The prognostic value of measuring the gross linear radial growth of pulmonary metastases and primary pulmonary cancers

The gross rates of growth of pulmonary cancers and pulmonary metastases may be reduced to clinically useful nomograms and graphs. The constructs are feasible because most neoplasms growing in the lung are observed only during a limited segment of their life history, often being observed too few times to permit the identification of the growth curve of best fit. Consequently, the parameter that can be calculated most quickly, namely linear radial growth rate in mm./day, may be most useful. The linear radial growth rates are plotted against observed survival. The nomograms permit easy approximation of the volume doubling time and the exponential radial growth rate in mm./mm./day. The mean of the log normal frequency distributions of doubling times for common primary and metastatic cancers found growing in the lung is plotted on one nomogram to put the information in perspective. The more widespread reporting and tabulation of such data should lead to a highly useful kinetic staging and treatment evaluation system.

John S. Spratt, Jr., M.S.P.H., M.D., F.A.C.S., and John Arthur Spratt, B.A., *Columbia, Mo.*

The one characteristic known to be common to all cancers is growth. Until recently, this characteristic has been described in subjective terms like "fast" or "slow," but the actual rate of growth has been recorded infrequently. A brief summary of the utility value of knowing the rates of growth is given in Table I.

Growth of any cancer fits into a kinetic model determined by many variables acting simultaneously to effect a net rate of increase or decrease in the total mass of a cancer. The kinetic model is depicted in Fig. 1.

Beginning in the early 1960's, we have been able to accumulate considerable data from several roentgen files. Clusters of observed growth curves measured for 22 primary lung cancers of different histologic types and of pulmonary metastases have been previously published.[6-8] The dimensions of roentgen shadows recorded at different times for growing cancers can be measured by calipers. Though radiographic geometric factors affect actual size, the rate of change is not significantly affected by these same factors if roentgen techniques remain constant. We have now measured hundreds of different cancers growing in the lung, the bones, the breast, the lymph nodes, and the colon. Furthermore, numerous review articles on compilations of similar observations are beginning to accumulate. The more completely and comprehensively such data are reported, the sooner it will be feasible to establish a kinetic classification for benign and malignant neoplasms that will explain many behavioral characteristics of cancers not elucidated by anatomic and morphologic classification systems. Correlation between kinetics and morphology remains highly desirable to make maximum use of past clinical experience largely based on gross anatomic and microscopic morphology.

The gross rates of growth are measurable in only a segment of the entire period of growth. This segment exists between the threshold diameter of radiographic visibility and the prelethal diameter which may

From the Cancer Research Center and the Ellis Fischel State Cancer Hospital, Columbia, Mo.

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Address for reprints: John S. Spratt, Jr., M.D., Cancer Research Center, Business 70 and Garth Ave., Columbia, Mo. 65201.

*Director, Cancer Research Center, and Chief Surgeon, Ellis Fischel State Cancer Hospital.

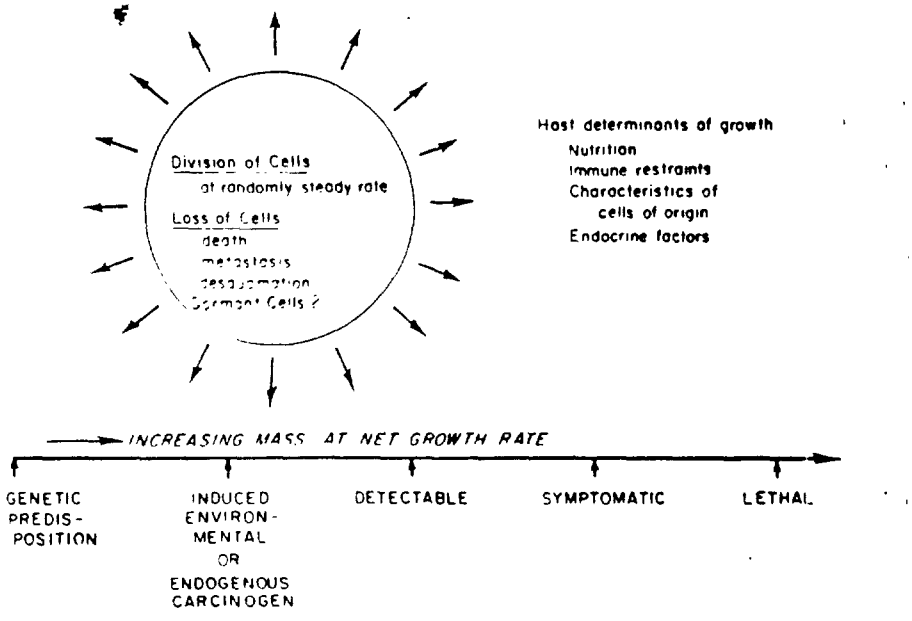

Fig. 1. Kinetic model of an untreated cancer. A solid cancer growing in the lung is a dynamic mass of tissue on which many factors are acting simultaneously. These variable factors produce a net effect on growth which produces grossly measurable growth rates characterizing various cancers (and pulmonary metastases) and affecting longevity.

become obscured by confluent growth of multiple metastases or by secondary events such as pneumonia and atelectasis in the lung.

A previous report[5] indicated that the radiologist rarely sees pulmonary metastases at sizes less than 6 mm (a size obtained by 26.7 net doublings of a 1,000 cμ cell) and never at sizes less than 3 mm. They are not regularly visible until they reach 10 mm. in diameter. As these metastases grow, the untreated host will not long survive the presence of pulmonary metastases or a pulmonary cancer larger than 10 cm. in greatest clinical dimension. Thus the segment of a growth curve grossly and consistently measurable by thoracic roentgenography exists between 10 mm. and 100 mm. All patients will be dead by the time the diameter has reached 200 mm. (a size obtained by 40.8 net doublings of a 1,000 cμ cell). Measurements of net growth rates are also possible for other organ sites, such as the skin,[2] colon,[9] bone,[8] breast,[3] and lymph nodes.[3]

When the growth rate is calculated over such a short and selected segment, the calculation of the line of best fit becomes hypothetical in most cases. Actually, the short segment of growth between 10 mm. and 10 cm. often approximates straight line growth and may be interpreted as a straight line when a site is measured two times, before and after a span of time adequate for growth, as is the situation in many cases. Thus arguments over whether the growth is logarithmic, Gompertzian, linear, or other are often impossible to resolve in the clinical setting because of the short period of observation relative to the total life history of the neoplasm. Furthermore, there are good animal models of solid tumors which suggest that radial growth really is linear during this segment of spherical cancerous growth if continued cell duplication is restricted only to an advancing margin of active growth while the center becomes dormant and necrotic. In fact, Mayneord[4] provides very sound observations that the radial growth of at least some cancers is linear. He observes that Jensen's rat sarcoma increases linearly with time, not exponentially. He developed a mathematical theory that satisfactorily explains the observed linear growth. The explanation hinges on the observation that active cellular proliferation occurs only in a thin outer shell of a spherical cancer with the central cells being either dormant or necrotic.

With these points in mind, we re-examined data previously reported. Several years ago, the foremost concept was doubling time. We have recalculated the growth in millimeters per day of radial growth and correlated that growth with observed survival from a

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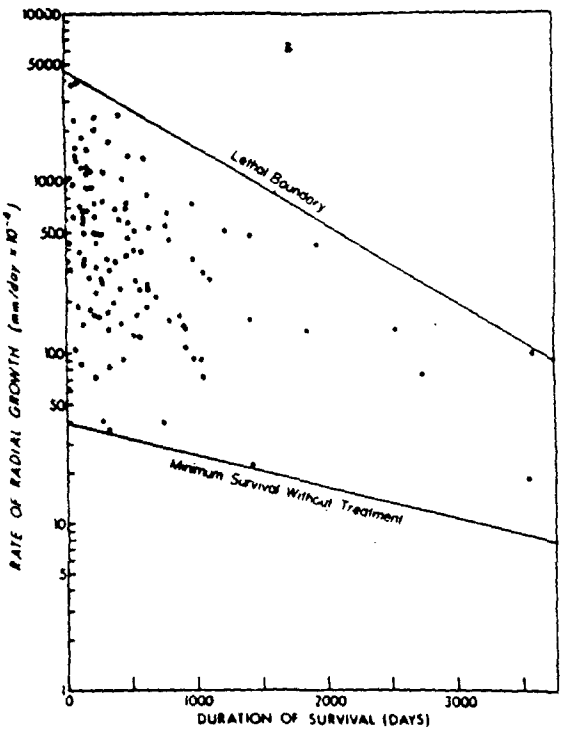

Fig. 2. This scatter diagram compares the correlation between the linear radial growth rate of the fastest growing pulmonary metastasis with the duration of host survival. The duration of survival has been corrected for the observed rate so that survival is plotted from a common size, a greatest chordal diameter of 10 mm. The scatter diagram defines the limits of lethality based on the linear growth rate.

Table I. *Clinical value of knowing the growth rate of pulmonary neoplasms (metastatic and primary)*

Differential diagnosis
Prediction of longevity
Evaluating and planning effective detection programs
Planning therapy
Evaluating therapy
Correlation of gross rates of growth with cellular kinetics
Improving understanding of the natural history of cancers with prevention or suppression of neoplastic growth being the ultimate objective

common point. The common point is a radiographic density with a diameter of 10 mm. (Fig. 2).

To calculate the linear radial growth of a cancer, one need only use a standard rate formula:

$$\text{radial growth rate (mm./day)} = \frac{\left[\frac{d_2 - d_1}{2}\right]}{t_2 - t_1}$$

where the diameter at the first measurement (d_1) is subtracted from the diameter of the second measurement (d_2). The difference is divided by 2 to give the radial change. This, in turn, is divided by the number of days elapsing between the first and second observation to give the linear growth rate in mm./day.

With exponential or geometric growth, the linear radial rate increases as the sphere enlarges. If the radial rate is expressed as a geometric rate (mm./mm./day), this apparent increase in growth rate with increasing size remains constant.

Several simple nomograms are needed to display the interrelations among time, size, rates of growth, and survival. The first nomogram developed relates radial growth rate in mm./mm./day and doubling times for tumors of different radii to the linear radial growth rate (mm./day) (Fig. 3).

This nomogram will permit the crude but rapid *approximation of the exponential growth rate* of spherical cancers for which two measurements of diameter or radius are available at two different points in time. Time intervals must be great enough to permit measurable growth. To use, calculate the linear radial growth in mm./day. Next, add the diameters measured at points *a* and *b* and divide by 2 to obtain the midpoint diameter. Divide this diameter by 2 again to obtain the midpoint radius. Select the point on the nomogram where a vertical line from the mm./day intersects the line most closely approximating the midpoint radius. Extend a line horizontally to intersect the equivalent exponential growth scales giving the exponential rate of growth of the cancer in mm./mm./day and the scale giving the doubling time in days.

The relation between the number of doublings to survival for pulmonary cancers and metastases has been published previously.[8] A scatter diagram showing the relation between linear radial growth (mm./day) and host survival is given in Fig. 2. This diagram is particularly useful for predicting the minimum and maximum duration of survival of persons having pulmonary metastases of known linear growth rate.

A second nomogram with added data of clinical value is given in Fig. 4. This nomogram permits the direct conversion of the exponential radial growth rate (mm./mm./day) and host survival is given in Fig. 2. This diagram is particularly useful for predicting the minimum and maximum duration of survival of persons having pulmonary metastases of known linear growth rate.

A second nomogram with added data of clinical value is given in Fig. 4. This nomogram permits the direct conversion of the exponential radial growth

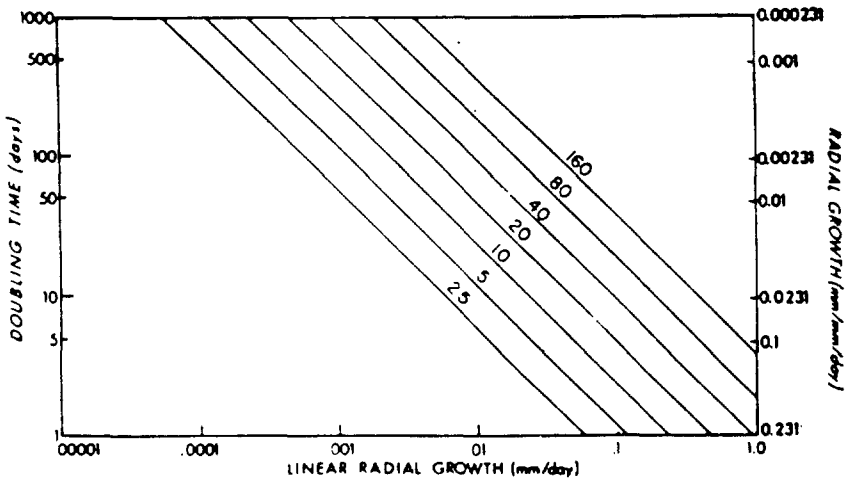

Fig. 3. To use this nomogram, calculate the linear radial growth rate in mm./day as described in the text. Similarly, determine the length of the radius midpoint between the two measurements of tumor size. The *slanted lines* are the nomograms for the midpoint radii. Project a vertical extension from the calculated growth rate (mm./day) to intersect the line most closely approximating the midpoint radius. From this intersect, extend a line horizontally to obtain an approximation of the doubling time on the left. By extending the horizontal line to the right, one can obtain the exponential radial growth in mm./mm./day.

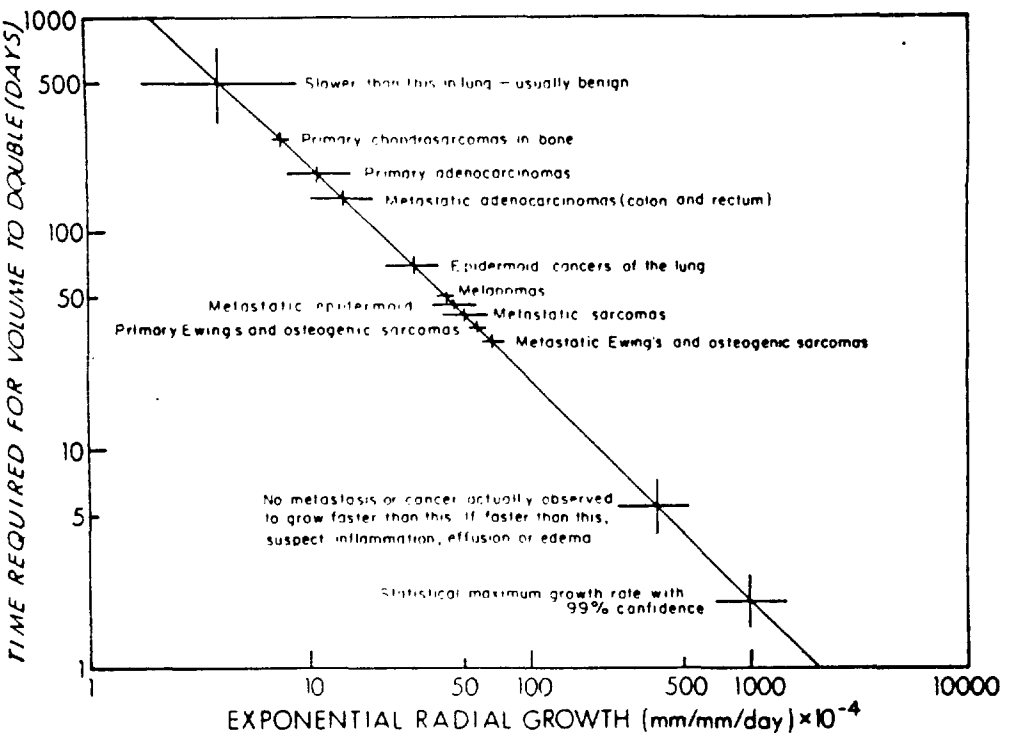

Fig. 4. This nomogram relates the time required in days for a growing spherical cancer to double its volume to the exponential radial growth rate in mm./mm./day. By multiplying the exponential radial rate by 3 and moving the decimal place to the right three places, still an additional parameter is obtained—the net gain in cancer cells per thousand existing cancer cells per day.

mm./mm./day to the time required for the volume to double, but the line of intersection reports the mean rates for various types of cancers and metastases that have been observed to grow in the lung.[6–8]

As a basis of comparing the linear radial growth rate of cancers to the linear growth of a non-neoplastic epithelial tissue in an adult, we can look at the data on the growth of William Bean's left thumbnail.

> Secular trends in growth of my thumbnail are reported. Various observations, including slowing on the rate of growth with infections, are recorded. The slowing of the rate of growth has progressed in somewhat irregular phases. This is a phenomenon that most people observe if they care to introspect themselves as they participate in the aging process. The average daily rate of growth has varied from 0.123 mm. per day when I was 32 to 0.100 mm. when I was 61.*

Throughout a 30 year period the growth was much faster than that observed for the cancers measured in this study. Cancer tissue may frequently grow more slowly than normal tissues, rather than more rapidly. The difference between cancerous and normal tissue is more a matter of control and organization than of rate.

During the period of clinical observation, it might prove useful to be able to quantitate a slowing of growth rate as a parameter of effective therapy. This might be particularly useful with chemotherapy. A slowing of rate might be an indication for continued therapy. An acceleration of rate would certainly merit a consideration of stopping the treatment. In the case of surgical resection of metastases, survival in excess of the maximum survival to be expected for a metastasis with a known growth rate would serve as an index of therapeutic success.

The data in this study all apply to untreated cancers. Short-term betterment of survival in categories of cases of similar size and linear growth rate would be necessary to show the longevity benefit of new types of therapy. When present, many of these benefits are short term. For example, 200 days of comfortable life at the end stage of cancer is superior to only 100 days of progressive dyspnea produced by the sustained growth of cancer. However, such short-term evaluation would be facilitated by a kinetic staging system based on growth rate and mass that is applicable to individual cases.

*From Bean, W. B.: Arch. Intern. Med. 134: 497, copyright 1974, American Medical Association.

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