Doubling time is one model used to predict how fast cancer cells grow. It may be used to defend physicians against liability in cases involving a delay in diagnosing cancer. Challenges to the theory can help you use it to support your client’s case.
The belief that the longer a cancer is allowed to grow, the more deadly it becomes, and that the sooner treatment is initiated, the better the chance of cure, has become common sense among the lay public. In many jurisdictions, jurors are instructed that they may use common sense gained from their experiences in evaluating what they see and hear during the trial.

Although the plaintiff bears the burden of proof that the doctor’s negligence was a proximate cause of the plaintiff’s injury in a case involving a delay in diagnosing cancer, the plaintiff has a natural advantage compared to the defense on the proximate cause issue.

To counter that advantage, the medical malpractice defense bar has embraced the concept of doubling time. Defense experts use it to argue that an earlier diagnosis of cancer would not have affected the patient’s outcome.

Most cancerous tumors begin as a single normal cell, in which multiple mutations occur in the genes that govern cell growth, cell differentiation, and programmed cell death. As a result, the cell begins to divide in an uncontrolled fashion, leading to a proliferation of malignant clones. Assuming that the original cancerous cell and its daughter cells divide at roughly a constant rate, the total number of cancerous cells in the tumor would grow exponentially, doubling at every division cycle: One cancer cell would develop into two, then four, eight, and so on. After 20 doublings, there would be approximately 1 million cancerous cells in the tumor; after an additional 10 doublings, there would be over 1 billion.

However, clinical evidence indicates tumor growth is not constant over the life cycle of a tumor, and the alternative Gompertzian model of tumor growth was developed. In this model, the doubling time varies as a function of the tumor’s volume, with increased doubling time and decreased growth over time. This model allows the tumor to approach, but not exceed, a maximum volume as it ages, consistent with the biological behavior of tumors in which tumor growth rate decreases as the metabolic demands of the enlarging tumor exceed the host’s capacities to provide nutrients.
The doubling time theory is often used in defending delay in diagnosis of cancer cases. Typically, the cancer is at an advanced stage at the time of diagnosis, with a poor prognosis. The plaintiff alleges that an opportunity to diagnose the cancer at an early stage with a better prognosis has been lost due to the defendant physician’s negligence.

The underlying message of most defense experts using the doubling time theory to bolster their opinions is that a cancerous tumor consists of millions if not billions of cells before it is detectable; metastasis occurs early in the tumor’s life, long before it becomes symptomatic; and therefore “early detection may not be early enough detection.”

**Fighting Doubling Time Defenses**

The medical and scientific literature provides the foundation for a defense expert to use the doubling time theory, but it also provides ways to undermine that foundation. There has been lively debate since the concept of doubling time was first introduced in the 1950s regarding its applicability to real-life tumors. Some of the most common criticisms follow.

**Assumption of a constant growth rate.** One of the strongest suppositions in the doubling time theory is constant and predictable tumor growth—and it also provides a major reservation. Animal and human tumors have been observed with varying patterns of growth: exponential, Gompertzian, and irregular patterns with periods of Gompertzian growth interspersed with quiescent periods and growth plateaus. Although some scientists have argued forcefully that the evidence for constant growth patterns is convincing, others have questioned the strength of the empirical evidence for this assumption.

**Heterogeneity in tumor doubling time.** It is well known that different cancer types exhibit different rates of growth and therefore, different doubling time. However, it is less well recognized that tumors of the same tissue type can exhibit wide-ranging growth rates.

For example, a retrospective analysis investigated the growth rate of primary breast cancer tumors of 122 patients in nine hospitals in Japan. Different histologic types of breast cancer (cancers arising from different types of cells) had mean doubling time ranging from 126 days for solid-tubular histologic type to 252 days for papillotubular carcinoma of the breast. Even patients with the same histologic type of cancer exhibited a wide range of doubling time. For instance, the distribution of doubling time for patients with solid-tubular tumors ranged from 11 days to more than three and a half years. Even if the most extreme values were excluded, the distribution of doubling time ranged from 60 days to 480 days.

A practice tip as you consider heterogeneity: Digest the specific studies the defense is relying on for the doubling time in your case.

**Variability in estimates of mean doubling time.** In most cases, not enough data is available on the growth behavior of the plaintiff’s tumor to estimate a specific doubling time for it. Instead, defense experts rely on published tissue-specific mean (or median) doubling time. Numerous studies have been conducted to estimate the mean doubling time of different types of tumors. However, published results of different studies often vary markedly in their estimates.

For instance, the growth rate of primary breast cancer has been reported in numerous studies. The mean doubling time in seven studies of primary breast cancers ranges from 80 days to 260 days. In another example, the mean growth rates of primary uveal melanoma (melanoma of the eye involving the iris, ciliary body, or choroid) have been reported in.
a broad range of 10 days to more than 1,000 days. Practice tip: Find other studies on comparable cancers that estimate doubling time that differs significantly from what the defense expert quotes.

**Measurement error in tumor volume.** To estimate a tumor’s growth rate, at least two measurements of tumor size at different times are needed. The size of an internal tumor is estimated using direct palpation; radiographic, mammographic, or ultrasonic visualization; or pathological examination.

Each approach introduces different sources and magnitudes of error. Direct palpation is probably the most error-prone. However, the most sophisticated and technologically dependent approaches are far from perfect. For example, sources of error in estimating the size of lung tumors using standard radiography include poor image quality, irregular lesion shape, and diffuse boundaries. The error rate in estimating the volume of primary lung tumors can be as much as 20 to 30 percent.

**Tumor composition.** Solid tumors are not composed of cancer cells alone but have a distinct structure including malignant cells, blood vessels, connective tissue, inflammatory cells, and plasma and other fluids.

The tumor’s density may change due to changes in cellular composition brought on by infection, changes in vascularity, or changes in the tumor’s connective framework. The proportion of cancerous to noncancerous cells in the tumor would have to remain relatively constant to calculate the doubling time based on the change in apparent tumor size. In any particular patient there is no way to know whether this proportion has remained relatively constant throughout the life of the tumor.

**Lack of routine use in clinical practice.** The doubling time concept has a long history in the medical literature, but the concept is used primarily in medical research and theoretical discussions of cancer progression, not in clinical practice. Therefore, the application of it to any particular patient is suspect and occurs almost exclusively in the context of litigation.

Practice tip: Comb the patient’s medical records and you will find no references to doubling time.

**Persuasiveness of the theory.** Probably the biggest weakness with using the concept of doubling time to defend a delayed diagnosis case is that it runs counter to the message of the medical, public health, and cancer survivor communities that early diagnosis and treatment are the keys to cure. The idea that earlier discovery of a cancer would not affect outcome—the basis of the doubling time defense—contradicts the logic of widely publicized cancer screening campaigns promoting breast self-examinations, regular mammograms, Pap smears, and colonoscopies. The equation of early treatment with greater chances for cure is firmly implanted in the minds of most jurors. A defense expert faces an uphill battle to convince jurors that earlier is not early enough.

**Plaintiff Uses of Doubling Time**

Plaintiffs can and do use the doubling time theory to their advantage. The following medical negligence case alleges a negligent delay in the diagnosis of cervical cancer. The plaintiff’s causation witness, a gynecologic oncologist, relied on the theory of doubling time to bolster his opinion.

The plaintiff underwent a Pap smear in 1993 and the result was reported as being within normal limits. In April 1996, the plaintiff underwent a second Pap smear that was again reported as normal. In September 1996, the plaintiff reported to her gynecologist that she had begun to experience spotting. She was instructed to perform a home pregnancy test and to wait and see if the spotting continued. In November 1996, the plaintiff was seen by the gynecologist’s partner with a complaint of continued spotting plus post-coital bleeding. The partner performed an endometrial biopsy, which was negative for malignancy.

In January 1997, the plaintiff was seen again by the partner and reported significant bleeding after intercourse. That doctor noted that her cervix was extremely friable. He obtained another Pap smear, which was again reported as being within normal limits, and he scheduled the plaintiff for a colposcopy and cervical biopsy. The biopsy showed infiltrating poorly differentiated squamous carcinoma of the cervix.

The plaintiff underwent a radical hysterectomy with bilateral pelvic lymph node dissection, which revealed micrometastases in three pelvic lymph nodes. A second look at the Pap smear slides by a pathologist at a nationally known cancer center where the plaintiff subsequently sought treatment revealed that all three Pap smears had been misread. Despite aggressive surgical treatment and chemotherapy, the plaintiff suffered a recurrence of her cervical cancer within two years of diagnosis and died from the disease. The plaintiff’s family
There has been lively debate since the concept of doubling time was first introduced in the 1950s regarding its applicability to real-life tumors. filed suit against the clinical laboratory that read the Pap smears as well as the two gynecologists for failing to diagnose cervical cancer.

The plaintiff’s causation witness testified at trial to the following, based in part on the known doubling time of cervical cancer cells:

- In 1993, the plaintiff’s cervical lesion was present as a high-grade dysplasia only. Cryosurgery, laser surgery, loop electrosurgical excision procedure (LEEP), or cone biopsy would have successfully treated the lesion.

- By April 1996, the cervical lesion had likely progressed to cervical cancer, but it was most likely confined to the cervix. If treated at this stage, the plaintiff’s prognosis would have been excellent and her chances for long-term survival would have approached 95 percent.

- Given the size of the tumor at diagnosis, and the known doubling time of cervical cancer cells, the lesion should have been visible when the defendant gynecologists examined the plaintiff’s cervix in the fall of 1996. Also, because the metastatic lesions were only microscopic at the time of lymph node dissection, it was probable that the lesion remained confined to the cervix. The case was tried to verdict and the jury found for the plaintiff.

Plaintiffs’ experts also have employed the doubling time theory in cases involving other forms of cancer, and even in noncancer cases. Recently, my firm represented a plaintiff who presented to a local emergency room complaining of a severe headache. Although the ER doctor considered bacterial meningitis in his differential diagnosis, antibiotics were not administered until more than seven hours after the plaintiff arrived at the emergency room. Ultimately, the plaintiff developed sepsis, multi-organ system failure, and disseminated intravascular coagulation leading to partial amputations in all four limbs and blindness in one eye.

The plaintiff’s infectious disease witnesses explained the impact of the delay by pointing to the published doubling time of the bacterial pathogen responsible for the infection. These experts testified that the infection was more than 500,000 times worse at the time of treatment than at the time when the plaintiff should have received antibiotics. Because the exponential growth of the bacteria was allowed to continue, the plaintiff developed the devastating complications that led to the permanent injuries he suffered.

The concept of doubling time as a measure of cancer growth patterns is not a creation of the courtroom, nor is it the exclusive possession of retained defense witnesses. Like many other scientific and medical principles, applying the concept mechanically and simplistically to a particular fact pattern, without an honest acknowledgement of its limitations, is an abuse of the science. Lawyers must be thoroughly versed in the relevant medical literature and comfortable with the underlying scientific principles to successfully rebut—or propound—the doubling time theory.

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NOTES
2. Id.
5. See James Michaelson et al., Estimates of Breast Cancer Growth Rate and Sojourn Time From Screening Database Information, 5 J. Women’s Imaging 11 (2003). See also Kuroishi, supra n. 4, Table X.
8. Id.