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A CLINICAL METHOD FOR ESTIMATING THE RATE OF GROWTH OF A CANCER†

The rate of growth of a human cancer is frequently discussed but seldom measured. The measurement would require the calculation of a proportion, or rate, in which the numerator represents a *change of growth,* and the denominator, an *interval of time* during which the change occurred. The necessary data for this calculation would be an assessment of the state of the cancer in its human host at each of two different points in time. The difference between the two states would be the numerator, and between the two times, the denominator.

Such measurements are rarely used for appraising rate of growth when a cancer is discovered in an individual patient. Instead, treatment is usually planned and reported on the basis of an anatomic staging system that cites the extensiveness of the tumor at the time of its detection. Although this citation of anatomic extensiveness is satisfactory for denoting an amount or direction of growth, it does not account for functional effects of growth, and it indicates neither a change in growth nor a rate.

One of the main reasons for not measuring these phenomena has been the difficulty of getting evidence that is satisfactory in both time and content. In time, the usable evidence must be restricted to what was learned during the temporal interval before the cancer received any treatment that might alter its natural rate of growth. Although the date of treatment can serve as the endpoint of this interval, no standard concepts have been established for the time to be cited as an opening date. In content of evidence, the structural aspects of a cancer's growth can be classified with the traditional system of anatomic staging, but no systems of classification have been available for the clinical manifestations that denote functional effects. And even the structural measurements are necessarily imprecise, because the exact size of a cancer can be determined only if it is removed at surgery — a procedure that can be done only once for most patients, and not at all for many.

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My purpose in this paper is to suggest specific points in time that can be used for these assessments, and to propose a method for estimating rate of growth of a cancer from conventional clinical evidence that can denote both the structural and functional effects of growth.

"Datemarks" in the natural history of a cancer

After a cancer has been diagnostically identified, the clinician can find several principal "datemarks" for the cancer's previous course in that patient. The time sequence of some of these "datemarks" is shown in Fig. 1, and is discussed in the sections that follow.

Date of onset; "latest negative"

The date of onset of a cancer can never be determined. Even if a person has continuous daily medical examinations from birth, the exact moment at which a cancer begins cannot be distinguished. The clinician would be unable to decide whether the newly discovered lesion began on the day it was first noticed, or whether its previous growth had now reached the point of detectability.

Since a date of onset cannot be determined, the clinician can look for an alternate date that may often be specifically demarcated: the *latest negative*. The *latest negative* refers to the date of the most recent time at which negative results were found during an appropriate examination of the site at which the current cancer is now detected. As shown in Figure 1, the *latest negative* examination may have occurred before or after the onset of the cancer.

For example, in lung cancer, the *latest negative* date would be the time of the most recent roentgenogram at which no evidence of the current tumor was visible; in breast cancer, this date would be the most recent examination of the breast (by any reliable observer, including the patient) at which no evidence of the current lump could be palpated.

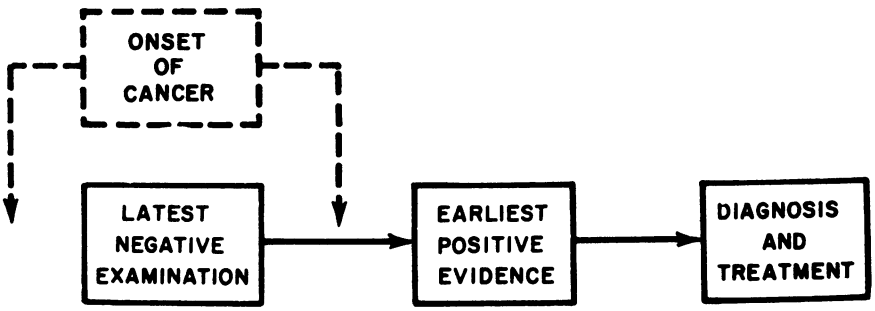

FIG. 1. "Datemarks" in the natural history of a cancer.
(For further details, see text.)

When the date of *latest negative* is selected from the available data, the compared examinations should be commensurate. For example, a previously normal digital palpation of the rectum should not be regarded as a negative examination for a cancer that is later visible at sigmoidoscopy but not palpable digitally. The details of criteria for "commensurate" examinations are described elsewhere.[1]

Date of first objective evidence; "earliest positive"

Objective evidence of a cancer's presence can be noted from roentgenograms, from endoscopy, from physical examination, and occasionally, from a laboratory test.* The *earliest positive* refers to the first test or examination at which objective evidence of the current tumor, or of an appropriate "ancestor," was noted to be present.

Date of first symptoms; "initial symptom(s)"

The date of the first symptom(s) attributable to the cancer is determined after careful history-taking and diagnostic appraisal of each of the patient's symptoms. This date is easily selected when the patient's symptoms have had a distinct, abrupt onset and when the patient has no other disease that may produce the symptoms ordinarily associated with the cancer under scrutiny. If the symptoms have had an insidious onset, an upper time limit for them can usually be found by reference to the presence or absence of the symptoms at notable previous dates in the patient's life. The techniques for performing such assessments have been discussed elsewhere.[2]

If the patient with cancer has an associated "simulating" disease, the decision about attribution of symptoms may be difficult. For example, when hemoptysis occurs in a patient who has chronic bronchitis and lung cancer, the source of the hemoptysis is uncertain; the attribution of blood in the stools may be uncertain in a patient with cancer of the rectum who also has hemorrhoids or diverticulosis.

With astute diagnostic reasoning, many of these difficulties can be resolved, but many other "attribution" decisions will remain uncertain. Of the totality of symptoms present in a patient with cancer, some will be unequivocally attributed to some other disease; some will be unequivocally attributed to the cancer; and others will be of uncertain attribution, in that the clinician cannot be sure of whether the symptoms are due to the cancer, to a co-existing disease, or to both. In selecting the *initial symptom(s)* due to the cancer, the clinician can restrict the list of candidates to those unequivocally attributable to the cancer, or he can also include the symptoms of uncertain attribution. The decision is often

* For example, an elevated acid phosphatase in cancer of the prostate, or certain abnormal serum proteins in multiple myeloma.

simplified when symptoms of "certain" attribution have begun earlier than, or contemporaneously with, those of "uncertain" attribution.

(The problem is not as difficult as it may seem. In studies of medical records of patients with lung cancer and rectal cancer,[3,4] this "attribution" issue was significant in only about 10 percent of cases, and the problem might have been less frequent if all the patients had been available for direct interview. Since no major difference in the general statistical distinctions were found[3,4] when the "uncertain attribution" group of symptoms was either excluded or included among the candidates for *initial symptom(s)*, the simplest general policy is to include such symptoms among the candidates.)

"Zero time"; the date of therapeutic decision

In addition to the three dates just cited, a fourth "datemark" can be used as a *"zero time,"* or index point of temporal reference, for comparing the biologic behavior and rate of growth of a cancer in different patients. The disadvantages and advantages of different "datemarks" for *zero time* have been discussed elsewhere.[1,2] In a survey of clinical course and therapy for a large series of cases, the best choice of *zero time* is the date of the first anti-neoplastic treatment for the cancer. In a prospective therapeutic trial, or in the selection of treatment for an individual patient, the reference date would be the time at which the therapeutic decision is made. In calculating some of the intervals to be cited later, and in assessing certain changes in size or functional effects of the cancer, the term *zero state* will refer to the patient's condition at *zero time.*

Anatomic and functional direction of a cancer's growth

The anatomic evidence obtained by physical examination, endoscopy, radiography, and biopsy enables clinicians to estimate the extent to which a tumor has physically disseminated in a patient's body. For example, metastases may be palpable in lymph nodes or liver, observable in roentgenograms of bones or other regions, or microscopically demonstrable in sites subjected to biopsy. Such anatomic evidence, however, does not necessarily indicate that the tumor has affected the function of the involved site. For example, despite small or large amounts of metastatic cancer, a liver may continue to function normally; a bone may remain painless and unbroken; and a brain may show no overt neurologic disturbance.

Not only does anatomic evidence often fail to indicate the clinical effects of a cancer, but the clinical manifestations of the patient often denote impairments for which no structural counterparts are possible or available in the patient's anatomic evidence. Some of the systemic functional effects — such as weight loss or fatigue — cannot be assessed

anatomically. Other functional effects of a cancer can occur systemically, remote from the primary site, as "endocrinopathies" or "neuropathies" that cannot be discerned from the conventional procedures used either to examine the cancer itself or to classify the anatomic "stage."

Other types of clinical effects imply anatomic lesions that may not be actually demonstrated in a particular patient during life, because the demonstration is undesirable or hazardous. For example, in a patient with cancer of the lung, the symptom of hoarseness and the endoscopic visualization of a non-moving vocal cord imply that the recurrent laryngeal nerve is involved by a neoplastic mass, but the mass may not be demonstrable by conventional roentgenography; a diagnosis of cerebral metastasis may be made on the basis of clinical and electroencephalographic manifestations although the ordinary skull roentgenogram shows no abnormalities. In the situations just cited, surgery or dye-contrast roentgenography might be therapeutically undesirable and not usable as a means of confirming the anatomic spread of the cancer. The anatomic inferences made from the functional clinical evidence in these patients would thus be the only indication of metastatic anatomic involvement — an involvement that is deduced clinically but not actually demonstrated with any anatomic form of examination.

Because the acquired items of evidence that indicate neoplastic *form* and *function* are so often "dissociated" in individual patients, the growth of a cancer cannot be appraised merely from its size or anatomic dissemination. The functional effects must also be classified and assessed.

The functional effects of a tumor are reflected in the clinical types of symptoms and signs that it produces. Each clinical manifestation due to a cancer can be toponymically categorized as *primary, systemic,* or *metastatic. Primary* clinical features are attributable to the tumor at its primary site, or to surrounding inflammation; and no primary feature implies *per se* that the tumor has spread beyond the primary site. Examples of primary symptoms are hoarseness in cancer of the larynx, hemoptysis in cancer of the lung, and alteration of stools in cancer of the rectum. *Systemic* clinical features arise in the body as a whole or at sites remote from the primary tumor, but these features also do not *per se* imply anatomic dissemination of tumor beyond the primary site. Anorexia, weight loss, and fatigue are examples of systemic symptoms in the three cancers just cited. *Metastatic* clinical manifestations imply physical spread of the tumor beyond the primary site. Examples of metastatic symptoms in the three cited cancers are pain due to metastasis in the bony pelvis, and jaundice due to neoplastic invasion in or near the liver.

Details of this functional toponymic classification of symptoms in cancer have been described elsewhere.[3] For describing the patient's *zero state,* these categories of clinical toponymy can be used as indexes (or "stages") of the functional growth of a tumor, supplementing the structural evidence used to indicate anatomic growth.[5]

Time intervals of growth of a cancer

The cited "datemarks" of *latest negative, earliest positive, initial symptom(s),* and *zero time* can be used for calculating the intervals shown in Figure 2. In these calculations, the *first manifestations* will be either the *earliest positive* objective evidence or the *initial symptoms,* according to whichever came first.

Inception interval

The *inception interval* is the time elapsed between the *latest negative* and the *first manifestations.* If a *latest negative* examination is not available, this interval cannot be calculated.

Progression interval

The *progression interval* is the time elapsed between the *first manifestations* and *zero time.* This interval can always be calculated, since a patient who receives the diagnosis of cancer must have either symptoms or some objective evidence of the cancer.

Deductions about rate of growth

For calculating rate of growth of the cancer found at *zero state,* the numerator of the ratio will represent *directional* changes in anatomic and functional growth of the tumor; the denominator will represent the time during which these changes occurred. A cancer is most likely to be biologically "benign" if it has had a favorable direction of growth—i.e., no anatomic dissemination, and no systemic or metastatic functional effects—over a long duration of time.

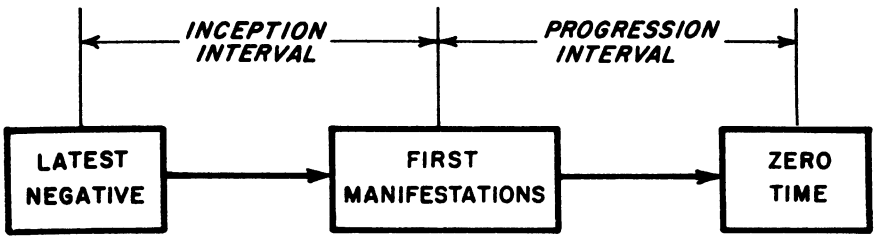

FIG. 2. Time intervals of growth of a cancer.
(For further details, see text.)

The change in growth, from one state to another, will reflect these directional aspects of the cancer, while the change in time will reflect the rapidity of the increment in growth. A cancer that has grown unfavorably, having already produced metastatic manifestations when it is detected, can seldom be "cured" no matter how slowly it has grown — but a long duration of growth may indicate that "palliative" surgery or other vigorous therapeutic procedures are particularly likely to be effective. On the other hand, a rapid rate of growth may be a harbinger of poor prognosis even though the direction of growth appears "favorable."

Since the intervals calculated in the previous section will be the critical denominators of the growth ratio, these intervals require thoughtful interpretation.

A long inception interval

A long inception interval has no significance. Since the length of this interval depends on when the *latest negative* examination occurred, the interval can be extremely long merely because the old examination took place many years previously. For example, in a patient whose *earliest positive* chest roentgenogram for lung cancer was noted when he was 58 years old, the only available previous negative film may have been taken when he was 22.

A short inception interval

A short inception interval generally implies a rapidly-growing tumor. The shorter the interval, and the greater the change in growth during that interval, the more likely is the tumor to be rapid-growing. For example, if a woman's breast showed no lump two months ago and a large lump now, the lump has grown rapidly. Similarly, in a patient who has chest roentgenograms taken every six months, a negative film at one examination followed by a large mass in the film of the next examination would suggest rapid growth. Thus, despite such "early discoveries" of cancer, the results of treatment may be poor because the cancer is rapid-growing.

A short progression interval

A short progression interval has no significance *per se* unless a large amount of change takes place during that interval. For example, the earliest positive evidence of a cancer in an asymptomatic patient may have been found only a week before the patient's admission to the hospital for treatment. In such circumstances, the short progression interval is attributable to the medical procedures of man, rather than to the biologic course of nature, and cannot be used to assess the growth of the cancer. In patients whose initial symptoms were the first manifestations of cancer,

no definite conclusion can be drawn from a short progression interval, unless a dramatic *increment* of systemic and metastatic symptoms has accrued during that interval. The interval may have been short because the tumor grows rapidly, but the brief duration may alternatively represent the "top of an iceberg" — resulting from a slow-growing tumor that has finally reached the point of symptomatic eruption.

A long progression interval

A long progression interval implies a slow-growing tumor. The only way in which a patient could still be alive for a long time after the first manifestations of the tumor is for the tumor to have grown slowly. With a long progression interval, the tumor may have grown in an unfavorable anatomic or functional direction, but its growth has been slow. For this reason, and because onset of symptoms is often the first manifestation used for calculating the progression interval, a reasonable aphorism about the rate of growth of tumors is that slow-growing tumors produce symptoms slowly.[4]

DISCUSSION AND CLINICAL APPLICATIONS

Most existing concepts of rate of growth for human cancers have been based on data obtained by three techniques, each of which has distinct disadvantages:

[1]. From observation of cellular types, pathologists have concluded that "differentiated" cancers tend to grow slowly and "undifferentiated" ones rapidly. The disadvantage of these histopathologic concepts is that they represent general conclusions, which might not apply to an individual patient; moreover, they are based on microscopic appearances, which do not contain direct appraisals of either growth or time.

[2]. The rate of growth of an excised cancer can be observed when part of it is grown in an animal or in some other medium outside the patient's body. This procedure has two disadvantages: a piece of the cancer cannot always be obtained during the patient's lifetime, and the *extra-corporeal* growth deprives the cancer of any constitutional resistance from the human host. Consequently, the results cannot readily be extrapolated to what happened when the cancer was part of the host.

[3]. A frequently used *endo-corporeal* approach has been based on wholly objective evidence, obtained from review of earlier examinations, via roentgenography, endoscopy, or palpation, of the region in which the cancer has now been detected. The disadvantage of this approach is that a preceding examination may not have been done, or may not have been performed or recorded in a manner suitable for comparison with the

current state. Moreover, the size of the cancer noted at these examinations may be difficult to interpret because of associated inflammation or observer variability.

The technique proposed in this paper is an attempt to improve the endocorporeal approach by analyzing the patient's symptoms as well as the more "objective" clinical and para-clinical evidence. The proposed method of estimating rate of growth cannot be illustrated with a plethora of supporting data, because relatively little appropriate information is available. The duration and other necessary distinctions of symptoms are often not given explicit attention in the histories taken from most patients, and previous objective evidence of a cancer — in either physical, endoscopic or roentgenographic examinations — is not regularly looked for. Moreover, even when satisfactory information is obtained about symptomatic distinctions and previous objective evidence of cancer, the information is seldom specifically classified and analyzed in large-scale statistical tabulations.

The foregoing discussion has therefore been concentrated on a methodologic rationale for future research, since most existing investigations of cancer have not provided data with which to test the concepts. The remaining discussion will be devoted to summarizing the supporting data contained in the few investigations where these problems have been explored, and to proposing a way of using these concepts to clarify some of the confusion that now exists in the study of breast cancer.

A short inception interval

Since roentgenograms of the chest are so easily obtained, cancer of the lung is one of the few neoplasms for which the inception interval has been studied systematically enough to warrant formal analysis. In particular, Weiss, Boucot, and Cooper[6] have appraised the post-therapeutic survival after detection of lung cancer during the semi-annual photofluorographic examinations of more than 6,000 men. The growth rate of the cancer was determined as a "doubling time" based on the increment of size during the 6-month inception interval from a "negative" to a "positive" radiographic examination. Smaller tumors had longer doubling times, and such patients survived generally longer than those with a short doubling time. In such circumstances, a large increment in growth during a relatively short inception interval indicated a rapidly-growing tumor.

A long progression interval

That cancers of the lung can often grow slowly — even with anaplastic cell types — has now been well established from many radiologic studies.[6-9] What has not been frequently quantified, however, is that survival rates in lung cancer may be no better in certain patients discovered sympto-

matically "early" rather than "late." For example, among patients who had only primary symptoms of lung cancer, the survival rates were actually somewhat higher in those who had a *long* rather than *short* duration of pre-therapeutic symptoms.[3-5] In particular, among patients who had no pre-operative anatomic evidence of dissemination beyond the primary site, the 5-year survival rate after resection of the cancer was 34 percent [10/29] in those with a long duration of only primary symptoms, and 21 percent [5/24] in those with a short duration.[10]

In a similar study of the symptomatic progression interval in patients with rectal cancer who had no evidence of anatomic dissemination of cancer beyond the primary site, the 5-year survival rate after surgical resection was 67 percent [29/43] in the group with "long primary" symptoms, and 54 percent [18/33] in the "short primary" group.[10] The importance of a long progression interval has also been noted in several cancers other than pulmonary or rectal neoplasms. In Hodgkin's disease,[11] and in cancer of the stomach,[12] recent investigators have reported the apparent paradox of good survival in patients with long "delays" before treatment.

Although such long survivals, despite "delays" in treatment, have often been noted in patients with cancer, the phenomenon has usually been considered a caprice of nature or an idiosyncrasy of the human psyche, rather than a clue to the biologic behavior of cancer.[4,5] Slow-growing, favorably-directed tumors can regularly be expected to have a long progression interval; and protracted primary symptoms, without the development of systemic or metastatic symptoms, can be used predictively as an index of relatively good prognosis.

Cancer of the breast

Despite volumes of statistics based on anatomic staging of breast cancer, the treatment of this disease is perhaps more controversial today than that of any other human neoplasm. One possible reason for the controversy is that the morphologic classifications, which depend on size, fixation, localization, and cellular type, make no provision for the rate of growth of the cancer. Consequently, slow-growing and rapid-growing tumors may be admixed in the same morphologic category, leading to undetected and unresolved discrepancies in the post-therapeutic data.

Since cancer of the breast seldom produces symptoms, its rate of growth must be assessed from physical signs of the length of time that the tumor was, or might have been, present before it was detected in its "zero state." A progression interval can always be calculated for the time elapsed between the patient's notation of the current lump and zero time. An

additional question should always be asked, however, of any patient with cancer of the breast. The question is: "When was your breast examined in the past, before this current lump was noted, and what was found?" After this question is answered, and after any previous examiners are consulted, the data may be arranged in three possible categories.

[1] No previous examination was done, or the results of previous examinations are unknown. In this case, no inception interval can be calculated. The clinician has no idea of how long the tumor might have been present before its recent discovery.

[2] A previous examination was performed, with negative findings. In this case, an inception interval can be calculated, and, if short, will imply a rapid-growing tumor.

[3] A previous examination was done, and showed the same lump as now, present in some ancestral form. Further questions should then be asked to elicit information about a *latest negative* examination of the breast. Regardless of the answer to the additional questions, this patient's progression interval can be calculated, and, if long, will imply a slow-growing tumor.

With this information, a breast cancer can be classified as slow-growing (long progression interval), rapid-growing (short inception interval), or of uncertain rate of growth (inception interval unknown or long, and progression interval not long). If patients with comparable "anatomic stages" were further subclassified according to these "clinical" or "biologic" stages, the results of different modes of therapy might be more effectively analyzed, because the comparisons would contain groups that are biologically more homogeneous and clinically more comparable.

SUMMARY

The rate of growth of a cancer in its human host is not assessed effectively from histopathologic inferences, anatomic "stages," or attempts to grow the cancer outside the host's body.

In measuring rate of growth, the numerator of the ratio (changes in growth) should deal with functional as well as structural effects of the cancer. The denominator (time of growth) must deal with measured intervals of time. Structural evidence of cancer, obtained during appropriate previous examinations, can provide some of the information needed for this calculation, but such previous examinations have not always been performed in all patients, and the data, even when available, are not always satisfactory for the necessary decisions. An alternative source of useful information is an account of the clinical manifestations of the

patient. These data help denote both the functional direction and duration of a growing cancer.

From the classified clinical symptoms and other evidence of cancer, two important intervals can be calculated: an *inception interval,* from the date of the latest negative examination to the first symptomatic or other manifestations of the cancer; and a *progression interval,* from the first manifestations of the cancer to the time of the first therapeutic decision. In general, a short inception interval implies a rapid-growing tumor, and a long progression interval implies a slow-growing tumor.

Further aspects of these principles are discussed, and an application is suggested to improve the analysis of data for cancer of the breast.

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