

Volume Doubling Measurement of Spherical and Ellipsoidal Tumors

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Volume doubling rulers are described for rapid estimation of tumor volume using projection areas of single-plane images such as chest radiographs. The potential utility of the rulers derives in part from the convenient relationships that exist for the interconversion of volume, volume doubling number, and decimal log growth or cell kill. The traditional approach to tumor volume doubling time determination, originated by Collins [1] uses the average diameter of approximately spherical tumors; analysis of the geometry of volume doubling shows this method to be nearly as accurate as methods that assume elliptical eccentricity, but only up to a tumor

image length/width ratio of 1.5. For ratios greater than 1.5, it is shown that the clinical practice of taking perpendicular diameters is inherently more accurate. Where two perpendicular radiographic views of a tumor ellipsoid are available, it is shown that calculation of volume using the longest projection radius should result in less than one single volume doubling underestimate due to out-of-plane orientation of the long axis of the tumor.

These methods should find greatest utility in measurement of multiple metachronous tumors that are well-circumscribed, convex in perimeter, and have low length/width ratios.

Key words: tumor measurement, tumor growth rate, volume doubling, image analysis, doubling time

INTRODUCTION

The time interval taken for one doubling of the volume of a tumor is the tumor volume doubling time (DT). The usefulness of DT as an index of tumor growth was first described by Collins, who also suggested that the number of volume doublings (the doubling number) a tumor has undergone since its inception as a single cell is a meaningful unit of tumor size [1]. Although the DT and doubling number do not correspond to the cell-cycle time and the number of cellular divisions, these terms have endured as descriptors of tumor behavior [2-10].

DT determination is traditionally done by use of serial measurements of single-plane image data, such as appear on chest radiographs, by the average diameter method of Collins [1,7]. The average diameter of an apparently spherical tumor shadow, ideally a "coin lesion," is plotted against time on semilog graph paper. The DT then equals one-third of the time interval taken for doubling of the diameter. Alternate published means of DT derivation from average diameter measurements are by formula [2], tables [11], or a complex calculator method [12]. With few exceptions, clinical studies of tumor growth rates have relied entirely on the average diameter method.

Nonetheless, DT values resulting from this method have been shown to be prognostically significant, perhaps as much as the tumor cell type [7]. A variety of correlations with DT estimates have been found, including tumor response to chemotherapy and radiotherapy, surgical resectability of pulmonary tumors, risk for metastatic disease, period of risk for recurrent disease, and remaining life span [1-9].

The preciseness and repeatability that characterize tumor measurements by a given observer are a function of the particular method of measurement which is applied, and of observer preference for the method [13]. It therefore seems likely that a method for direct visualization of the dimensions of a tumor image in volume-doubling units will facilitate DT calculation. Conversion of linear measurements into base 2 logarithmic doubling units without such a method invites error. In addition, the

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greater the number of observations that can be made on a given tumor, the greater will be the accuracy with which growth curve determination is made. It is the clinical ease with which frequent single view films can be obtained and combined with use of simple volume doubling rulers that has prompted the present report.

METHODS

Volume Doubling Relationships

The number of doublings that defines the difference in size (Δn , the change in volume doubling number) between two volumes V_x and V_y for any two masses of the same shape and orientation is given in the relationship:

$$V_x/V_y = 2^{n_x} - 2^{n_y} = 2^{\Delta n} \quad [I]$$

Because of the exponential relationship between radius (R), area (A), and volume (V), for spherical and ellipsoidal masses:

$$A_x/A_y = 2^{2/3(\Delta n)} \quad [II]$$

$$\text{and } R_x/R_y = 2^{\Delta n/3} \quad [III]$$

These relationships are shown graphically in Figure 1, which depicts successive volume doublings of a sphere. Thus, a single volume doubling shows an increase in radius by a factor of 1.26, which is the cube root of 2. Because $\log_{10} 2 = 0.301$, and therefore may be approximated to 0.3, these useful relationships obtain:

$$\begin{aligned} \Delta n &= \frac{\log (V_x/V_y)}{0.3} = \frac{\log (A_x/A_y)}{0.2} \\ &= \frac{\log (R_x/R_y)}{0.1} \quad [IV] \end{aligned}$$

Ellipsoid Models

The Figure 2 solid-line isobars are based on the formula for the volume of an ellipsoid, by equating the unknown depth of the ellipsoid, c , with $(a + b)/2$, the average of the two known dimensions of the projection ellipse. Volumes calculated on the basis of the average diameter method of measurement are based on $V = (4/3\pi [(a + b)/2]^3)$. The geometric mean method is based on $V = 4\pi [ab(ab)^{1/2}]/3$.

Rotation Effects on Projection Size

The change in projection radius as a function of degrees θ rotation of an ellipse is derived in the following manner. Any point on an ellipse, centered at the origin, is defined by x , abscissa, and y , ordinate, values as a function of the major (a) and minor (b) axes [14]:

$$\frac{x^2}{a^2} + \frac{y^2}{b^2} = 1 \quad [V]$$

The eccentricity of an ellipse is given by $a/b = \text{length/width}$ ratio. Thus, as a function of eccentricity,

$$x = [(a/b)^2 (b^2 - y^2)]^{1/2} \quad [VI]$$

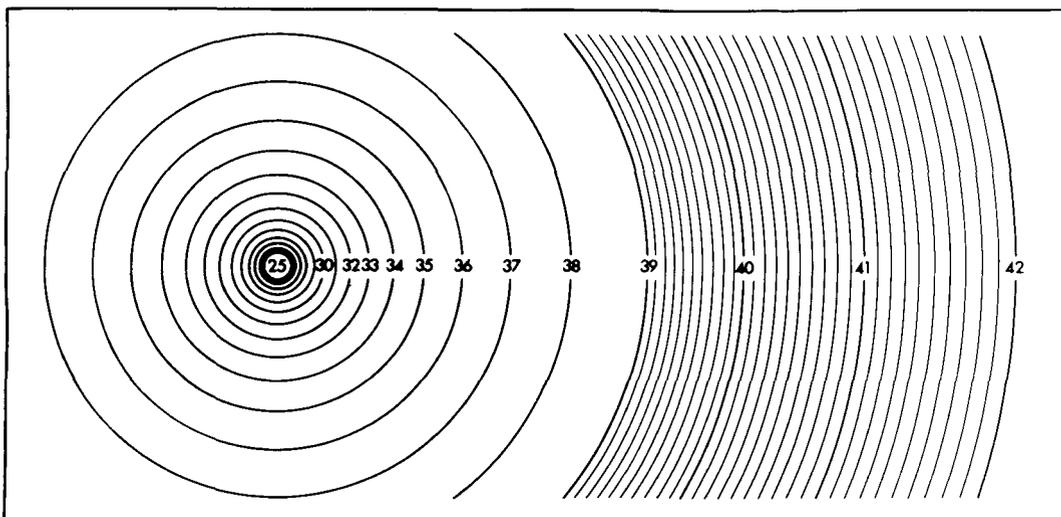


Fig. 1. Projection areas that correspond to volume doublings of a sphere (10) shown as successive volume doubling numbers (n) such that the 30th doubling is 1 cm³.

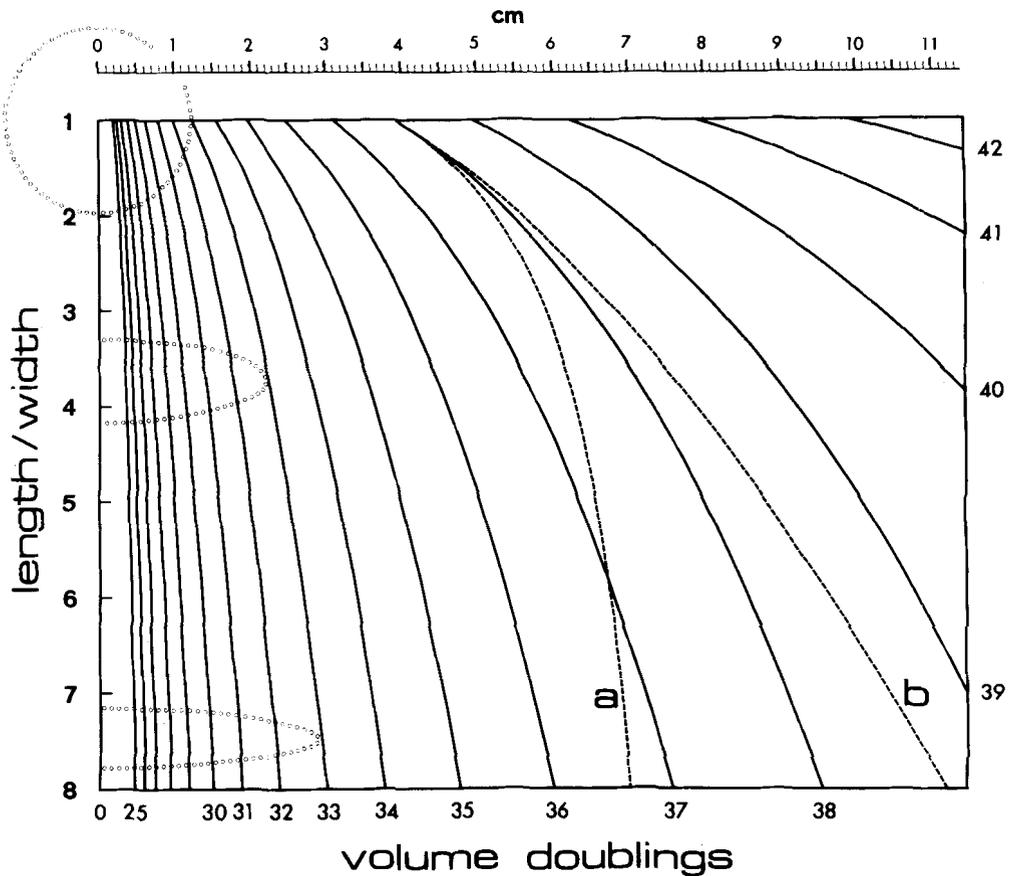


Fig. 2. Isovolumetric ruler, modified from Figure 1, for measurement of volume and volume doubling number of an elliptical tumor image, from the eccentricity (length/width) and the long radius (abscissa). The assumption is made that tumor depth is the average of the length and width. Curves (a) and (b) at the 38th doubling represent alternate calculations, using the traditional average diameter method of Collins [1], or the geometric mean [2], respectively.

The slope of a tangent to the ellipse [14] is given by Eq. [VII], in which θ is also the angle made by the tangent at the Y-intercept:

$$\frac{1}{\tan\theta} = -\frac{b^2x}{a^2y}, \quad \text{[VII]}$$

and, therefore:

$$y = -(b/a)^2 (x \tan\theta). \quad \text{[VIII]}$$

It is easily demonstrated that the projection radius, e , is related to θ and the parameters of an ellipse by:

$$e = (x^2 + y^2)^{1/2} \cos(\theta - \arctan [-y/x]). \quad \text{[IX]}$$

Since the relative decrease in radius is equal to $e/a = 2^{\Delta n/3}$,

$$\Delta n = \frac{\log e - \log [(a/b)b]}{(\log 2)/3}. \quad \text{[X]}$$

Substitution of Eqs. [VI], [VIII], and [IX] into Eq. [X], yields the decrease in apparent volume, Δn , in terms of eccentricity (a/b) and the angle of rotation (θ) from an in-plane orientation.

RESULTS AND DISCUSSION

Spherical Doubling

Figure 1 shows a volume doubling ruler for sequential doublings of the projection area of a sphere. The assignment of doubling number in Figure 1 results from the unique relationships that exist between volume, \log_{10} volume, \log_{10} cell number, and volume doubling number (n), when the 30th doubling is set equal to 1 cm³ (about 1 gm). The 31st, 32nd, and 33rd doublings then denote tumor volumes of 2, 4, and 8 cm³ and so on. Because $\log_{10} 2$ nearly exactly equals 0.3, and 1.0 cm³ may be assumed to contain about one billion cells, these simple and useful formulae result:

$$\frac{\text{time period of observation}}{\Delta n} = DT. \quad \text{[XII]}$$

TABLE I. Doubling or Halving of Algebraic Parameters of a Spherical or Ellipsoidal Mass: Corresponding Changes in Remaining Parameters*

	Tumor growth				Tumor regression			
	Number of volume doublings increase	Percentage additional			Number of volume halvings: Decrease in volume doubling number	Percentage decrease in		
		Volume	Area ^a	Diameter ^b		Volume	Area ^a	Diameter ^b
Doubling of					Halving of			
Volume	1.0	100.0	58.7	26.0	Volume	1.0	50.0	37.0
Area	1.5	182.8	100.0	41.4	Area	1.5	64.6	50.0
Diameter	3.0	700.0	300.0	100.0	Diameter	3.0	87.5	75.0

*assuming no change in eccentricity (length/width ratio) of the tumor ellipsoid, or in its orientation relative to the projection plane.

^arepresents either cross-sectional, projection, or surface area.

^bor any given radius.

$$0.3 n - 9 = \log_{10} (\text{cm}^3) . \quad \text{[XIII]}$$

$$0.3 n = \log_{10} (\text{cell number}) . \quad \text{[XIV]}$$

$$0.3 \Delta n = \log_{10} (\text{cell kill or growth}) . \quad \text{[XV]}$$

The volume doubling ruler, Figure 1, holds additional interest in that, in principle, it unifies some disparate criteria of tumor response to therapy. Tumor response is usually reported as a 50% (or greater) decrease in either the diameter, the product of perpendicular diameters (area), or the volume. Since 1 doubling of diameter = 2 doublings of area = 3 doublings of volume (Eq. [IV]), these criteria are related in an integral way, in doubling number units (Table I). The Table I relationships are also true for nonspherical tumors which show no change in shape or orientation during the course of growth or shrinkage.

Ellipsoidal Doubling

The popularity that the “product of the perpendicular diameters” method enjoys in chemotherapy response reporting suggests that projection images of tumors may be more appropriately modeled after the ellipse than the circle. Attempts have been made to measure tumors as ellipsoids by taking three diameters of lesions, which can be measured on both posterior–anterior and lateral chest radiographs [15–17]. Preliminary results have indicated that this approach results in tumor growth curve data with significantly less scatter than those calculated using the average diameter method [17].

The spherical doubling approach to estimation of tumor volume (Fig. 1) can be modified to include elliptical tumor images on single-plane films. However, the size estimate will vary according to the assumption that is necessarily made concerning the unknown depth of the tumor. Moreover, deviation of the anatomical axes of an ellipsoidal tumor mass from an in-plane orientation on the radiograph(s) is likely.

Several algebraic models for volume estimation from a single-view elliptical tumor image have been employed by different investigators. The average diameter method is one possible solution: Stated otherwise, volume is proportional to the cube of the average diameter of the projection ellipse. This process normalizes all elliptical images to sphericity. Alternatively, ellipticity may be preserved—the two perpendicular axes used without modification—by use of the assumption that the third axis is equal to either the arithmetic [15], or the geometric [2], mean of the two measured axes.

Figure 2 shows a volume-doubling ruler for ellipsoids that describes the arithmetic mean method. Figure 2 is an isovolumetric ruler, in which the solid-line isobars represent radii of the long axes of projection ellipses of ellipsoids of the same volume. Eccentricity is expressed by the length/width ratio of the elliptical image. The assumption is made that the unknown, third tumor radius is the average of the two observable radii. The isobars are drawn to represent volumes corresponding to the same doubling numbers shown in Figure 1. Thus, in the example shown, volumes of the sphere (circle) and ellipsoids (shown as hemi-ellipses) are identical. Equations [XII] to [XV] also apply to Figure 2.

Curvatures of the isobars in Figure 2, at the 38th doubling, that result from use of the alternative, average diameter method, or from the geometric mean approach, are represented by the dashed lines (a) and (b), respectively. It is clear that up to an image length/width ratio of 1.5, little difference in volume occurs on calculation by any of the three methods. At ratios greater than 3, however, the average diameter method—which is the cornerstone of present day human tumor growth rate information—is remarkably insensitive to variation in eccentricity of the tumor ellipse.

Thus, if only a single radiographic view of a tumor image is available, the average diameter method of tradition is inherently as valid as the elliptical models, but only up to a length/width ratio of 1.5. Below a ratio of

1.5, the volume of an elliptical lesion may nearly equally be taken from the average diameter and the spherical doubling ruler (Fig. 1). At greater length/width ratios the Figure 2 method (solid isobars) should be more accurate.

Orientation Effects

A specific advantage is obtained if two views of an ellipsoidal tumor mass are available; for example, if a lesion is well-delineated on both posterior-anterior and lateral chest films. By use of the longer of the two major axes seen on the two views, the tendency for the major axis of the projection ellipse to always be shorter than the anatomic major axis can be greatly minimized.

Figure 3 demonstrates the effects of rotation of a tumor ellipsoid on the size of its projection ellipse. The rotation is perpendicular to the plane of the projection image, with one semi-minor axis parallel to the projection plane, so that these effects can be given in doubling number units of apparent volume decrease from the true value. For angles of rotation less than 45° , the resulting volume underestimate is small and does not vary greatly

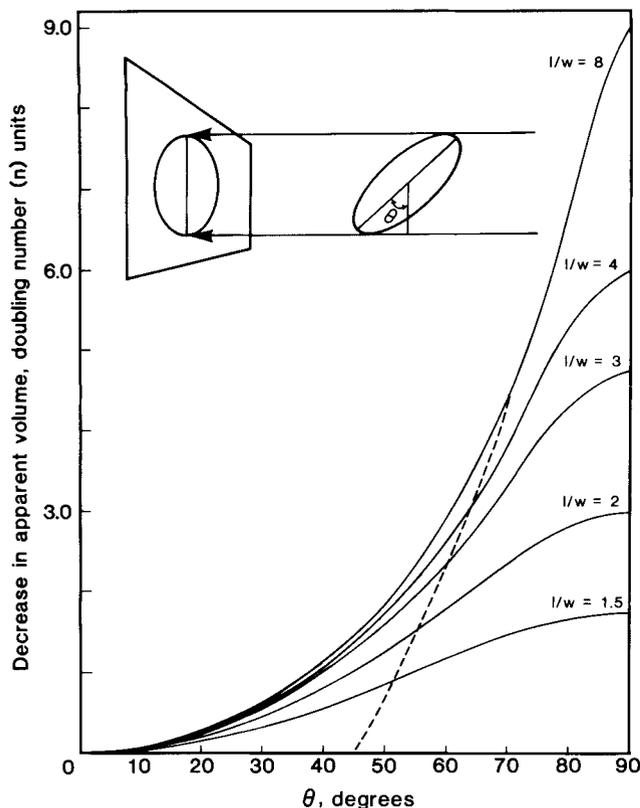


Fig. 3. Effect of spatial orientation of a tumor ellipsoid on the size of its projection ellipse as a function of the length/width ratio, in units of volume doublings. The dotted line shows the geometric mean, the only out-of-plane orientation at which the product of projection diameters taken from perpendicular radiographic views correctly represents the minor radii of the ellipsoid.

with the eccentricity of the tumor ellipsoid. The major axis of a tumor ellipsoid physically cannot be greater than 45° rotation out-of-plane on both posterior-anterior and lateral radiographs. Therefore, by taking for measurement the longest diameter of the tumor ellipses seen on the two views, the underestimate in volume resulting from major axis foreshortening will generally be no greater than one single volume doubling.

By contrast, with the major axis of the tumor ellipsoid held in any fixed orientation, rotation of the two semi-minor axes about the major axis will tend to result in an overestimate of tumor volume, by use of two, perpendicular radiographic views, each of which provides a minor radius measurement. The shortening of the projection radius of the larger of the two semi-minor axes, which occurs for a given angle of rotation on one view, will be accompanied by a relatively greater lengthening of the projection radius of the smaller axis (at $90^\circ - \theta$) on the other, perpendicular view. Only in the case of an in-plane orientation of the minor axes, and at the half-maximal points (dotted line in Fig. 3) is the minimum, and correct, product of the two semi-minor axes obtained from the minor radii of the two radiographic views. A net result of these projection effects on a tumor ellipsoid is a rounding-up process, which logically must contribute to the relative frequency with which "coin lesions" are observed.

Thus, if two perpendicular radiographic views of an ellipsoidal tumor mass are available, its volume may be best approximated as described by Mattson and Holsti [16] using the formula for the volume of an ellipsoid ($V = 4\pi abc/3$), by which the longest radius of either view is multiplied by the semi-minor radii of each view. The volume doubling number can then be calculated by Eq. [XIII]. Assuming a completely random probability of spatial orientation of the true, anatomical axes of a tumor ellipsoid, the tendency for the longest radius to be an underestimate should generally be partly offset by the tendency of the product of the minor radii to overestimate the true volume.

Volumetric measurement of tumors by the present methods considerably shortens the time and reduces errors over conventional methods that convert linear measurements into logarithmic, volume data. These methods should find greatest utility in measurement of multiple metachronous tumors that are well-circumscribed, convex in perimeter, and have low length/width ratios. Examples include multiple hematogenous metastases to lung from a variety of primary sites, and the multiple subcutaneous metastases of malignant melanoma. For small subcutaneous metastases, however, some attempt at minimizing the error due to skin thickness should be made [18]. In non-Hodgkin's lymphoma patients, measurement of the rate of regression of multiple lymph node masses may be helpful in planning chemotherapeutic strategies

[19]. In the experimental situation with animal tumor models, the volume doubling rulers should be useful in measuring volume changes in subcutaneous tumors, since ellipsoidal shape is typically assumed (eg [20]); and as optical reticles for measurement of multicellular spheroids in vitro [21].

CONCLUSIONS

1. Measurement of tumor volume, growth, or regression may be described directly in terms of doubling number; volume doubling rulers (Figs. 1 and 2) should facilitate estimation of these parameters from single-view radiographic data.

2. The average diameter method of Collins [1] for measurement of volume doubling time, heuristically represented by spherical doubling (Fig. 1) should be restricted to elliptical tumor images with length/width ratios of 1.5 or less. For elliptical images with length/width ratios greater than 2, some account of the eccentricity should be made, as in the method of Figure 2, in which the nonvisualized third diameter is taken to be the average of length and width.

3. Volumes of tumors well seen on two perpendicular radiographic views are best calculated from the product of the longest radius and the two minor radii, as suggested by previous workers [15-17] and converted to doubling number by Eq. [XIII].

4. Volume determination of single-plane images is also dependent on adequate standardization of radiographic magnification, but if this is constant through a series of radiographs, no effect on tumor growth rate determination will result. Highly accurate measurement of the size and growth rate of tumor present in a given radiographic lesion will depend on finding practical solutions to the formidable problems of cellular pleomorphism and tissue heterogeneity, densitometry and edge-analysis, and repeated CT application [22, 23].

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REFERENCES

1. Collins VP, Loeffler RK, Tivey H: Observations on growth rates

- of human tumors. *Am J Roentgenol* 76:988-1000, 1956.
2. Schwartz M: A biomathematical approach to clinical tumor growth. *Cancer* 14:1272-1294, 1961.
 3. Meyer JA: The concept and significance of growth rates in human pulmonary tumors. *Ann Thorac Surg* 14:309-322, 1972.
 4. Spratt JS, Spratt TL: Rates of growth of pulmonary metastases and host survival. *Ann Surg* 159:161-171, 1964.
 5. Weiss W: Peripheral measurable bronchogenic carcinoma. Growth rate and period of risk after therapy. *Am Rev Respir Dis* 103:198-208, 1971.
 6. Steele JD, Buell P: Asymptomatic solitary pulmonary nodules. Host survival, tumor size, and growth rate. *J Thorac Cardiovasc Surg* 65:140-151, 1973.
 7. Straus M: The growth characteristics of lung cancer and its application to treatment design. *Semin Oncol* 1:167-174, 1974.
 8. Schackney SE, McCormack GW, Cuchural GJ: Growth rate patterns of solid tumors and their relation to responsiveness to therapy. An analytical review. *Ann Intern Med* 89:107-121, 1978.
 9. Steel GG: "Growth Kinetics of Tumors." Oxford: Clarendon Press, 1977.
 10. Spears CP: U.S. Patent 4, 131, 998. Jan. 2, 1979.
 11. Twardzik FG, Sklaroff DM: Growth analysis of pulmonary metastases from salivary gland tumors. *Am J Roentgenol Rad Ther Nucl Med* 126:493-499, 1976.
 12. Maggs PR: Determining tumor doubling time using HP-27 calculator. *Ann Thorac Surg* 24:595, 1977.
 13. Gurland J, Johnson RD: How reliable are tumor measurements? *JAMA* 194:125-130, 1965.
 14. Wilson WA, Tracey JJ: "Analytic Geometry." Boston: DC Heath, 1949, pp 109-121.
 15. Brenner MW, Holsti LR, Perttala Y: The study by graphical analysis of the growth of human tumors and metastases of the lung. *Br J Cancer* 21:1-13, 1967.
 16. Mattson K, Holsti LR: Prognostic value of doubling time in cancer. *Strahlentherapie* 156:632-636, 1980.
 17. Mattson K, Salmo M, Holsti LR: Accuracy of determination of doubling time in lung cancer. *Br J Cancer* 41:49, 1980.
 18. Moertel CG, Hanley JA: The effect of measuring error on the results of therapeutic trials in advanced cancer. *Cancer* 38:388-394, 1976.
 19. DeVita VT, Hellman, S: In DeVita VT, Hellman S, Rosenberg SA (eds): "Cancer: Principles and Practice of Oncology." Philadelphia: J.B. Lippincott, 1982, p 1387.
 20. Spears CP, Shahinian AH, Moran RG, Heidelberger C, and Corbett TH: In vivo kinetics of thymidylate synthetase inhibition in 5-fluorouracil-sensitive and -resistant murine colon adenocarcinomas. *Cancer Res* 42:450-456, 1982.
 21. Conger AD, Ziskin MC: Growth of mammalian multicellular tumor spheroids. *Cancer Res* 43:556-560, 1983.
 22. Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M: Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Intern Med* 90:185-187, 1979.
 23. Friedman MA, Resser KJ, Marcus FS, Moss AA, Cann CE: How accurate are computed tomographic scans in assessment of changes in tumor size? *Am J Med* 75:193-198, 1983.