then, DT_e approached zero for very short time intervals down to a few days.

Figure 3 shows the values of DT_m, DT_{log}, and DT_e as a function of the relative uncertainty of SGR. It shows that, regardless of the uncertainty of the volume estimation, DT_m, DT_{log}, and DT_e gave similar results for similar uncertainties of SGR.

DT_m, DT_{log}, and DT_e values estimated from the previously published clinical data on several types of tumors are presented in Fig. 4. The measurement time intervals varied between 13 and 1,212 days. The estimated DTs from these articles were between −1,350 and 1,172 days. The only study containing negative growth rates was that of adenocarcinoma and squamous cell lung carcinoma (31). For all studies, including only positive growth rates, DT_e was lower than DT_{log}, which was lower than DT_m (Fig. 4*A*). On average, DT_{log} and DT_m were 25% (range, 3–88%) and 76% (range, 6–317%) higher than DT_e, respectively. If the negative growth rates were included, negative DT_m was obtained, whereas DT_e was still positive (data not shown).

The SGR values from clinical data are summarized in Fig. 4*B*. Because SGR and DT are reciprocally related (Eq. E), a higher SGR

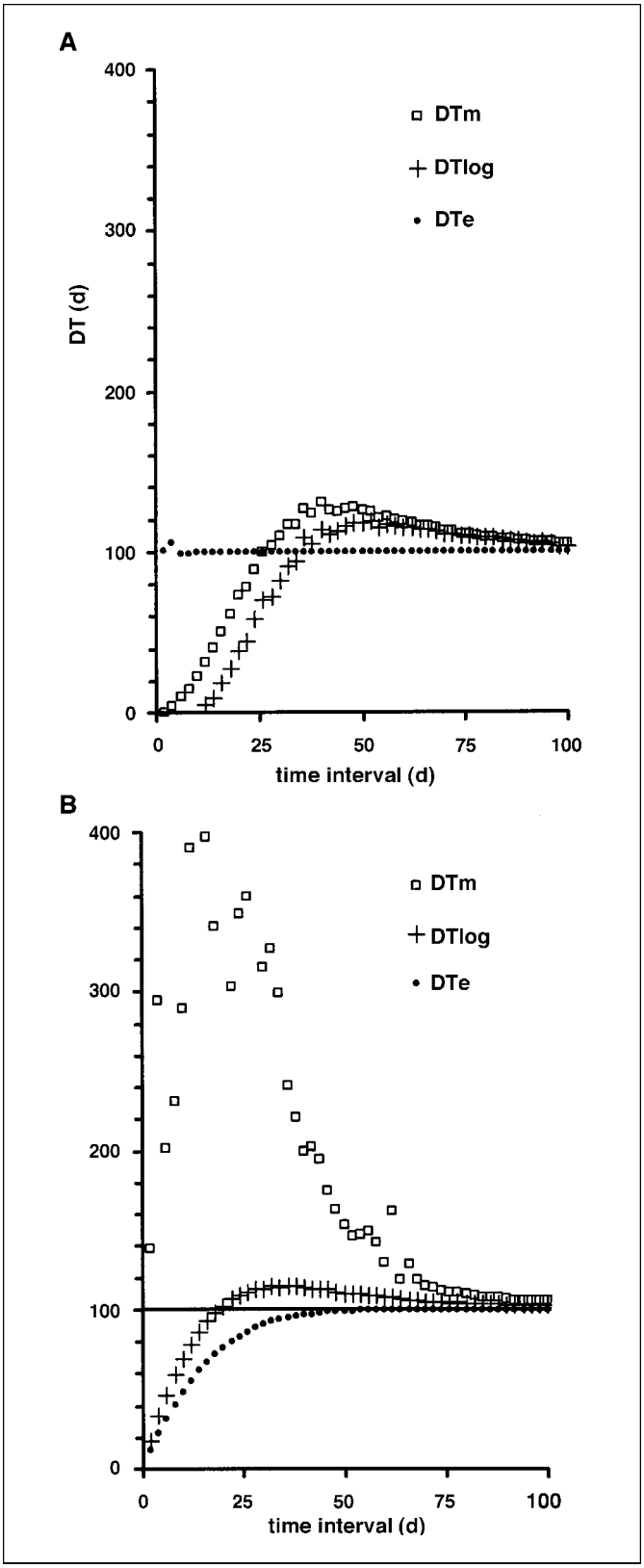

Figure 2. Simulation results of DT_m, DT_{log}, and DT_e for 10% volume measurement uncertainty and different measurement time intervals. The true DT value was 100 days. Negative values of growth rate were included in (*A*) and excluded in (*B*). For proper scaling of the DT axis and clear presentation of deviations from true DT, DT_m values of 454, 471, and 776 at 28-, 20-, and 14-day time intervals were excluded from (*B*), respectively.

value in Fig. 4*B* corresponds to a shorter DT_e in Fig. 4*A* and vice versa. Such trend was not always seen for DT_m and DT_{log} values because they may overestimate or underestimate the true DT of tumors depending on volume measurement uncertainties and the time interval (Figs. 2 and 3).

Discussion

This study clearly shows the importance of selecting a correct quantification method for proper evaluation of tumor growth rate. There are at least three advantages of using SGR instead of DT:

(1) Reduced errors. Errors are encountered with DT_m and DT_{log}, which may cause either overestimation or underestimation of DT_{true}. DT_m can correctly estimate the average growth rate of tumors when the frequency distribution of DT is symmetric, that is when the uncertainty of tumor volume estimation is relatively low (e.g., 10%), or the time interval is considerably longer than DT_{true} (e.g., 2 DT_{true}). With increasing volume uncertainty, or decreasing time interval, the frequency distribution of DT becomes positively skewed. DT_m will then overestimate DT_{true} due to this asymmetry and the size of the error depends on the uncertainty of volume estimations and the measurement time interval. The logarithmic transformation of DT will decrease this asymmetry but is not symmetrical either. With time intervals shorter than DT_{true}, negative DT values appear and increase in number with decreasing time interval. Therefore, the overestimation of DT_{true} by DT_m is limited to a maximum of $\sim$30%. Further decrease of the time interval causes decrease of DT_m toward zero. Negative growth rates would have been excluded if the tumor was not detected at the second investigation. If negative growth rates are excluded, none of the average growth rate estimators will indicate the true growth rate (Figs. 2*B* and 3*B*). Assuming that the volume of undetected tumor equals the detection limit, one may include negative values of DT for proper evaluation. However, DT_m and DT_{log} may still give incorrect estimates of the true growth rate (Figs. 2 and 3). DT_m and DT_{log} can thus overestimate or underestimate DT_{true}, depending on the degree of uncertainty of the volume measurement and the time interval. DT_e is the only estimator that can give the true average growth rate of tumors. All measurement results, including negative SGR values, should be included in the calculation of mean SGR (Fig. 2*A*). Otherwise, DT_e will deviate from DT_{true}, as DT_m and DT_{log} do (Fig. 2*B*). It should be noted that the inclusion of negative values does not mean that such values must exist. Winer-Muram et al. (30) observed the erroneous estimation of the average growth rate with DT_m and made a better estimation by the reciprocal of the average of reciprocals of DT values. The results of that method are comparable with those using SGR as growth rate variable.

(2) No problem when $V_2 \approx V_1$. If the estimated volume at the second measurement is only slightly larger, or smaller, than the volume at the first measurement, then the calculated DT will result in a very high positive or negative value (e.g., $-$1,350 days for lung adenocarcinoma; ref. 30). Furthermore, DT is not defined if the estimated volumes are equal ($V_2 = V_1$ in Eq. E). No problem is encountered in the calculation of SGR and DT_e when $V_2 = V_1$.

(3) Suitable frequency distribution and statistical testing. When DT is used for quantification of tumor growth rate at time intervals used clinically, with an uncertainty in the volume measurement, an asymmetrical frequency distribution of DT is

obtained (Fig. 1). This fact was shown by the computer simulations and is similar to observed DT distributions from clinical studies (17). The frequency distribution of the logarithm of DT is not symmetrical either. Most of the common statistical tests are based on the assumption of normally distributed variables. Therefore, DT and log(DT) are not suitable variables for such statistical analyses. SGR is the growth rate estimator, which is least influenced by uncertainties of the measurement procedure. Its frequency distribution is symmetrical for an exponentially growing tumor (i.e., SGR is suitable for common statistical tests).

The difference between exponential and nonexponential growth models is that SGR is constant for exponential growth, whereas it is related to tumor volume for nonexponential growth. Therefore, to make statistical analysis, the SGR values can be normalized for a specific volume with access to the nonexponential growth variables of the tumor. Nevertheless, dependency or nondependency of SGR on tumor volume, or time, does not degrade the superiority of SGR over DT.

Several assumptions were made in the computer simulations done in this study. The relative uncertainty of volume was assumed to be equal for all tumors, realistic for some applications (25), but is probably not the case for all imaging modalities. However, the effect of volume uncertainty is modulated by the time interval (Eq. I). The variable, which generates the differences between different growth rate estimators, is the relative uncertainty of SGR (Fig. 3). If two different sets of volume uncertainties and time intervals generate the same relative uncertainty of SGR, the estimated values of DT_m, DT_{log}, and DT_e will be similar in both settings (Fig. 3). Therefore, different relative volume uncertainties at different volumes will only change the relative uncertainty of SGR without affecting the main results and conclusions of this study. The same discussion is valid for the assumption of DT equal to 100 days. According to Eq. I, the SGR uncertainty depends on the ratio between the measurement time interval and DT. Therefore, the results are also valid for tumors with different DTs but with equal ratios between time interval and DT. Furthermore, the exclusion of SGR values between −0.0000693 and +0.0000693 (i.e., truncation) seems realistic because it practically excludes zero values of SGR, which may be excluded by investigators as nongrowing tumors (i.e., DT = $\pm\infty$; ref. 30). When the simulation was repeated without truncation, DT_m generated extremely large positive or negative values, whereas there were no problems to calculate SGR and DT_e without truncation.

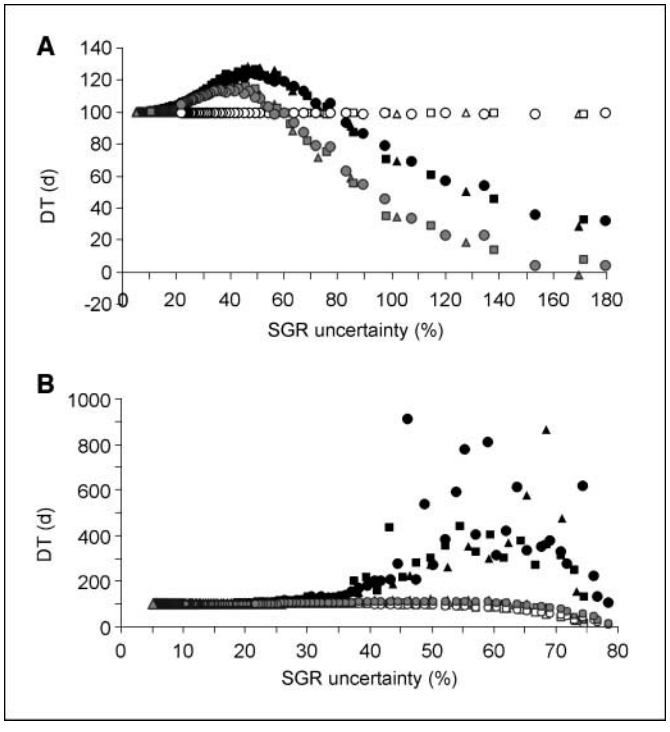

Figure 3. Simulation results of DT_m (*black*), DT_{log} (*gray*), and DT_e (*white*) versus the relative uncertainty of SGR. The relative uncertainty of volume determination was 5% (*triangle*), 10% (*square*), and 20% (*circle*). Negative values of growth rate were included in (*A*) and excluded in (*B*). Note the different scales of the *X*-axis and *Y*-axis.

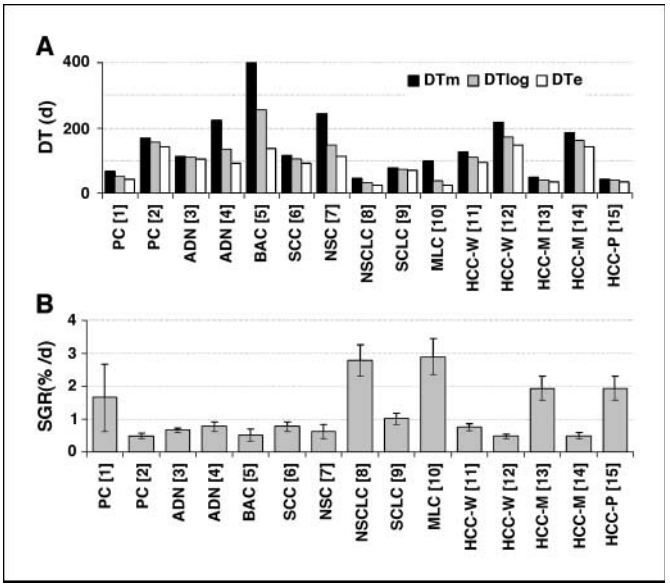

Figure 4. DT_m, DT_{log}, and DT_e (*A*) and SGR (*B*) values determined from previously published clinical data. Numbers in brackets show the study number according to Table 1. *PC,* pancreatic carcinoma (3, 28). Primary lung cancers: *ADN,* adenocarcinoma (9, 30); *BAC,* bronchioalveolar (30); *SCC,* squamous cell carcinoma (30); *NSC,* non–small cell carcinoma (30); *NSCLC,* non–small cell lung cancer (2); *SCLC,* small cell lung cancer (9); *MLC,* metastatic lung cancer from bone and soft tissue (21); *HCC,* hepatocellular carcinoma (27, 29). *W, M,* and *P,* well, moderately, and poorly differentiated tumors, respectively.

Differences in growth rates of tumors is mainly a result of different growth fractions (GF; fraction of tumor volume that consists of proliferating cells) and cell loss rates (CLR). Thus, the duration of cell cycle does not play a major role in the varying kinetics of tumor growth (26, 31). Such a growth pattern can quantitatively be described using SGR. If the absolute value of CLR is added to the SGR of tumor volume, the SGR of the entire tumor in the absence of cell loss is obtained. The SGR of the proliferating cells can then be obtained by dividing the result by GF. In general, the volumetric SGR of a tumor with polyclonal cell population (a heterogeneous SGR distribution within the tumor) is the mean of SGR values weighted by the fraction of each cell component, including stromal and tumor cell populations (i.e., for a tumor with n cell components: $V = V_1+V_2\ldots+V_n$, then $V\cdot SGR_V = V_1\cdot SGR_1+V_2\cdot SGR_2\ldots+V_n\cdot SGR_n$). Similar to DT_m within a population, calculation of volumetric growth rate of tumor as mean DT of its components will result in erroneous estimations of the growth rates.

The SGR values for the clinical data ranged between 0.5%/d and 3%/d. Our recalculations of data from these studies clearly show that the DT_e values always were the lowest ones for each study and tumor type. These results are comparable with simulation results in Fig. 3*B*. This means that when using routine methods today, DT might be overestimated; hence, the tumor might in reality grow faster than estimated when using DT_m and DT_{log}.

In conclusion, to correctly quantify the growth rate of tumors, the variable SGR must be used. The average growth rate must also be estimated by the mean SGR or DT_e. The uncertainty of SGR can be reduced with increasing measurement time interval or decreasing volume uncertainties. In addition, SGR is a suitable variable for common statistical testing based on the assumption of normally distributed variables.

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