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Growth of Testicular Neoplasm Lung Metastases: Tumor-Specific Relation Between Two Gompertzian Parameters

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Abstract—*Sequential chest roentgenograms obtained in ten selected cases of testicular tumor having multiple lung metastases were considered. Different nodules were regarded as independently growing and it was assumed that each followed the same growth curve. The Gompertzian equation was found to carefully describe experimental data and a strong linear correlation between two equation parameters was identified. Growth patterns predicted by equations were consistent with observed clinical data and with the natural history of testicular tumors. These findings confirm that the method used leads to satisfactory results in studying multiple metastases. The existence of a linear correlation between two Gompertzian parameters supports previously reported data on tumor-specificity of growth patterns.*

INTRODUCTION

FIRST proposed by Laird [1], the Gompertzian function was successsfully used to describe tumor growth in laboratory animals. Sullivan and Salmon [2] utilized such a model to describe tumor growth and drug induced tumor regression in a series of 11 patients with IgG multiple myeloma. They were also able to quantitatively predict the tumor's drug sensitivity.

In the Gompertzian model, specific instantaneous growth rate $\alpha(t)$ decreases at a constant rate β from an initial value α_0 dropping asymptotically to zero.

In some species of laboratory animals and utilizing data from the above-mentioned series of human IgG multiple myeloma, Norton *et al.* [3] and Bruton *et al.* [4, 5] showed that although α_0 and β varied from one tumor to another, the two parameters are not independent. In fact, it has been verified that they exhibit a strong linear correlation of the form

$$\alpha_0 = K\beta + C \qquad (1)$$

where the regression slope K is a tumor-specific constant and the intercept C is found to be very close to zero. In practice this fact means that: (a) tumors having highest initial specific instantaneous growth rate have highest retardation factor; (b) tumors of the same particular kind approach the same theoretical upper limit N_1 (Fig. 1).

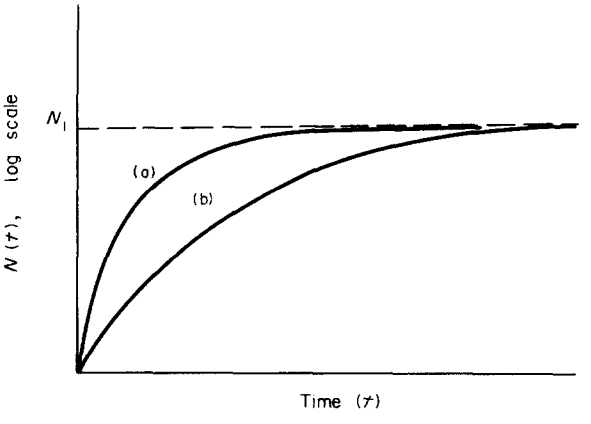

Fig. 1. Gompertzian growth in two hypothetical tumors having different specific instantaneous initial growth rate α_0. Tumor a starts with higher growth rate but slows down swifter than tumor b.

Brunton *et al.* [5] even suggest the hypothesis that K may be not only a tumor-specific, but also a species-specific growth constant. The hypothesis states, in other words, that a particular species has the ability to support a tumor of a certain maximum size.

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Extension of these kinds of investigations to human neoplasms carries some obstacles: protracted observation of tumor's free growth is required to verify the existence of a characteristic growth relation. Ethical considerations minimize this time, so that available data are generally too poor to identify anything other but exponential growth pattern; tumor mass measurements are almost always difficult and imprecise; clinical investigators give too little attention to such a matter and underestimate its usefulness in clinical problems.

The present preliminary report shows that tumor growth investigations may be carried out, without ethical problems, during 'staging' time, in human neoplasms having multiple measurable metastases and a sufficiently high growth rate.

MATERIALS AND METHODS

Patients

Chest roentgenograms, obtained during 'staging' in nine cases of non-seminomatous testicular tumors and one case of pure seminoma, all histologically proven, having lung metastases, were considered. Availability of roentgenograms and measurability of lesions determined patient selection. In each case many parenchymal lung localizations were present and two or more chest roentgenograms had been performed before starting treatment. In Table 1 are reported some data about material that was analyzed.

Minimum and maximum diameters of all clearly measurable lesions were recorded. An easily measurable distance among osseus fixed points was also assessed to identify a correction factor to reduce errors arising from geometrical differences in roentgenograms execution.

Tumor volumes were computed by corrected diameters a and b using relation

$$V=\frac{\pi}{6}a\,b\frac{a+b}{2}. \qquad (2)$$

Tumor mass was measured by considering a cellular density of 10^9 cells/cm^3.

Table 1. Main characteristics of selected patients' roentgenograms

Patient	No. of lung metastases	Diameter range of metastases (mm)	No. of roentgenograms	Time between roentgenograms (days)
1	8	9–69	2	10
2	5	13–21	2	13
3	3	18–48	2	24
4	3	18–25	2	20
5	12	9–30	3	6–7
6	4	10–18	3	12–7
7	24	8–34	2	16
8	11	9–30	2	26
9	11	11–28	2	15
10	3	8–16	2	9

Table 2. Coefficients of eq. $\alpha(t)=-\beta[\ln N(t)\times 10^{-9}]+\gamma$ *and significance of linearity in 10 cases of testicular tumors (lung metastases)*

Patient	Histological diagnosis	β (day^{-1})	γ (day^{-1})	Significance of linearity (P)
1	Eca+T(m)	0.0048	0.0224	<0.025
2	Eca	0.0080	0.0528	>0.1
3	Eca	0.0084	0.0496	<0.05
4	Eca	0.0120	0.0386	>0.1
5	Eca	0.0124	0.0570	<0.05
6	Eca+T(m)	0.0126	0.0204	>0.1
7	S	0.0129	0.0779	<0.01
8	Eca	0.0147	0.0493	<0.005
9	Eca+S	0.0159	0.0620	<0.05
10	Ch+Eca+T(i)	0.0493	0.1416	>0.1

Eca = embryonal carcinoma; T(m) = teratoma (mature); T(i) = teratoma (immature); S = seminoma; Ch = choriocarcinoma.

Table 3. Gompertzian constant and growth parameters in 6 cases of testicular tumors (lung metastases)

Patient	Specific instantaneous initial growth rate $\alpha_0(day^{-1})$	Retardation factor $\beta(day^{-1})$	Generation time (days)	Growth fraction* (%)
1	0.1212	0.0048	5.7	12.5
3	0.2243	0.0084	3.1	15
5	0.3132	0.0124	2.2	13
7	0.3450	0.0129	2.0	16
8	0.3540	0.0147	2.0	10
9	0.3901	0.0159	1.8	11

*At $N(t)=10^9$ cells.

From the Gompertzian equation it may be shown (see Appendix) that

$$\alpha(t)=-\beta[\ln N(t)\times 10^{-9}]+\gamma \qquad (3)$$

where $N(t)$ represents the total number of tumor cells present at time t and γ is a constant.

This means that, if the Gompertzian model is acceptable, computing $\alpha(t)$ (as $(\ln 2)/(DT)$ where DT is the doubling time) and $N(t)$ for different lung metastases, as suggested by Akanuma [6], and plotting those values in semilogarithmic scale, a straight line should be obtained.

All ten examined cases showed such a pattern and the linear regression gave statistically significant results ($P\leqq 0.05$) in 6/10 cases (Table 2). Four cases (Nos. 2, 4, 6, 10), having an inferior number of measurable metastases, could also be described by a linear equation like (3), although linearity was not statistically significant.

Utilizing Eq. (3), the specific instantaneous initial growth rate α_0, and the 'generation time' $t_g=(\ln 2)/(\alpha_0)$ (that is the theoretical doubling time from one cell to two cells) were computed (Table 3).

Assuming t_g to be constant, the growth fraction

$$g_f(t)=\alpha(t)\cdot t_g \qquad (4)$$

at $N(t)=10^9$ cells was assessed (this mass is considered to be the lowest limit clinically detectable).

Time of lung metastatization and time required to reach $N(t)=10^9$ cells, that is duration of subclinical disease, were also computed (Table 4).

RESULTS AND DISCUSSION

The leading hypothesis of the method is that metastatic nodules grow independently and each follow the same growth curve. According to this hypothesis, different sizes reflect only different times of metastatization. Therefore, different nodules can be regarded as kinetically different situations of the same nodule. Two observations will thus be sufficient to compute kinetical variables of the same growth curve and one will be able to identify Gompertzian parameters α_0 and β.

Table 4. Clinical history in 6 cases of testicular tumors (lung metastases): calculated vs real times

Patients	Month of 1st symptom	Month of diagnosis	Calculated month of metastatization	Duration of subclinical disease (months)*
1	9/78	12/78	1/77	11.5
3	9/77	12/77	3/77	6
5	9/78	11/78	6/78	4.5
7	3/79	7/79	2/79	4
8	2/77	9/77	5/77	4.5
9	1/79	1/79	7/78	4

*Time required to reach $N(t)=10^9$ cells.

In testicular tumors histological type of metastases can sometimes differ from the primary and perhaps from each other. This disadvantage, nevertheless, does not deprive previous consideration because a single non-homogeneous localization cannot significantly alter the results. Presented data confirm this assumption. On the other hand the high growth rate of this kind of neoplasm allows a satisfactory determination of volumetric changes.

Table 2 shows that in all examined cases a linear regression with positive coefficients was found. A statistical significance of linearity was demonstrated in 6 cases. Figure 2 shows a

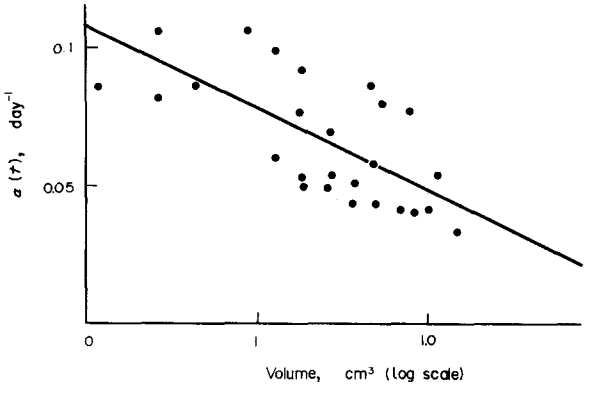

Fig. 2. Quantitative relation between specific instantaneous growth rate and volume in lung metastases of pure seminoma. Linear regression gives $\alpha(t) = -0.0129\ [\ln N(t) \times 10^9] + 0.0779$.

graphical representation of linear quantitative relation between $\alpha(t)$ and $\ln N(t)$ in patient No. 7. Experimental data are distributed both according to the Gompertzian model and the previously described hypothesis.

Computed values of the specific instantaneous initial growth rate, α_0, and corresponding retardation factor, β, are collected in Table 3, where one can easily verify an evident correlation between such values. This correlation can be quantitatively analyzed: a linear regression gives:

$$\alpha_0 = (23.9 \pm 1.5)\,\beta + (0.016 \pm 0.023) \quad (5)$$

with $r = 0.992$ and a highly significant linearity ($P \ll 0.005$) (Fig. 3).

This finding confirms previous published data [4, 5] and support the tumor-specific character of K constant. Furthermore, keeping in mind histological differences among examined testicular tumors, this result seems to support, in part, species-specificity hypothesis.

For human multiple myeloma $K = 28.5 \pm 0.6$.

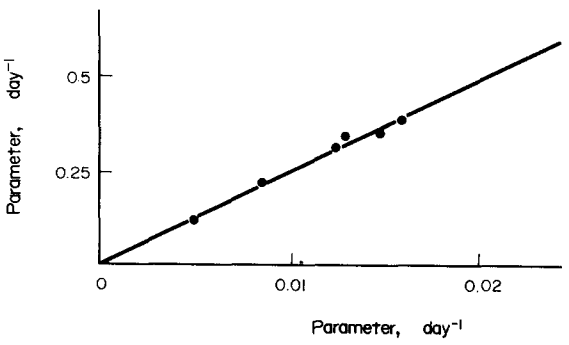

Fig. 3. Quantitative relation between Gompertzian parameters α_0 *and* β *in six cases of testicular tumors (lung metastases) having statistically significant linearity of Eq. (3) (see text). A linear regression gives* $\alpha_0 = (23 \pm 1.3)\,\beta + (0.016 \pm 0.023)$; $r = 0.992$.

The discrepancy between the two numerical values can be explained in at least two ways: (a) experimental data used for computing K constant in multiple myeloma were collected monitoring total malignant cell number: conversely, the present report deals with a limited portion of whole disease. (b) K is not a species-specific constant, therefore different tumors have different K values.

Point (a) seems to be the most reasonable explanation for the noticed difference.

Straight line of Fig. 3 may be assumed to pass through the origin [that is $C = 0$ in Eq. (1)]. Equation (5) then becomes.

$$\alpha_0 = (25.2 \pm 1.6)\beta \quad (6)$$

with $r = 0.9992$ and a very significant linearity ($P = 0.005$).

This equation reduces the drawing of the Gompertzian curve to a very easy task. The Gompertzian equation may be written in non-secular form:

$$\frac{1}{N(t)}\frac{dN(t)}{dt} = \alpha_0\left[1 - \frac{1}{25.2}\cdot \ln\frac{N(t)}{N(0)}\right] \quad (7)$$

which has α_0 as the only unknown parameter that can be estimated without protracted observation. The complete undisturbed growth pattern may now be well predicted. This facility, as other authors have emphasized, may have important practical applications in investigating the possibility of predicting the response to therapy on an individual basis, in designing treatment schedules, and so on.

In Fig. 4 cases that were not utilized in calculations ($P > 0.05$) are reported. Representative points pattern follow the straight line of equation (5) very well, giving further support to the previously explained rationale.

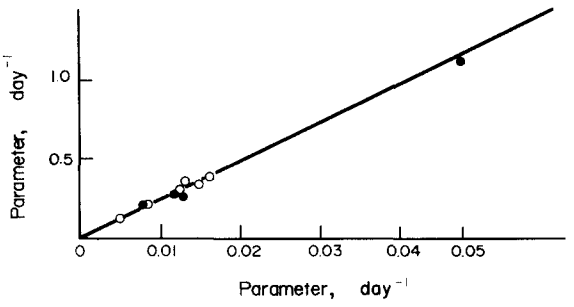

Fig. 4. Gompertzian parameters of four cases of testicular tumor (lung metastases) not having a statistically significant linearity of eq. (3) (●) are compared with regression line computed from six significant cases (○).

Generation times, t_g, and growth fractions at 10^9 cells, $g_f(t)$, (Table 3) were found to be comparable with corresponding data reported by Sullivan and Salmon for human multiple myeloma [2]. They have computed t_g values ranging from 0.92 to 5.94 days and $g_f(t)$ values ranging from 5.9 to 7.1%.

Table 4 shows time data that are consistent with the natural history of testicular tumors: early metastatization and rapid development. Subclinical disease duration seems to be very much shorter than previously assumed. This evidence is also supported by preliminary data of labeling index measures reaching 40–50% (investigation in progress at I.N.T.—Milan, personal communication). Similar observations on subclinical disease are reported in human multiple myeloma [2].

These facts are also consistent with previous investigations of the growth patterns of solid tumors. Charbit [7] has analyzed 530 human solid neoplasms showing that embryonal carcinomas are the fastest ones, followed by lymphomas and mesenchymal malignant tumors.

CONCLUSION

The method utilized in this report leads to satisfactory results in studying multiple lung metastases. With careful standardization in data survey (e.g., fixed geometry, multiple projections etc.) it can be extensively used. Multiple skin lesions seem furthermore to be a promising field of more precise investigation (a skin nodule is easier to measure than a lung metastasis). The use of a computer to obtain estimations of the parameters α_0 and β would obviously minimize the influence of measurement-errors and other random fluctuations.

The Gompertzian model seems to provide an adequate mathematical description of lung metastases of testicular tumors. Individual Gompertzian parameters α_0 and β exhibit a strong linear correlation that greatly simplifies the task of predicting the tumor growth pattern. There is now the background to investigate kinetic prognostic factors, quantitative drug–tumor interaction and other factors of clinical relevance in this kind of neoplasm.

The species-specificity of relation between α_0 and β needs to be further investigated.

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APPENDIX

The Gompertzian equation may be written in the integrated form

$$N(t)=N(o)\exp\left\{\frac{\alpha_0}{\beta}\left[1-\exp(-\beta t)\right]\right\} \qquad (1)$$

where $N(t)$ represents the total number of tumor cells present at time t; $N(o)$ the corresponding population at the chosen time origin and α_0 and β are positive parameters.

The term α_0 has the meaning of 'specific instantaneous initial growth rate' and

$$\alpha(t)=\alpha_0\exp(-\beta t) \qquad (2)$$

is the specific instantaneous growth rate at time t.

Differential form of (1) is

$$\frac{1}{N(t)}\frac{dN(t)}{dt}=-\beta\cdot\ln\left[\frac{N(t)}{N_t}\right] \qquad (3)$$

where $N_t=N(o)\exp\left(\frac{\alpha_0}{\beta}\right)$.

Putting

$$\frac{1}{N(t)}\cdot\frac{dN(t)}{dt}=\alpha(t) \quad \text{and} \quad \beta\ln N_t=\gamma$$

we have

$$\alpha(t)=-\beta\ln N(t)+\gamma \qquad (4)$$

where $\alpha(t)$ and $N(t)$ are measurable parameters.