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Growth Kinetics of Small Cell Carcinoma of the Lung*

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Abstract—*Tumor volumes prior to initial therapy for 33 patients with small cell carcinoma of the lung were determined from serially measurable roentgenographic lesions. Tumor doubling times were calculated for 20 patients who had two or more serial measurements. Pretreatment tumor volumes ranged from <5 to 485 cm³, with a median of 87 cm³, a log mean of 61 cm³, and an arithmetic mean of 103 cm³. The tumor doubling times (DT) ranged between 12 and 209 days, with a median of 53 days, a log mean of 59 days, and an arithmetic mean of 79 days. The tumor growth rate, expressed by tumor doubling time, was correlated with the tumor volume* ($r = -0.533$, $P < 0.05$); *and volume dependency of the tumor growth rate, as specified in Gompertzian growth, was demonstrated. Patients with DT < 79 days had a median duration of survival of 15 months, which was significantly longer* ($P = 0.046$) *than the median survival of 8 months for patients with DT > 79 days.*

INTRODUCTION

TUMOR growth is a dynamic process in which the rate of growth of tumor masses is determined by cell proliferation and cell death in response to a variety of internal and external factors. The growth rates of human solid tumors may be important determinants of response to therapy and curability [1, 2]. Rapidly growing tumors are more often responsive to therapy than slowly growing tumors. Responsiveness to treatment appears to change over time as rapidly growing tumors in advanced stages are similar in their response behavior to more slowly growing tumors; and these responses are generally not durable [2].

The relationship between tumor size and sensitivity to therapy also may exert an influence on the design of cancer treatment protocols [1, 3]. It was previously reported that small tumors, due to their large fraction of actively dividing cells, are more sensitive to cytotoxic therapy than tumors of equivalent histology but larger size [1]. This concept has been questioned, and evidence for the relative resistance of small tumor masses has led to the suggestion that intensification of therapy for smaller masses may be a more appropriate strategy [3].

The increasing use of intensive dose schedules, timed sequential administration of chemotherapy and other therapeutic strategies based on tumor growth kinetics requires a more precise measurement of the dynamics of growth and regression of tumor masses in patients with malignancy. The growth characteristics of small cell carcinoma of the lung (SCC) have been studied [4–7] and related to responsiveness to therapy with anti-tumor drugs or radiation [7, 8]. Recent studies of growth rate assessed in terms of the doubling time of SCC showed that SCC is a relatively slowly growing tumor in which both the rate of cell production and the rate of cell loss are higher than in non-small cell lung cancers [7, 8].

During the past several years, the medical and radiation oncology divisions of The Johns Hopkins Oncology Center have been exploring the use of intensive combined modality therapy of SCC [9, 10]. In this report, we present an analysis of the doubling time of SCC determined by a retrospective examination of serial chest X-ray films of patients with SCC. Clinical correlates have been made of pretreatment primary tumor volume and tumor doubling time, with overall patient survival. The tumor growth rate has been related to the tumor volume to characterize the growth pattern of SCC using a Gompertzian function growth model [11].

MATERIALS AND METHODS

Patient selection

The patient population consisted of 33 newly diagnosed patients with SCC. The diagnosis of

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SCC was established on the basis of lung, lymph node, liver, or other tissue biopsies. Of the 33 patients studied, all had measurable tumor volumes prior to therapy, and 20 had serial pretreatment X-ray films with the time span of observation of at least 3 weeks. Our estimate of tumor doubling time is based upon an analysis of these patients. The majority of patients were subsequently entered onto therapeutic protocols at The Johns Hopkins Oncology Center.

Determination of growth rate

Serially measurable roentgenographic lesions were chosen to determine tumor volume and growth rate. The longest and shortest perpendicular diameters were carefully measured with calipers. Tumor volume, V, was calculated by the following formula [12],

$$V = \frac{4}{3}\pi\left(\frac{d}{2}\right)^3 \quad (1)$$

where d is the mean value of the longest and shortest perpendicular diameters. Tumor growth rate, A, was assumed to be constant over the period of observation. When measurements from two time points were employed, tumor growth rate could be calculated from the equation,

$$V = V_0 e^{At} \quad (2)$$

where V and V_0 are tumor volume at time t, and initial tumor volume, respectively. Tumor doubling time, DT, was derived from equation (2) for $V = 2V_0$, and was expressed by

$$DT = \frac{\ln 2}{A}. \quad (3)$$

A wide range of pretreatment tumor volumes was assessed in relation to variation in tumor growth rate to examine whether tumor growth of SCC follows a Gompertzian function growth model.

The method of Kaplan and Meier was used to calculate survival curves. The statistical significance of differences in survival curves was tested using the generalized Wilcoxon test [13, 14].

RESULTS

Table 1 summarizes tumor volume measurements immediately prior to initial therapy of 33 patients, including 20 patients who had two or more serial measurements which enable the determination of tumor doubling time. Pretreatment tumor volumes ranged between <5 and 485 cm^3 with a median of 87 cm^3, a log mean of 61 cm^3, and a linear mean of 103 cm^3. Figure 1 illustrates serial tumor volume measurements obtained for 19 patients who had tumor volumes >5 cm^3; and 1 patient with <5 cm^3 was not included. The tumor doubling times in these 20 patients ranged between 12 and 209 days, with a median doubling time of 53 days, a log mean of 59 days, and a linear mean of 79 days.

Tumor growth rate, expressed in terms of tumor doubling time, was evaluated from two serially determined tumor volumes. Figure 2 shows the relationship between tumor growth rates and the mean values of these two serially determined tumor volumes for 19 patients. The correlation coefficient, r, was -0.533 ($P < 0.05$). When measured tumor volumes from all patients are combined and analyzed, a retardation of tumor growth with increasing tumor volume [11] is demonstrated.

Correlation between tumor volume at the time of initial therapy and tumor doubling time was calculated. This showed a negative correlation but no statistical significance. The number of patients may be too small to fully evaluate this finding; however, this concurs with a previous report on breast carcinoma [15].

Tumor volumes immediately prior to initial therapy were evaluated in relation to patient survival using actuarial survival curves (Fig. 3). Patients were divided into two groups using the mean tumor volume of 103 cm^3 as the discriminant. There were 12 patients with the pretreatment tumor volume larger than the discriminant volume, and 18 patients with tumor volume smaller than the discriminant value. The difference between the curves is not significant ($P = 0.787$).

Figure 4 shows the relationship between tumor doubling time and survival. The mean doubling time of 79 days for 20 patients was chosen as a discriminant to study patient survival. Of a total of 20 patients, 17 patients had survival data in which 6 patients had longer doubling time, and 11 patients had shorter doubling time than the discrimant value. The median survival duration for patients with DT < 79 days was 15 months, whereas for patients with DT > 79 days survival was 8 months. The difference between two survival curves is statistically significant ($P = 0.0461$).

DISCUSSION

The calculated median tumor doubling time of 53 days determined from this study of serial

Table 1. The pretreatment tumor volumes and doubling times and the survival of patients with small cell carcinoma of the lung (patient number = 33)

Patient No.	Tumor volume* (cm^3)	Tumor doubling time (days)	Survival† (months)
1.	243.7	63.0	26
2.	75.8	—	32
3.	22.5	—	27
4.	87.1	37.2	7+
5.	8.2	—	6
6.	27.6	40.6	10
7.	2.5	—	31+
8.	200.2	—	25
9.	99.5	—	14
10.	22.5	130.9	7
11.	75.8	105.8	7
12.	220.9	52.5	15
13.	99.5	—	7
14.	143.8	34.7	30
15.	87.1	208.6	3
16.	143.8	144.0	8
17.	56.1	—	14
18.	220.9	—	33+
19.	143.8	—	12
20.	47.7	177.2	8
21.	8.2	—	10
22.	161.0	31.5	8
23.	4.2	27.8	19+
24.	161.0	—	11
25.	22.4	28.9	11+
26.	485.3	80.8	5
27.	143.8	70.5	8
28.	27.6	—	8+
29.	104.8	12.0	4+
30.	56.1	99.0	22
31.	99.5	40.8	—
32.	89.5	19.8	—
33.	14.1	180.6	—

*Tumor volumes determined at the time of initial therapy.
†Survival with + indicates patients who were alive at the time of evaluation.

chest X-ray films of patients with SCC is comparable with those results obtained by Brigham *et al.* [7] and Tubiana and Malaise [8], but longer than those reported by Chahinian [16]. A review of growth rate patterns of human solid tumors identified SCC as an intermediate or slowly growing tumor[2], and noted that the tumor doubling times are negatively correlated with the labeling indices [4]. Because of the relatively high labeling indices obtained [5, 6] and the higher rate of cell loss calculated [8], the long tumor doubling time with the high labeling index in SCC would indicate that there is a higher rate of both cell production and cell death.

The prognostic value of the pretreatment tumor doubling time was assessed in this study by relating it to survival of 17 patients (Fig. 4). The number of patients under evaluation was relatively small. Nevertheless, a statistically significant difference in survival was observed ($P = 0.0461$) when patients with DT > 79 days was compared to patients with DT < 79 days. Patients with shorter doubling times had longer survival than those with longer doubling times.

On the other hand there have been a number of studies reporting that the survival of patient was positively correlated to the duration of doubling times [15, 18, 19, 20]. Kusama *et al.* [15] reported that in the assessment of five-year

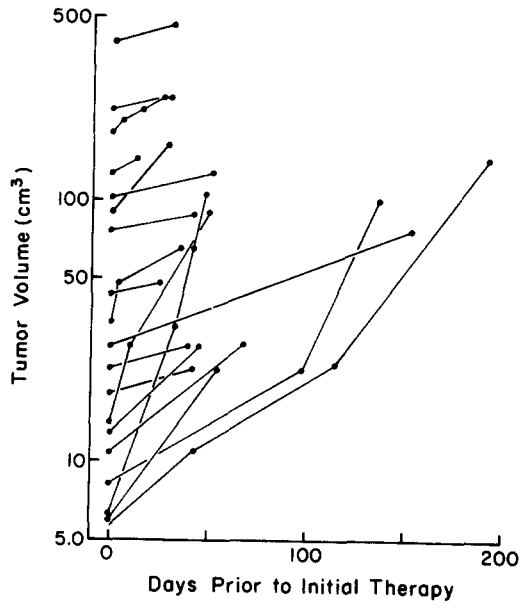

Fig. 1. Serial measurements of pretreatment tumor volumes for 19 patients. One patient with tumor volumes $<5\,cm^3$ was not included.

survival rates for patients with breast carcinoma, rapidly growing tumors were associated with a poor prognosis and more slowly growing tumors with a relatively favorable prognosis. Within a group of patients with the same anatomic spread in breast cancer, the prognosis in those whose tumors have slow growth rates is much better than in those whose tumors have rapid growth rates [20].

These differences in the growth rate and survival relationships between SCC and other tumors may be explained by higher responsiveness of SCC to initial therapy. Results similar to those of SCC have been previously reported, indicating that tumors with shorter doubling times tend to be more responsive to chemotherapy, and that tumors with long doubling times respond poorly to chemotherapy [2, 7]. Breur [17] observed that tumors characterized by a short doubling time were more radiosensitive. Shackney [2] pointed out the importance of the rate of tumor cell

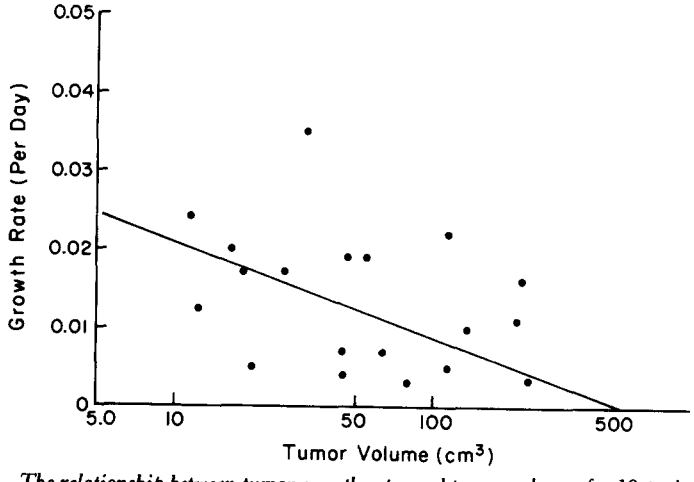

Fig. 2. The relationship between tumor growth rates and tumor volumes for 19 patients. Volume dependency of the tumor growth rate, as specified in Gompertizan growth [11], is expressed by $A = -R\,ln\,(V/Vm)$, *where R is the retardation factor, and* Vm *is the maximum tumor volume for the limitation of tumor growth. In the present study,* $A = 0.0053\,ln\,(V/525)$, *with the correlation coefficient* $r = -0.533$ $(P < 0.05)$.

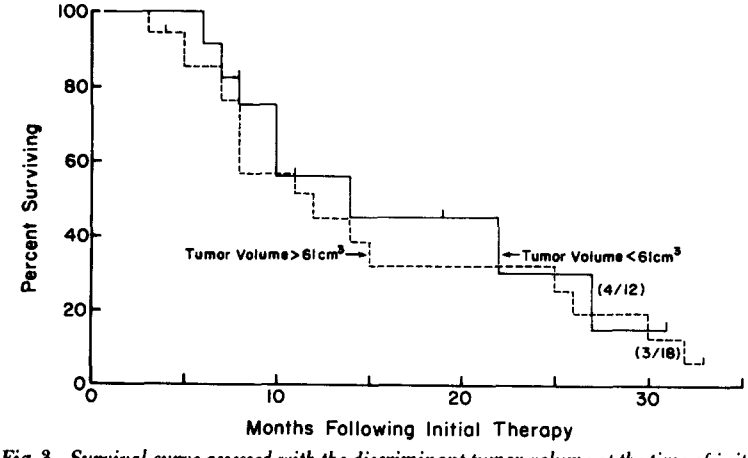

Fig. 3. Survival curve assessed with the discriminant tumor volume at the time of initial therapy of $103\,cm^3$ *utilizing the method of Kaplan and Meier. Short vertical lines on the survival plots indicate living patients. The fractions represent the number of patients who have survived/total number of patients in the life table plots.*

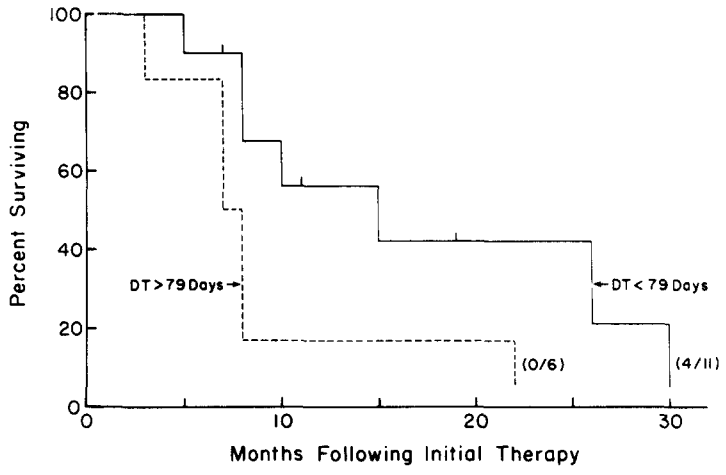

Fig. 4. Survival curves assessed with the discriminant tumor doubling time (DT) of 79 days *utilizing the method of Kaplan and Meier. Short vertical lines on the survival plots indicate living patients. The fractions represent the number of patients who have survived/total number of patients in the life table plots.*

production in relation to therapeutic responsiveness. The relationship is between the tritiated-thymidine pulse-labeling index and the tumor doubling time and low rates of cell production in tumors with short doubling time and low rates of cell production in tumors with long doubling time. However, the high labeling index in SCC [5, 6] reflects the high rate of cell production, and the long doubling time of measured tumor volumes implies a balancing effect of the high cell loss rate.

The growth characteristics of SCC, which indicate that growth rates were faster at smaller volumes and slower at larger volumes (Fig. 2), were demonstrated in this study. Such retardation of tumor growth, while it was determined by tumor volume measurements from different patients, may be indicative of Gompertzian growth characteristics [3, 11]. The tumor size and sensitivity to therapy has been of interest in designing treatment schedules for human solid tumors [1, 3, 9], and a study on this relationship in SCC will be presented elsewhere.

In our analysis, the size of primary tumor immediately prior to therapy was not a sensitive prognostic parameter of patient survival (Fig. 3). The shape of the survival curves based on tumor volumes were similar to that of our previous study which was based on the pretreatment discriminant CEA of 5.0 ng/ml [23]. In SCC, the initial response to therapy was a sensitive indicator for patient survival [23]; however, both the CEA discriminant of 5.0 ng/ml and the volume discriminant of 61 cm^3 were unable to classify patients into different therapeutic responses, subsequently unable to separate survival curves. On the other hand, the therapeutic responsiveness was related to the growth rate of tumor [1, 2, 21, 22, 24]; and the efficacy of pretreatment DT as a sensitive prognostic parameter was illustrated with SCC in the present study.

In summary, this study reports a potential prognostic value of the determination of tumor growth rate prior to initiation of therapy in SCC. The observed volume dependency of tumor growth rate suggests that the growth of SCC may follow Gompertzian kinetics. These observations may in the future provide a guide to therapeutic decisions and direct the intensity and duration of treatment. A prospective study is presently under way to further evaluate the prognostic value of pretreatment tumor growth rate and to estimate the therapeutic efficacy utilizing tumor regression rate following initial therapy.

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