NOWOTWORY Journal of Oncology • 2005 • volume 55
Number 1 • 1–22

Artykuł na zaproszenie redakcji • Invited article

On the growth rates of human malignant tumors: Implications for medical decision making

Sten Friberg

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 sub-clinical period, to grow at constant rates for long periods of time, to often start to metastasize even before the primary is detected, to often have metastases that 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:
- *Screening programs. Most tumors are several years old when they become detectable by present-day diagnostic methods. This makes the term 'early detection' questionable.*
- *Legal trials. The importance of so-called doctor's delay is often discussed, but the prognostic value of "early" detection is overestimated.*
- *Analysis of clinical trials. Analysis of clinical trials 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.*
- *Analyses of epidemiological data. If searches are made for the causes of malignant tumors in man, the time of exposure must be extended far back in the subject's history.*
- *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.

Rozrost nowotworów złośliwych u ludzi
Implikacje dotyczące podejmowania decyzji

Raki jąder, nowotwory dziecięce i niektóre guzy mezenchymalne to przykłady bardzo szybko namnażających się populacji komórek, w przypadku których czas do podwojenia objętości guza (tumour volume doubling time – TVDT) bywa wyrażany w dniach. Z drugiej strony raki piersi, gruczołu krokowego czy jelita grubego rosną powoli, a ich TVDT wyraża się w miesiącach, a nawet w latach.
Niezależnie od dynamiki rozrostu większość nowotworów napotykanych u ludzi posiada następujące cechy: wywodzi się z jednej komórki, charakteryzuje się długim przebiegiem bezobjawowym, rozrasta się w jednostajnym tempie przez długi czas, często daje przerzuty, zanim dojdzie do rozpoznania guza pierwotnego, często daje przerzuty charakteryzujące się takim samym tempem wzrostu jak guz pierwotny.
Znajomość podstawowych elementów kinetyki guza jest niezbędna dla wypracowania współczesnej strategii postępowania w nowotworach. W niniejszej pracy położono szczególny nacisk na następujące elementy:
- *Programy przesiewowe. W momencie, kiedy przy użyciu nowoczesnych technik można stwierdzić obecność nowotworu, rozrasta się on już zazwyczaj od kilku lat. Podważa to zasadność terminu „wczesne rozpoznanie".*
- *Zagadnienia medyko-legalne. Często rozważa się znaczenie tak zwanego „opóźnienia zawinionego przez lekarza", ale w istocie znaczenie prognostyczne „wczesnego" rozpoznania jest znacznie przeceniane.*

Department of Oncology
Karolinska University Hospital
Stockholm, Sweden

– *Analiza badań klinicznych. Analizę badań klinicznych można zróżnicować w zależności od dynamiki wzrostu badanego typu nowotworu. Co więcej, bezkrytyczne podejście do wyników badania, przedstawionych w aspekcie długości przeżycia, może być bardzo mylące, jeśli nie bierze się pod uwagę TVDT.*
– *Analiza danych epidemiologicznych. Jeśli poszukuje się czynników odpowiedzialnych za wystąpienie nowotworu u danego chorego, to analizą należy objąć okres sięgający nawet wiele lat wstecz.*
– *Ocena ryzyka prowadzona przez ubezpieczyciela. W przypadku większości nowotworów spotykanych u ludzi pięcioletnie przeżycie nie jest adekwatnym miernikiem wyleczenia.*

Podsumowując, można stwierdzić, że znajomość kinetyki nowotworu ma istotne implikacje nie tylko w zakresie planowania narodowych strategii zdrowotnych, ale również podczas prowadzenia spraw sądowych dotyczących postępowania medycznego, w kontekście badań naukowych, a nawet w odniesieniu do ubezpieczeń zdrowotnych.

Key words: neoplasm, human, growth rate, doubling time, diagnostic level, lethal burden, period of risk
Słowa kluczowe: nowotwór, ludzie, dynamika wzrostu, czas podwojenia, poziom diagnostyczny, śmiertelność, okres ryzyka

Introduction

In 1997, Stefan Mattson and I published a review on the growth rates of human malignant tumors [1]. Since then, further information and more models for growth curves have been published. Upgrading of the previous review is thus of timely importance. The purpose of this review is to consider the gross growth rates of various human malignancies, as studied in their hosts. It will not deal with in vitro studies, or studies in animals, since their relevance for human spontaneous malignancies is questionable. Nor will it deal with experimental studies in humans (i.e. labelling indicies, incorporation of radio-labeled nucleotides, immunological markers, etc) since these studies do not take cell loss (mainly through apoptosis) into consideration [2]. In this review, the growth rate is defined as the rate of increase of volume (or the number of cells) in relation to time. It is based on studies of more than 2,500 individual cases, with a total of more than 7,000 observations of the growth rate.

Data mining

The database "Medline" was searched back to the beginning of 1966. Search words were the same as the key words in this review. Articles prior to 1966 were identified through perusal of the reference lists in the articles found. Exclusion criteria of the articles were reports on individual cases, or cancers with uncommon or unclear pathology, or cases with only a few observations.

If the examination methods were other than radiological, they were also excluded. Special focus was placed on reports dealing with cancers of the breast, cancers of the lung, and ocular malignant melanomas. Whenever the suspicion has arisen that the same patient cases had been published more than once, that particular clinical material is referred to only once.

Background

Monoclonality

A primary tumor starts from one single cell, 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 [3]. One hundred years later, in 1962, Waldenström gave the hypothesis support from studies on human multiple myeloma [4]. Today, monoclonality has been shown for the majority of human malignant tumors [5-8]. Even multicentric tumors – such as cancer of the urinary bladder [9] or cancer of the breast [10] – have been shown by modern methods in molecular genetics to be originally monoclonal.

Also, even tumors in paired organs – like the testes – seem to stem from one basic genetic alteration during embryogenesis [11, 12]. The same genetic alteration also appears to be the underlying cause of extra-gonadal germ cell tumors (in the thymus or the pineal gland) [13]. Heterogeneous clones are likely to occur later during the life-span of a tumor. It will be shown in this review that most malignant tumors in humans are many years old when clinically detectable. Polyclonality at the time of diagnosis does therefore not contradict a monoclonal origin: the tumor cell population has had ample time to diversify during the pre-clinical period. To make a comparison, every newborn being is polyclonal, but its origin (the fertilized egg) is monoclonal. Attempts at disproving monclonality of origin for clinical tumors will always 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 approximately 1 cm^3 after 32 cell generations. If the tumor cells are 25 μm in diameter, 26 doublings are required to reach that volume, and at that size, it consists of 10^9 cells.

For calculations of growth curves in this review the following simplifications have been 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 fill completely the sphere. The cellular composition of tumors will be discussed below. If the size of a tumor is given in two dimensions [cm x cm] and is

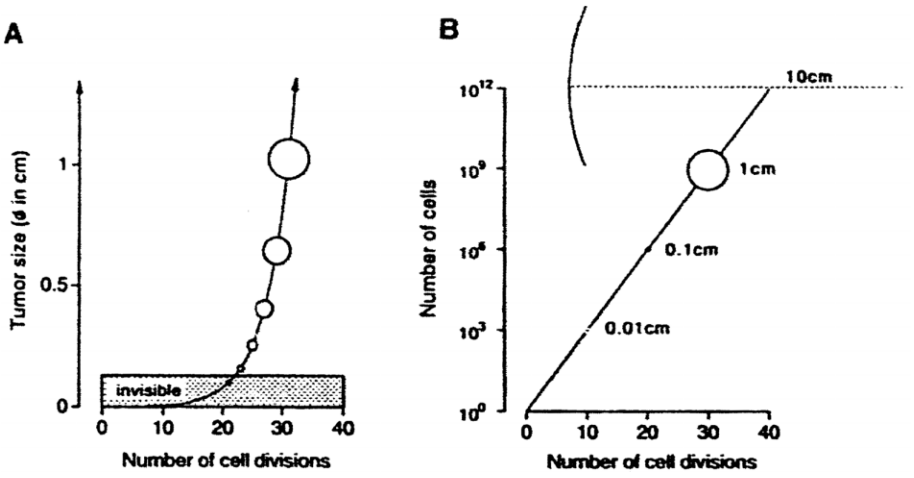

Figure 1.
Figure 1 A. Gross growth rate of a tumor.
Abscissa: Number of cell divisions.
Ordinate: Tumor size (diameter in centimetres).
Note the number of cell divisions required for the tumor to reach diagnostic level (0.2 – 1 cm in diameter). The pitfall of plotting tumor growth on a non-logarithmic scale gives the false impression that the tumor grows at an increasing speed.

Figure 1 B. Gross growth rate of a tumor.
Abscissa: Number of cell divisions.
Ordinate: Number of cells (logarithmic scale).
The growth rates are identical in Figures 1A and 1B, 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 it weighs 0.52 gram. With a TVDT of 150 days, and assuming a constant generation time, the tumor is then around 12 years old.
The straight line indicates a constant growth rate, in contrast to the false impression that Figure 1A gives.

plotted against time, the curve depicted in Figure 1A is obtained. It gives the reader the impression that a tumor grows at an accelerating speed. But this is an illusion which will be commented on below. The increase in the number of cells in a tumor is determined mainly by three principal parameters [14]: 1. The cell cycle time of the proliferating cells, 2. The fraction of cells proliferating, 3. The amount or fraction of spontaneous cell loss. The spontaneous cell loss in vivo may be as high as 50% [14] in each cell cycle or even higher [15] and is therefore of profound importance for the growth rate. Refsum and Berdal [15] 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 constant during the visible stage [16-35]. Plotted on a semi-logarithmic 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 centimeter] but as the number of cells on a logarithmic scale. Tumors grow in 3 dimensions, not 2. In this review, linear growth is defined as a constant increase of tumor volume on a logarithmic scale, in relation to time. The distinction between Figures 1A and 1B are not always made. This has probably led to one of the myths in oncology, which will be examplified below.

Growth curves

An early contribution to the theory of growth curves – although not intended for tumors – was made by Gompertz in 1825 [36]. Several other mathematical models useful for studying tumor growth exist [37-40]. Most growth curves are characterized by an upper horisontal asymptote. For human malignant tumors, this upper horisontal asymptote is the upper limit which the cancer cannot exceed because the tumor burden has become lethal to its host. This limit has been termed the "lethal burden", and it is illustrated in Figure 2, where the period during which human tumors are measurable in vivo is that above the detection level. More recent growth models are published by Plevritis [41], by van Leeuwen et al [42], and by Kopans et al [43].

The growth curves in Figure 2 were obtained in the following way: the slope of the linear growth curve was calculated for 3 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 is then added.

In Figure 2, a retardation of growth (deceleration) is seen at the upper limit. This is likely to be true for the primary tumor, due to diminishing nutrients, blood supply, growth factors, hormones and so forth. Such measurements, however, are rare, because the patient

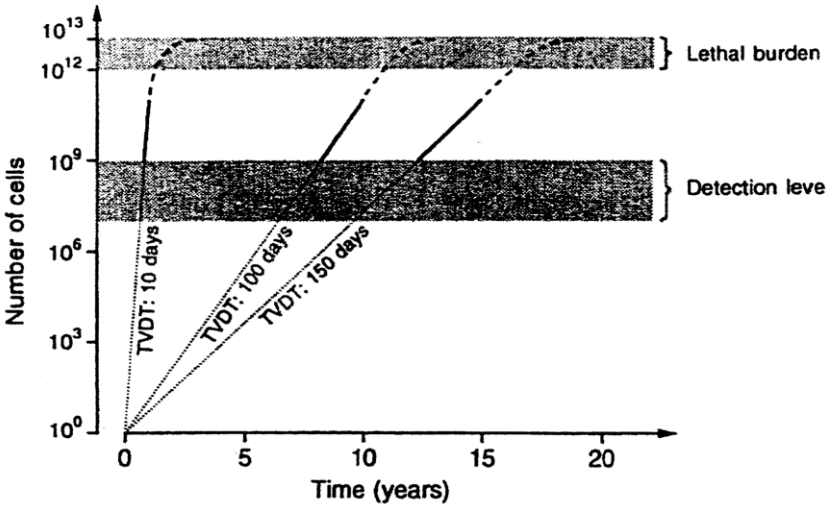

Figure 2. Growth rates for three different tumors.
Abscissa: Time (years). Ordinate: Number of tumor cells (logarithmic scale).
The diagnostic level (from 10^7 to 10^9 cells), and the lethal burden (10^{12}-10^{13} cells, or 1 kilogram – 10 kilograms) limit the visible phase of a human tumor.
The three tumors have been given TVDTs 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.

is close to death. It would be unethical to investigate for only scientific purposes a patient who is beyond treatment. If extrapolation back to the one-cell origin starts near the asymptotic level, this can explain the absurd results indicating that the tumor started to grow some 30 years before the patient was born. The majority of human malignant tumors display constant growth rates – albeit individually highly different – in the medium size range (10^7-10^{11} cells).

However, when the total number of tumor cells in a patient are considered, then the contribution by microscopical metastases should be included. But their weight will never be known. If they are added, the curve will become straighter and steeper. It may be argued that since the growth rate during the pre-clinical period is not known, the extrapolation back to the one-cell level is uncertain. For the growth rate of a tumor during the pre-clinical period, three theoretical possibilities exist: 1. it can be faster than, 2. it can be identical to, or 3. it can be slower than the growth rate during the visible phase, see Figure 3.

Facing these three possibilities, the present author has chosen the intermediate one (= identical growth rate). In Figure 2 the total 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 a relatively small tumor. It is at that size that a tumor may give rise to the first symptoms. It is also at that size that a tumor may become detectable by palpation, or by the use of tumor markers such as Prostate Specific Antigen (PSA) [44], or on radiographs.

Cellular origins of metastases

Metastases can also be assumed to start from one 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 semi-logarithmic scale. Therefore, determinations of the TVDT of a secondary tumor followed by extrapolation back to the one-cell origin, may allow estimation of the starting time of that secondary tumor.

There is a widespread opinion among physicians that metastases grow faster than their primaries, through

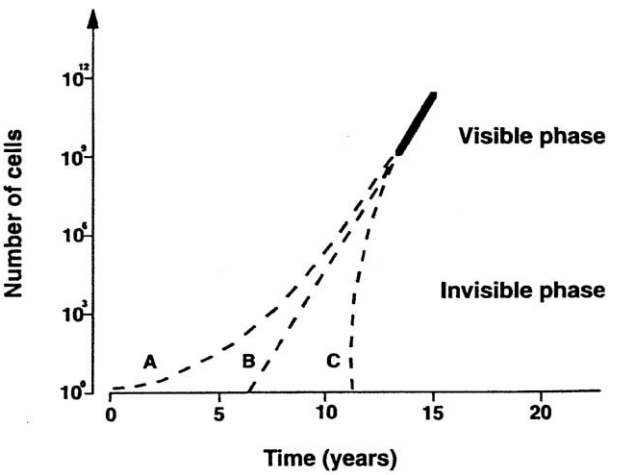

Figure 3. Hypothetical growth during the pre-clinical phase.
Abscissa: Time (years).
Ordinate: Number of tumor cells (logarithmic scale).
A: Slower than,
B: Equal to,
C. Faster than during the measurable phase (2 x 10^7-10^{11} cells)

a selection of the fast-growing clones. This may be true, but support for this idea in the medical literature is scarce. A more likely explanation is that the growth rates of the metastasis are plotted on a arithmetic scale and not on a logarithmic. In the clinical setting, the size of a tumor is usually given in only 2 dimensions, whereas growth is 3-dimensional.

Whenever growth rates of tumors are studied, the authors and readers must think in terms of logarithms. If a sphere has increased its size from 1 to 2 centimeters in diameter, it has not doubled its volume; it has increased its volume 8 times.

Methods

Radiological

The TVDT of various untreated solid malignant human tumors has been the subject of several studies, and serial radiograms have usually 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. Irregular shapes, unsharp boundaries and inhomogeneity are some of the major obstacles. In a careful analysis of the possible errors, Brenner et al [25] 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 non-neoplastic elements contribute to the volume. It can be assumed, however, that for a given tumor the proportion of neoplastic to non-neoplastic 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 around 30 doublings from the first cell. If the tumor consisted also of 50% non-tumorous 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 non-tumorous cells has only a marginal influence of the tumor volume on the time scale.

Levels of radiological detection

The crucial point is the minimal detection level of radiologists. This was experimentally tested by Spratt et al [18]. They 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 as follows. "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 [45]. For conventional X-rays of the lungs, 6 mm has been stated to be the lower detection limit [46].

Errors in calculation of TVDT

The basis for this calculation has been clearly stated by Shackney et al [47]: "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 1×10^{11} cells (= 100 g of tissue) instead of 1×10^{9} cells (= 1 g), 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.

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

All estimations of the duration of the pre-clinical phase are handicapped by the fact that the growth rates are not known. Comparisons with experimental tumors in animals or in vitro situations are questionable, and therefore omitted here. Much of the confusion regarding various growth curves is due to the fact that many investigators try to apply one single formula to three basically incommensurable types of tumors: 1. Human spontaneous tumors, 2. Experimentally induced tumors in animals, and 3. Tumors grown in vitro. Trying to unify these three is not only a gross oversimplification: it is incorrect. Experimentally induced tumors have different properties than spontaneous tumors, and cells growing in vitro can be regarded as laboratory artefacts. They are selected to grow under highly specialized conditions, and also for their fast growth rates (in order to give fast results?).

As mentioned, three theoretical possibilities exist for the growth rates of spontaneous human tumors during the pre-clinical phase as was shown in Figure 3. An identical growth rate was chosen, basing the choice on values from the measurable phase.

Evidence has been presented supporting slower as well as faster growth rates during the pre-clinical phase. Slower growth rates (curve A in Figure 3) may occur prior to the production of angiogenetic factors by the tumor cells. During the quiscent period, the production 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 [2]. Evidence for faster growth rates during the pre-clinical phase (curve C in Figure 3) is based on indirect calculations [45]. The reader is referred to Steel and Lamerton [38], Dethlefsen et al [39] and Steel [40] for a more detailed discussion of these models and on the possible errors in extrapolations from growth curves.

Results

Historical comments

The first observations were made by Collins et al [16], who studied the growth rates of pulmonary metastases from a variety of primary tumors. Their initial observations resulted in the identification of three fundamental

principles for the growth rates of human tumors: 1. It is constant for long periods of time, 2. It is often slow, 3. It varies from one histological type to another.

Collins' three principles have been repeatedly confirmed [17-35]. Wilms' tumor [32], acute leukemias [48] and non-seminomatous germ cell tumors (NSGCT) [49] are examples of rapidly (a TVDT of days) proliferating cell populations. Most adeno-carcinomas and some mesenchymal tumors have considerably slower growth rates (a TVDT of months or years) [17-28, 30-32, 34-37, 50-51].

Linearity of increase in volume

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 will be given later in this article. Some representative cases have been selected to illustrate this. Selection criteria have been: 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, 4. No local or general treatment. The first two criteria were utilized to minimize methodological errors in extrapolations.

From the references in this review a total of 58 untreated primary tumors were found which where measured more than four times during at least three years. All 58 of these tumors show linearity of increase in volume.

von Fournier et al [33] were able to follow 12 women with untreated cancer of the breast for 3-9 years with 5 or more mammograms in each case: all tumors showed a linear increase in volume during the observation period. Garland et al [19] 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, Spjut and Roper [20] studying 118 cases with pulmonary metastases from various primary tumors observed linear increase in volume with multiple measurements for many years. Breur [23, 24] studying 16 cases of pulmonary metastases from mesenchymal malignancies, noted linearity during the whole observation period (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 [51] studied cases with renal cell carcinomas. In 6 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 7 measurements during a period of 6 years. A remarkable case has been published by Spratt and Ackerman [50]. They were able to follow a patient with a well differentiated adenocarcinoma of the colon for more than 7.5 years. All of their 9 observations on the growth rate fell on a straight line. Numerous examples of cases displaying linear growth will be found below. On the other hand, exceptions to linear growth are common. Spontaneous regression, no growth, irregular growth rates and accelerations of growth can all occur. However, 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.

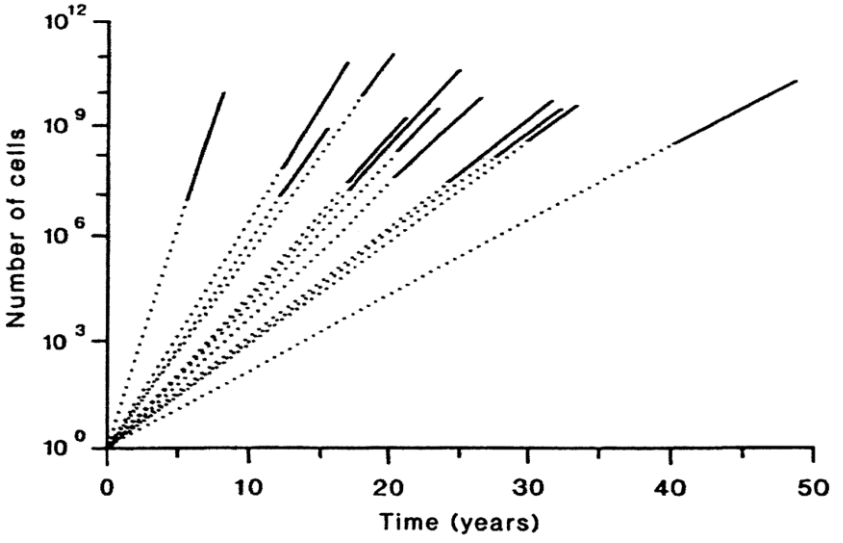

Figure 4. Growth rates for twelve cases with primary cancer of the breast.
Abscissa: Time.
Ordinate: Number of tumor cells (logarithmic scale).
Each curve represents one case. The solid line indicates the period of observation.
Dotted lines mark the invisible phase. Modified from von Fournier et al [33] with the kind permission of the Lippincott-Raven Publishers.

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 to 9 years. The curves have been adjusted to the one-cell origin, which arranges the curves in a "fan-like" fashion. Figure 4 shows the great interindividual variability of the growth rates for different cancers of the breast, with TVDTs ranging from 88 to 523 days. The average doubling time is 280 days, which means that more than 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 have been redrawn from the study by von Fournier et al [33]. 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 around 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 around 2 mm (≈10^7 cells). The largest cancer that was measured had a diameter of around 45 mm (≈10^{11} 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. This was discovered in a woman when she was 60 years of age, and it was observed for 8 years with 8 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 more than 800 patients. All patients were untreated. For obvioius reasons detailed information of the histological classification is usually not given, but the malignancy was confirmed, either cytologically, histologically or at autopsy. 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.

Table I. Growth rates for cancer of the breast

Estimated TVDT (days)	Number of cases studied	Reference
105*	199	Kusama [52]
150†	200	Peer [53]
174†	122	Kuroishi [54]
212‡	147	von Fournier [33]
270*	158§	Arnerlöv [55]

*= median
†= geometric mean
‡= arithmetic mean
§= four cases with infinite growth have been excluded
The mean TVDT for these cases cannot be calculated (for explanation, see text). The estimated weighted median value is around 150 days. The range varies from 30 days [52] to infinity [54]. The range has been illustrated in Figure 4.

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 [23, 24, 30, 45, 56-66]. Galante et al [67] 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 Figure 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 ways. So-called interval and inflammatory cancers – which are fast-growing – are omitted by some authors since these tumors are not measurable on mammograms. On the other hand, 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 non- growing cancers can not 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 approximately 32 cell doublings, and 100% viability of the cells, are required for the first cancer cell to reach a volume of 1 cubic centimeter, 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 detectable cancer of the breast detectable measures 2.1 mm [45]. With a TVDT of 150 days, such a cancer is 8 years old and it consists of 10^7 cells. An excellent mathematical model for invasive cancer of the breast, which also takes ductal cancer in situ (DCIS) into consideration, is given by Kopans et al [43]. An excellent mathematical algoritm for cancer of the breast detected by mammography is given by Plevritis [41].

Studies on cancer of the lung

The first reviews of cancers of the lung and their growth rates was given by Geddes [68]. This elegant publication has been confirmed several times. However, not all of the published data 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, in which 12 of the largest studies are included.

Table II is based on more than 300 completely untreated patients. The histology of these tumors were often determined at autopsy. The number of observations of the volume of the tumor is at least 2, and in many cases 5 to 10. Several of the patients were observed for years or almost a decade, as will be illustrated later (Figures. 5, 6 and 7). Median values for the TVDTs of the various histological types can be estimated to be around 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 epidermal carcinomas (non-small cell carcinomas, NSCC), and Figure 6 shows four cases with adenocarcinomas. All cases were selected to illustrate constant growth rates over prolonged periods of time, occasionally more than 10 years.

Spratt, Spjut and Roper [20] 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 around 40 years old, and it would still be invisible when he was 55 years old. That patient would reach a lethal tumor burden from the time of diagnosis after 10 more doublings of the tumor cells, i.e. when he is 69 years old. If these somewhat theoretical figures are put into clinical realities, both size at the time of diagnosis and the TVDT have a profound influence on prognosis. If two smokers both develop the first cell of lung cancer at the age of 40 years, and the TVDT is 30 days for one of them (SCLC), and 300 days for the other (adenocarcinoma), the first patient will reach diagnosible level after almost 4 years, whereas the other can be detected only after 30 years. The first patient will have an aggressive cancer at 44 years of age, and the other an almost benign tumor at 70.

Table II. Growth rates for cancer of the lung divided according to histological type TVDT (days)

Histological type				Reference
Epidermoid	Small-cell	Anaplastic/ Undifferentiated	Adenocar-cinoma	
70 (13)		93 (13)	118 (8)	Spratt [20]
78 (8)		109 (7)	214 (11)	Weiss [69]
79 (11)			71 (2)	Schwartz [17]
80 (97)			207 (19)	Charbit [70]
92 (16)	64 (23)		144 (21)	Steele [28]
93 (6)		90 (9)	269 (7)	Spratt [20]
95 (21)	39 (3)		61 (3)	Chahinian [71]
103 (6)				Meyer [27]
107 (7)			232 (5)	Weiss [22]
126 (22)		123 (9)	219 (7)	Garland [19]
141 (14)	46 (3)	86 (7)	257 (2)	Mattson [72]
			77 (12)	Brigham [73]

Numbers within brackets denote number of cases. The range is not given.
Only publications with five or more cases have been included.

The latest reports on the growth rates of cancers of the lung, where more modern and sensitive radiological methods than conventional radiographs have been used [74, 75, 46], indicate that small cancers grow at similar

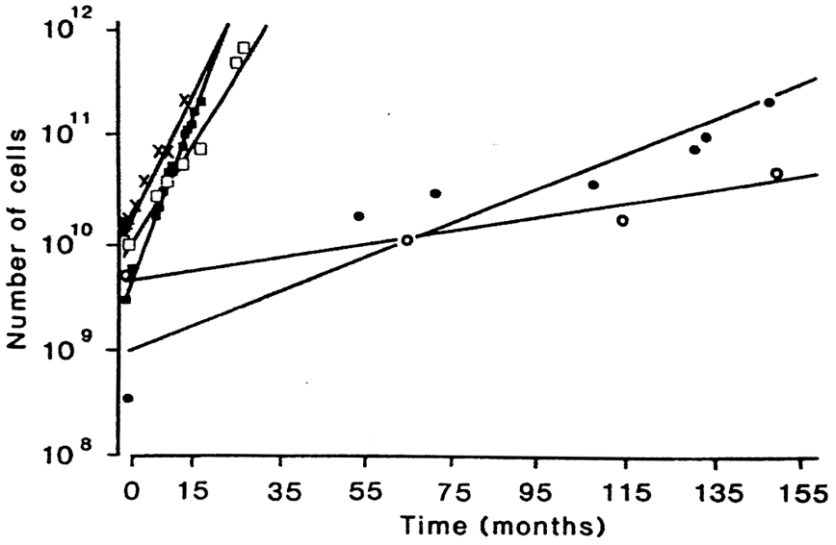

Figure 5. Growth curves for five cases of primary epidermoid cancer of the lung.
Abscissa: Time.
Ordinate: Number of tumor cells (logarithmic scale).
Each curve represents one case, and each point one observation.
The three more rapidly growing tumors have been adjusted slightly in parallell to facilitate visualization. Note that the observation extends over more than 10 years. The data have been extracted and modified from Spratt & Spratt [20], Schwartz [17], and Brenner et al [25] with the kind permission of the editors.

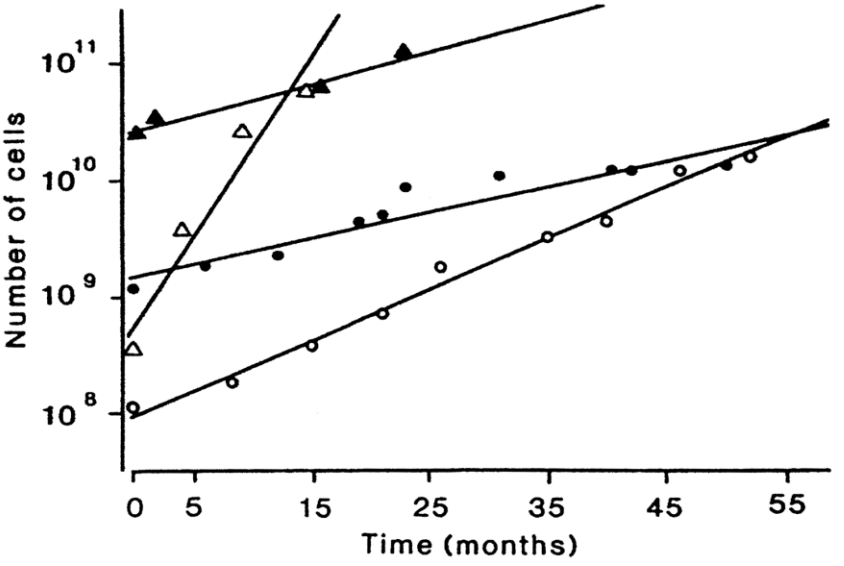

Figure 6. Growth curves for four cases of primary pulmonary adenocarcinoma.
Abscissa: Time.
Ordinate: number of tumor cells (logarithmic scale).
Each curve represents one case, and each point one observation.
Curves have not been fitted to the one-cell origin. Note the linearity for all the cases during the observation period. Two cases are from Weiss et al [69]. The two others are from Spratt et al [20]. Modified and reproduced with the kind permission of the editors.

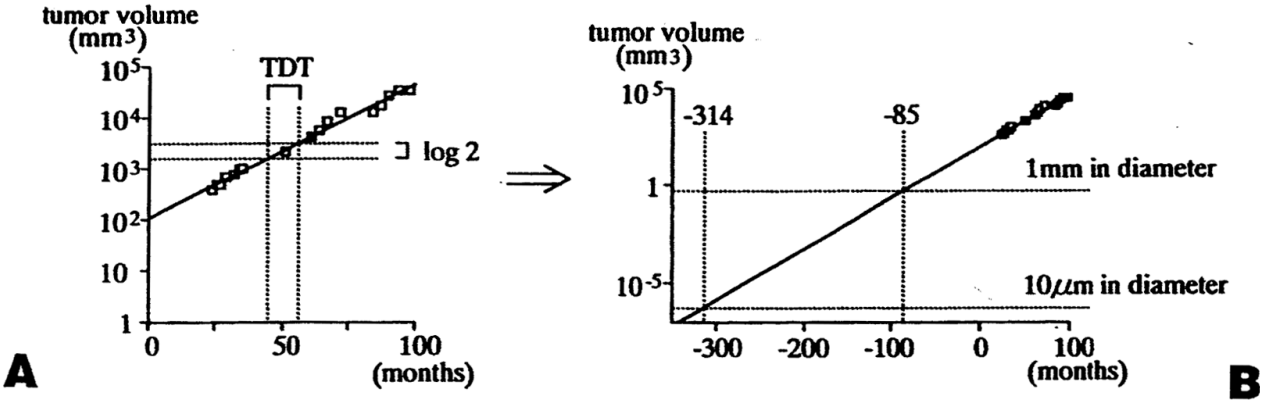

Figure 7. Growth curves for acinic cell cancers.
A. Logarithm of volume of a malignant tumor in proportion to time after onset. TDT = TVDT in this publication.
B. The onset time (10 μm) and the time when the tumor grew to 1 mm in diameter are calculated on the same graph paper.
From the publication by Umeda et al [82], reproduced by the kind permission of the author.

rates as bigger ones, again indicating that linearity of growth is maintained over time.

Studies on malignant melanomas

The ophtalmologists have given a very elegant demonstration of how knowledge of tumor kinetics can influence clinical practice. In 1980, McLean et al [76] calculated that it took 7 years for a "small" (≤10 mm) melanoma of the eye to grow to a "large" one (≥15 mm). They observed a higher mortality rate during the first two years after enucleation. They hypothesized that this was due to dissemination during the operation. This altered the treatment philosophy from the previous extreme to the other; from "when in doubt, take it out" to "avoid enucleation as long as possible, since it may harm the patient". The need for treatments other than surgery became imminent. In 1985, Gass [77] in a study of 34 patients noted: "Each melanoma grew at a constant rate that varied widely in different patients, ranging from 2 to 30 months". The analysis did not indicate that enucleation was responsible for dissemination of metastases, rendering collegues uncertain of what to do with their patients.

This is where tumor cell kinetics came into the picture. Manschot and van Strik [78] in 1992 presented a summary of the growth rates for 39 patients. 36 of the melanomas had a TVDT of 60 days or more. Metastatic death occurs after 40 doublings after the first cell. If the

metastases were seeded during enucleation, it would take 60 x 40 days (around 7 years) to reach lethal burden. Thus, enucleation could not be responsible for the mortality during the first 6 years after treatment. All deaths among patients earlier than 7 years post-operatively must therefore be due to dissemination prior to enucleation. And enucleation was again accepted as the treatment of choice.

In a study of ocular malignant melanomas with solitary metastases to the lungs in 45 patients, Ollila et al [79] found the TVDT to be 66.9 days (range 14-287 days). All patients underwent resection, and were followed until death. A multivariate analysis showed that the only prognostic variable was the TVDT. Patients with a TVDT less than 60 days did not benefit from surgery. Finally, Eskelin et al [80] in 2000 reported on 37 cases where they tried to determine the time for the first metastasis in patients with ocular malignant melanomas. The growth rates of untreated metastases ranged from 34 to 220 days with a median of 63. Eskelin's et al data indicated that the first metastases started to grow around 5 years before the diagnosis was made. The growth rates for the metastases had a mean TVDT of 63 days (range 34-220 days), which is remarkably similar to those of Ollila's et al: 67 days (range 14-287 days).

Thus, calculations of the TVDT's of ocular malignant melanomas led to a series of evolutionary steps. First, it re-established a discarded treatment of the primary tumor. Second, it provided the identification of patients who would benefit from resection of a solitary metastasis. And third, the TVDT's gave an explanation of the natural history of the disease.

The growth rates for the primary of 17 ocular malignant melanomas were presented by Augsburger et al [81]: a mean of 205 days (range 23-540 days). The figures are incorporated in Table III.

Acinic cell cancer

Acinic cell cancer (ACC) is a very slow growing malignancy from the salivary glands. The average interval between initial treatment and the appearance of distant disease is 8.1 years. Umeda et al [82] gave a TVDT of 393 days. All their tumors showed linearity of growth, in some cases for up to 70 months and 14 measurements. They calculated that: "the time of onset of pulmonary metastases was much earlier (average of 227 months) than the patient's first visit. ACC growth rates are included in Table III, and Umeda's growth curves are shown in Figure 7.

Table III. Growth rates for three types of primary malignancies

Type	TVDT	+range (days)	Numer of cases	Reference
Hepatocellular	94	(35-496)	49	Kubota [84]
"	102	(41-305)	15	Okazaki [85]
"	117	(29-398)	28	Sheu [86]
Acinic cell cancer	393	(86-1064)	30	Umeda [82]
Malignant melanoma (ocular)	205	(23-540)	17	Augsburger [81]

Hepatocellular carcinomas

Since long, primary hepatocellular cancer has been the most common malignant tumors in Asia and parts of Africa. The frequency is now increasing also in the Western Civilization [83]. The growth rates for these cancers have been reported in three publications [84, 85, 86]. Kubota et al [84] gave a TVDT of 94 days (range 45-496 days) for their 49 cases. All growth curves were straight lines. The other two publications gave similar figures (see Table III).

Studies on pulmonary metastases

The growth rates of primary tumors other than cancers of the breast, cancers of the lungs and ocular malignant melanomas have not been studied to the same extent. The obvious reason is that there are few other malignancies that lend themselves to accurate measurements of the tumor volume.

However, the growth rates of solid human malignant tumors originating from organs other than these 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 will be discussed below.

Table IV lists some of the histologically better defined metastases which 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 any systemic therapy.

Table IV also 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 8. The selection criteria were the same as for Figures 5 and 6.

In Figure 8 only four of the cases display linear growth during the observation period. The other two cases exemplify non-linear 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 9 and 10. These cases were selected because they provide unusually beautiful examples of linearity of growth. Both cases are from Breur [23]. One explanation of the observed effect of radiotherapy on the metastases is that it is a "partial response" and a true effect on the tumor cell population. Another explanation is that the radiotherapy diminishes the number of non-neoplastic cells (lymphocytes, vascular endothelium, etc.), leaving the tumor cells unaffected.

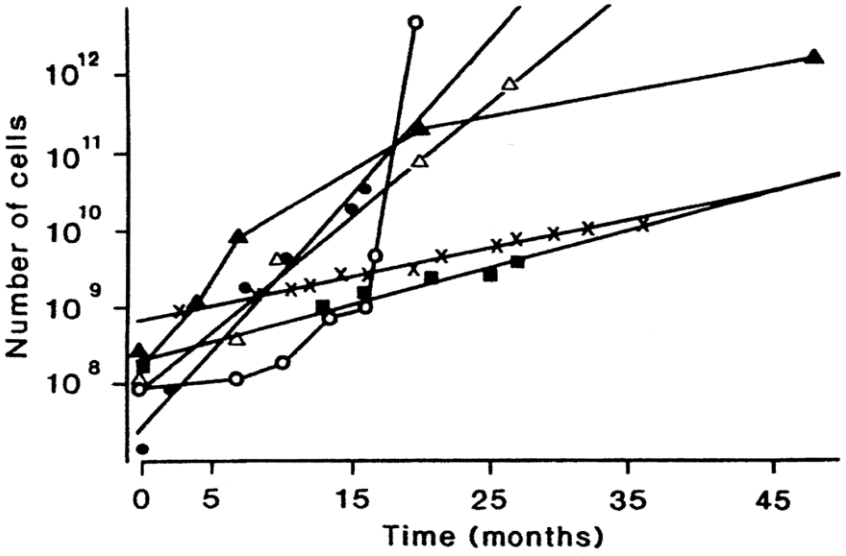

Figure 8. Growth rates for some pulmonary metastases.
Abscissa: Time.
Ordinate: number of tumor cells (logarithmic scale).
Each curve represents one case, and each point one observation.
Symbols: ■——■ = leiomyosarcoma (Rööser et al [34])
●——● = Ewing sarcoma (Pearlman [30])
×——× = hypernephroma (Brenner et al [25])
The other three cases are metastases from colon carcinomas (Spratt & Spratt [23]). Four of the cases display linearity of growth. Two cases of colon carcinoma show non-linearity. One case shows acceleration, the other retardation of growth. All cases reproduced with the kind permission of the editors.

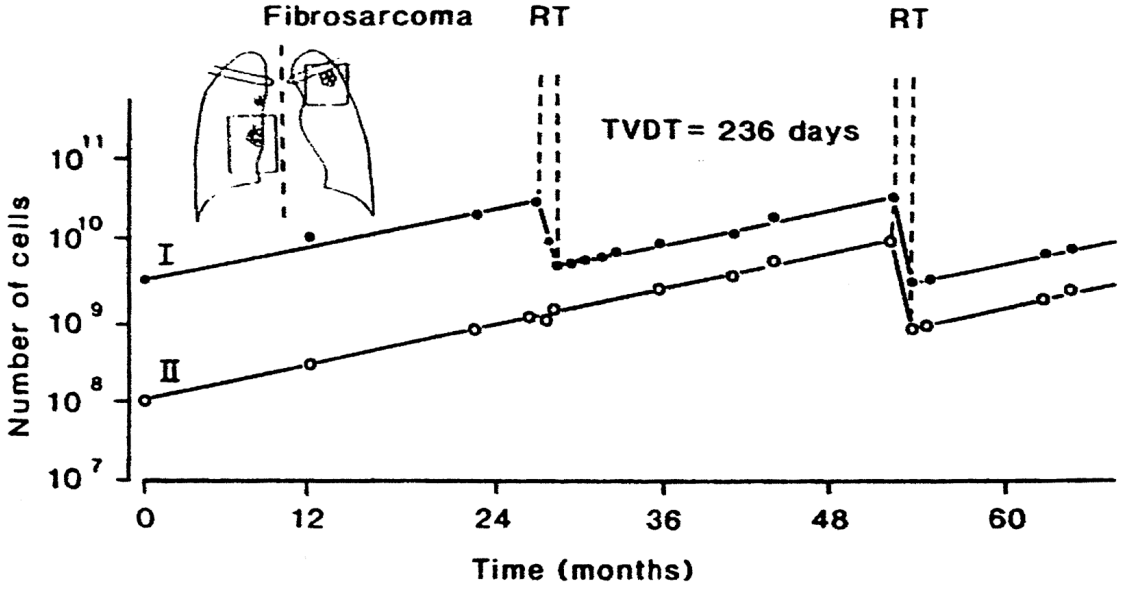

Figure 9. Growth curves for two pulmonary metastases from a fibrosarcoma in one patient.
Abscissa: Time (in months).
Ordinate: Number of cells (logarithmic scale).
Each curve represents one metastasis, and each point one observation. RT= Radiation therapy. One of the metastases was irradiated (=RT) once (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 [23]. Reproduced with the kind permission of the editor.

Figure 9 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 pre-treatment period. Figure 10 depicts a case

Table IV. Growth rates of pulmonary metastases divided according to the site of the primary tumor

Primary	TVDT (days)	Numer of cases	Reference
Testis*	15	8	Breur [23]
”	3	5	Demicheli [49]
”	19	6	Collins [16]
”	43	13	Spratt [21]
Malignant melanoma (cuteaneous)	48	10	Knutsson [87]
Malignant melanoma (ocular)	35	18	Schötterl [88]
“	49	18	Plesnicar [89]
“	63	37	Eskelin [80]
Thyroid			
anaplastic	29	4	Combes [90]
follicular	148	7	Combes [90]
Breast	82	29	Spratt [21]
”	83	6	Combes [90]
”	199	6	Breur [23]
Colon	106	14	Combes [90]
”	109	10	Spratt [23]
”	116	25	Collins [16]
Kidney	66	5	Chahinian [71]
”	89	12	Fujimoto [51]
”	132	8	Brenner [25]
Cervical uteri	89	5	Combes [90]
Mesenchymal†	8 – 198	11	Rööser [34]
”	11 – 120	15	Band [91]
”	3.9 – 352	21	Blomqvist [35]
”	5 – 200	25	Pearlman [30]
”	5 – 340	23	Spratt [21]
”	13 – 257	38	Breur [23]
”	5 – 360	64	Joseph [92]

* = NSGCT (Non-Semitomatous Germ Cell Tumors)
† = Various sites. Most cases were stated to be high-grade malignant. The inter-individual variations in TVDT are so great that the range is given rather than the mean

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. There is a widespread belief that metastases grow at rates faster than their primaries through a selection of more aggressive clones. There is very little support to this belief in the medical literature. It cannot be excluded that this is based on the incorrect plotting of the growth rates on an arithmetic scale (as in Figure 1A) and not a semilogarithmic scale (as in Figure 1B).

For example, Spratt [93]. studying 3 cases with osteogenic sarcomas, found that the secondary tumors in 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 [23] made the same observation in a case with a sarcoma. Fujimoto et al [51] studied 18 cases with renal cell carcinoma. The TVDT of the 6 primary tumors ranged from 372 to 579 days (468±43.0). The TVDT of the 12 pulmonary metastases ranged from 20 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 (>1 year). The reason cannot be that the tumors were measured during the decelerating asymptotic phase: all tumors were less than 5 cm in diameter, which is well below the asymptotic level in Figure 2.

MacDonald [94] observed that the pulmonary metastases from cancer of the breast grew somewhat faster than the primary tumor. Tubiana et al [95], studying

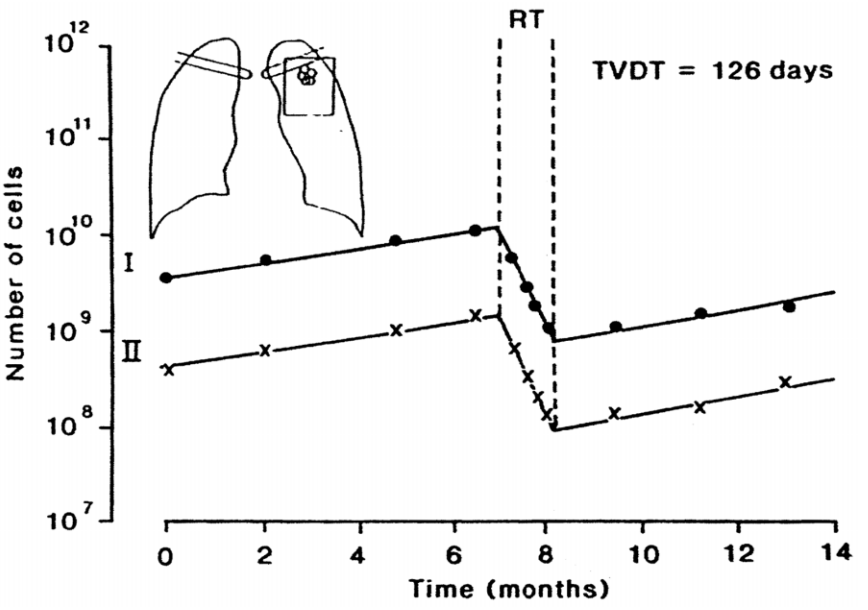

Figure 10. Growth curves for two pulmonary metastases from a case with bladder carcinoma. All explanations, abbreviations and comments are as in Figure 8. Radiation dose was 56 Gy. Copied and slightly modified from Breur [23]. Reproduced with the kind permission of the editor.

cancer of the breast, noted a TVDT of 105 days for the primary tumor, and 66 days for the pulmonary metastases.

Kusama et al [52], 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 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 [96], 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 for TVDT in Tables I, II and IV, and based on the assumption of a close relationship between the growth rates of the primary tumors and their metastases, the diagram in Figure 11 can be constructed. In this diagram, the growth rates for testicular cancers and sarcomas are taken from Table IV. The slope of the line in Figure 11 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 IV 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, non-seminomatous 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 metastasise?

In humans, it is impossible to obtain experimental evidence to answer this question. However, by measuring the TVDT of metastases, and extrapolating back to one cell, an approximation of the time of dissemination can be obtained. 10 investigators have made attempts at calculating the start of dissemination. The first of these are summarized by Davies in 1977 [97]. 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 [95], 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 [96] were able to measure both the primary tumor and multiple metastases to the lung from seven cases of carcinoma of the breast. By backwards extrapolation, 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 [98] 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 less than 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, can not be early enough to precede

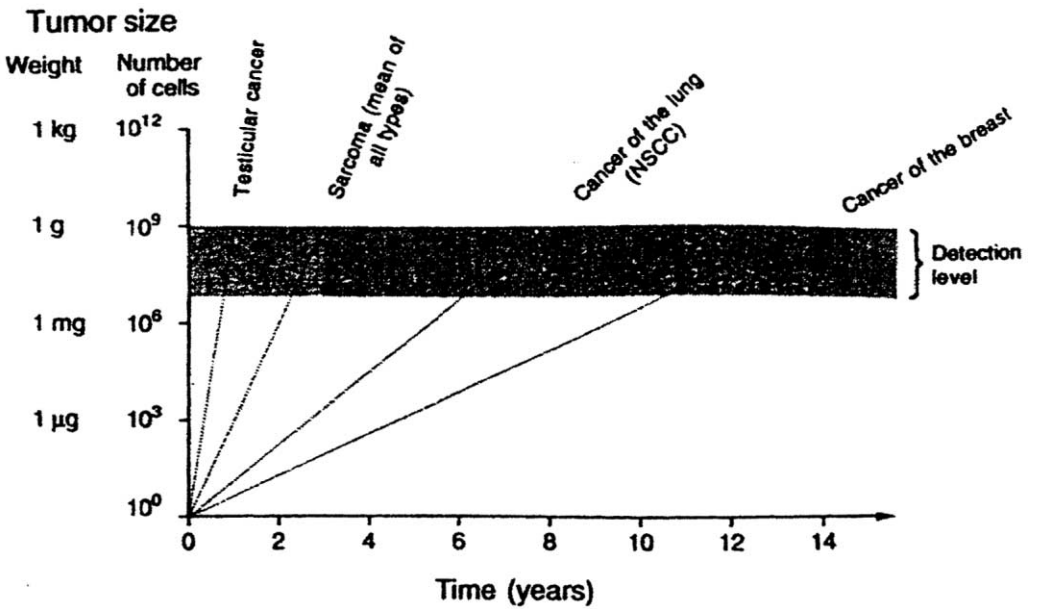

Figure 11. Hypothetical growth rates for various malignant human tumors.
Abscissa: Time (years).
Ordinate: Tumor size (log number of cells or weight of tumor).
The level of detection is indicated by the shaded area.

lymphatic spread." Breur [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 [34] 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 ten studies cited above have come to similar conclusions: in the majority of 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. Eskelin et al [80], in their study of pulmonary metastases from ocular malignant melanomas, calculated the secondaries to precede the diagnosis of the primary by 5 years. Schötterl and Paul [88] came to the same conclusion in their study of pulmonary metastases from cutaneous malignant melanomas, as did Umeda et al [82] for acinic cell carcinomas. Umeda's et al growth curves can explain why metastases from this type of cancer can occur as much as 20 years after the removal of the primary tumor.

The impression obtained from these ten studies can not 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 present author is fully aware of the fact that many tumors do not give rise to metastases until late in their life span. Such tumors have usually 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: period of risk

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 [16, 99] 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 [32] examined 95 patients with Wilms' tumor and 68 patients with neuroblastoma. They found one single exception to Collins' period of risk.

Knox and Pillers [100] examined 87 cases with Wilms' tumor, 126 cases with neuroblastoma, and 31 cases with rhabdomyosarcoma. Among the 244 cases, all 192 recurrencies 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 [101]. In a review by Brown et al [102], the authors identified only 38 (0.17%) exceptions from 2,233 non-astroglial pediatric cases. These results give strong support to the concept of constant growth rates.

It may be argued that pediatric tumors differ in their behaviour from adult tumors. However, support for the assumption of constant growth rate comes also from studies of cancer of the breast in adults. Allan [103], presented data from "late" recurrencies (over 5 years) of cancer of the breast in 139 cases. He found a close correlation between the latent period (up to more than 20 years) and the survival time (>10 years) after the "late" recurrence. Allan's cases would correspond to the 3 or 4 most slow-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 tumours".

Only tumors with a TVDT of less than 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 x 60 days = 1,800 days ≈ 5 years). Of the more than 800 cases of cancer of the breast summarized in Table I, only around 15% have a TVDT of less than 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 over 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 cure"). Such a long period of risk is consistent with the observed excess mortality from cancer of the breast more than 30 years after the primary treatment [104-108].

NSGCT (non-seminomatous germ cell tumors) have a TVDT of around 20 days (Table IV). 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 malignancies than late recurrencies [109].

Discussion

The facts given in this review are not new. Furthermore, they are well documented: since the original studies by Collins et al 40 years ago, almost 100 articles, seven reviews [17, 40, 47, 68, 97, 110, 111,] and two books [40, 112] 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 which can be drawn from Figure 11 can be extended, as illustrated in Figure 12.

In Figure 12 it is demonstrated that when a malignant tumor can be detected by present-day diagnostic methods it has consumed more than half of its life span, 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 45^{th} tumor cell generation) for an adult individual may be regarded as lethal (10% of the body weight). This level seems to be valid for both solid tumors and haematological malignancies [7, 17, 18, 21, 29, 48, 113]. If the TVDT of the primary tumor is known, antegrade extrapolation – Figure 12 – 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 [114]. In contrast, a patient with a slow-growing cancer of the breast or the prostate, can be expected to have around 5 years to survive from the detection level, even if untreated.

Which patients will benefit from so-called "early diagnosis"?

Some patients actually do benefit from "early diagnosis" (the term is never properly defined), and this is illustrated in Figure 13. As can be seen from this figure, the three most rapidly growing cancers (A, B, and C) have given rise to metastases before the new diagnostic level is reached. These patients will not benefit from "earlier" diagnosis.

The two most slow-growing tumors will start to metastasise late, and after the old diagnostic level has been passed by the primary (tumors H and J). These patients will not benefit from the new diagnostic method since the tumor can be detected by the old method. The only patients who will benefit from "early" diagnosis are those whose tumors start to disseminate in the interval between the two diagnostic levels (tumors D – G); in this example 1/3 of the tumors.

This illustrates why a new screening method will not be of benefit to all patients. For cancers of the breast (in plural!), Figure 13 could explain why 1/3 of the patients have metastases to the bone marrow already at the time of diagnosis, according to Braun et al [115]. Local therapy cannot affect the outcome of a generalized malignancy.

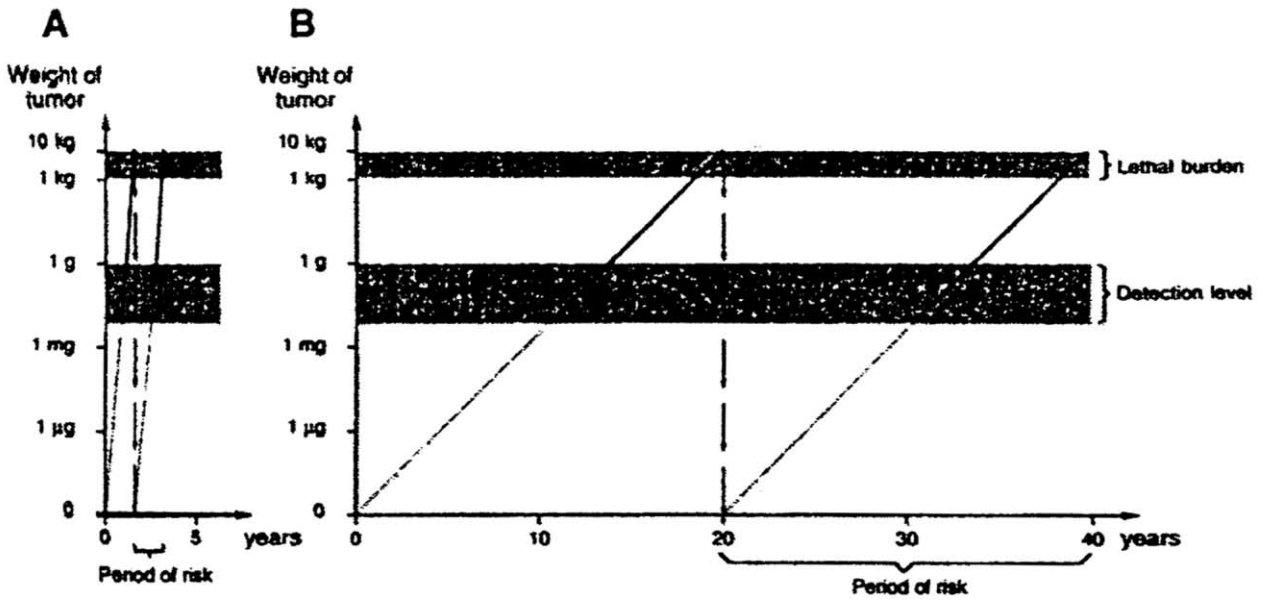

Figure 12. "Period of risk" for two human malignant tumors.
To the left (A): a hypothetical line for a malignant tumor with a TDVT of 10 days.
To the right (B): the corresponding line for a tumor with a TVDT of 150 days.
Both tumors are assumed to be untreated. In the diagram, the total tumor burden (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.

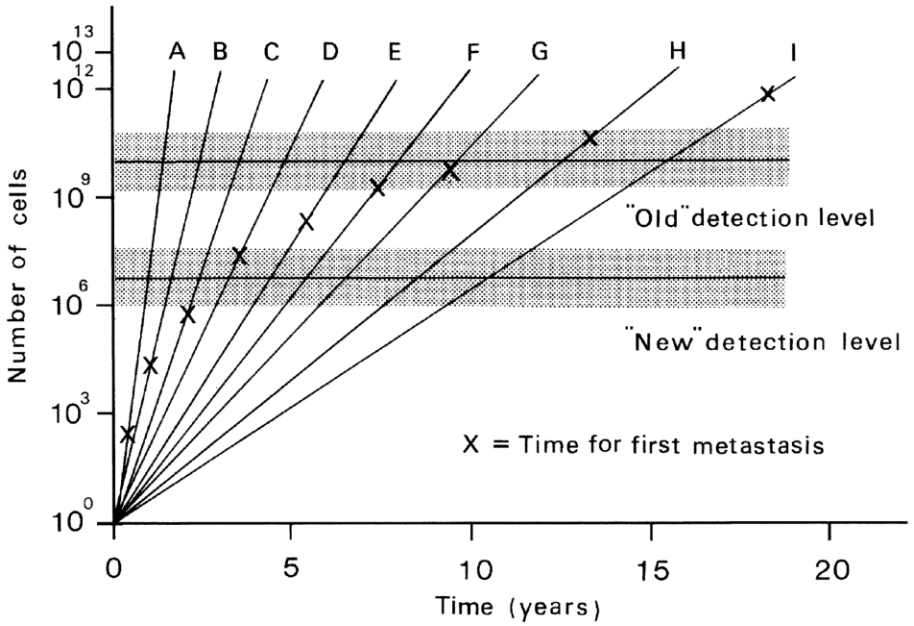

Figure 13. Time for first metastasis for a hypothetical group of tumors.
Ordinate: Time.
Abscissa: Size of tumor.
Each curve represents one tumor growing at constant rate.
On each curve there is an X, indicating time for first metastasis. The slower the growth rate, the later the tumor starts to give rise to metastases. In this figure, the two levels indicate the old and the new, more sensitive level of detection, respectively.

The 5-year survival rate: partially a myth?

For long, the cliché "early diagnosis leads to better prognosis" has echoed in the medical world. But to a large extent it is a myth, based on a misunderstanding which is termed "lead time bias". The term is best explained by an illustration (Figure 14).

The term "lead time bias" was introduced already in the 1960's [116]. If the lead time is not corrected for, the outcome of several clinical trials will be misinterpreted. This mental trap was pointed out already in the 1940's by statisticians [117], by the legal profession (since this trap is of profound importance in malpractice claims) [118, 119], but only occasionally by the medical profession.

The 5-year survival rate has for a long time been used as an index of the effectiveness of the treatment for cancer. It has been widely used since the end of the 19th century, and thousands of scientific publications have utilized it. Basically, the 5 year survival rate is a statistical tool for characterizing the survival of a certain group of individuals. It is somewhat primitive, since it does not utilize all available information from a survival analysis. It only tells how large a proportion has survived for a limited time span – arbitrarily put to 5 years. It is not even a true rate, but simply a value at a fixed point of time [120, 121].

The 5-year survival can even be misleading: It is easy to give examples of quite different survival patterns with identical five-year survival rates (Figure 15). However, if the original intention with the "five-year survival" had been maintained – as a mere value in time – then no harm would have been done. But over the years a change has occurred in the meaning (interpretation?) of the term "five-year survival rate". It has gradually shifted to become the equivalent to "five-year-cure rate". This is a gross misconception because "survival" is not synonymous with "cure". It is only for fast-growing tumors (e.g. acute leukemias and testicular non-seminomatous germ cell tumors) that surviving for five years after the diagnosis is likely to indicate a true cure. This is illustrated by curve B in Figure 15. Most human malignancies, however, are slow-growing, (i.e. most cancers of the breast, colon or prostate) and require many years or even decades to kill their host. For such cases, survival for five years is not indicative of cure. For example, of the women who survive their breast cancer diagnosis for five years, 1/3 will succumb to their disease, and for those women who have survived for 10 years, as much as 1/4 will still die from their malignancy. Even as long as 30 years after the diagnosis, this patient population shows an over-mortality from cancer of the breast. Consequently, some clinicians have posed the question: "Do we ever cure cancer of the breast?" (For summary, see ref 107). The cliché "earlier diagnosis leads to better prognosis" and the misconception "five-year cure" have done more harm than good. The cliché lacks firm scientific support, and the words "early" and "cure" are often used without being defined. If "early" is supposed to mean "before the tumor has metastasised", this is another illusion: most human tumors have metastasised when diagnosable by present-day methods, as summarized in this article. Further, the word "cure" should be used with caution. Many adult malignant tumors have a long natural course extending over two or three decades. This means that there are many individuals who, after having had thir primary tumors removed, live

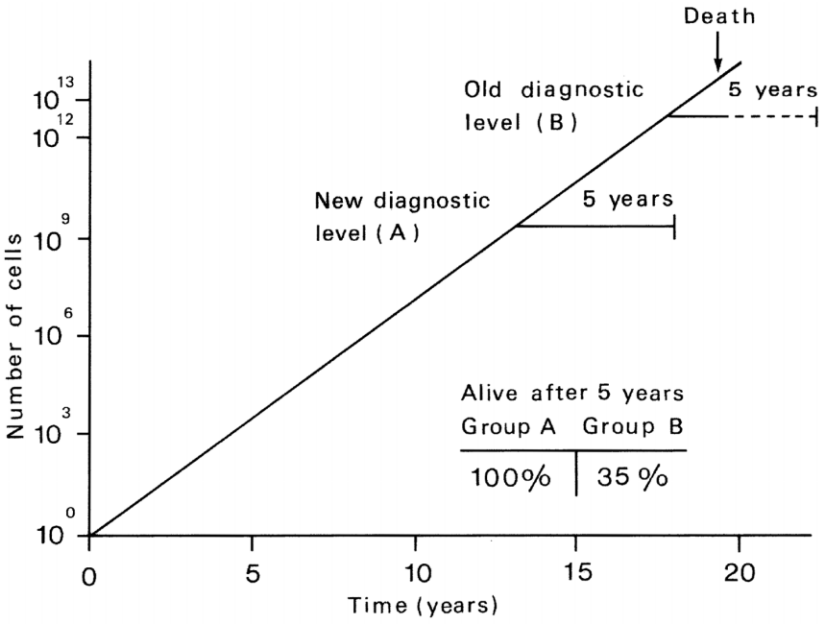

Figure 14. "Lead time bias".
Ordinate: Time.
Abscissa: Amount of disease.
The straight line depicts the evolution of a lethal disease, starting at origo and killing its host at the level of the arrow. The disease must not necessarily be a malignant tumor; it can be any lethal disease with a protracted course (amyotrophic lateral sclerosis, AIDS, Parkinson's disease, etc.). The outcome for two groups of patients is followed for 5 years. In group A observation starts "early". After 5 years (the lower of the two horizontal bars), the number of deaths amounts to zero. In the "late" group (B), 50% of the patients are dead after 5 years. The obvious conclusion is that "early" detection leads to better prognosis, which is an illusion. Shifting the time of diagnosis to an earlier date will only provide longer observation time. Disease specific mortality, however, will not be affected.

with asymptomatic, microscopic disease (like many other chronic diseases). These patients have not been cured, but they live seemingly healthy with "no evidence of disease".

In clinical oncology a wholly satisfactory definition of the term "cure" is therefore regarded as difficult – if not impossible [122]. There are three current definitions of cure: 1. statistical, 2. clinical, and 3. personal. "Statistical cure" means that the study population dies at the same rate as the "normal" population (regardless of diagnosis). "Clinical cure" designates the situation in which the study population dies of its malignancy at the same rate as the "normal" population (with the same diagnosis). "Personal cure" means that the study population dies with its disease, but not from it (i.e. death from a cardiovascular disease, but with known active tumor). It is a paradox that whatever definition of "cure" is chosen, the patient must die – and be autopsied – before he or she can be declared healthy. This is of particular importance in clinical trials [123].

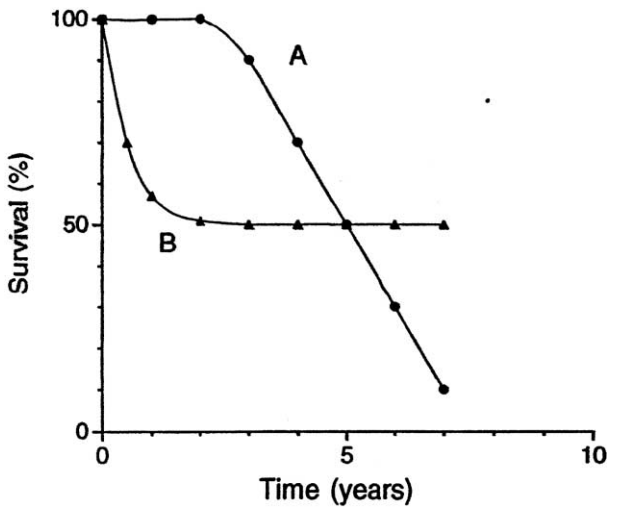

Figure 15. Two series with identical five year survival rates (50%). Survival in series A is better for the first four years, but practically nil after seven years. Survivor in series B can be regarded as cured after three years.

Thus – regardless of which of these definitions is intended – a five-year survival period should not be equated with "cure" for most malignancies. In spite of this, the "five-year cure rate" has been hammered into the heads of the public, the medical profession, the journalists, the legal profession, and many others, for so long that it has become an axiom. It is written in the minds of the people, in publications and in text-books.

Nevertheless, we tend to hold fast to the clichés of our teachers, enjoying the comfort of popular opinion, simultaneously avoiding the discomfort of thought.

If a false statement (i.e. surviving for five years means cure) is repeated sufficiently often, it will be accepted as a truth. It is noteworthy that clearsighted

criticism of the medical clichés, terms and misconceptions does not come from a profession with a medical education, but from one without such an education: the legal profession [118, 119].

The illusion created by the five-year cure rate gives false promises based on false premises: bitter frustration among patients (who experience recurrences and/or metastasis 10 or 15 years after the first five-year period), confusion and denial in the medical profession and law suits against doctors [124, 125]. The delayed diagnosis of breast cancer is now the most frequent medical malpractice claim in the United States, and "it is the second most expensive condition for insurers to indemnify" [125].

In Figure 16, the evolution of one and the same tumor detected on two different occasions is illustrated. The two growth curves are linked with a 5-year observation period for the prognosis. This is a somewhat complicated attempt to combine growth curves of tumors with the pit-fall "lead time bias", trying to explain why the cliché "early detection leads to better prognosis" to a large extent is a myth. The numerical comparison between the two situations for the same tumor is condensed in Table V (which is inserted in Figure 16), where the size of the primary tumor, the number of metastases detected (which is not the same as the number of metastases existing) and the 5-year survivals are compared. The obvious conclusion from Table V is that "early detection leads to better prognosis" if the survival figures are compared. However, this conclusion is erroneous: If the observation period is not truncated at 5 years but extended to 7 years, the prognosis is identical for the two situations. This is an illustration of how myths and illusions are created.

If we are to make any progress in the war against cancer, we must first recognize the limitations set by nature [126, 127].

Conclusions

Knowledge of the above facts is important for several reasons. First, the value of so-called "early" diagnosis has become questionable. The word "early" is not even defined in most publications. Whatever definition is used, the word "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 [128] titled an article: "The invalid evidence for faith in early treatment." So-called "early" detection is in fact "biologically late", as stated by MacDonald in 1966

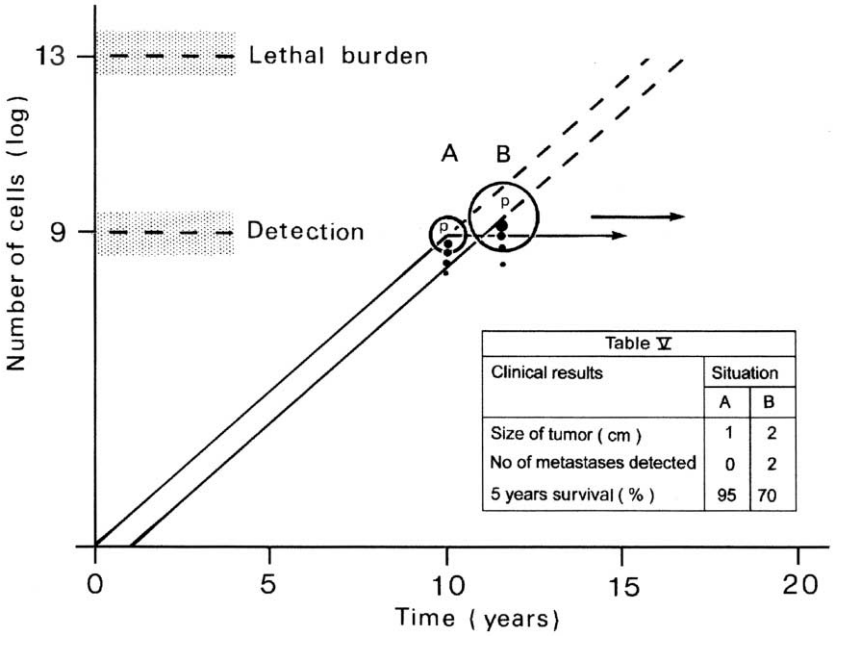

Figure 16. "Lead time bias", graphically and numerically illustrated.
Abscissa: Time.
Ordinate: Size of tumor.
The detection level and the lethal burden are indicated.
P = primary. M = metastases. → = 5 years.
The graph shows the same tumor on two different occasions. In situation A, the primary tumors is detected at a size of 1 cm in diameter, and no metastases are found (although they exist). The 5-year survival is 95%. In situation B, the primary tumor is 2 cm's in diameter, 2 metastases are found and the 5-year survival is 70%. Note that in situation A there are as many metastases as in situation B, but none of those in A are detected. Table V is a numerical presentation of the curves depicted. If the observation time is not truncated after 5 years but extended to 7 years, then all patients will have died. No survival benefit for situation A ("early detection") would remain.

[94]. 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 life-span. This may explain why mammography has not been able to reduce 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 [129].

A recent meta-analysis from the Cochrane Institute based on the six largest mammography trials concludes: "Mammography is not justifiable" [130]. The mere fact that 40 years after the introduction of mammography we are still discussing its possible benefits; an indication as good as any of its questionable value. To give another example, screening for lung cancer in order to obtain "early" detection has not reduced mortality from these diseases [131]. Screening for lung cancer is therefore advised against [132].

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 occured long before the diagnosis of the primary tumor.

Moreover, a delay of one or two 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 life-span of that tumor. Displacing the diagnosis to an earlier date will prolong the observation period without influencing the time of death for a non-treated 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 a 2 mm in diameter ($\approx 10^7$ cells), this would increase the observation time with almost 3 years "lead time". Such patients will live longer as cancer cases, but not as individuals. 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 [133].

"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 is 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 of the primary. Whatever type of surgery for cancer of the breast is used, it does not affect survival. Local treatment cannot affect 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.

But there are examples where "early" detection really results in a decrease of mortality: malignant melanoma of the skin, cervical cancer of the uterus, and cancer of the breast. These three malignancies share two characteristics. First, they have a long pre-clinical phase in the form of pre-cursor lesions: dysplastic naevi, cancer in situ and ductal cancer in situ (DCIS), respectively. Second, they can relatively easily be detected: the first two by the eye, and the latter with mammography. If removed while still in the pre-cursor phase before they are invasive, mortality from these three malignancies will be reduced.

Third, the design and analysis of clinical trials may be affected by knowledge of tumor kinetics [123]. 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 (curve B in Figure 15). 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 [107]. The long-term survival curves from cancer of the breast and renal cell cancer [134] are particularly striking. Moreover, if the TVDT is not taken into consideration, an uncritical interpretation of survival curves may be misleading [120]. 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 (Figure 16).

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 may also 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 [135].

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 centimetre, it is likely that some of the secondaries will need the same period of time to reach detectable levels. Some "late recurrencies" or so-called "dormant cells" – appearing decades after removal of the primary – may be neither late nor dormant. 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 [120, 121].

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 survival is a more realistic measure of treatment efficacy than 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 pulmonary metastasis 20 mm in diameter has a 95% probability of dying within 11 more tumor doublings [20]. The duration of his 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.

Sten Friberg MD, PhD
Banérgatan 21, VII
SE-115 22 Stockholm
Sweden

References

1. Friberg S, Mattson S. On the growth rates of human malignant tumors: Implications for medical decision making. *J Surg Oncol* 1997; 65: 284-97.
2. Holmgren L, O' Reilly M, Folkman J. Dormancy of micrometastases: Balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nature Medicine* 1995; 1: 149-53.
3. Virchow R. "Vorlesungen über Pathologie". *Berlin: A Hirchwald Verlag*, 1862, p 1.
4. Waldenström J. Hypergammaglobulinemia as a clinical hematologic problem: A study in the gammopathies. *Progr Haemotol* 1962; 3: 266-93.
5. Fialkow PJ. The origin and development of human tumors studied with cell markers. *N Engl J Med* 1974; 291: 26-34.
6. Hobbs JR. Growth rates and responses to treatment in human myelomatosis. *Brit J Haemat* 1969; 16: 607-17.
7. Hobbs J. Immunocytoma o' mice an' men. *Br Med J* 1971; 2: 67-72.
8. Gilliland DG, Blanchard KL, Levy J et al. Clonality in myeloproliferative disorders: Analysis by means of the polymerase chain reaction. *Proc Natl Acad Sci USA* 1991; 88: 6848-52.
9. Sidransky DS, Frost P, von Eschenbach A et al. Clonal origin of bladder cancer. *N Engl J Med* 1991; 326: 737-40.
10. Noguchi S, Aihara T, Koyama H et al. Discrimination between multicentric and multifocal carcinomas of the breast through clonal analysis. *Cancer* 1994; 74: 872-77.
11. Wang N, Perkins KL, Bronson DL et al. Cytogenetic evidence for premeiotic transformation of human testicular cancers. *Cancer Res* 1981; 41: 2135-40.
12. Skakkebaekk NE, Berthelsen JU, Giwercman A et al. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursors of all types of germ cell tumors except spermatocytoma. *Int J Urol Androl* 1987; 10: 19-28.
13. Chaganti RSK, Rodriguez E, Mathew S. Origin of adult male mediastinal germ-cell tumors. *Lancet* 1994; 343: 1130-2.
14. Steel GG. Cell loss as a factor in the growth rate of human tumours. *Eur J Cancer* 1967; 3: 381-7.
15. Refsum SB, Berdal P. Cell loss in malignant tumours in man. (Letter to Editor). *Eur J Cancer* 1967; 3: 235-236.
16. Collins VP, Loeffler RK, Tivey H: Observations on growth rates of human tumors. *Am J Roentgen* 1956; 76: 988-1000.
17. Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer* 1961; 14: 1271-94.
18. Spratt JS, Ter-Pogossian M, Long RTL. The detection and growth of intrathoracic neoplasms. *Arch Surg* 1963; 86: 283-8.
19. Garland LH, Coulson W, Wollin E. The rate of growth and apparent duration of untreated primary bronchial carcinoma. *Cancer* 1963; 16: 694-707.
20. Spratt JS, Spjut HJ, Roper CL. The frequency distribution of the rates of growth and the estimated duration of primary pulmonary carcinomas. *Cancer* 1963; 16: 687-93.
21. Spratt JS, Spratt TL: Rates of growth of pulmonary metastases and host survival. *Ann Surg* 1964; 159: 161-71.
22. Weiss W, Boucot KR, Cooper DA. Growth rate in the detection and prognosis of bronchogenic carcinoma. *JAMA* 1966; 198: 108-14.
23. Breur K. Growth rate and radiosensitivity of human tumors – I. *Eur J Cancer* 1966; 2: 157-71.
24. Breur K. Growth rate and radiosensitivity of human tumors – II. *Eur J Cancer* 1966; 2: 173-188.
25. Brenner MW, Holsti LR, Perttala Y. The study by graphical analysis of the growth of human tumours and metastases of the lung. *Br J Cancer* 1967; 21: 1-13.
26. Rambert PE, Malaise E, Laugier A et al. Donnés sur la vitesse de croissance de tumours humaines. *Bulletin du Cancer* 1968; 55: 323-42.
27. Meyer JA The concept and significance of growth rates in human pulmonary tumors. *Am Thorac Surg* 1972; 14: 309-22.
28. Steele JD, Buell P. Asymptomatic solitary pulmonary nodules. Host survival, tumor size and growth rate. *J Thorac Cardiovasc Surg* 1973; 65: 140-51.
29. Pearlman AW. Growth rate investigation and tumor lethal dose in Ewing's sarcoma. *Acta Radiol* 1973; 12: 57-70.
30. Pearlman AW. Breast cancer: Influence of growth rate on prognosis and treatment evaluation. *Cancer* 1976; 38: 1826-33.
31. Pearlman AW. Fibrosarcaoma: The biomathematical approach to late metastases – a case report. *Mount Sinai J Med* 1979; 46: 255-60.
32. Pollock WF, Hastings N, Snyder WH. The Collins "period of risk" formula for malignant tumors in children, with particular reference to Wilms' tumor and neuroblastoma. *Surgery* 1960; 48: 606-9.
33. Fournier D v, Weber E, Hoeffken W et al. Growth rate of 147 mammary carcinomas. *Cancer* 1980; 45: 2198-207.
34. Rööser B, Petterson H, Alvegård T. Growth rate of pulmonary metastases from soft tissue sarcoma. *Acta Oncol* 1987; 26:189-92.
35. Blomqvist C. Wiklund T, Tarkkanen M et al. Measurement of growth rate of lung metastases in 21 patients with bone or soft-tissue sarcoma. *Brit J Cancer* 1993; 68: 414-7.
36. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Phil Trans Roy Soc London* 1825; 115: 513-83.
37. Winsor CP. The Gompertz curve as a growth curve. *Proc Nat Acad Sci* 1932; 18: 1-8.
38. Steel GG, Lamerton LF. The growth rate of human tumours. *Br J Cancer* 1966; 20: 74-86.
39. Dethlefsen LA, Prewitt JMS, Mendelsohn ML. Analysis of tumor growth curves. *J Natl Cancer Inst* 1968; 40: 389-405.
40. Steel GG. *Growth Kinetics of Tumours: Cell Population Kinetics in Relation to the Growth and Treatment of Cancer*. Oxford: Clarendon Press; 1977.
41. Plevritis SK. A mathematical algorithm that computes breast cancer sizes and doubling times detected by screening. *Mathematical Biosciences* 2001; 171: 155-78.
42. van Leeuwen IMM, Zonneveld C, Kooijman SALM. The embedded tumour: host physiology is important for the evaluation of tumour growth. *Brit J Cancer* 2003; 89: 2254-63.
43. Kopans PB, Rafferty E, Georgian-Smith D et al. A simple model of breast carcinoma growth may provide explanations for observations of apparently complex phenomena. *Cancer* 2003; 97: 2951-9.
44. Stamey TA, Kabalin JN, McNEal JE et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate II. Radical prostatectomy treated patients. *J Urol* 1989; 141: 1076-83.
45. Spratt JS, Greenberg RA, Heuser LS. Geometry, growth rates and duration of cancer and carcinoma in situ of the breast before detection by screening. *Cancer Res* 1986; 46: 970-4.
46. Yankelevitz DF, Kostis WJ, Hensche CI et al. Overdiagnosis in chest radiographic screening for lung carcinoma – Frequency. *Cancer* 2003; 97: 1271-5.
47. Shackney SE, McCormack GW, Cuchural GJ. Growth rate patterns of solid tumors and their relation to responsiveness to therapy. *Ann Int Med* 1978; 89: 107-21.
48. Frei E, Freireich EJ. Progress and perspectives in the chemotherapy of acute leukaemia. *Adv Chemother* 1965; 2: 269-98.
49. Demicheli R. Growth of testicular neoplasm lung metastases: Tumor-specific relation between two Gompertzian parameters. *Eur J Cancer* 1980; 16: 1603-8.

50. Spratt JS, Ackerman LV. The growth of a colonic adenocarcinoma. *Am Surg* 1961; 27: 23-8.
51. Fujimoto N, Sugita A, Terasawa Y et al. Observations on the growth rate of renal cell carcinoma. *Int J Urol* 1995; 2: 71-6.
52. Kusama S, Spratt JS, Donegan WL et al. The gross rates of growth of human mammary carcinoma. *Cancer* 1972; 30: 594-9.
53. Peer P, van Dijk J, Hendriks J et al. Age-dependent growth rate of primary breast cancer. *Cancer* 1993; 71: 3547-51.
54. Kuroishi T, Tominaga S, Morimoto T et al. Tumor growth rate and prognosis of breast cancer mainly by mass screening. *Jpn J Cancer Res* 1990; 81: 454-62.
55. Arnerlöv C, Emdin SO, Lundgren B et al. Breast carcinoma growth rate described by mammographic doubling time and S-phase fraction. *Cancer* 1992; 70: 1928-34.
56. Ingleby H, Moore L, Gershon-Cohen J. A roentgenographic study of the growth rate of 6 "early" cancers of the breast. *Cancer* 1958; 11: 726-30.
57. Ingleby H, Gershon-Cohen J. *Comparative Anatomy, Pathology and Roentgenology of the Breast*. Philadelphia: University of Pennsylvania Press; 1960.
58. Gershon-Cohen J, Berger SM, Klickstein HS. Roentgenography of breast cancer moderating concept of "biologic predeterminism". *Cancer* 1963; 16: 961-4.
59. Spratt JS, Kaltenbach ML, Spratt J. Cytokinetic definition of acute and chronic breast cancer. *Cancer Res* 1977; 37: 226-30.
60. Lundgren B. Observations on growth rate of breast carcinomas and its possible implications for lead time. *Cancer* 1977; 40: 1722-5.
61. Heuser L, Spratt JS, Polk HC. Growth rates of primary breast cancers. *Cancer* 1979; 43: 1888-94.
62. Heuser L, Spratt JS, Polk HC et al. Relation between mammary cancer growth kinetics and the interval between screenings. *Cancer* 1979; 43: 857-62.
63. Spratt JS, Chang AFC, Heuser LS et al. Acute carcinoma of the breast. *Surg Gynecol Obstet* 1983; 157: 220-2.
64. Buchanan JB, Spratt JS, Heuser LS. Tumor growth, doubling times and the inability of the radiobiologist to diagnose certain cancers. *Radiol Clin N Am* 1983; 21: 115-26.
65. Heuser LS, Spratt JS, Kuhns JG et al. The association of pathologic and mammographic characteristics of primary human breast cancers with "slow" and "fast" growth rates and with axillary lymph node metastases. *Cancer* 1984; 53: 96-98.
66. Spratt JS, Spratt JA. What is breast cancer doing before we can detect it? *J Surg Oncol* 1985; 30: 156-60.
67. Galante E, Guzzon A, Gallus G, et al. Prognostic significance of the growth rate of breast cancer: preliminary evaluation on the follow-up of 196 breast cancers. *Tumori* 1981;67:333-340.
68. Geddes DM. The natural history of lung cancer: a review based on rates of tumour growth. *Br J Chest Dis* 1979; 73: 1-17.
69. Weiss W. Tumor doubling time and survival of men with bronchogenic carcinoma. *Chest* 1974,65: 3-8.
70. Charbit A, Malaise EP, Tubiana M. Relation between the pathological nature and growth rate of human tumors. *Eur J Cancer* 1971; 7: 307-15.
71. Chahinian P, Israel L. Survival gain and volume gain: Mathematical tools in evaluating treatments. *Eur J Cancer* 1969; 5: 625-9.
72. Mattson K, Holsti LR. Prognostic value of doubling time in lung cancer. *Strahlentherapie* 1980; 156: 632-6.
73. Brigham BA, Bunn PA, Minna JD et al. Growth rates of small cell bronchogenic carcinomas. *Cancer* 1978; 42: 2880-6.
74. Hasegawa M, Sone S, Takashima S et al. Growth rate of small lung cancers detected on mass CT screening. *Brit J Radiol* 2000; 73.1252-9.
75. Winer-Muram H, Jennings SG, Tarver RD et al. Volumetric growth rate of stage I lung cancer prior to treatment: Serial CT scanning. *Radiology* 2003; 223: 798-805.
76. McLean IW, Foster WD, Zimmerman LE et al. Inferred natural history of uveal melanoma. *Invest Ophthalmol Vis Sci* 1980; 19: 760-70.
77. Gass, JDM. Comparison of uveal melanoma growth rates with mitotic index and mortality. *Arch Ophtalmol* 1985; 103: 924-31.
78. Manschot WA and van Strik R. Uveal melanoma: Therapeutic consequences of doubling times and irradiation results; a review. *International Ophtalmology* 1992; 16: 91-9.
79. Ollila DW, Stern SL, Morton DL. Tumor doubling time: A selection factor for pulmonary resection metastatic melanoma. *J Surg Oncol* 1998; 69: 206-11.
80. Eskelin S, Pyrhönen S, Summanen P et al. Tumor doubling times in metastatic malignant melanoma of the uvea. *Ophtalmology* 2000; 107: 1443-9.
81. Augsburger JJ, Gonder JR, Amsel J et al. Growth rates and doubling times of posterior uveal melanomas. *Ophthalmology* 1984; 91: 1709-15.
82. Umeda M, Nishimatsu N, Masago H et al. Tumor-doubling time and onset of pulmonary metastasis from adenoid carcinoma of the salivary gland. *Oral Surg Oral Med Oral Pathol Radiol Endod* 1999; 88: 473-8.
83. El-Serag HB and Mason AC.Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; 340: 745-50.
84. Kubota K et al. Growth rate of primary single hepatocellular carcinoma. Determining optimal screening interval with contrast enhanced computed tomography. *Digestive Diseases and Sciences* 2003; 48: 581-6.
85. Okazaki N et al. Evaluation of the prognosis for small hepatocellular carcinoma based on tumor volume doubling time. A preliminary report. *Cancer* 1989; 63: 2207-10.
86. Sheu JC et al. Growth rate of asymptomatic hepatocellular carcinoma and clinical implications. *Gastroenterology* 1985; 89: 259-66.
87. Knutson CO et al. Melanoma. Review. *Curr Probl Surg* 1971; 12: 3-55.
88. Schötterl H-D and Paul E.Growth dynamics of malignant melanoma. Tumor duplication time morphometrically measured in X-ray pictures of pulmonary metastases. *Zeitschrift für Hautkrankenheiten* 1988; 63: 481-7.
89. Plesnicar S, Klanjscek G, Modic S: Actual doubling time values of pulmonary metastases from malignant melanoma. *Aust N Z J Surg* 1978; 84: 23-5.
90. Combes PF, Douchez J, Carton M et al. Etude de la croissance des métastases pulmonaires humaines comme argument objectif d'evaluation du prognostic et des effets thérapiques. *J Radiologie et d'Electrologie* 1968; 49: 893-902.
91. Band PR, Kocandrle C. Growth rate of pulmonary metastases in human sarcomas. *Cancer* 1975; 36: 471-4.
92. Joseph WL, Morton DL, Adkins PC. Prognostic significance of tumor doubling time in evaluating operability in pulmonary metastatic disease. *J Thor Cardiovasc Surg* 1971; 61: 23-32.
93. Spratt JS. The rates of growth of skeletal sarcomas. *Cancer* 1965; 18: 14-24.
94. MacDonald JS. Radiological methods of measurement. In: *Clinical Evaluation of Breast Cancer*. New York: Hayward & Bulbrock; 1966, 11-34.
95. Tubiana M, Chauvel P, Renaud A et al. Vitesse de croissance et histoire naturelle du cancer du sein. *Bulletin du Cancer* 1975; 62: 341-58.
96. von Fournier D, Hoeffken W, Junkermann H et al. Growth rate of primary mammary carcinoma and its metastases. In: Zander J, BaltzerJ (eds). *Early Breast Cancer*. Berlin: Springer-Verlag; 1985.
97. Davies JNP. Overview of the biology and pathology of metastasis. In: Day SB, Myers WPL, Stansly P et al (ed), *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy: Progress in Cancer Research and Therapy*. New York: Raven Press; 1977; 5: 15.
98. Bauer W, Igot JP, Le Gal Y. Chronologie du cancer mammaire utilisant un modèle de croissance de Gompertz. Annales d'Anatomie Patologique 1980; 25: 39-56.
99. Collins VP. The treatment of Wilms`s tumor. *Cancer* 1958; 11: 89-94.
100. Knox WE, Pillers EMK. Time of recurrence or cure of tumours in childhood. *Lancet* 1958; 188-91.
101. Austin EJ, Alvord EC. Recurrences of cerebellar astrocytomas: A violation of Collins' law. *J Neurosurg* 1988; 68: 41-7.
102. Brown WD, Tavaré CJ, Sobel EL et al. Medulloblastoma and Collins' law: A critical review of the concept of a period of risk for tumor recurrence and patient survival. *Neurosurgery* 1995; 36: 691-7.
103. Allan E. Breast cancer: The long latent interval. *Eur J Cancer* 1977; 13: 839-45.
104. Duncan W, Kerr GR. The curability of breast cancer. *Br Med J* 1976; 2: 781-3.
105. Rutqvist LE, Wallgren A, Nilsson B. Is breast cancer a curable disease? *Cancer* 1984; 53: 1793-800.
106. Rutqvist LE, Wallgren A. Long-term survival of 458 young breast cancer patients. *Cancer* 1985; 55: 658-65.
107. Joensuu H, Toikkanen S. Cured of breast cancer? *J Clin Oncol* 1995; 13: 62-9.
108. Cuzick J, Stewart H, Rutqvist LE et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994; 12: 447-53.
109. Borge N, Fosså SD, Stenwig AE. Metastatic testicular cancer and extragonadal germ cell tumor presenting with neurological symptoms. *J Neurooncol* 1990; 8: 145-8.
110. Spratt JS, Meyer JS, Spratt JA. Rates of growth of human solid neoplasms: Part I. *J Surg Oncol* 1995; 60: 137-46.
111. Spratt JS, Meyer JS, Spratt JA. Rates of growth of human solid neoplasms: Part II. *J Surg Oncol* 1996; 61: 68-83.
112. Oeser H v. *Krebsbekämpfung: Hoffnung und Realität*. Stuttgart: Georg Thieme Verlag; 1974.
113. Salmon SE, Smith BA. Immunoglobulin synthesis and total body tumor cell number in IgG multiple myeloma. *J Clin Invest* 1970; 49: 1114-21.

114. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Int Med* 1977; 87: 293-8.
115. Braun S, Pantel K, Muller P et al. Cytokeratin-positive cells in the bone marrow and survival patients with stage I, II, or III breast cancer. *N Engl J Med* 2000; 342: 525-33.
116. Hutchison GB, Shapiro S. Lead time gained by diagnostic screening for breast cancer. *J Nat Cancer Inst* 1968; 41: 665-81.
117. Boag JW. Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *J Roy Stat Soc* 1949; 11: 15-53.
118. Michels P, Mirra J. Attacking the doubling time defense in breast cancer cases. *Medical Trial Technique Quarterly* 1981; 28: 301-321.
119. Parver CP. Defence of delayed diagnosis and treatment of breast cancer. *Medical Trial Technique Quarterly* 1983; 30: 34-63.
120. Friberg S. 5-year cure rate: Yet another myth. *J Surg Oncol* 1997; 65: 73-5.
121. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *JAMA* 2000; 283: 2975-8.
122. Haybittle JL. Curability of breast cancer. *Br Med Bull* 1990; 47: 319-23.
123. Friberg S. Critical Analysis of Clinical Trials. In: Donegan WL, Spratt JS (eds.), *Cancer of the Breast*. Philadelphia: Saunders; 1998.
124. Spratt J. Realities of breast cancer control, public expectations, and law. *Surg Oncol Clin North Am* 1994; 3: 25-34.
125. Kern KA. The anatomy of surgical malpractice claims. *Bull Am Coll Surg* 1995; 80: 34-9.
126. Bailar III JC and Smith EM. Progress against cancer? *N Engl J Med* 1986; 314: 1226-32.
127. Bailar III JC, and Gornik HL. Cancer undefeated. *N Engl J Med* 1997; 336: 1569-74.
128. McKinnon NE. Cancer of the breast: the invalid evidence for faith in early treatment. *Canad J Publ Health* 1951; 42: 218-23.
129. Wright CJ, Mueller CB. Screening mammography and public health policy: the need for perspective. *Lancet* 1995; 346: 29-32.
130. Gotzsche PC and Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; 355: 129-34.
131. Fry WA, Phillips JL, Menck HR. Ten-year survey of lung cancer treatment and survival in hospitals in the United States. *Cancer* 1999; 86: 1867-76.
132. Eddy DM. Screening for lung cancer. *Ann Int Med* 1989; 111: 232-7.
133. Spratt JS and Spratt SW. Medical and legal implications of screening and follow-up procedures for breast cancer. *Cancer* 1990; 66: 1351-62.
134. McNichols D, Segura J, DeWeerd J. Renal cell carcinoma: Long-term survival and late recurrence. *J Urol* 1981; 126: 17-23.
135. Mueller CB: Stage II breast cancer is not simply a late stage I. *Surgery* 1988; 104: 631-8.

Paper received and accepted: 19 October 2004