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On Growth Rate of Lung Tumor in Two Cases

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肺腫瘍の症例における発育速度に関する考察

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我々は以前よりX線学的に肺腫瘍の増殖速度の観察を行つてゐるが、日常遭遇する悪性腫瘍の増殖速度は exponential growth と見なし得ない場合が多い。もし exponential growth ならば growth rate は constant であるべきである。即ち generation time (g.t) 及び doubling time (d.t) は一定でなければならない。2例の肺腫瘍についてX線 film 上の陰影の大きさを経日的に graph に plot しその growth curve から g.t. を求めた。一方手術で剔出し、その腫瘍の組織学的観察及び DNA 合成 ($^3\text{H-TdR}$) 使用による invitro labeling

の面から g.t を測定し d.t. と比較した。d.t 及び g.t は腫瘍の増大につれて次第に延長して行く、組織学的には腫瘍の中心部は壊死におちいり周辺部の一部が活性である。 $^3\text{H-TdR}$ labeling も周辺部のみが陽性である。この事は growth rate が constant でない事を立証している。我々が観察し得る肺腫瘍は、大きく中心部は壊死を示している。host と tumor 間、tumor 間の影響により、腫瘍の増殖は exponential ではなく Linear growth であることを観察した。

Introduction

Growth rate of malignant tumor can be determined by various methods—tissue culture, DNA precursor, roentgenography, etc— and many data obtained by these methods are reported¹⁾⁻¹¹⁾.

Previously we reported on a method to determine the growth rate of lung tumor by observing change in the size of the lung shadow in roentgenogram¹²⁾. In this case we took the same assumption with Collins *et al*¹³⁾ that the tumor is an aggregate of asynchronous cells, and that usually they proliferate at a constant rate, that is, they made exponential growth. In many cases, however, pulmonary tumors which we encounter in daily practice, are not pliable to determination of the growth rate by the exponential equation, because, owing to their extreme growth, many factors between the host and tumor as well as within the tumor may exert their influence to modify the pure exponential growth. In order to know the exact growth rate it is of course necessary to make histological examination. At the same time it is desirable to trace the change in the size of tumor in roentgenogram during a period when the various factors are not yet influential on it. But to perform these two with one same patient is of course impossible. Incidentally we encountered two patients who were relatively adequate for making these two examination respectively. We made observation on the growth rate of their tumors and discussion on the obser-

vations. These are reported in this paper.

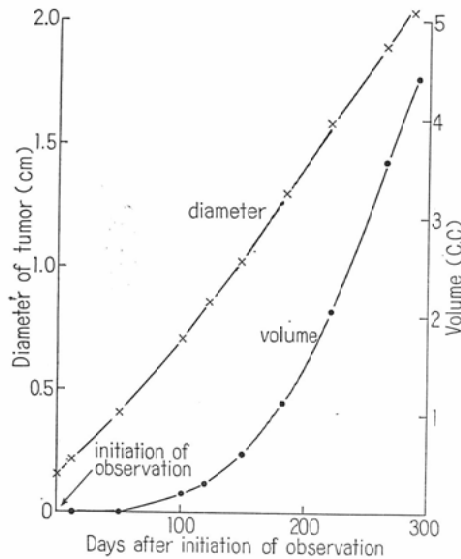
Method of Observation

In two cases of pulmonary tumor which exhibited in their chest roentgenograms circular shadows of distinct contour, and which could successively be observed more than twice, their growth rates were examined by determining the doubling time and DNA synthesis rate, the latter by means of *in vitro* labeling of excised tumor (from one case) with $^3\text{H-TdR}$. In measuring the size of the circular shadow, the arithmetic mean of its two perpendicular diameters was calculated. The roentgenogram was taken by irradiation in the standard dorsoventral direction, and distance of roentgenography was not constant for each, but the resulting error was too negligible to require any correction in measured values with respect to the distance.

Case 1. A male aged 17. The past and family histories were both noncontributory. Since about the middle of January 1966, he had complained of pain in the left knee joint, and at the same time he noticed swelling at this part. The pain and the swelling gradually increased. He visited a certain physician in the early May and received explanatory excision. The swelling was histologically found to be osteogenic osteoblastic sarcoma. On May 20 he was admitted into a hospital to undergo the amputation of the left femur. The postoperative course was satisfactory, and x-ray examination on June 23 disclosed no abnormalities. About a month later, a circular shadow of tumor was observed in the upper field of the left lung, and diagnosed as the pulmonary metastasis of the osteosarcoma. Thereafter thoracic roentgenography was performed about once a month to observe increase in the size of the tumor shadow.

Determination of doubling time (d. t.) by growth curve (Fig. 1).

Fig. 1. Growth curve of tumor (lung metastasis) postoperative osteosarcoma.



Since a circular shadow was noted in the thoracic roentgenogram, its two diameters had periodically been measured and their arithmetic mean calculated, and measured values were plotted on the ordinate against days on the abscissa. The resultant curve was not exponential but linear. The d.t.'s at various time

were determined from the curve.

The anamnesis and x-ray film of this case were supplied by Dr. S. Niizuma, chief of roentgen section of Takasaki National Hospital. Deep gratitude is due to his kindness.

Case 2. A male aged 68. The past and family history were noncontributory. About the late July, 1965, he began to develop cough and sputum. On August 2, he was examined by a physician, who found an abnormal shadow in his thoratic roentgenogram. He was introduced by this physician to Ishihara Department of Surgery, Gunma University. He visited this department on September 13, and as the result of detailed examinations, diagnosis of pulmonary cancer was made. On October 27 he received operation (lobectomy of the right lower lobe). Histological diagnosis was Squamous cell carcinoma.

i) Growth curve (determination of d.t.)

The growth curve was obtained by plotting the means of two diameters of the tumor shadow in the roentgenogram, and from it were calculated average d.t. (\bar{T}) at various time points. In Fig. 2 the abscissa was day of observation, and the ordinate the mean of the diameters.

ii) Histologic and autoradiographic examinations (determination of generation time and histological findings)

The tumor was excised, and its segments were placed into the incubating tube together with medium 1 cc (Eagle's medium + 10% calf serum + penicillin) and 3H-TdR (specific activity 2.5Ci/mM) ($0.02\mu\text{Ci}/5 \times 10^4$ cells), and the tube was kept in the water bath at 36.5 °C for one hour to perform *in vitro* labeling. From the segments were prepared 2-3 μ samples (with Fuji ET-2E stripping film), and after exposure in a dark box at 4°C for 2 weeks, and 5-minutes development (with Fuji Fix), they were stained with hematoxylin-eosin to be examined microscopically. In this case, labeling index (L.i.) was determined at 1 mm intervals in the band-forming range as to its right and left periphery to the depth of 100 μ (since the radioactivity attains to the depth of 100 μ in 1 hour incubation with 3H-TdR), and g.t. was computed by giving the Mayneord's formula various measured values (average Li, Ri (radius of the tumor), and D (thickness of active zone in the periphery)).

Results

Case 1.

When the means of the 2 diameters of the tumor shadow in the chest roentgenogram were plotted, a nearly linear curve was obtained. namely, the growth of the tumor was not exponential but linear. By means of this curve, d.t.'s in various time points were determined as follows: Doubling times at 130, 230 and 260 days after the initial day of the observation are 30, 50 and 60 days, respectively. In this way, d.t. was increased with time. This means that with the growth of the tumor, the growth rate lowers as a whole.

Case 2.

i) Growth curve

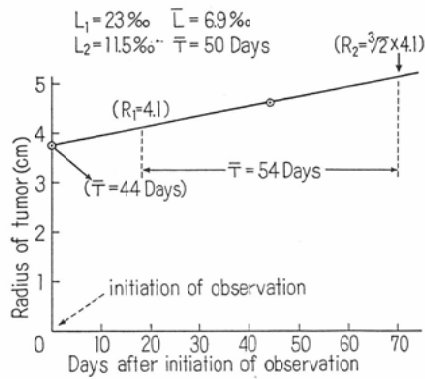
The \bar{T} values were obtained from the observation curve (Fig. 2) on the assumption that a portion of it between 2 time points is approximately linear.

They were 44 and 54 at 0 and 44 days respectively.

ii) Histological findings

The central necrotic focus (4.5 cm in radius) was distinguished from the peripheral part (1.2 cm wide).

Fig. 2. Growth curve of lung tumor
— Sq. c. carcinoma —



Microscopically, capsule was observed in the outermost, and relatively large necrotic foci were intermingled in the active zone.

iii) Autoradiogram

$^3\text{H-TdR}$ uptake was not demonstrated at all in the central necrotic focus, the outermost capsule, and necrotic foci sporadically present in the active zone. In the remainder, the active zone, L_1 (L_1) was 23%. Since the active and the inactive part in the peripheral zone occupied nearly the same areas the average L_i for the total peripheral zone (L_2) is 11.5%. The average L_1 for the total tumor (L) as computed by the formula was 6.9%, and g.t. at 44 days was 50. This value well agrees with that obtained from the growth curve.

The formula for computing g.t. at 44 days:

$$\bar{L} = L \times \{R^3 - (R-D)^3\} / R^3 \quad (1)$$

$$\bar{T} = 0.693 \times S / \bar{L} \quad (2)$$

The values 11.5%, 4.6 cm, 1.2 cm, 0.5 days (suppositional) are given to L , R , D and S , respectively.

$$\bar{L} = 11.5 \times \frac{4.5^3(4.5-1.2)^3}{4.5^3} = 6.9$$

$$\bar{T} = 0.693 \times \frac{0.5}{0.069} = 50$$

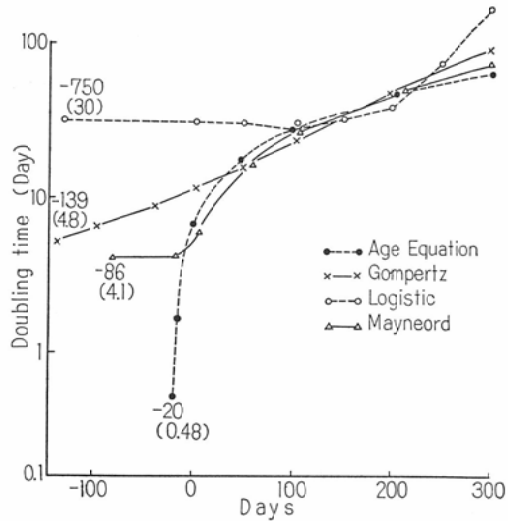
Discussion and Summary

The limit of observable size of the tumor on roentgenogram is said to be 0.5 cm or 1.0 cm. In case 1 the presence of the tumor was first recognized in a size of about 0.5 cm in later roentgenogram, and then retrospectively confirmed in the early stage one. When the tumor shadow is such a small one, it is apt to be overestimated owing to the overlapping of other shadow. As previously stated we made every effort to evade such errors. It is very natural that when the shadow is small, a slight difference in observed value will significantly affect the form of the curve. But, be it as may, we could not consider in any way that the growth curve plotted on a semi-logarithmic section paper was strictly exponential, if we judge from the form of the whole curve, though this may be rather qualitative assessment. When 4 formulas of growth (fig. 3) are applied to such growth curve, diverse values are computed for each of the indices as seen in Fig. 4. We refrain from giving any conclusion as to which of these values is most pertinent from the

Fig. 3. Equation of tumor growth

- 1) Age Equation: $\frac{dv}{dt} = dt^B v$
 - 2) Gompertz: $\frac{dv}{dt} = de^{-\mu^t V}$
 - 3) Logistic: $\frac{dv}{dt} = CV (K-V)$
 - 4) Mayneord: $\frac{dv}{dt} = \alpha \left(\frac{4\pi}{3} [R^3 - (R-D)^3] \right)$
-
- Exponential $\frac{dv}{dt} = \alpha V$

Fig. 4. Change of growth rate.



viewpoint of medical common sense. But at least the following can be said concerning the present 2 cases: Since, as seen in growth curve in Fig. 4, the 4 formulas gave nearly the same growth rates for a period of 100–200 days after the start of observation, the growth rate of the tumor of 1 cm in diameter (mean for the range of 0.75–1.5 cm) can be regarded as clinically representative.

Case 2 was primary lung cancer, and histologically diagnosed as squamous cell carcinoma. It is widely known that the cancer of this kind is apt to produce central necrotic part.

Only 2 roentgenograms were available as the base of plotting the growth curve. We assumed 2 possibilities—exponential growth curve and approximately linear growth curve. And the result, as afore described, was obtained. What we can say grossly is that the estimated value for the one cell stage, which is used as a mark of the time when the tumor starts the growth as malignant one, is remarkably varying dependent on the hypothetical growth model. And this was true with the present case 1.

We have discussed on the basis of the observations on 2 cases. We want to continue investigation whenever we have a chance, and will be perform through atudies on this problem by accumulating the relevant cases.

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