How is a 19th century amateur mathematician contributing to a 21st century advance in breast cancer treatment that could result in a 26% decrease in the annual odds of recurrence and a 31% decrease in the annual odds of death?

Dr. Larry Norton of Memorial Sloan-Kettering Cancer Center tells the story of this remarkable connection in his manuscript, “Conceptual and Practical Implications of Breast Cancer Tissue Geometry: Toward a More Effective, Less Toxic Therapy” [1]. The Oncologist is honored to publish this paper, which is based on Dr. Norton’s recently delivered Brinker Award Lecture as the recipient of the Susan G. Komen Breast Cancer Foundation’s Brinker Award for Scientific Distinction. Established by the Foundation in 1992 to recognize leading researchers and clinicians involved in the study and treatment of breast cancer, Dr. Norton’s lecture was delivered on December 9, 2004, during the Charles A. Coltman, Jr., San Antonio Breast Cancer Symposium.

The tale begins in 1825, when London East End insurance actuary Benjamin Gompertz theorized that life and aging follow a mathematically predictable curve. Rapid growth occurs first, followed by slower growth. From this insight, Dr. Norton, whose breast cancer research career spans three decades, developed with colleague Dr. Richard Simon their related cancer-centric hypothesis: “Therapy results in a rate of regression in tumor volume that is proportional to the rate of growth that would be expected for an unperturbed tumor of that size.”

The Norton-Simon Hypothesis then led to the “dose-dense” approach to breast cancer chemotherapy, shown in multiple studies to achieve those promising drops in cancer recurrence and death.

Dose-dense chemotherapy seeks to maximize “cell kill” by maximizing the rate of drug delivery – not the level of dosing. As he describes in his article, Dr. Norton and his fellow researchers found that by dosing at two-week rather than the conventional three-week intervals, they could interrupt the rapid growth phase, as it were short-circuiting the Gompertzian growth curve before the tumor regrowth achieved its mathematically greatest size gains.

Enabling this compressed dosing schedule was the development of granulocyte-colony stimulating factor, or G-CSF (filgrastim, Neupogen®). G-CSF serves to protect the patient’s ability to make vital white blood cells during strenuous chemotherapy.

This new therapy approach has not been without its share of controversy, notes Dr. Norton, largely because the term “dose-dense” has been misinterpreted to mean “more toxic.” In fact it may be just the opposite – as you will read. And dose density, with its compressed schedule, also holds promise of a shorter overall treatment time.

The Gompertzian curve also provided the seed for Dr. Norton’s observations on a new understanding of cancer metastasis and cancer stem cell biology. He postulates that “self-metastasis” is responsible for small clumps of cell growth that together comprise a tumor, with each clump following the initial rapid growth of the Gompertzian model prior to distant metastasis.

“The bottom line is this,” he writes, “We have tended to think that cancers metastasize because they are large; the reality may be that they are large because they are self-metastatic.”

Dr. Larry Norton’s recognition and appreciation for the utility of Gompertzian mathematics, spanning as it does the 19th and 20th centuries, is now during the early years of the 21st century being recognized for both its theoretical and practical importance. So this story really bridges three centuries. It also reflects the creativity and insightfulness of Dr. Norton – and his persistence too!

REFERENCE

1 Norton L. Conceptual and practical implications of breast tissue geometry: toward a more effective, less toxic therapy. The Oncologist 2005;10:370-381.