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# REVIEW ARTICLE

# On the Growth Rates of Human Malignant Tumors: Implications for Medical Decision Making

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Testicular carcinomas, pediatric tumors, and some mesenchymal tumors are examples of rapidly proliferating cell populations, for which the tumor volume doubling time (TVDT) can be counted in days. Cancers from the breast, prostate, and colon are frequently slow-growing, displaying a TVDT of months or years. Irrespective of their growth rates, most human tumors have been found: to start from one single cell, to have a long subclinical period, to grow at constant rates for long periods of time, to start to metastasize often even before the primary is detected, and to have metastases that often grow at approximately the same rate as the primary tumor. The recognition of basic facts in tumor cell kinetics is essential in the evaluation of important present-day strategies in oncology. Among the facts emphasized in this review are: (1) *Screening programs.* Most tumors are several years old when detectable by present-day diagnostic methods. This makes the term ''early detection'' questionable. (2) *Legal trials.* The importance of so-called doctor's delay is often discussed, but the prognostic value of ''early'' detection is overestimated. (3) *Analyses of clinical trials.* Such analysis may be differentiated depending on the growth rates of the type of tumor studied. Furthermore, uncritical analysis of survival data may be misleading if the TVDT is not taken into consideration. (4) *Analyses of epidemiological data.* If causes of malignant tumors in humans are searched for, the time of exposure must be extended far back in the subject's history. (5) *Risk estimations by insurance companies.* For the majority of human cancers, the 5-year survival rate is not a valid measurement for cure. Thus, basic knowledge of tumor kinetics may have important implications for political health programs, legal trials, medical science, and insurance policies.

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**KEY WORDS: neoplasm; human; growth rate; doubling time; diagnostic level; lethal burden; period of risk**

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## INTRODUCTION: ON THE GROWTH RATES OF HUMAN MALIGNANT TUMORS

The purpose of this review is to consider the gross growth rate of various human malignancies, as studied in their hosts. It does not deal with experimental tumors in vitro or in animals, since their relevance for human spontaneous malignancies is questionable. Nor does it deal with experimental studies in humans (i.e., labeling indices, incorporation of radio-labeled nucleotides, immunological markers), since these studies do not take cell loss (mainly through apoptosis) into consideration [1].

In this review, the growth rate is defined as the rate of increase in volume (or the number of cells) in relation to time. This review is based on studies in >2,000 individual cases, with a total of >6,000 observations of the growth rate.

### Collection of Information

The database Medline was searched back to the beginning of 1966. Search words were the same as in this review. Articles prior to 1966 were identified through perusal of the reference lists from the articles found.

Reports on individual cases, or cases with uncommon or unclear histology, or cases with only a few observations were excluded. Examination methods other than radiological (which allow repeated measurements from a single observation) also have been excluded. All other articles are included. Special focus was placed on reports dealing with cancer of the breast or lung. Whenever the suspicion arose that the same patient cases had been published more than once, that particular clinical material is referred to once only. Studies on the growth rates of human tumors based on indirect methods, such as monitoring of serum markers, are to be the subject of a future report.

## BACKGROUND

### Monoclonality

A primary tumor starts from one single cell, in the same way that all human beings originate from a single cell, the fertilized egg. The notion that a tumor develops from a single cell (monoclonality) was anticipated by Virchow in 1862 [2]. A century later, in 1962, Waldenström [3] gave the hypothesis support from studies on human multiple myeloma. Today, monoclonality has been shown for the majority of human tumors [4–7]. Also multicentric tumors, such as cancer of the bladder [8] or of the breast [9], have been shown by modern methods in molecular genetics to be originally monoclonal.

Even tumors in paired organs, such as the testes, seem to stem from one basic genetic alteration during embryogenesis [10,11]. The same genetic alteration also appears to be the underlying cause of extragonadal germ cell tumors (in the thymus or in the pineal gland) [12]. Heterogeneous clones are likely to occur later during the lifespan of a tumor.

As this review shows, most human malignant tumors are many years old when clinically detectable. Polyclonality at the time of diagnosis, therefore, does not contradict a monoclonal origin: The tumor cell population has had ample time to diversify during the preclinical period. To make a comparison, every newborn being is polyclonal, but its origin (the fertilized egg) is monoclonal. Attempts at disapproving monoclonality of origin for clinical tumors always will be hampered by the fact that diagnosable tumors are not at their origin.

### Cell Kinetics

The first tumor cell multiplies exponentially with time: 1-2-4-8-16-32, and so forth. If the tumor cells have a diameter of 10 μm, the clone will have reached a volume of ~1 $cm^3$ after 32 cell generations. If the tumor cells are 25 μm in diameter, 26 doublings are required to reach that volume. At that size, it consists of $10^9$ cells. For calculations of growth curves in this review, the following simplifications are made: tumor cells have a diameter of 10 μm ($10^{-6}$ meters), macroscopic tumors consist of tumor cells only, and the tumor cells are densely packed to completely fill the sphere.

If the growth of a tumor is plotted against time, the curve depicted in Figure 1A is obtained. The curve in Figure 1A gives the impression that a tumor doubles its volume at accelerating speed.

The increase in the number of cells in a tumor is determined mainly by three principal parameters [13]: (1) the cell cycle time of the proliferating cells, (2) the fraction of cells proliferating, and (3) the amount or fraction of spontaneous cell loss. The spontaneous cell loss in vivo may be as high as 50% [13] in each cell cycle or even higher [14] and is therefore of profound importance for the growth rate. Refsum and Berdal [14] calculated the cell loss in 61 cases of oropharyngeal cancers to be as high as 96%, explaining the slow increase in net volume.

Related to time, the net growth of the tumor volume is fairly exponential during the visible stage [15–34]. Plotted on a semilogarithmic scale, it is linear. The inclination of the slope may be called the tumor volume doubling time (TVDT). This is shown in Figure 1B.

The growth curve in Figure 1B is identical to that in Figure 1A, except that the size of the tumor has been given not as the diameter (in centimeters), but as the number of cells on a logarithmic scale. In this review, linear growth is defined as a constant increase of tumor volume on a logarithmic scale, in relation to time.

### Growth Curves

An early contribution to the theory of growth curves was made by Gompertz in 1825 [35]. There are other

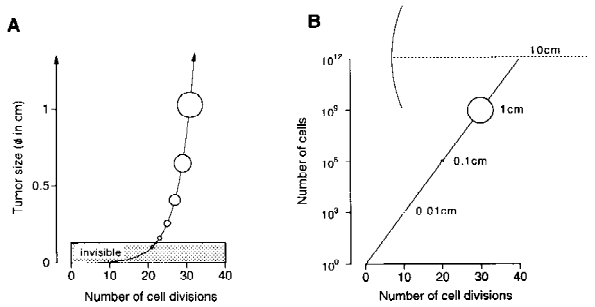


Fig. 1. **A.** Gross growth rate of a tumor. Abscissa: number of cell divisions. Ordinate: tumor size (diameter in centimeters). Note the number of cell divisions required for the tumor to reach diagnostic level (0.2–1 cm in diameter). **B.** Gross growth rate of a tumor. Abscissa: number of cell divisions. Ordinate: number of cells (logarithmic scale). Growth rates are identical in A and B, but the units on the ordinates are different. It takes more than 30 doublings for the tumor cells to reach a population size of $10^9$ cells. At that point the tumor has a diameter of 1 cm and weighs 0.52 g. With a tumor volume doubling time of 150 days and assuming a constant generation time, the tumor is then ~12 years old.

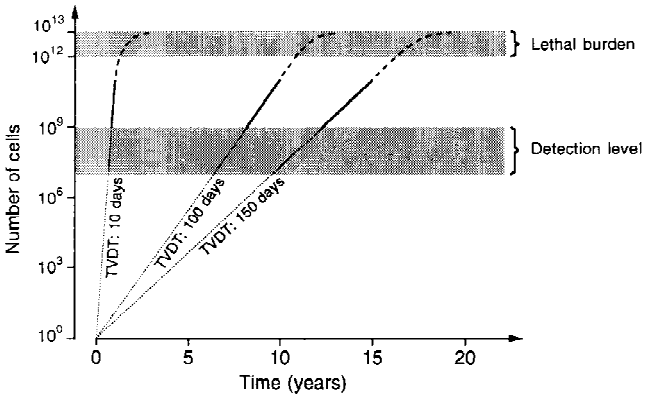


Fig. 2. Growth rates for three different tumors. Abscissa: time (years). Ordinate: number of tumor cells (logarithmic scale). The diagnostic level ($10^7$–$10^9$ cells), and the lethal burden ($10^{12}$–$10^{13}$ cells, or 1 kg − 10 kg) limit the visible phase of a human tumor. The three tumors have been given tumor volume doubling times of 10, 100, and 150 days, respectively. Symbols: ·····= invisible phase (extrapolated); —— = visible (and measurable) phase; ------- = estimated asymptote. The number of cells is assumed to be produced by the primary tumor alone. If the addition to the total tumor burden from the metastases is also included, the curve approaches a straight line.

mathematical models useful for studying tumor growth as well [36–39]. Most growth curves are characterized by an upper horizontal asymptote. For human malignant tumors, this upper horizontal asymptote is the upper limit that the cancer cannot exceed because the tumor burden has become lethal to its host. This limit has been termed the ''lethal burden,'' and is illustrated in Figure 2. The period during which human tumors are measurable in vivo is that above the detection level (Fig. 2).

The growth curves in Figure 2 were obtained in the following way: the slope of the linear growth curve was calculated for three different arbitrary TVDTs (10, 100, and 150 days). Each curve was then inserted as a straight line in the interval from $10^9$ to $10^{11}$ cells (measurable phase). This is the interval in which human tumors are measurable and where linear growth has been found to occur. Each curve was then extrapolated back to the one-cell origin and adjusted in relation to time. From $10^{11}$ to $10^{13}$ cells, the estimated asymptote was then added.

It may be argued that since the growth rate of tumors during the preclinical period is not known, extrapolations back to the one-cell origin are uncertain. For the growth rate of a tumor during the preclinical period, three theoretical possibilities exist: (1) it can be faster than, (2) it can be identical to, or (3) it may be slower than the growth rate during the visible phase. Facing these three possibilities, the present authors have chosen the intermediate one (= identical growth rate). In Figure 2, the total tumor burden is provided exclusively by the primary tumor.

In the clinical setting, a tumor with a volume of 1 cubic centimeter (≈$10^9$ cells) is regarded as relatively small. It is at this size that a tumor may give rise to the first symptoms. It is also at this size that a tumor may become detectable on palpation, or by use of laboratory tests such as the tumor marker prostate specific antigen (PSA) for cancer of the prostate [40].

### Cellular Origin of Metastases

Metastases also can be assumed to start from a single cell, or a small complex of cells. The TVDT of a secondary tumor has likewise been found to be constant during the first part of the visible phase and thus linear on a semilogarithmic scale. Therefore, determinations of the TVDT of a secondary tumor followed by linear extrapolation back to the one-cell origin may allow estimation of the starting time of that secondary tumor.

## REVIEW STRUCTURE: METHODS AND RESULTS

This review summarizes some of the available information under the headings Methods and Results. Methods includes: radiological methods, methodological errors in radiological determinations of tumor volumes, cellular composition of macroscopic tumors, radiological levels of detection, errors in calculations of TVDTs, and errors in extrapolations. Results includes: historical background, linearity of growth, studies on cancer of the breast, lung, and pulmonary metastases, relation between the growth rates of a primary tumor and its metastases, when cancers start to metastasize, and clinical support for the concept of constant growth rates.

### Methods

**Radiological.** The TVDT of various untreated solid malignant human tumors has been the subject of several studies. Usually, serial radiograms have been the method of choice. The growth rates of primary cancers of the

breast can be directly observed with mammography. Likewise, the growth rates of primary cancers from the lung can be directly followed from serial X-ray examinations of the chest.

**Methodological errors in diagnostic radiology.** The exact measurement of the volume of tumors from radiograms can be difficult to ascertain. Irregular shape, unsharp boundaries, and inhomogeneity are some of the major obstacles. In a careful analysis of the possible errors, Brenner et al. [24] concluded that the methodological error for a single determination amounted to ±11% of the volume.

**Cellular composition of macroscopic tumors.** Macroscopic tumors are not composed of cancer cells alone. Stroma, vessels, blood, and other nonneoplastic elements contribute to the volume. It can be assumed, however, that for a given tumor, the proportion of neoplastic to nonneoplastic cells remains constant during long periods of growth. If a macroscopic tumor with a diameter of 1 cm consists of tumor cells alone, it must have gone through ~30 doublings from the first cell. If the tumor consisted also of 50% nontumorous cells, it would have reached 1 cm in diameter in 26 doublings of tumor cells. Thus, even a 1:1 proportion of tumor cells to nontumorous cells has only a marginal influence of the tumor volume on the time scale.

**Radiological levels of detection.** The crucial point is the minimal detection level of radiologists. This was experimentally tested by Spratt and coworkers [17], who placed lucite balls having a radiopacity approximating that of solid tumors and ranging in diameter from 1.6 to 12 mm randomly upon the posterior and anterior thorax of patients. Radiographs were taken and examined by a group of radiologists. The conclusions were: ''Radiologists could distinguish 10–12 mm diameter balls regardless of their location; 6 mm balls could be detected when the shadow was in a favourable site, and 3 mm shadows could only be found when the radiologist was shown precisely where to look. Radiopacities smaller than 3 mm were indistinguishable.'' For mammography, the lowest level of detection is stated to be 2.1 mm [41].

**Errors in calculations of TVDT.** The basis for this calculation has been clearly stated by Shackney et al. [42]: ''Because the number of cell doublings in the subclinical stage of growth is so large, any error in calculating the doubling time that might be introduced by underestimating tumor size at diagnosis would be relatively small. For example, if the tumor at diagnosis consisted of $1 \times 10^{11}$ cells (= 100g of tissue) instead of $1 \times 10^9$ cells (= 1g), the actual number of doublings would be a little more than 36 instead of 30, introducing an error of little more than 20% in the doubling time calculation.''

**Errors in extrapolations.** The nature of exponential growth places a practical limitation on the magnitude of possible errors in determination of tumor volume. An error by a factor of 2 is compensated for by one single cell population doubling. An error by a factor of 100 is compensated for by only 6.75 doublings. Thus, even a rather large error in measurement and calculation of the volume leads to a much smaller error in the estimation of the duration. Any inaccuracy in determination of growth rate at worst only produces a scale error not affecting the order of events.

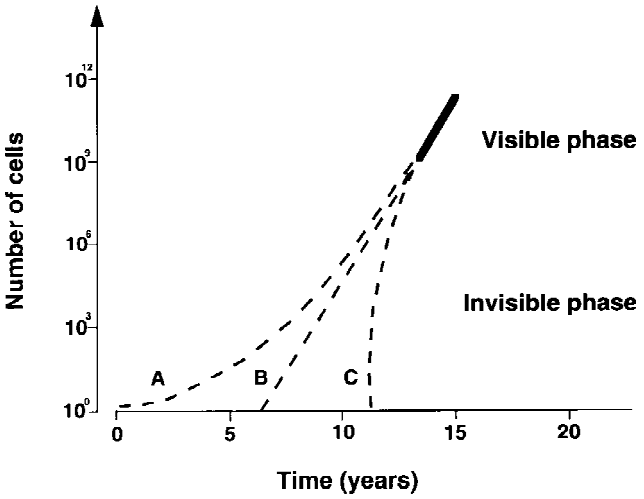


Fig. 3. Hypothetical growth during the preclinical phase. Abscissa: time (years). Ordinate: number of tumor cells (logarithmic scale). A. Slower. B. Equal to. C. Faster than during the measurable phase ($2 \times 10^7$–$10^{11}$ cells).

If the point of origin (= the first cell) is obtained by extrapolation backward in time, the position of that point on the time scale will depend on whether extrapolation starts from the linear visible phase ($2 \times 10^7$ to $10^{11}$), or from the brief asymptotic phase. In this review, all extrapolations were performed from the visible phase, assuming a constant growth rate.

All estimations of the duration of the preclinical period are handicapped by the fact that the growth rates are not known. Comparisons to experimental tumors in animals or in vitro situations are questionable and are, therefore, omitted here.

As noted earlier, three theoretical possibilities exist for the growth rates of spontaneous human tumors during the preclinical period: slower than, equal to, or faster than during the visible and measurable phase (see Fig 3). In choosing between the three possibilities, the present authors have selected linear growth. Thereby, we base our assumption on what can be observed, trying to minimize speculations.

Evidence has been presented supporting slower growth rates, as well as faster growth rates during the preclinical phase. Slower growth rates (curve A in Fig. 3) may occur during a period prior to the production of angiogenetic factors by the tumor cells. During this

quiescent period, the generation of new cells is counteracted by the loss of cells through apoptosis, resulting in a slow or no net increase in the volume of the tumor [1]. Evidence for faster growth rates during the preclinical phase (curve C in Fig. 3) is based on indirect calculations [41]. The reader is referred to Steel and Lamerton [37], Dethlefsen et al. [38], and Steel [39] for a more detailed discussion of these models and on the possible errors in extrapolations from growth curves.

## Results

**Historical background.** The first observations were made by Collins et al. [15], who studied the growth rates of pulmonary metastases from a variety of primary tumors. Their initial studies resulted in the identification of three fundamental principles for the growth rate of human tumors: (1) it is constant for long periods of time, (2) it is often slow, and (3) it varies from one histological type to another. These three principles have been repeatedly confirmed [15–26,28–30,32–34].

Wilms' tumor [42], acute leukemias [43], and nonseminomatous germ cell tumors (NSGCT) [15,20,22,23,44] are examples of rapidly (a TVDT of days) proliferating cell populations. Most adenocarcinomas and some mesenchymal tumors have considerably slower growth rates (a TVDT of months or years) [15–26,28–30,32–34,45].

**Linearity of growth.** Linearity of increase in volume on a logarithmic scale has been observed for several types of human malignancies. In many instances, linearity has been maintained during several years and with numerous observations. Examples of linear growth are given later in this review. Some representative cases have been selected as illustrations. Selection criteria were: (1) numerous determinations of tumor volumes (usually more than four), (2) observation of growth rates over long periods (years), (3) well-defined histology of tumors, and (4) no local or general treatment. The first two criteria were utilized to minimize methodological errors in extrapolations. From the references in this review, we found 58 untreated tumors that where measured more than four times during at least 3 years. Of those tumors, 58 show linearity of increase in volume.

Von Fournier et al. [32] were able to follow 12 women with untreated cancer of the breast for 3–9 years with five or more mammograms in each case: all tumors showed a linear increase in volume during the observation period. Garland et al. [18] studied primary pulmonary malignancies in 41 patients over several years and noted linear increase in volume. In one case, linearity was maintained for 9 years. Spratt et al. [19], studying 118 cases with pulmonary metastases from various primary tumors, observed linear increase in volume with multiple measurements for many years. Breur [22,23], studying 16 cases of pulmonary metastases from mesenchymal malignancies, noted linearity during the whole observation period

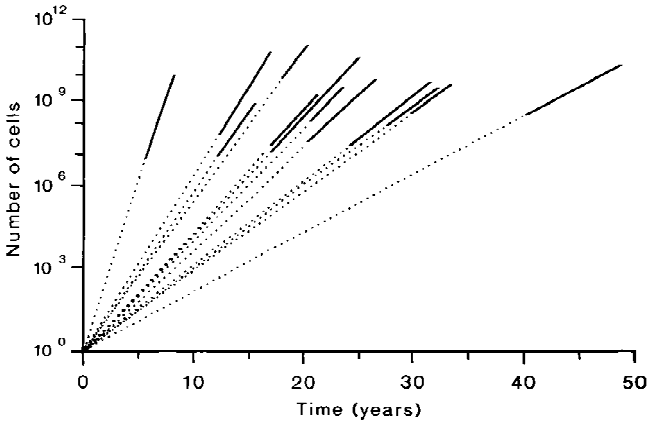


Fig. 4. Growth rates for 12 cases with primary cancer of the breast. Abscissa: time. Ordinate: number of tumor cells (logarithmic scale). Each curve represents one case. The solid line indicates the period of observation. Dotted lines mark the invisible phase. Modified from Von Fournier et al. [32] with the kind permission of Lippincott-Raven Publishers.

(years) for all cases. One patient was examined radiologically 11 times during a 44-month period. All measurements of tumor volume fell on a straight line (on a logarithmic scale).

Fujimoto et al. [46] studied cases with renal cell carcinomas. In six cases, the primary tumors were followed, and in 12 (different) cases metastases to the lungs were monitored. The growth rate showed great interindividual variability, but in each case the growth rate was constant during the observation period. In one case, linearity of growth was noticed for all seven measurements during a period of 6 years.

A remarkable case was published by Spratt and Ackerman [45]. They were able to follow a patient with a well-differentiated adenocarcinoma of the colon for >7.5 years. All of their nine observations on the growth rate fell on a straight line.

Numerous examples of cases displaying linear growth are found below. However, exceptions to linear growth are common. Spontaneous regression, no growth, irregular growth rates, and accelerations of growth can all occur. Even so, the general impression remains that most human malignancies grow at a slow and steady rate for long periods of time during the clinical (and measurable) phase.

**Studies on TVDT of cancer of the breast.** Figure 4 shows the growth rates for 12 primary cancers of the breast. All cases were untreated, and each patient was examined radiologically at least five times. The observation period ranged from 2 years to 9 years. The curves have been adjusted to the one-cell origin, which arranges the curves in a ''fanlike'' fashion. Figure 4 shows the great interindividual variability of the growth rates for different cancers of the breast, with TVDTs ranging from 88 days to 523 days. The average doubling time is 280

**TABLE I. Growth Rates for Cancer of the Breast**

| Estimated TVDT[a] (days) | Number of cases studied | References |
|---|---|---|
| 105[b] | 199 | Kusama et al. [47] |
| 150[c] | 200 | Peer et al. [48] |
| 174[c] | 122 | Kuroishi et al. [49] |
| 212[d] | 147 | Von Fournier et al. [32] |
| 270[b] | 158[e] | Arnerlöv et al. [50] |

[a]Tumor volume doubling time. The median TVDT for these cases cannot be calculated (for explanation, see text). The estimated weighted median value is ~150 days. The range varies from 30 days (46) to infinity (49). The range is illustrated in Figure 4.
[b]Median.
[c]Geometric mean.
[d]Arithmetic mean.
[e]Four cases with infinite growth have been excluded.

days, which means that >18 years were required from the first tumor cell (≈10 μm in diameter) to produce a tumor with a diameter of 2 mm (≈the lowest detection level).

The curves in Figure 4 were redrawn from the study by von Fournier et al. [32]. In that study there was no correlation between the growth rate of the cancer and the age of the patient at the time of diagnosis. The lowest age of a patient when a cancer was detected was 36 years. That cancer had a TVDT of 196 days, indicating that it started to grow when the patient was ~20 years old. The highest age of a patient at the time of diagnosis was 70 years. That cancer had a TVDT of 297 days. The smallest detectable cancer had a diameter of 2 mm (≈$10^7$ cells). The largest cancer that was measured had a diameter of ~45 mm (≈$10^{10}$ cells). The fastest growing cancer had a TVDT of 88 days, and it was detected in a woman when she was 55 years old. It was observed for 4 years with five mammograms. The slowest growing cancer had a TVDT of 521 days, discovered in a woman when she was 60 years of age. It was observed for 8 years with eight mammograms.

Table I gives a summary of TVDT for cancer of the breast, as measured from serial mammograms. The Table is based on observations from >800 patients. All patients were untreated. Detailed information of the histological classification is usually not given. Many of these patients were followed for several years and subject to repeated mammograms. All tumors had diameters between 2 mm and 10 cm. In this range the growth can be expected to be linear before the asymptote in Figure 2 is reached.

Only the five largest studies on cancer of the breast have been included in Table I. Several authors give similar figures, but their number of patients is lower, and their results have therefore not been included [22,23,29,41, 51–61]. Galante et al. [62] reported observations on 196 cases with cancer of the breast. Their results were presented in such a way that the median TVDT could not be calculated, and their observations are therefore not included.

When comparing the TVDT in individual patients, considerable differences are found (see Fig. 4). However, relevant studies give results of the same order of magnitude as the estimated TVDT of cancer of the breast, as seen in Table I. In the five publications listed in Table I, the TVDT values center around 180 days. The exact median TVDT from the five publications in Table I cannot be calculated, since the data presented are not always complete, and they are also presented in various different manners. So-called interval and inflammatory cancers, which are fast-growing, are omitted by some authors since these tumors are not measurable on mammograms. However, cancers not showing any increase in size at all during the observation period (TVDT = >5,000 days) are also excluded by some authors. The proportion of fast-growing cancers to nongrowing cancers cannot be calculated from data in the literature because definitions of ''fast'' and ''slow'' vary from one author to another. It can be assumed to be in the same order of magnitude. It is therefore likely that the two categories ''fast'' and ''slow,'' when excluded, to some extent compensate each other when the median value of TVDT is estimated. Since ~32 cell doublings are required for the first malignant cell to reach a population size with a volume of 1 $cm^3$, a cancer of the breast with a TVDT of 150 days has an age of 12 years or more when discovered clinically by palpation.

The smallest cancer of the breast detectable by mammography measures 2.1 mm [41]. With a TVDT of 150 days, such a cancer has an age of 8 years and it consists of ~$10^7$ cells.

**Studies on cancer of the lung.** The growth rates of primary cancer of the lung have been the subject of several studies. However, not all of these lend themselves to comparison, since the histopathology is not always given. Some of the studies on histologically better defined primary carcinoma of the lung are listed in Table II, which summarizes 12 of the largest studies on cancer of the lung.

Table II is based on >300 untreated cases. The histology of the tumor was often determined at autopsy. The number of observations of the volume of the tumor is at least 2, and in many cases 5–10. Several of the patients were observed for years, or almost a decade, as illustrated later in this review (Figs. 5–7). Median values for the TVDTs of the various histological types can be estimated to be ~90 days for epidermoid carcinomas, 65 days for small cell carcinomas, and 185 days for adenocarcinomas.

Growth rates for primary cancers of the lung are illustrated in Figures 5 and 6. Figure 5 shows five cases with epidermoid carcinomas, (nonsmall cell carcinoma, NSCC), and Figure 6 shows four cases with adenocarcinomas. All cases were selected to illustrate constant

**TABLE II. Growth Rates of Cancer of the Lung Divided According to Histological Type***

| Epidermoid[a] | Small cell[a] | Anaplastic/ undifferentiated[a] | Adenocarcinoma[a] | References[b] |
|---|---|---|---|---|
| 70 (13) | | 93 (13) | 118 (8) | Spratt et al. [19] |
| 78 (8) | | 109 (7) | 214 (11) | Weiss [63] |
| 79 (11) | | | 71 (2) | Schwarz [16] |
| 80 (97) | | | 207 (19) | Charbit et al. [64] |
| 92 (16) | 64 (23) | | 144 (21) | Steele and Buell [27] |
| 93 (6) | | 90 (9) | 269 (7) | Spratt et al. [19] |
| 95 (21) | 39 (3) | | 61 (3) | Chahinian and Israel [65] |
| 103 (6) | | | | Meyer [26] |
| 107 (7) | | | 232 (5) | Weiss et al. [21] |
| 126 (22) | | 123 (9) | 219 (7) | Garland et al. [18] |
| 141 (14) | 46 (3) | 86 (7) | 257 (2) | Mattson and Holsti [66] |
| | | | 77 (12) | Brigham et al. [67] |

*Tumor volume doubling time (TVDT) in days, average/median for different histological types.
[a]Numbers in brackets denote number of cases; range is not given.
[b]Only publications with five or more cases are included.

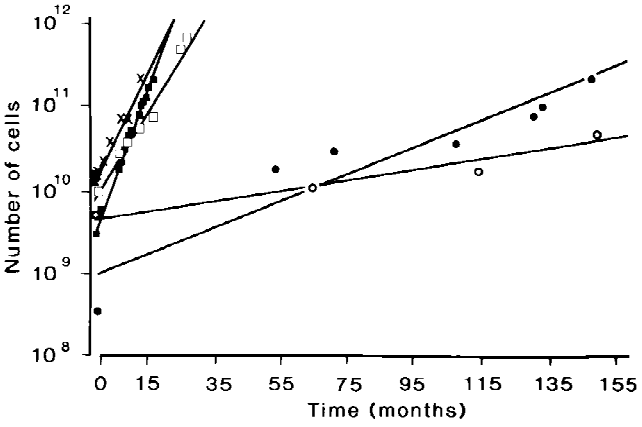


Fig. 5. Growth curves for five cases of primary epidermoid cancer of the lung. Abscissa: time. Ordinate: number of tumor cells (logarithmic scale). Each curve represents one case and each point one observation. The three more rapidly growing tumors have been adjusted slightly in parallel to facilitate visualization. Note that the observation extends over >10 years. The data have been extracted and modified from Spratt and Spratt [20], Schwartz [16], and Brenner et al. [24] with the kind permission of Lippincott-Raven Publishers.

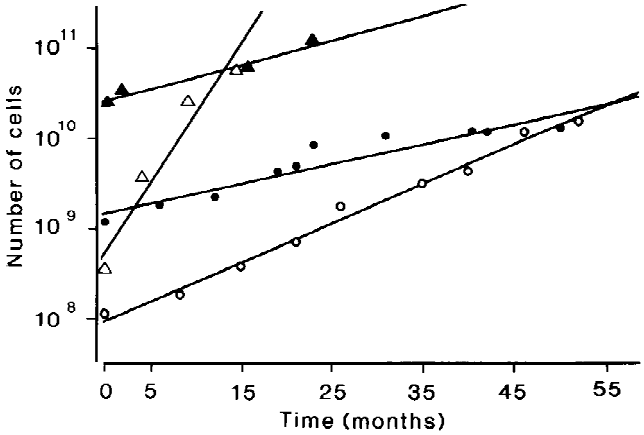


Fig. 6. Growth curves for four cases of primary pulmonary adenocarcinoma. Abscissa: time. Ordinate: number of tumor cells (logarithmic scale). Each curve represents one case and each point one observation. Curves have not been fitted to the one cell origin. Note the linearity for all the cases during the observation period. Two cases are from Weiss et al. [21], two others from Spratt et al. [20]. Modified and reproduced with the kind permission of Lippincott-Raven Publishers.

growth rate over prolonged periods of time (occasionally >10 years).

Spratt et al. [19] noted: ''The number of years required for a cancer to grow from $10^0$ to $10^9$ cells is 7.8 years for an epidermoid carcinoma, and 22.5 years for an adenocarcinoma.'' This means that if an adenocarcinoma with a volume of 1 $cm^3$ is found in the lung of a man 63 years old, the tumor started to grow when he was ~40 years old, and it would still be invisible when he was 55 years old. That patient will reach lethal tumor burden from the time of diagnosis after 10 more doublings of the tumor cells, i.e., when he is 69 years old.

**Studies on pulmonary metastases.** The growth rates of primary tumors other than cancer of the breast or the lung have not been studied to the same extent. The obvious reason is that few other malignancies lend themselves to accurate measurements of the tumor volume. However, the growth rates of solid human malignant tumors originating from organs other than the breast and lung can be estimated indirectly by monitoring their metastases to the lungs, where serial X-ray examinations allow observations. This indirect estimation of the growth rates of the primary tumor is based on the assumption that metastases grow at rates similar to that of the primary tumor. This supposition is discussed below.

Table III lists some of the histologically better defined metastases that have been studied. The majority of these originated from mesenchymal neoplasms—for which no effective general therapy is available—or from testicular tumors before the introduction of cis-platinum treatment. In these studies, the growth rates were not influenced by

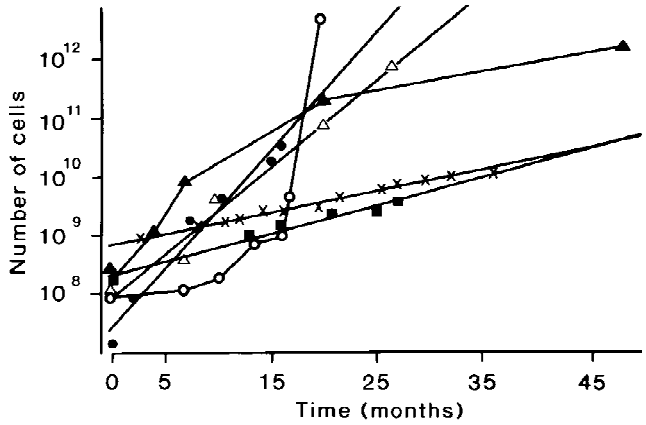


Fig. 7. Growth rates for some pulmonary metastases. Abscissa: time. Ordinate: number of tumor cells (logarithmic scale). Each curve represents one case, and each point one observation. Symbols: ■—■ = leiomyosarcoma (Rööser et al. [33]); ●—● = Ewing sarcoma (Pearlman [28]); X—X = hypernephroma (Brenner et al. [24]). The other three cases are metastases from colon carcinomas [Spratt and Spratt, 20]. Four of the cases display linearity of growth. Two cases of colon carcinoma show nonlinearity. One case shows acceleration, the other retardation of growth. All cases reproduced with the kind permission of the publishers.

**TABLE III. Growth Rates of Pulmonary Metastases Divided According to Site of Primary Tumor**

| Primary | TVDT[a] (days) | Number of cases | References |
|---|---|---|---|
| Testis[b] | 15 | 8 | Breur [22] |
| " | 3 | 5 | Demicheli [44] |
| " | 19 | 6 | Collins et al. [15] |
| " | 43 | 13 | Spratt and Spratt [20] |
| Malignant melanoma | 48 | 10 | Knutsson et al. [68] |
| Thyroid | | | |
| anaplastic | 29 | 4 | Combes et al. [69] |
| follicular | 148 | 7 | Combes et al. [69] |
| Breast | 82 | 29 | Spratt and Spratt [20] |
| " | 83 | 6 | Combes et al. [69] |
| " | 199 | 6 | Breur [22] |
| Colon | 106 | 14 | Combes et al. [69] |
| " | 109 | 10 | Spratt and Spratt [20] |
| " | 116 | 25 | Collins et al. [15] |
| Kidney | 66 | 5 | Chahinian and Israel [66] |
| " | 89 | 12 | Fujimoto et al. [46] |
| " | 132 | 8 | Brenner et al. [24] |
| Cervical uteri | 89 | 5 | Combes et al. [69] |
| Mesenchymal[c] | 8–198 | 11 | Rööser et al. [33] |
| " | 11–120 | 15 | Band and Kocandrle [70] |
| " | 3.9–352 | 21 | Blomqvist et al. [34] |
| " | 5–200 | 25 | Pearlman [29] |
| " | 5–340 | 23 | Spratt and Spratt [20] |
| " | 13–257 | 38 | Breur [22] |
| " | 5–360 | 64 | Joseph et al. [71] |

[a]Tumor volume doubling time. The interindividual variations in TVDT are so great that the range is given rather than the mean.
[b]NSGCT (nonseminomatous germ cell tumors).
[c]Various sites. Most cases were stated to be high grade malignant.

any systemic therapy. Table III includes published data on more than five cases studied by the same investigator. Singular observations have been omitted. Growth rates for six pulmonary metastases are illustrated in Figure 7. The selection criteria were the same as for Figures 5 and 6. In Figure 7, only four of the cases display linear growth during the observation period. The other two cases exemplify nonlinear growth: one case showing acceleration and the other retardation. It can be noted that the retarding growth rate occurs when the volumes are smaller than would be expected at the level of the asymptote in Figure 2.

Two more cases of pulmonary metastases are illustrated in Figures 8 and 9. These cases were selected because they provide unusually good examples of linearity of growth. Both cases are from Breur [22,23].

Figure 8 shows one case of fibrosarcoma with two pulmonary metastases, growing at identical and constant rate. One of the metastases was irradiated (= RT) once and the other twice. Both responded to the treatment, but rapidly resumed growth after completion of therapy. When growth was resumed, it was at a rate identical to that in the pretreatment period. In Figure 9, a case is depicted with two pulmonary metastases from a carcinoma of the bladder.

**Relation between the growth rates of the primary tumor and its metastases.** Secondary tumors may grow at a different rate from that of the primary tumor. It has only been possible to study this in a few cases. For example, Spratt [72], studying three cases with osteogenic sarcomas, found that the secondary tumors to the lungs were similar or slower in growth rate than the primary tumors in the same patient, but the observed differences were not large. Breur [22,23] made the same observation in a case with a sarcoma.

Fujimoto et al. [46] studied 18 cases with renal cell carcinoma. The TVDT of the six primary tumors ranged from 372 days to 579 days (468 ± 43.0). The TVDT of the 12 pulmonary metastases ranged from 20 days to 154 days (89.4 ± 43.0). It should be noted, however, that the patients in whom the primary tumors were measured were not the same patients in whom the metastases were measured. The TVDT of the primary tumors were exceptionally long. The reason cannot be that the tumors were measured during the decelerating asymptotic phase: all tumors were <5 cm in diameter, which is well below the asymptotic level in Figure 2. MacDonald [73] observed that the pulmonary metastases from cancer of the breast grew somewhat faster than the primary tumor. Tubiana et al. [74], studying cancer of the breast, noted a TVDT of 105 days for the primary tumor and 66 days for the pulmonary metastases.

Kusama et al. [47], studying 34 cases with cancer of the breast, noted that the TVDT for the primary tumor did not differ significantly from the TVDT of metastases to the lungs or the lymph nodes in the same individual. If

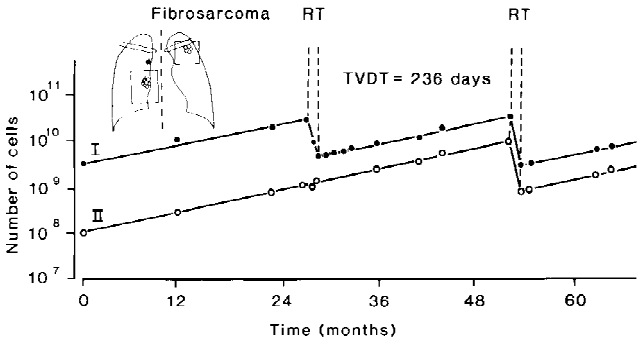


Fig. 8. Growth curves for two pulmonary metastases from a fibrosarcoma in one patient. Abscissa: time (in months). Ordinate: number of cells (logarithmic scale). Each curve represents one metastasis and each point one observation. RT = radiation therapy. One of the metastases was irradiated (= RT) once (II), and the other twice (I): the radiation doses were 37 and 50 Gray (Gy), respectively. The ikon in the top left corner depicts the lungs, the localization of the metastases, and the fields of irradiation. Copied and slightly modified from Breur [22,23]. Reprinted from European Journal of Cancer, Vol. 2, Breurk, ''Growth Rate and Radiosensitivity of Human Tumours, I and II,'' pp. 157–171 and 173–188, 1966, with permission from Elsevier Science, Ltd, Pergamon Imprint, The Boulevard, Langford Lane, Kidlington OX51GB, UK.

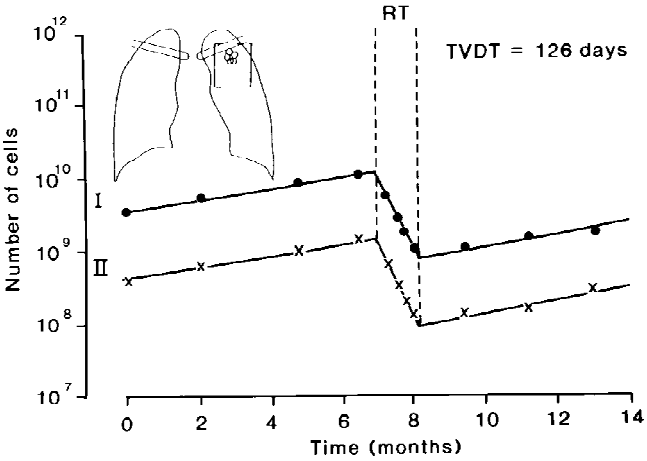


Fig. 9. Growth curves for two pulmonary metastases from a case with bladder carcinoma. All explanations, abbreviations, and comments are as in Figure 8. Radiation dose: 56 Gy. Copied and slightly modified from Breur [22,23]. Reprinted from the European Journal of Cancer, Vol. 2, Breur K, ''Growth Rate and Radiosensitivity of Human Tumors, I and II'', pp. 157–171 and 173–188, 1966 with permission from Elsevier Science, Ltd, Pergamon Imprint, The Boulevard, Langford Lane, Kidlington OX51GB, UK.

the primary tumor grew fast, then the secondaries also grew fast. Conversely, if the primary tumor grew slowly, then the metastases grew slowly as well. Von Fournier et al. [75], studying the same type of malignancy, made the same observation in 16 cases with untreated breast cancer and simultaneous measurements of their metastases to the lungs. The impression from these studies is that the growth rates of the metastases are similar to those of the primary tumors.

If linear growth curves are constructed from the values

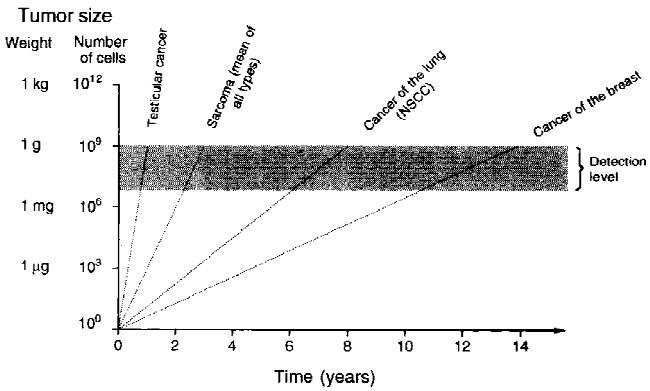


Fig. 10. Hypothetical growth rates for various malignant human tumors. Abscissa: time (years). Ordinate: tumor size (log number of cells or weight of tumor). The level of detection is indicated by the shaded area.

for TVDT in Tables I, II, and III, and are based on the assumption of a close relationship between the growth rates of the primary tumors and their metastases, the diagram in Figure 10 can be constructed. In this diagram, the growth rates for testicular cancers and sarcomas are taken from Table III.

The slope of the line for sarcomas is based on the mean of all observations of TVDT of the various types. This is an obvious oversimplification. The range of the TVDT for the 197 mesenchymal tumors in Table III varies from 3.9 days to 360 days. Consequently, the time period from the first tumor cell to reach detection level varies from 117 days to some 30 years.

The growth rate for epidermoid carcinomas of the lung is calculated from the mean value in Table II. The growth rate for cancer of the breast is the estimated median value from Table I.

Fast-growing tumors (acute leukemias, nonseminomatous testicular tumors, anaplastic thyroid carcinomas, and some pediatric tumors) will ''surface'' in a year or two. Slow-growing tumors (breast, prostate, colon, and several others) will require several years or even decades to reach detection level.

**When do cancers start to metastasize?** In humans, it is impossible to obtain experimental evidence to answer the question of when cancers start to metastasize. But by measuring the TVDT of metastases and extrapolating back to one cell, an approximation of the time of dissemination can be obtained.

Six investigators have made attempts at calculating the start of dissemination. Collins et al. [15] concluded from their studies on 23 cases with pulmonary metastases from various primary tumors: ''. . . the establishment of pulmonary metastases was earlier than the first symptoms of the primary lesion in all but one of the 23 cases studied.'' Tubiana et al. [74], studying cancer of the breast, concluded that ''50% of the metastases started to grow two years before the detection of the primary tumor.''

Von Fournier et al. [75] were able to measure both the primary tumor and multiple metastases to the lung from seven cases of carcinoma of the breast. By extrapolation backward, they concluded that ''metastases start their growth many years before the diagnosis of the primary tumor.'' These authors also imply that already after 21 doublings, (≈0.6 mm in diameter) tumors have the ability to generate metastatic cells.

Bauer et al. [76] concluded that for women with axillary lymph-node metastases from the primary in the breast, 90% of the metastases started to grow when the primary was <6 mm in diameter. They based their conclusion on a study of 337 cases. They end their summary: ''The earliest diagnosis, taking technical possibilities into account, cannot be early enough to precede lymphatic spread.''

Breur [22,23] studied the growth rates of various malignant human tumors. In 76 of his 86 cases, the pulmonary metastases ''originated well before the treatment of the primary tumor, and in most cases before the first symptoms were detected.'' Rööser et al.[33] studied 11 cases with pulmonary metastases from soft tissue sarcoma. ''In all but one case microscopic pulmonary spread was calculated to be present when the primary tumor was diagnosed.''

All of the six studies cited above have come to similar conclusions: in many cases (>75%) the metastases started to grow years before the primary tumor was even detected. In many of these cases the primary had been removed, and there were no signs of local recurrence, even at autopsy. The metastases must therefore have been deposited before the removal of the primary tumor.

The impression obtained from these six studies cannot be valid for all types of human tumors, because local therapy (surgery and/or radiotherapy) is still a curative treatment for the majority of patients where permanent cure really is achieved. The term ''cure'' is almost impossible to define [77]. In this review, the term is used to mean ''dead from intercurrent disease'' (= ''personal cure'').

The present authors are fully aware of the fact that many tumors do not give rise to metastases until late in their lifespan. Such tumors usually have not been reported in the literature, since they do not offer any possibility of studying the growth rates of their secondary tumors. The extremes of biological behavior of malignant tumors range from rapidly metastasizing tumors, which begin to disseminate from the start, to tumors that never give rise to visible metastases, no matter how large the primary tumor grows.

**Support for the concept of constant growth rate.** Perhaps the strongest biological support for the assumption of constant growth rate has been in the area of malignant tumors in infants and children. Wilms' tumor, as an example, may be present at birth or appear within the first months of life. Collins [15,78] reasoned that if a tumor were found in a 3-month-old infant, the maximum age of the tumor from the single cell stage would be the host's age plus 9 months (gestation). If recurrence or metastases should occur after resection and start regrowth from the minimum of one single cell, then the tumor would reach diagnostic size within the same period. In this case, at 15 months of age. Collins was able to test his hypothesis in 340 cases. Of 75 children who had passed the *period of risk*, 73 remained free of disease. In a similar study, Pollock et al. [31] examined 95 patients with Wilms' tumor and 68 patients with neuroblastoma. They found one single exception to Collins' period of risk.

Knox and Pillers [79] examined 87 cases with Wilms' tumor, 126 cases with neuroblastoma, and 31 cases with rhabdomyosarcoma. Among the 244 cases, all 192 recurrences appeared within the period of risk. In total, only 3 (0.6%) exceptions to Collins' rule of the period of risk were found in the first 482 cases studied. Not all pediatric tumors follow Collins' rule: astroglial tumors seem to be an exception [80]. In a recent review by Brown et al. [81], the authors identified only 38 (0.17%) exceptions from 2,233 nonastroglial pediatric cases. The results give strong support to the concept of constant growth rates.

Concerning late recurrences, it may be argued that pediatric tumors differ in their behavior from adult tumors. However, support for the assumption of constant growth rate also comes from studies of cancer of the breast in adults. Allan [82] presented data from late recurrences (>5 years) of cancer of the breast in 139 cases. He found a close correlation between the latent period (up to >20 years) and the survival time (>10 years) after the ''late'' recurrence. Allan's cases would correspond to the three or four slowest growing cases in Figure 4. He concluded that there is ''no justification for the concept of . . . a dormant state during the latent interval, and that the results are consistent with the theory of constant growth rate of the tumors.''

Only tumors with a TVDT of <60 days can be calculated to recur within 5 years if stemming from one single cell at the time of removal of the primary tumor (30 generations × 60 days = 1,800 days ≈ 5 years). Of the more than 800 cases of cancer of the breast summarized in Table I, only ~15% have a TVDT of <60 days.

Recurrences appearing within 5 years after removal of the primary can be explained in two ways: (1) they grow faster than the primary tumor, or (2) they grow at the same rate as the primary tumor, but they started to grow before removal of the primary tumor.

The period of risk for the 12 cancers in Figure 4 can be calculated to vary from a minimum of 9 years (a TVDT of 88 days) to a maximum of >50 years (a TVDT of 512 days). A patient with such a slow-growing tumor is likely to die with, but not from, her cancer (= ''personal

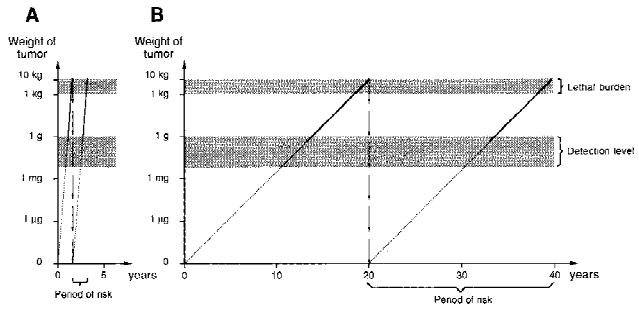


Fig. 11. ''Period of risk'' for two human malignant tumors. To the left **(A),** a hypothetical line for a malignant tumor with a TDVT of 10 days. To the right **(B),** the corresponding line for a tumor with a TVDT of 150 days. Both tumors are assumed to be untreated. In the diagram, the total tumor burden (1–10 kg) is assumed to be provided by the primary tumor *plus* its metastases. The period of risk is defined as the period beginning with removal of the primary just prior to reaching the lethal burden and recurrence stemming from one single cell, growing at a rate similar to the primary tumor and starting when the primary tumor was removed. The period ends when the recurrent cell population has reached the lethal burden.

cure''). Such a long period of risk is consistent with the observed excess mortality from cancer of the breast >30 years after the primary treatment [77,83–87].

NSGCT (nonseminomatous germ cell tumors) have a TVDT of ~20 days (Table III). With such a short doubling time, the tumor will kill its host in a year or two. This means that recurrences of testicular carcinomas many years after the primary treatment are more likely to be new primary malignancies than late recurrences [88].

## DISCUSSION

The facts given in this review are not new. Furthermore, they are well documented. Since the original studies by Collins et al. [15] some 40 years ago, almost 100 articles, five reviews, [16,37,42,89,90] and two books [39,91] have been published on the topic. Yet, the conclusions from biological data are not always drawn in extenso, and the medical and legal implications are usually not taken fully into consideration. The practical medical conclusions that can be drawn from Figure 10 can be extended, as illustrated in Figure 11.

In Figure 11, it is demonstrated that when a malignant tumor can be detected by present-day diagnostic methods, it has consumed more than half of its lifespan, if left alone or unaffected by treatment. A total tumor burden of $10^{12}$ (≈1 kg) in children to $10^{13}$ cells (≈10 kg or around the 45th tumor cell generation) for an adult individual may be regarded as lethal. This level seems to be valid for both solid tumors and hematological malignancies [6,16,17,20,28,43,92]. If the TVDT of the primary tumor is known, antegrade extrapolation (Fig. 11) can, therefore, be used for prognostication. For example, a patient with a malignant tumor with a TVDT of 10 days has a maximum of 450 days from the first tumor cell to survive if untreated.

However, the lifespan of that patient ought to be shorter, since the metastases (and their secondaries) will contribute to the total tumor burden of the host. Recurrences from testicular carcinomas, which are fast-growing tumors, hardly ever occur later than 24 months after treatment of the primary tumor [93]. In contrast, a patient with a slow-growing cancer of the breast or the prostate, as in Figure 11, can be expected to have ~5 years to survive from the detection level, even if untreated.

## CONCLUSIONS

Knowledge of the above facts is important for several reasons.

First, the value of so-called early diagnosis has become questionable. As a matter of fact, the word ''early'' is not even defined in most publications. Whatever definition is used, ''early'' can be regarded as a misnomer when used to describe a tumor that is actually 5 or 10 years of age when detected. Screening the healthy population for malignant tumors—be it cancer of the breast by mammography or cancer of the prostate by measurement of PSA—may, therefore, not reduce the mortality from these diseases as much as expected. Already in 1951, McKinnon [94] titled an article: ''The invalid evidence for faith in early treatment.'' So-called early detection is in fact ''biologically late,'' as stated by MacDonald [73] in 1975. The most common mistake is to regard a small tumor as an ''early'' tumor. This is not so; when a malignant tumor is detected, it has already existed for at least half of its lifespan.

This may explain why mammography has not been able to reduce the mortality from cancer of the breast as much as initially expected. The number of women screened to achieve one less death per year ranges from 7,068 in one study to 63,264 in another study to infinity in a third [95]. To give another example, screening for lung cancer in order to obtain ''early'' detection has not reduced mortality from these diseases. Screening for lung cancer is, therefore, advised against [96].

Second, knowledge of human tumor kinetics may influence the outcome of legal trials in which the possible influence of patients' or doctors' delays on the prognosis of the patient is at stake. The importance of ''early'' detection of tumors for the prognosis of the patient has been grossly overestimated, because clinically detectable tumors are not early. Dissemination may have occurred long before the diagnosis of the primary tumor.

Moreover, a delay of 1 or 2 months in the diagnosis of a slow-growing malignant tumor such as cancer of the breast will amount to 1% or 2% of the total consumed lifespan of that tumor. Displacing diagnosis to an earlier date will prolong the observation period without influencing the time of death for a nontreated patient. If the diagnostic level of an untreated tumor with a TVDT of

150 days was shifted from 1 cm diameter ($\approx 10^9$ cells) to 2 mm in diameter ($\approx 10^7$ cells), this would increase the observation time with almost 3 years. Such patients will live longer as cancer cases, but not as individuals. This pitfall has been termed ''lead time bias'' [97]. The medico-legal problem of malpractice claims for doctor's delay is increasing, but has so far received but little attention in the medical literature. One notable exception is the article by Spratt and Spratt [98].

''Early'' therapy of a primary tumor will lead to a reduction in mortality only if the primary tumor can be eliminated before dissemination begins. And as shown in this review, dissemination frequently begins prior to the detection of the primary tumor. In such cases, local treatment of the primary tumor will not prevent dissemination. Nor will local treatment improve the long-term prognosis of the patient. This emphasizes the need for better generalized treatment, not the need for better diagnostic methods or better local treatment.

But there are two examples where ''early'' detection (with prompt removal of the primary tumor) has resulted in a true decrease in mortality: malignant melanoma of the skin and cervical carcinoma. These two malignancies share two unique characteristics: (1) they both have a long preinvasive period, and (2) they can be inspected by eye.

Hence, a suspected precursor lesion can be removed during the preinvasive phase. Under those conditions, local treatment may prevent metastases. In contrast, when generalized malignancies are cured—like some leukemias or testicular tumors—it is not because they are detected early, but because the tumor cells are susceptible to treatment.

Third, the design and analysis of clinical trials may be affected by knowledge of tumor kinetics. If cancer-specific death is used as an end-point in individual cases, then that point will be reached in a few years for fast-growing tumors. For slow-growing malignancies, in contrast, a 5- or 10-year observation period may not even cover the natural course of the disease. For cancer of the breast, the prostate, and the kidney, for example, the excess mortality from the diseases remains as long as 20 years after the primary treatment [90]. The long-term survival curves from cancer of the breast [87] and renal cell cancer [99] are particularly striking. Moreover, if the TVDT is not taken into consideration, an uncritical interpretation of survival curves may be misleading [28]. For example, survival curves from patients with one clinical stage may not be directly compared to patients with another clinical stage of a similar tumor, because the two groups of patients are at different levels on the growth curve when the observation starts.

The two groups of patients may also represent different types of malignancies originating in the same organ, but lumped together under the same diagnosis. The wide range of growth rates for cancer of the breast illustrated in Figure 4 also may reflect highly variable biological properties, like metastasizing potential. It is possible that ''stage II breast cancer is not simply a late stage I,'' as stated by Mueller [100].

Fourth, interpretation of some epidemiological data may be reconsidered. If a tumor reaches the diagnostic level when it is 10 years old, it is not likely to have been initiated by a suspected carcinogen to which the patient was exposed only 5 years earlier. The causative agent must be searched for more than 10 years before the diagnosis.

Fifth, as stated above, insurance policies may be affected by awareness of tumor kinetics. There is ample evidence that metastases progress at roughly the same rate ( = similar TVDTs) as the primary tumor. Therefore, if 12 years are required for the primary tumor to reach a size of 1 cubic centimeter, it is likely that some of the secondaries will need the same period of time to reach detectable levels. Some ''late recurrences'' or so-called dormant cells, appearing decades after removal of the primary, may not be late or dormant at all. They may simply reflect the natural history of a slow-growing neoplasm. For slow-growing cancers—and many cancers of the breast, prostate, colon, and kidney belong to this category—these facts lead to the conclusion that the 5-year survival rate is no reliable measure of cure [101]. However, if the TVDT of a tumor is known, the ''period of risk'' can be estimated relatively accurately. The use of TVDT as a yardstick of prognosis is a more realistic measure of treatment efficacy than the number of survivors at arbitrary units of time. If the TVDT—and hence the period of risk—is doubled by treatment, this may be a more appropriate measure of treatment efficacy than an increase in the number of 5-year survivors. A host having a pulmonary metastasis 20 mm in diameter has a 95% probability of dying within 11 more tumor doublings [20]. The duration of his or her life, however, may vary from some 100 days with a TVDT of 10 days to 2,160 days (≈6 years) with a TVDT of 200 days. This, in turn, may have implications for insurance companies and their risk estimations.

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