Tumor Doubling Time and Survival of Men with Bronchogenic Carcinoma*

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The relationship between tumor volume doubling time and survival was studied in 28 patients with histologically confirmed bronchogenic carcinoma with the following characteristics: the cancers presented radiographically as circumscribed peripheral nodules first observed at a diameter of 0.6 to 1.4 cm, and follow-up was maintained until death or for at least 8.5 years from the time the tumor was 1.0 cm in diameter. Among eight patients whose cancers were not resected, survival was longer in the four treated with radiation than in the four who were not. Among 20 patients whose cancers were resected, 18 who died showed a fair correlation between tumor doubling time and survival; the other two patients were still alive 116 and 143 months after the tumors were 1 cm in diameter, presumably cured. These observations indicate that tumor growth rate is an important factor in the prognosis of patients with bronchogenic carcinoma.

Growth is one of the most important biologic characteristics of cancer. Quantitation of gross tumor growth in human disease is difficult except in selected cases because the patients must have cancers in which size is readily measurable in a serial fashion. For superficial cancers this may be done by palpation. For deep cancers occasional cases may be studied radiographically when the tumor casts a discrete shadow with defined borders.

In 1956, Collins et al1 proposed a simple exponential model of cancer growth in which one cell divides into two, two become four, four become eight, etc. If the rate of growth is constant it can be described in terms of volume doubling time, i.e., the time it takes for the tumor to double its volume. While there is some doubt about the validity of such a model for human cancers,2 the doubling time may be useful if it correlates with survival so that some degree of prediction may be derived from it.

In 1966, my associates and I2 made the first report in a continuing study of lung cancer growth rate beginning with eight men whose tumors presented as solitary peripheral nodules measurable on serial chest roentgenograms. As the series enlarged, subsequent publications included 18,4 19,5 20,6 and 537 cases, with emphasis on different associated host and cancer characteristics in the several reports. The most important observation in these papers concerned the inverse relationship between tumor growth rate, measured in terms of volume doubling time, and survival of the host. The correlation between doubling time and survival was fairly good in the earlier reports but as the series of cases grew, it became apparent that this relationship was complicated by factors other than growth rate.

One factor had to do with therapy. Cases in which the tumors were resected divided themselves into two populations: (1) a majority in which the relationship between doubling time and survival persisted; and (2) a minority in which survival far exceeded that predictable from growth rate.7 A small number of cases in which there was either no therapy or the patients received radiation and/or chemotherapy showed no clear relationship between doubling time and survival, perhaps because nonsurgical modalities of treatment sometimes lengthened life without effecting cure.

Another factor was methodologic. For compara-
tive purposes, survival had to be measured from the same point on the growth curve in every case. In most patients only a small segment of the growth curve was actually observed, so extrapolation was often necessary to determine the time when the tumor was a given size and from which survival could be measured. The number of measurements available on the growth curve was so limited in many cases that the slope of the curve could not be established with much confidence. Even the reliability of the tumor measurements was invested with some doubt, especially when the cancer was small and errors were relatively more important. Therefore, extrapolation of the growth curves was somewhat dangerous. In our first reports, survival was measured from the time when the cancer was estimated at 1 cm in diameter. Some of the cancers were not observed until their diameters were greater than 1 cm, and extrapolation backward along the growth curve might have created a spurious association between doubling time and survival since longer periods were added to survival by calculation in patients whose cancers had longer doubling times. When survival was measured from the time the cancer size was 1.5 cm$^4$ or 2.0 cm$^3$, in order to minimize extrapolation, the association between doubling time and survival did not seem to be so strong.

The size of the series has now grown to 61 patients and 31 had cancers which were 0.6 to 1.4 cm in diameter when first observed so that extrapolation of the growth curve could be minimized, while survival was measured from the time the cancer was 1 cm in diameter. Twenty-eight of the 31 patients were observed until death or for at least 102 months (8.5 years), and these provide the material for this study.

**METHOD**

The 61 cases of bronchogenic carcinoma were collected because they satisfied the following criteria: the tumors presented as solitary nodules in which the diameter was measurable on two or more chest roentgenograms taken at suitable intervals; histologic confirmation was obtained; prolonged follow-up was available; and death, if it occurred, was not obviously due to some mishap or disease other than lung cancer. Fifty-two of the 61 cases occurred among 286 men who developed histologically confirmed bronchogenic carcinoma during the course of three prospective population studies in which 103,259 older men were examined every six months with chest photofluorograms for three to ten years. The remaining nine cases were collected over a 12-year period on the pulmonary disease service of the Philadelphia General Hospital.

The maximal diameter of the tumor and the diameter at right angles were measured on each posteroanterior film and the mean of these was calculated. The measurements were used uncorrected when obtained from 14×17 inch films. In many cases the measurements were made on miniature photofluorograms with a 7X magnifier containing a millimeter scale and converted to actual size by using a factor derived from a study of lead phantoms. The factor was 4.0 for 100 mm films, 5.9 for 70 mm films, and 14.9 for 35 mm films.

The tumor doubling time was estimated by the method of Collins et al. The mean tumor diameter for each case was plotted on semilogarithmic paper as a function of time. A straight line was fitted to the points by eye. The assumption was that the tumor was a sphere so that one doubling of the diameter represented three doublings of the volume. Vertical lines were dropped from the curve at diameters of 1 and 2 cm, and the interval encompassed by these verticals on the baseline was divided by three to obtain the volume doubling time.

The histologic type of cancer was obtained from the report of the hospital pathologist on the basis of tissue which was usually acquired by resection of the primary tumor. In a few of the cases tissue was obtained by biopsy or autopsy.

The current study was limited to 28 cases in which the cancer was observed initially at a mean diameter between 0.6 and 1.4 cm and for which there was at least 102 months (8.5 years) follow-up if the patient was alive. Survival was measured from the time the cancer was 1.0 cm in diameter. Slight extrapolation of the growth curve was required in those patients whose observed growth curves did not include the diameter of 1.0 cm.

**RESULTS**

Pertinent information pertaining to the 28 patients, arranged in order of increasing doubling time from 0.9 to 10.0 months, is given in Table 1. Age when the cancer was 1.0 cm in diameter is not included because there was no correlation with doubling time. When initially observed, 13 cancers had a mean diameter ranging from 0.6 to 0.9 cm, five measured 1.0 cm, and the remaining 10 were 1.1 to 1.4 cm in diameter. Initial diameter was unrelated to doubling time. Comparing the 14 most rapidly growing cancers with the 14 most slowly growing ones, initial mean diameter averaged 0.94 and 1.00 cm, respectively.

The number of points on the growth curve was two in 11 cases, three in six cases, four to six in nine cases, and nine in two cases. The slowly growing cancers tended to have more measurements than the rapidly growing ones: there were more than four points in only two of the first 14 cases compared with six of the last 14 cases.

Squamous cell and undifferentiated carcinomas were predominant among the more rapidly growing tumors, with adenocarcinomas predominant among the more slowly growing ones. Thus, there were only two adenocarcinomas among the first 14 cases and nine among the last 14. Indeed, among the nine tumors with doubling times of 6.9 to 10.0 months, all but one were adenocarcinomas.

Eight of the 28 patients did not have operations. The lack of surgery was unrelated to doubling time. Four (patients 4, 9, 19, and 21) received no therapy and survived 10 to 28 months. Four (patients 1, 7, 14, and 28) were treated with radiation; three sur-
TUMOR DOUBLING TIME AND SURVIVAL IN BRONCHOGENIC CARCINOMA

Table 1—Characteristics of 28 Lung Cancers, in Order of Increasing Doubling Time, and Survival of the Host

<table>
<thead>
<tr>
<th>Patient, No.</th>
<th>Initial Diameter, Cm</th>
<th>Pointe on Growth Curve, No.</th>
<th>Histologic Type</th>
<th>Doubling Time, Mos.</th>
<th>Resected</th>
<th>Survival,* Mos.</th>
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<tr>
<td>1</td>
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<td>+</td>
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</tr>
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<td>+</td>
<td>102**</td>
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<td>+</td>
<td>116**</td>
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<td>9.0</td>
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<td>6</td>
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*Measured from time cancer was 1 cm in diameter.

**Patient is still alive.

vived 43 to 54 months and one was still alive after 102 months. These samples are too small to relate survival to growth rate, but they suggest that survival was longer in the patients treated with radiation than in those who were untreated.

The growth curve of the cancer in patient 1 is shown in Figure 1 to illustrate the effect of radiation. This 67-year-old man had active tuberculosis in 1956. The disease healed by October, 1957, but follow-up revealed a new lesion in the form of a nodule measuring 1.0 cm in diameter in the left upper lobe on June 23, 1958. Serial films showed a rapid growth rate, with a volume doubling time of 0.9 month. Cells indicative of oat cell carcinoma were found in bronchial washings. The patient refused surgery, but he was treated with radiation from January 5 to February 16, 1959, and the nodule shrank from 4.5 to 2.2 cm in diameter in a period of nine months. One year after therapy was completed a new irregular infiltrate appeared in the right upper lobe contiguous with the mediastinum and worsened until his death at home on April 3, 1962. The cause of the new disease was not established. It may have been a second primary carcinoma or extension of metastases in mediastinal lymph nodes. The patient died 45 months after his oat cell carcinoma was 1.0 cm in diameter. Since the tumor was doubling its volume.

RESPONSE OF LUNG CANCER TO RADIATION

MALE, 67, WITH INACTIVE TB & SMALL CELL CA

Figure 1. Growth curve of small cell carcinoma of left lung in 67-year-old man with inactive pulmonary tuberculosis. Prior to radiation therapy cancer had doubling time of 0.9 month. One year after therapy new infiltrate appeared in contralateral lung. Etiology of this lesion was not determined, but appearance and course suggested neoplasm.

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every 0.9 month before radiation therapy was given and would have grown to a diameter exceeding 20 cm within a year, survival was considerably longer than expected.

The cancers were resected in 20 cases, and in this group there was a significant relationship between cancer growth rate and survival. The shortest survival was 15 months in patient 5, with a tumor doubling time of 2.0 months. The longest survival occurred in patient 23, still alive after 143 months, with a tumor doubling time of 7.8 months.

Survival was plotted against doubling time for the 20 patients treated by resection of the primary cancer (Fig 2). There appeared to be two separate populations. For 18 patients who died within the 8.5-year minimum follow-up period, the longer the doubling time, the longer the survival. The Spearman rank correlation coefficient was 0.65, and this was statistically highly significant ($t = 3.47, P < 0.005$ df = 16). The other two patients were still alive after 116 and 143 months. Thus, 18 or 90 percent of the patients showed a fairly strong inverse relationship between tumor growth rate and survival, while two (10 percent) were apparently cured by resection without relation to growth rate.

Six (30 percent) of the 20 patients lived five years or more. The median survival was 34 months in four patients with squamous cell carcinoma, 56 months in six with undifferentiated carcinoma, and 70 months in nine with adenocarcinoma.

**Discussion**

Although it seems obvious that the survival of ineffectively treated patients with cancer must depend to a large extent on how fast the cancer grows, there is little information in the literature on human disease concerning the correlation between these two variables. One reason is that observations are necessarily limited to measurable tumors, i.e., those which are superficial, as in the breast, or can be seen on roentgenograms, as in the lung. In 1948, Richards60 reported a striking decrease in five-year survival rates among 324 patients with breast cancer as growth rate increased, but he provided no details for his method of measuring tumor growth rate.

Additional observations in breast cancer have been recorded. Delario11 reported that 19 patients in whom the cancer was “not growing” before resection had a four-year survival rate of 73.6 percent, while 40 patients in whom the tumor was “growing” before resection had a survival rate of 52.5 percent. Delario11 also gave no information on his method for measuring the presence or absence of tumor growth.

Recently Kusama et al12 collected doubling time measurements for breast cancers in 199 patients selected from a total series of 912 having a radical mastectomy between 1940 and 1960. The tumor measurements included 163 primary cancers and 51 metastatic lesions. Survival depended on doubling time, especially during the first six years after mastectomy. Afterward, survival rates were much the same in all growth rate groups except the patients with the most slowly growing cancers having doubling times of eight months or more. In this group, survival was more favorable than in all other groups up to the limit of follow-up at 15 years.

Perhaps the first data on tumor doubling time and survival for primary lung cancer appeared in a report by Schwartz.13 Two of 13 bronchogenic carcinomas were first observed at a diameter between 0.6 and 1.4 cm. One had a doubling time of 56 days, and the patient lived 1.3 years after the tumor was 1.0 cm in diameter. The other had a doubling time of 200 days, and the patient lived 4.3 years.

14 have reported more extensive observations on the relationship between doubling time and survival in bronchogenic carcinoma. There was a fair correlation: the Spearman coefficient was 0.76 for 17 cases.4 However, the data suffered from the disadvantage that survival was measured from the time the cancer was 1.0 cm in diameter, and in some cases considerable extrapolation of the growth curve was required to calculate survival from this point.

![Figure 2. Survival in months from time cancer was 1.0 cm in diameter plotted against tumor doubling time in 20 patients whose cancers were resected and who were observed until death or for at least 8.5 years. In 18 patients who died, survival increased with increasing doubling time of tumor. Two patients were still alive at 116 and 143 months.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20946/)
series of cases in this study has increased in number sufficiently to circumvent this problem by emphasizing those cases in which the observed tumor growth curve begins very close to a diameter of 1 cm. The correlation coefficient of 0.65 for the patients in whom death occurred confirms the importance of growth rate as a factor in prognosis.

Using a slightly different method of analysis, Steel and Buell have recently corroborated this principle with data on 57 cases divided into two groups according to tumor doubling time. Survival was measured from the time of resection rather than the time when the cancer was 1 cm in diameter. This may account for the observation that growth rate was more important in patients whose cancers were resected when the diameter was 2.5 cm, or less than in patients operated on when the cancer was larger.

Chest roentgenograms provide another source of data for correlating tumor growth rate and survival, since pulmonary metastases from cancers in other organs usually grow as spherical nodules. Spratt and Spratt plotted the survival in terms of the number of volume doublings, using the doubling time of the most rapidly growing pulmonary metastasis, against the diameter of the metastasis when first observed in 118 patients. They found that maximum survival varied inversely with initial size of the metastatic tumor.

Edlich et al. reported a series of 61 patients who had resection of pulmonary metastases at various intervals after resection of a primary malignancy. There was a positive association between the length of the interval and survival rate following removal of the metastatic lesion. Similar observations have been made by Thomford et al. This might have been due to variations in tumor growth rate, but it also might have been due to variation in the time of metastatic implantation.

The former explanation is supported by a study of Joseph et al., because there was a correlation between the doubling time of the pulmonary metastasis and the interval between resection of the primary cancer and the onset of metastasis in 113 patients. In 89 patients who received no therapy for the pulmonary metastases, survival varied directly with the tumor doubling time. A similar relationship was observed among 24 patients whose pulmonary metastases were resected and survival seemed to be unusually good in 11 whose tumor doubling times were over 40 days, despite the fact that some patients had multiple and bilateral metastases.

In 1968, Combes et al. recorded the doubling times of pulmonary metastases and survival from the beginning of treatment in 90 cases. There was a fair correlation between doubling time and survival in the 77 patients observed until death. Thus, if one divides their series into 26 patients with doubling times under 45 days, 25 with doubling times of 45 to 89 days, and 26 with doubling times of 90 days or more, the proportions surviving 0-19 months were 89 percent, 36 percent, and 15 percent, respectively, while the proportions surviving 40 months or more were 0 percent, 12 percent, and 38 percent, respectively. One can calculate the Spearman rank order correlation coefficient between doubling time and survival from the data of Combes et al: it is 0.69 and this is statistically highly significant (t = 8.32, P < 0.001, df = 75).

In the present study of bronchogenic carcinoma, the confirmation of the relationship between growth rate of the primary cancer and survival was limited to the patients whose tumors were resected. There are several reasons for this. First, the number of unresected cases was small and half of them were treated with radiation. This therapy is seldom curative but may prolong life, thus distorting the relationship between the two variables under study. Second, resection produces an all-or-none phenomenon in terms of cure, dividing the cases into two clear-cut groups if follow-up is long enough. If there are no metastases at the time of resection, prolonged survival can be expected, barring unrelated accidents. Such prolonged survival was demonstrated in two of the 20 resected cases in this series. In the remaining patients survival was presumably primarily dependent on the growth rate of metastatic lesions.

There is almost no information in the literature on the relationship between the doubling time of the primary lung cancer and the doubling times of its metastases. I have seen only two patients in whom measurements of growth rate of both the primary tumor and its pulmonary metastases were possible, and there was considerable variation. Circumstantial evidence must be brought to bear on this problem. There are experimental data showing that rapidly growing tumors metastasize more often and earlier than do slowly growing ones. This may be evidence of a positive association between the growth rate of the primary cancer and the growth rates of its metastases. The demonstrable association between the doubling times of metastases and survival in patients with various types of cancer discussed above and the similar degree of association between the doubling time of primary bronchogenic carcinoma and survival shown in this report provide additional evidence that there is correlation between the growth rate of the primary tumor and the growth rates of its metastases in at least a general sort of way.
REFERENCES