Clinically disturbed tumor growth and feasibility of Gompertzian function growth model

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再発腫瘍の成長曲線とゴンペルツ関数モデルの効用

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悪性腫瘍の治療にあたつては，腫瘍成長のパターンを理解する必要がある．一般的な腫瘍成長のモデルとして，増殖率の一定な指数関数モデルが利用されているが，我々臨床家でも，大きな腫瘍はそれほど増大しないことに気づくことがある．このことを説明するには，実験腫瘍の成長観察から得られた，ゴンペルツ関数モデルを用いるのがよいであろう．臨床的に照射した皮膚転移のデータを示すが，これによると，

1．用いた線量は過少で，すべて再発した．

2．線量が大きいほど，最小腫瘍体積は小さくなる．

3．最小体積は，3週間後にあらわれるが，最初の腫瘍体積により，異つているようである．

4．腫瘍が縮小すればするほど，再発時の増殖率は大きいが，どれもだいたい同じ最大体積に近づいていく．

5．再発時の最大体積は照射前のそれにより少し小さい．

ゴンペルツ関数の特性を利用することにより，これらのことを，たやすく説明することができた．よつて，ゴンペルツ関数の特性は腫瘍の性質の一部を近似すると，結論する．

In the treatment of malignant tumors, it is helpful to understand the growth of tumors. Clinicians often encounter the deviation of tumor growth from the conventional exponetial growth model in which the growth rate is constant. To explain this deacceleration of tumor growth, several models have been proposed. Among those, Gompertzian function model is analysed to explain clinically disturbed tumor

growth. The analysis reveals that the maximum tumor volume exists which is asymptote of the function and that the growth rate is the function of tumor volume. This is consistent with biological facts that cell population determines cell increase rate. Hence the model can be defined as "differential of growth rate is proportional to differential of logarthmic of tumor volume" with a negative constant. A set of data of clinically disturbed tumor growth is shown. The results are explained with the characteristics of Gompertzian function. The method to estimate the time of tumor origination is also discussed.

I. Introduction

A. Necessity of tumor growth model.

In the practice of clinical oncology, one often encounters the problem of whether or not to treat a particular malignant tumor. This is due to the realization that treatment occasionally stimulates the growth of the tumor or its metastases. James, A.P. (1961), observed that irradiated cells show an increased mitotic index. Partial removal of cells from a culture causes abundant mitoses (Todaro 1965), which suggests that partial resection of a tumor causes an increase of the growth rate. Simple application of conventional constant growth rate is not feasible in clinical practices.

The factors to be considered prior to the treatment of a primary tumor are, for example:

1. What is the pattern of the tumor's growth and its metastases?
2. Will the treatment of the primary tumor provoke or prevent metastases?
3. How will the expected growth rate influence the vigor with which the chosen modality is applied?

In addition, when a metastasis is discovered during a follow-up visit to the clinic, it would be desirable to learn whether it originated before, during, or after the treatment to the primary lesion. The above questions are difficult to answer without the establishment of tumor growth patterns.

In palliative cases, therapy is frequently initiated without sufficient justification of the treatments. The mere presence of a tumor is not sufficient reason to irradiate. Palliative treatment of a tumor should be considered when:

1. It is undesirably symptomatic: or
2. It is the apparent source of further metastases: or
3. It is active and growing, and subsequent undesirable symptoms are expected.

The argument for reasons 2 and 3 requires an estimate of tumor growth.

B. Gompertzian function model

Gompertzian function model is fairly practical and is commonly employed for growth analysis. Laird (1964) proposed a Gompertzian function tumor growth model based on her empirical observations and analysis of the literatures. The basic idea of this model is that a tumor grows exponentially, but the growth rate is reduced exponentially, which results in an asymptote of the tumor volume (see equation 3).

In spite of criticisms, (Steele and Lamberton 1966) to Gompertzian model, it is analyzed to obtain the growth characters from this function.

II. Analysis of Gompertzian Function

A) Assumption of "retardation of growth rate"

Gompertzian function is explained by Laird (1965) as an "Exponential growth process limited by

exponential retardation", which means that growth is essentially exponential but the growth rate is exponetially reduced.

This can be expressed mathematically as follows:

(1) $dV/dT = A*V$

(2) $dA/dT = -R*A$

where V stands for tumor volume,

A for growth rate

R for retardation factor.

These two equations lead to

(3) $V = VI*EXP(AI/R*(1 -EXP(-R*T)))$

Where VI and AI are tumor volume and growth rate at the beginning of the observation, respectively.

B) The implications of Gompertzian function

Equation (3) implies the followings:

1) Maximum volume

Tumor does not grow bigger than a certain volume which is the asymptote of the equation. (Maximum volume or asymptote volume is symbolized with VM). Various reasons have been reported which account for the limitation of tumor growth. Laird (1964) simply conjectures "This retardation effect might be due to an increase in mean generation time without change in the proportion of proliferating cells, or it might be due to a loss in reproductive cells without change in the mean generation time of cells, or it is possible that these two might be combined". This retarding effect limits tumor size according to equation (4).

(4) $VM = VI*EXP(AI/R)$

In practice of tumor therapy, it would be convenient to know the maximum size of each tumor type. The maximum size is dependent on more than just the pathology of the tumor. Equation (4) indicates that the maximum volume also varies according to the value of R, which would characterize the relationship between host and tumor and between primary and metastases.

2) Volume dependency of growth rate

In equation (3) AI is the growth rate at the first observation and is the greatest growth rate observed. (The greatest growth rate is at the time of initiation which obviously can't be observed.) Growth rate (A) decreases acvording to the equation:

(5) $A = AI*EXP\ (-R*T)$

Growth rate (A) is easily obtained by measuring the tumor at least twice within a short interval since:

$$A = (dV/dT)/V$$

$$= dLOG(V)/dT \qquad \text{(Natural Logarithm)}$$

(6) $$= \frac{LOG(V1)-LOG(V2)}{T1-T2}$$

This growth rate has conventionally been considered a clinical parameter to judge the necessity of therapy, particularly in palliation. It should be pointed out that growth rate (AI) is only the initial value, which may sometimes retard quickly (as observed in skin metastases of breast carcinoma). In cases where tumor size is important, an estimate of the maximum size rather than the growth rate is desirable, viz., vena cava syndrome. Growth rate would not play a big role.

3) Relationship of growth rate and tumor volume

VI is the volume at first observation and the magnitude of VI is a function of the time elapsed between the tumor's origin to the first observation. The first observed growth rate (AI) is also a function of the time elapsed since the the tumor's origin.

A relationship exists between V and A. At time T, after the observation of tumor growth is initiated:

$V = VI*EXP(AI/R*(1-EXP(-RT))$.....(3)

$A= AI*EXP(-RT)$.....(5)

These two equations above lead to:

(7) $A-AI = -R*LOG(V/VI)$

When $VI = VM$, then $AI = O$

(8) $A= -R*LOG(V/VM)$

As equation (5) shows, A is a function of T and at the same time, equation (8) shows, A is also a function of V. Clinical experience substantiated this fact.

III. Disturbed tumor growth

Equation (3) indicates uniterrupted tumor growth. When the tumor growth is disturbed, for example, when one half of the tumor is excised, how does this affect the maximum size the tumor will achieve? The equation itself does not answer this question. Todaro (1965) reports that partial removal of cells from a contact inhibted culture of normal cells induces abundant mitosis. Breur (1966) reports a case mammary carcinoma, with a doubling time of about 700 days, which underwent a course of chemotherapy. After the therapy the mass became remarkably small, but the growth rate became very high. These facts support the assumption that the growth rate is tumor size dependent. When the size of a tumor is artificially reduced, then, if the individual cell characteristics are not altered, the value of A increases. If the value of A before and after the excision were the same, the maximum size of the tumor attained fater the excision would be one half of that before excision, which is difficult to believe from knowledges of daily clinical experience. Equation (7) shows that the retardation occurs not because of the elapsed time, but because of the increased cell population in a tumor. The term (V/VM) (here called volume factor) must be an indicator of cell population pressure in a tumor. So the growth rate is proportional to logarithmic of volume factor (V/VM), and the proportion constant is negative, and is the retardation factor. It has to be emphasised that clinical efforts have to be made not to decrease growth rate but to reduce the maximum volume.

A set of data of disturbed tumor growth is incidentally obtained in my clinical practice. Metastatic skin nodules from breast carcinoma of a 62 years old female patient are irradiated on a 250 KVp X-ray unit. The nodules are radiated individually with a three centimeter diameter cone. Daily two fractionation schedules are employed which are shown in Table 1. Longer and shorter diameters of each irradiated nodules are measured weekly. Since exact tumor shape is not easily determined, we assume that it is ellipsoid of rotation around the longer diameter. The volume is computed from the diameters of each nodules. The results are shown in Table 1 and are graphically displayed in Figure 1. The results indicates the followings.

1. The doses are too low and all nodules recurred.
2. The larger dose yields the lower minimum volume.

Table 1 Volume change after irradiation

Nodule No.	Weeks Dose	0	1	2	3	4	5	6	7	8	9
1.	900× 2	980	335	256	132	301	268	523	301	382	424
2.	900× 2	680	628	523	179	205	301	301	268	268	301
3.	1100× 2	760	424	205	50	205	301	576	335	424	382
4.	1100× 2	628	424	301	33	301	423	760	424	523	382
5.	1300× 2	1503	1055	680	65	0	132	424	231	301	205

unit cubic milimeter

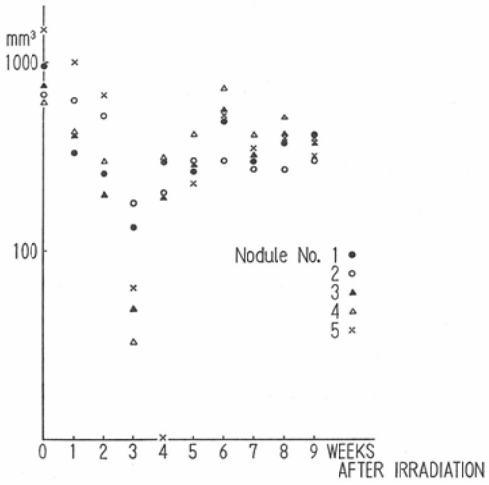

Fig. 1

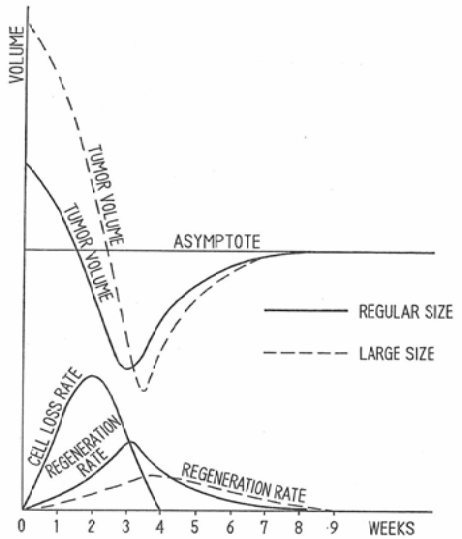

Fig. 2

3. The minimum volume, which is the equibilium of cell loss and regeneration, comes approximately three weeks after irradiation.

4. The more regression yields the larger growth rate. But the all recurrence curves show flattening and appear approaching the same asymptote which is the maximum volume.

5. The asymptote of the recurrence curve appears approximately 75 percent of the original size. 25 percent decrease of asymptote size has to be the merit of irradiation. The result No 4 is clear from the volume dependency of growth rate. The magnitude of radiation dose does not appear to determined the asymptote size. The possible mechanism to explain the result No. 3 is illustrated in Fig. 2. The minimum volume of nodule No. 5 took place a little later than the others. This phenomenon can be also explained with the volume dependency of growth rate. The cell loss pattern of the larger nodule won't be much different from those of the others. But the original volume of the nodule is approximately as double times larger as the others, therefore, the growth rate becomes slower. The dotted line in Fig. 2 illastrates this explanation schematically.

IV. Discussion

For clinical judgement of malignant tumors, being aware of the growth rate is not critical. Breur (1966 II) reported cases of breast carcinomas with doubling times of 23, 39, 59, 159, 177, and 745 days.

What causes these variations in doubling times among tumors of the same kind? This diversity is due to differences in tumor volume or variations in retardation factors among the cases.

As equation (7) shows, as the retardation factor (R) increases, the growth rate (A) decreases. It is not necessary to treat a tumor with a large retardation factor even if it has a high growth rate.

What causes the retardation is still not clear. Laird (1969) states it is due to genetically preprogrammed cell death. In addition, the factors which produce constant cell loss or differentiation of proliferating cells may also affect the retardation factor (R) e.g. hormone therapy, chemotherapy or radiation. By measuring the retardation factor (R), the effect of treatment can be evaluated. Cell contact can also influence the retardation factor. It is known that cell contact is an efficient method of cell communication Lowenstein, Kanno (1967). Immunological relationships of host and tumor also influence retardation. The retardation factor can be considered to vary with changes in the tumor host relationship. Constant observation is required even in cases which appear to be "steady" tumors; particularly in the cases where tumors remain steady with treatments.

It is of clinical interest to know the maximum volume of a tumor. Small nodules are not significant significant in the treatment of a malignant disease if they are not the source of further metastases. A hilum metastasis should be carefully evaluated, whether it will or will not eventually cause superior vena cava syndrome. If the metastasis, because of its location and the expected maximum volume, would not be expected to cause the syndrome, the treatment is not necessary.

There is no substantiation that tumor development necessarily results from the presence of a single cell. The presence of several cells could be required for tumor but at beginning doubling time is short, so the assumption that a tumor starts from a single cell does not cause significant difference in the results. On the other hand if the malignant cell or cells remains resting for a certain period, then the time when that cell or cells are activated is the origin of the tumor. Hence the origin can be calculated assuming that the tumor originates from a single cell and that cell cycle time remains constant.

It is assumed that a 1 CM^3 tumor consists of 10^9 cells. It takes approximately 10 days that a single cell grows up to 10^8 cells since majority of cell types has more or less than 24 hours dobling time (Okada 1970). The length of time (T days) required for a tumor to grow from 10^8 cells or 10^6 CM to the measured volume V in CM- is calculated from the following equation which is derived from equations (5) and (8)

(9) $T = 1/R*LOG((LOG(VM)+6*LOG(10))/(LOG(VM)-LOG(V)))+10$

T gives us an apporximate idea of the time required for the tumor to grow to the size.

V. Conclusion

1. Majority of clinical tumors follow the growth model of Gompertzian function of which analysis proves that the growth rate is a function of the tumor volume. Growth rate is not constant as in conventional exponential growth model and is determined by tumor volume.

2. The model can be better defined as follows. Change of growth rate is proportional to change of logarithmic of tumor volume.

Mathematically

$dA/dT = -R*dLOG(V)/dT$

3. This definition leads gompertzian function which shows a tumor has the maximum volume.

And the effect of tumor therapy has to be evaluated with the change of the maximum volume.

Litterature

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