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EXHIBIT**
MON-289

The Detection and Growth of Intrathoracic Neoplasms

*The Lower Limits of Radiographic Distinction, the
Antemortum Size, the Duration, and the
Pattern of Growth as Determined by
Direct Mensuration of Tumor Diameters from
Random Thoracic Roentgenograms*

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The purpose of this investigation was to explore the applicability of repetitive non-simultaneous and nonsystematic mensuration of the roentgen shadows of malignant neoplasms in the lung to the betterment of our understanding of the growth and behavior of malignant neoplasms in man and a better definition of the limitations of the roentgenographic detection of pulmonary tumors.

Material

Consecutive patients attended at the Ellis Fischel State Cancer Hospital between 1940

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and 1961 and having 2 or more thoracic roentgenograms showing intrathoracic primary or metastatic cancers were included in the study. When multiple thoracic roentgenograms were taken on the same day, only the best study was considered. Roentgenograms taken by some technique other than the standard 72 in. target-film distance, posterior-anterior projection, were excluded. Cases meeting the initial conditions included 21 patients having 22 primary pulmonary cancers and 176 patients with cancers metastatic to lung. All roentgenograms were reviewed, and all of the primary cancers and 138 of the metastatic cancers showed circular radiopacities having diameters measurable simply with dividers and a millimeter scale (Table 1, Fig. 1). That these circular radiopacities measured on posterior-anterior projections were in fact spheres could be ascertained in

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TABLE 1.—Histological Types of Measurable Intrathoracic Neoplasms Observed and Number of Posterior-Anterior Thoracic Roentgenograms Taken per Patient

	Types of Intrathoracic Neoplasms	No. of P-A Thoracic Roentgenograms per Patient												Totals *
		2	3	4	5	6	7	8	9	10	11	12	13	
Metastases from Known Primaries	Adenocarcinoma	27 *	24	6	7	1	1	1	4					71
	Transitional Ca.	2	1											3
	Epidermoid Ca.	6	5	5	1	3	1							21
	Soft Tissue Sarc.	8	5	2		1		1				1		18
	Osteous Sarc.	1	3		1									5
	Lymphomas	3		3		1	3	1						11
	Melanoma	1	2											3
	Unclassified Ca.	3	1	2										6
	Subtotal for Metast.	51	40	19	9	6	5	3	4			1		138
	Primary Pulm. Ca.†	7	5	3	1	1	1	2					1	21
	Totals *	58	45	22	10	7	6	5	4			1	1	159

* No. of patients.

† Ref. 4.

many cases by observing that these opacities were also circular on lateral projections, and the diameters of the circles were the same in both views. The reasons why 38 of the metastatic cancers were not measurable are given in Table 2.

The tumors of the patients were observed on from 2 to 13 separate thoracic roentgenograms taken on different dates at intervals of time between dates varying from 1 to 1,200 days, with a median interval between 51 and 100 days and a wide dispersion of the numbers of days within various intervals. No system has governed how frequently thoracic roentgenograms were ordered in the follow-

up of cancer patients attended at Ellis Fischel during the 21 years of the study. Many of the primary pulmonary cancers and the pulmonary metastases were observed during periods when the host was free of symptoms, though the development of symptoms probably influenced the obtaining of some examinations.

The diameters of the primary pulmonary cancers were measurable at 92 different times. Among the 138 patients with measurable intrathoracic metastatic cancers (Table 1), 6 patients had but 1 metastasis measured, 40 patients had 2 distinct and separate metastases, 10 patients had 3 metastases, and 1

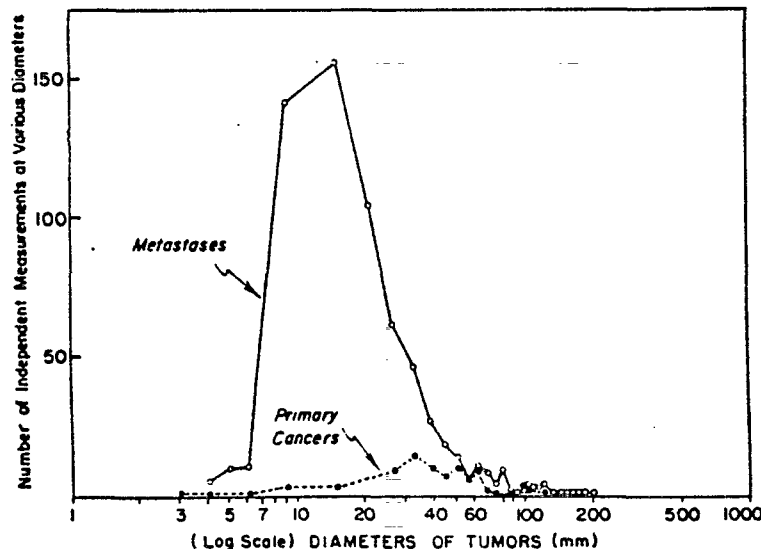


Fig. 1.—Frequency distribution of the measurements of the serial diameters of intrathoracic neoplasms of man observed repeatedly but randomly by 72 in. posterior-anterior thoracic roentgenograms: 656 independent measurements of 1 or more intrathoracic metastasis in 138 persons and 92 independent measurements of 22 primary pulmonary cancers were made.

Fig. 2.—Cumulative frequency measurements of various plotted successive linear and logarithmic probability paper horizontal lines that indicate the confidence limits normal or Gaussian distribution. Linear better approximation the 95% confidence limits on the logarithmic plot, suggesting a log distribution.

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TABLE 2.—Types of Inmeasurable Pulmonary Metastases Observed on Sequential Thoracic Roentgenograms

Type of Cancer	Reason Metastases Inmeasurable					Total
	Diffuse or Lymphangitic	Hilar	Pleural Effusion	Indistinct	Combination	
Epitheliocarcinomas						
Breast	9	1	1		2	13
Large Bowel	1			2		3
Stomach	1					1
Kidney	2					2
Endometrium	1					1
Ovary	2					2
Subtotal	16	1	1	2	2	22
Epithelioid Carcinomas						
Soft Palate	1					1
Cervix	1					1
Lip	1					1
Subtotal	3					3
Melanocarcinoma	1					1
Fibrosarcoma				1		1
Lymphomas						
Hodgkins Disease	1				1	2
Lymphosarcoma	1	2				3
Lymphocytic Leukemia	1					1
Subtotal	3	2			1	6
Grand Total	23	3	1	3	3	33
Film missing from files						
Rhabdomyosarcoma	1					1
Osteogenic sarcoma	2					2
Adenocarcinoma, large bowel	1					1
Chorionic ca., uterus	1					1
Total	5 (2.8% of cases)					

Totals •

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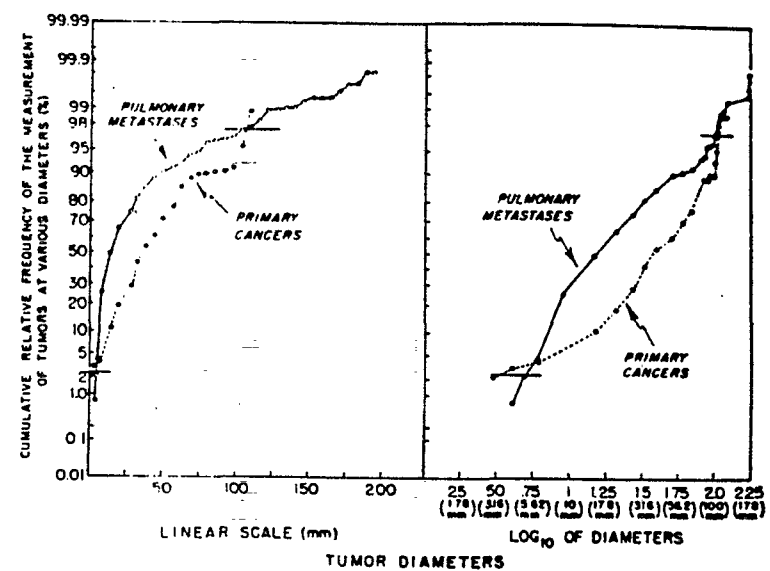
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1 of 656 diametric measurements of the
astases are given in Figure 1. The cumu-
lative relative frequencies of the respective

diameters are plotted successively on linear
and logarithmic probability paper in Figure 2.
The closer a probability paper plot of the
cumulative relative frequency of a distribu-
tion of events approaches a straight line, the
closer is the frequency distribution of the

Fig. 2.—Cumulative relative frequency of the measurements of tumors of various diameters plotted successively on linear and logarithmic probability paper. The 2 horizontal lines on each plot indicate the 95% confidence limits of a normal or Gaussian distribution. Linearity is better approximated between the 95% confidence limits on the log probability plot, supporting evidence of a log normal distribution.



events to a normal or Gaussian distribution.³ Linearity is approximated better in the log-probability plot of Figure 2, and the equations of a Gaussian distribution were used to determine the parameters of a log normal distribution of the diameters (Table 3).³

The diagnostic acumen of the radiologists was tested in 2 ways. One test was made by the random placement, upon the posterior and anterior thorax, of balls of lucite having a radiodensity approximating that of solid tumors and ranging in diameter from 1.6 to 12 mm. Posterior-anterior thoracic roentgenograms were taken of each arrangement of the lucite spheres at 72 in. target-film distance, 70 kv., 200 ma., and 0.05 sec. The radiologists then examined these films, attempting to locate the circular shadows. The second method of testing the acumen consisted of having the roentgenologists examine films that had been interpreted as normal before the location of the tumors became evident on subsequent examinations.

The radiologists could locate the opacities of lucite balls 10-12 mm. in diameter regularly regardless of the location. They could locate the radiopacities of balls 6 mm. in diameter only when the opacities were located in intercostal spaces contrasted against aerated lung. They could distinguish the radiopacities of 3 mm. diameter balls from normal pulmonary shadows in these same areas of favorable contrast only when they were shown precisely where to look. Radiopacities of balls smaller than 3 mm. in diameter were indistinguishable from anatomical pulmonary radiopacities.

No single primary pulmonary cancer nor single pulmonary metastasis smaller than 6 mm. in diameter was interpreted as an abnormal shadow initially by the radiologist. By the review of earlier films taken before the location of tumors had become evident, the smallest primary cancer detectable was 2.6 mm. in diameter, and the smallest metastasis was 3.5 mm. in diameter, both of these measurements being equivocal. Even after this review there remained a group of 60 patients having had thoracic roentgenograms which were taken before the location of tumors became evident and which were read as "nega-

tive" initially and were still interpreted as "negative" at the review. The time between the taking of the thoracic roentgenogram interpreted as "negative" and the taking of the first examination showing tumor varied from 11 to 1,200 days with a median interval of 300 days.

Comment

The diameters of spherical intrathoracic neoplasms observed by the repetitive and nonsystematic mensuration of the shadows of these tumors seen on standard 72 in. target-film distance posterior-anterior thoracic roentgenograms have been shown in Figures 1 and 2 to approximate a log-normal frequency distribution. If the cancers were observed randomly between the limits of radiographic distinction at one extreme and antemortem size at the other extreme, and if the cancers grew by a geometric progression in size, then observations of size between the 2 limiting conditions might be expected to distribute into a normal or Gaussian distribution on a size scale of geometric progression, i.e., a logarithmic scale. Since no system seems to have determined how frequently "chest x-rays" were ordered at Ellis Hospital during the past 21 years and since there is such a wide dispersion of the span of time between examinations, there is every reason to suppose that we have collected a group of random measurements. That the frequency distribution of these measurements forms a log normal distribution is in support of the concept that these intrathoracic cancers of man were indeed growing by a geometric progression in size as postulated by Collins.¹¹ However, other as yet unrecognized factors could have produced the log normal distribution. The parameters of the log normal distribution of the measurements is given in Table 3. These parameters state that the probability of observing on a standard thoracic roentgenogram a tumor smaller than 6 mm. in diameter would be 0.025 and smaller than 3 mm. would be 0.005. This is in agreement with the direct tests of the radiologists' diagnostic acumen by using the lucite balls and

TABLE

Calculation of Standard Deviation

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TABLE 3.—The Parameters of the Log Normal Distribution of the Diameters of Randomly Measured Primary Pulmonary Cancers and Pulmonary Metastases *

	Primary Pulmonary Cancers		Pulmonary Metastases		% of All Observations
	Log Distribution *	Diameter Mm.	Log Distribution *	Diameter Mm.	
Mean -2 S.D. †	0.4190	2.6	0.4877	3.07	
Mean -2 S.D.	0.7393	6.3	0.8030	6.35	
Mean	1.5290	36.4	1.4336	27.1	
Mean +2 S.D.	2.3205	200	2.0642	116.9	
Mean +2 S.D.	2.7008	602	2.3785	239.6	
S.D.	0.3801		0.3153		

* Calculated from material in Figure 1
† Standard deviation.

viewing films previously read as negative
after the locations of tumors were known.

The parameters in Table 3 also state that the probability of observing a primary pulmonary cancer larger than 200 mm. or an intrathoracic metastasis larger than 116 mm. would be less than 0.025. The largest cancer and metastasis observed were respectively 123 mm. and 200 mm. in diameter. Larger tumors were not observed because the patients died, and intrathoracic cancers between 12 and 20 cm. in diameter may be considered antemortem size, requiring either definitive therapy or the death of the host.

By expressing cancer size by the number of neoplastic cells rather than by diameters, a cancer of 6 mm. in diameter contains about 1.13×10^8 cells, a cancer of 123 mm. in diameter about 9.7×10^{11} cells, and a cancer of 200 mm. in diameter about 1.86×10^{12} cells. If growth occurs predominantly by the random division of the cancer cells followed by a period of growth of the daughter cells to approximately the size of the parent cells before cellular division again occurs, then these cancers are equivalent respectively to 37, 39.8, and 40.8 binary divisions or "doublings" of a single cell. We then have evidence that the duration of an intrathoracic neoplasm between the lower limit of radiographic visibility (6 mm. in diameter) and antemortem size (200 mm. diameter) would be equal to no more than 11 binary divisions of the cells originally within a cancer 6 mm. in diameter (40.8 - 26.7 = 14.1). The maximum duration of the life of the untreated host between these same limiting conditions

would therefore be equal to the time required for all the cells to divide once, i.e., the doubling time, multiplied by 14. For undifferentiated and epidermoid cancers of the lung having mean doubling times of about 90 days,⁴ the duration of the life of the untreated host between the limits of radiographic visibility and antemortem size of the intrathoracic tumor would be about 1,260 days, or 3.45 years. Among the metastases measured in this study the most rapid doubling time observed was 5 days. For this tumor the life expectancy of the host would not and did not much exceed 70 days after the appearance of the metastasis (5 day doubling time $\times$ 14 doubling intervals = 70 days). Collins has reported measurements of doubling times of metastases in the same range as observed for metastases in this study,^{1,2,5} and from these the prognosis placed on the life of the host by more slowly growing metastases can be estimated similarly.

Summary and Conclusion

The frequency distribution by seriated tumor diameter of 92 random, repetitive, and nonsimultaneous radiographic measurements on 22 primary pulmonary cancers and 656 such measurements of 1 to 4 pulmonary metastases in 138 consecutive patients having metastasizing cancers and sarcomas of different types is reported. The distribution of the measurements of tumors of different sizes is randomized in a log normal distribution, and the parameters of this distribution are reported. A log normal distribution of random observations measured between the lower

limits of radiographic resolution and the upper limits of morbid tumor size would be expected of tumors that grow by geometric progression.

The lower limits of resolution achieved by standard thoracic radiographic techniques is about 3 mm., but tumors are not generally diagnosed by the radiologist until their diameter exceeds 6 mm., a size equivalent to the 26.7 doublings of a 1,000 cubic micron cell. A malignant intrathoracic neoplasm that has attained a diameter of 200 mm., a size equivalent to 40.8 doublings of a 1,000 cubic micron cell, requires definitive therapy or else the cancer will generally kill the host during the next interval of the doubling of tumor volume. The maximum life expectancy of the untreated host between the radiographically visible size and the antemortem size of an intrathoracic tumor is equal to about 40.8 doublings (200 mm. tumor) minus 26.7 doublings (6 mm. tumor) or about 14 doublings multiplied by the doubling time of the cancer.

We wish to express our appreciation to Dr. C. M. Waggoner, Chief of Diagnostic Radiology at the Ellis Fischel State Cancer Hospital, for permission to review the accumulated radiographic files of that institution and for radiographic consultation.

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REFERENCES

1. Collins, V. P.; Loewler, R., and Tivey, H.: Observations on the Growth Rates of Human Tumors. *Amer. J. Roentgenol.* 76:988-1000, 1956.
2. Collins, V. P.: Time of Occurrence of Metastases from Carcinoma of Colon and Rectum. *Cancer* 15:387-395, 1962.
3. Spiegel, M. R.: *Outline and Theory and Problems of Statistics*, New York: Schaum Publishing Co., 1961.
4. Spratt, J. S., Jr.; Spjut, H. J., and Roper, C. L.: The Frequency Distribution of the Growth Rates and the Estimated Duration of Primary Pulmonary Carcinomas. *Cancer*, in press.
5. Unpublished data on the growth rates of pulmonary metastases from human cancers and sarcomas observed at the Ellis Fischel State Cancer Hospital, 1940-1961.