

CANCER GROWTH

Implications for Medicine & Malpractice

by Michael Retsky, PhD *



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Consider a hypothetical situation. On routine examination, a physician detects a breast lump by palpation on a 62 year old woman. There is a history of fibrocystic disease and mammography shows nothing suspicious. No biopsy is done. Ten months later the tumor has grown. Mammography now shows suspicion for carcinoma which is confirmed by biopsy. Lumpectomy and axillary dissection are done. Pathology reports a 2.2 cm moderately differentiated adenocarcinoma with 6 of 20 nodes positive, estrogen and progesterone receptors are 50 and 75 fm/mg. Tumor cells are aneuploid and S-phase fraction is 2%.

What is the prognosis for the patient as diagnosed and what would the prognosis have been if the patient's tumor was diagnosed at the earlier opportunity?

After millions of mammograms have been studied and hundreds of thousands of breast cancer patients have been treated, one would expect that the growth and development of breast cancer should be understood well enough to provide clear answers to such straightforward questions. Unfortunately, that is not the case. To illustrate the problems encountered, I will discuss primary tumor growth which is just one aspect of the larger issue.

I am not referring to complex and fundamental gene regulated biochemical mechanisms that control cellular growth. That is very difficult and may never be completely understood. I am referring to simple formulations that within reasonable accuracy describe the size of a primary breast tumor as a function of time. That is, if the tumor size is known at one or more times, simple equations would allow the interpolation or extrapolation of sizes at other times.

The growth rate (or kinetics as it is sometimes called) of breast tumors remains a debated subject. As will be shown, the scientific implications are quite important in the treatment of breast cancer. While less important in the scheme of things, attorneys sometimes need to establish if and to what extent a patient has suffered a loss of survivability due to delayed diagnosis of breast cancer. In large measure, that is dependent on estimates of tumor size at the time at which the disease could have been diagnosed.

A tumor consists of some normal tissue plus cancer cells that are descendants of one cell that had undergone a malignant transformation. The number of cells is described by the equation 2^n where n

is the number of doublings that have taken place. Tissue density is approximately a billion cells per cubic centimeter (cc). A billion is approximately 2^{30} . Ignoring the normal cells, a 1 cc tumor started as a single cancer cell that has divided 30 times. Data show the time for a breast cancer to double in volume is 25 days to at least 1000 days with a typical value of about 100 days. Depending on breast tissue density and structure, mammography is usually capable of finding breast tumors at approximately 1 cc. Combining this information, we can estimate the usual preclinical time of breast cancer as 30 doublings at 100 day doubling time or a total of 8 years.

If left untreated, a primary breast cancer 1 liter (1000 cc) in size is typically lethal. That size is 40 doublings of a single cell (1 liter or 10^{12} cells is approximately 2^{40} cells). Thus the possible observation times in breast cancer is limited to between the 30th and 40th doublings or at most only the last 25% of the growth history of a tumor. That plus realistic limitations due to dealing with human cancers accounts for the relatively sparse data of multiple measurements on many individual growing tumors which is what would be needed to develop well documented growth equations.

Exponential growth, the simplest possible growth, is cellular division with a constant dividing time. One cell divides into two and then four, etc., with each doubling taking the same time. This growth is easily recognizable when graphed. It is a straight line on a semi-log scale (logarithmic on the vertical scale and linear on the horizontal scale).

Models are needed to study cancer. An animal model is developed from an original spontaneous tumor. The tumor is harvested and injected into an immune compromised animal. This new tumor is allowed to grow and is then harvested and further passaged. This process continues many times. There are data showing the change in growth of the tumors as the passaging process takes place (1). The original tumor shows some slow erratic growth which gradually becomes smoother, rampant and exponential.

While they are small, multipassaged animal tumor models grow exponentially and are very reproducible. The doubling time of an animal model tumor is usually 1 or 2 days. A doubling time of 1 day allows a tumor growth and treatment experiment to be done in a month which is a convenient time. The reproducibility allows the same experiment to yield the same results on different animals and in different laboratories.

Exponential growth cannot continue indefinitely since it is boundless. Beyond a size where the tumor is a few percent of the host size, the host cannot fully sustain the tumor. At that point exponential growth gradually slows and may approach a Malthusian asymptotic limit. Growth that is exponential at small time and limited to an asymptotic level at large time is called Gompertzian growth. Multipassaged animal tumors grow in a Gompertzian fashion with slowly increasing doubling time as the tumor becomes large. Even in this situation where the growth rate is not constant, the concept of a doubling time is still useful.

A very important scientific issue that has to be considered in this discussion is the chemosensitivity of a growing tumor. Most chemotherapeutic drugs interfere with cell division processes and are thus most effective on growing tumors and in general the faster tumors grow, the more effective is the drug. The logic used in chemotherapy of breast cancer patients is intimately tied to growth patterns of breast cancer. According to the 1991 American Cancer Society Textbook of Clinical Oncology (2), Gompertzian growth accurately describe the growth of breast cancer. When cancer is found in a patient, the tumor lies high on the growth phase of the Gompertz curve and is thus relatively slowly growing. Debulking the tumor by surgical removal and radiation puts any residual tumor in the smaller thus faster growing section of the Gompertz curve and makes it more chemosensitive. This reasoning is valid in animal models. Since human breast cancer is assumed to grow similarly, intensive chemotherapy is given shortly after surgery with the hope of eradicating all residual breast cancer cells. Treatment is given until limited by toxicity and then stopped. Then we hope for the best. Compelling though this model is, only modest improvements in survival rates have been made over the years.

While it is often claimed that breast tumors grow in a Gompertzian manner, not all believe that. Consider these comments by Steel (1):

"Tumour growth is often irregular: Before going on to consider the mathematical form of the growth curves of tumours it is necessary to indicate that regularity is not a universal characteristic of malignant growth, and may indeed be less common than often supposed. Much has been written about the equation of growth of tumours and Mayneord (3) even used the term 'law of growth' in regard to a rat sarcoma. Such terms tempt one to imagine that every tumour has a specific equation of growth which may ultimately be understood in terms of biophysical parameters. As medical oncologists are all too aware, however, unpredictability or lawlessness is often the most noticeable characteristic of primary growths. 'Unpredictability', like the word 'spontaneous', is of course merely an admission that our knowledge is limited, but this itself should warn us against the attempt to imagine that all tumours conform to simple rules.

"Irregularity, as with the 'intermittent' fault in electronic devices, is one of the hardest phenomena for a scientist to deal with, and no doubt the requirement for uniform and interpretable results has often caused investigators to select regular, in preference to irregular, biological material. Irregularity in the growth of experimental tumors may be avoided in two principal ways: first, by the use of frequently passaged transplanted tumours whose cell populations have undergone selection for rapid and regular growth; secondly, by averaging growth data for a group of similar tumours. ... Whilst averaging improves the reliability and precision of the data it loses the detailed behavior of tumours..."

I began studying breast cancer growth with some colleagues in 1982. This research using computer simulation of clinical data predicted that tumor growth was mostly erratic, with alternating growth phases and periods of no growth or temporary dormancy (4-7). Since this work challenged the Gompertzian model, I examined the evidence in support of it. I am perhaps the first person to ever read all the references provided in support of Gompertzian kinetics for breast cancer.

Due to limitations of human experimentation, there is little hard data. Publications that use Gompertzian kinetics directly (8-11) or indirectly (2,12,13) cite a paper by Laird (14) as evidence that Gompertzian kinetics is valid for tumors. Laird measured growth of "19 examples of 12 different tumors of the rat, mouse, and rabbit" and concluded: "the pattern of growth defined by the Gompertz equation appears to be a general biological characteristic of tumor growth." That is a far reaching statement based on only 18 rodents and one rabbit.

I discussed the deficiencies of the Gompertz model including the Laird data during an invited talk to an international audience of 800 breast cancer clinicians and researchers in St. Gallen, Switzerland (15). The evidence to support the Gompertzian model in breast cancer is very weak. On the other hand, there is much well documented evidence to support temporary dormancy in the natural history of breast as well as other cancers. For reviews, see Hadfield (16), Meltzer (17), Stewart et al (18), Retsky et al (19).

In my searching of the cancer literature, I have been able to find only one case with more than two measurements over more than one year on an untreated primary breast cancer (20). This 78 year old patient's husband previously died of carcinoma of the larynx after spending their savings in futile treatment. She then refused any treatment except for occasional x-rays of her breast over a two year period. The tumor was detected with a cross-sectional area of 4.5 sq. cm. essentially in a growth plateau (7200 day doubling time) for almost a year and then it began to grow (180 day doubling time) before it was removed and examined after another year. A 4.5 sq. cm. tumor with a constant doubling time of 7200 days leads to the impossible result that the tumor started growing 655 years earlier. The tumor must have grown faster initially and then slowed and finally faster again. That is impossible to explain by Gompertzian growth. The authors did not select this patient as an example of unusual growth. They did not even graph the growth data. It was simply a rare opportunity to report tumor growth in the absence of treatment for an extended time. The analysis of this case has

been debated in the literature (15,21).

Perhaps the most exciting cancer research in the world today is in tumor angiogenesis. This strategy differs from conventional chemotherapy in that it is designed to attack the vasculature that supports a tumor rather than to kill cancer cells directly (22). That is like fighting a war by destroying the factories and supply lines instead of killing soldiers in the field. There are new non-toxic drugs under development that are very promising (23,24). Judah Folkman of Harvard is the person who founded this field. To learn about angiogenesis, I have been attending Dr. Folkman's lab meetings at Harvard for the past year. He spoke at a plenary session at the 1996 American Society for Clinical Oncology meeting in Philadelphia, attended by over 8000 medical oncologists (25). Folkman began by discussing a node negative breast cancer patient who relapses 10 years after surgery with an aggressive metastasis. "What was that tumor doing all those years?" he asked rhetorically and answered: "It was temporarily dormant until it became vascularized by the host."

I am sure that we have not heard the end of discussions on tumor growth. It is a very important and scientifically fascinating subject. A new paper of mine just came out last month on growth of metastasis in breast cancer (26) in collaboration with a distinguished Milan oncology group. This work has been discussed as a news feature in an issue of *The Lancet* (27).

As mentioned at the start of this letter, there are aspects of this subject of interest to attorneys. One issue facing the attorney trying to establish if a delayed diagnosis made any difference in outcome to a patient is whether the tumor grew appreciably between the time it could have been detected and when it was actually detected. If growth is continuous and deterministic as in the Gompertzian model, then every day of delay produces a measurably worse prognosis. If growth is discontinuous and erratic, then some periods of time delay in diagnosis produce no worsening of prognosis while other periods of time delay will produce significant worsening of prognosis.

As I have indicated, my research predicts the latter. We do not know exactly when these growth periods occur but we can predict the probability of such events with some precision. Patient data that can be used to make such calculations are 1) clinical information (patient age, all reports of tumor size including palpation and mammography, and if estrogen supplements have been taken) and 2) pathology and histology information (nodes positive and examined, lymphatic and vascular invasion, tumor grade, receptor status, DNA content and %S phase of tumor cells).

To the attorneys representing either the plaintiff or the accused in a case of delayed diagnosis of breast cancer, it often cannot be established with absolute certainty whether survivability was compromised due to delay. However the probability and the likely extent of damage to survivability can be calculated.

Referring to the hypothetical case presented in the beginning, the long term prognosis of the patient as diagnosed is 28% chance of long term survival. If the patient were diagnosed 10 months earlier, the chance of survival would be 41% to 65%.

FOOTNOTES

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*** Mr. Retsky is a leading authority on tumor growth. This Article was Provided by the Technical Assistance Bureau.**



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