Doubling Time: Friend or Foe? Did the Delay Make a Difference?

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Doubling Time Basics

- All solid tumors are present in three dimensions
- Approximate volume can be calculated if you know the length, width and height (doesn't account for ragged edges, but this doesn't matter)
- Typically the volume is known at two different moments in time
- The "doubling time" is the amount of time necessary for the tumor to double in volume

Calculating Doubling Time

- Find the interval between first and second measurements (in days)
- Create a ratio between the earlier and later volume
- Calculate the growth rate required for the tumor to change volume according to that ratio
- The doubling time is a function of that rate
- Example…

Example of Doubling Time Calculation in a Lung Cancer Case

- A chest xray taken on January 1, 2005 showed a spot on the lung; the radiologist read the film correctly, reported the findings to the PCP who failed to act on it. Looking at the spot on the PA and lateral views one can measure the lesion at 3 x 2 x 2 cm
- On March 15, 2007 the patient was admitted to the hospital with a severe headache; CT showed several brain metastases, the largest 0.8 cm. The lung lesion is now 6 x 4 x 4 cm. Biopsy of the lung lesion showed adenocarcinoma. Special stains confirmed a lung primary
- What is the doubling time of the primary tumor? Why does it matter?

Doubling Time Calculations

- Time from one x-ray to the next: 803 days
- Ratio of two volumes: 8
- 3 doublings produce an 8-fold change in volume
- Doubling time therefore 803/3 or 268 days
- When calculations are not so simple one can use exponential equations:

Equations

$V_f=V_i\ (e^{kT})$

K=ln(2)/DT

e is universal growth constant $e=(1+1/n)^n$ as $n\rightarrow\infty$ (or about 2.718)

ln2 is natural log of 2 or about 0.693

T is time elapsed

V_f and V_i are final and initial volumes

Solve for DT

- With the calculator supplied by Windows OS one can actually solve these equations, if so inclined

Back to Our Case…

- What information can be gleaned by knowing the DT is 268 days?
  - This DT is quite slow for lung cancers
  - There is a literature which relates survivability of lung cancer to doubling time: if the DT is > 5 months, this results in better survival. What does this information tell us about the curability of the cancer given that the patient developed brain metastases 26.5 months later?

Relationship of Growth Rate of the Primary Tumor to that of the Metastases

- In general metastases grow 1.5-3 x faster than the primary from which they arose
- Sample data follow from Spratt et al.
- Not an area of contemporary investigation
- Data tend to be decades old and based on small numbers

Relation of Growth Rate of Metastatic Tumor to that of the Primary

TABLE I. Rates of Growth of Pulmonary Metastases as Observed on Thoracic Roentgenograms*

Type of cancer	No. cancers	Mean (natural log)	SD (natural log)	Doubling times (days)			Exponential growth constant (b) equivalent to doubling times		
				Mean	95% Range	99% Range	Mean	95% Range	99% Range
Epidermoid	21	3.83819	0.93068	46	7–298	3–750	0.0151	0.0023–0.0990	0.0009–0.2311
Testicular	10	3.88130	0.77827	48	10–230	5–501	0.0103	0.0007–0.0533	0.0001–0.1386
Colon and rectum	10	4.68811	1.24431	109	9–1,300	3–4,540	0.0064	0.0005–0.0770	0.0002–0.2311
Osseous and soft tissue sarcomas	23	3.74191	1.04420	42	5–340	2–967	0.0064	0.0020–0.1386	0.0007–0.3466
Breast	29	4.41117	0.82199	82	16–426	7–969	0.0085	0.0015–0.0433	0.0007–0.0990
Adenocarcinomas, other sites	13	4.62337	0.97566	102	14–716	5–1,900	0.0068	0.0009–0.0495	0.0004–0.1386
All others	12	4.06197	1.09587	58	6–519	2–1,560	0.0120	0.0013–0.1155	0.0004–0.3466
Totals	118	4.17432	1.03269	65	8–512	3–1,440	0.0107	0.0013–0.0866	0.0005–0.2311

* Adapted with permission from Table 1, p 166, from Spratt JS and Spratt TL [1].

TABLE II. Rates of Growth of Primary Pulmonary Cancers as Observed on Thoracic Roentgenograms*

Type of cancer	No. cancers	Mean (natural log)	SD (natural log)	Doubling times (days)			Exponential growth constant (b) equivalent to doubling times		
				Mean	95% Range	99% Range	Mean	95% Range	99% Range
Adenocarcinoma	8	4.77652	1.11437	118	13–1,100	1–3,360	0.0055	0.0006–0.0533	0.0002–0.1733
Epidermoid	13	4.24818	0.60070	70	21–233	12–424	0.0099	0.0028–0.0330	0.0015–0.0578
Undifferentiated	13	4.53033	0.66828	93	24–353	13–689	0.0075	0.0019–0.0289	0.0010–0.0533
Total all lung cancer	34	4.48038	0.80195	88	18–439	8–979	0.0079	0.0015–0.0385	0.0007–0.0866

* Adapted with permission from Table 1, p 166, from Spratt JS and Spratt TL [1].

Spratt et al *J. Surg Oncol* 61:68-83, 1996

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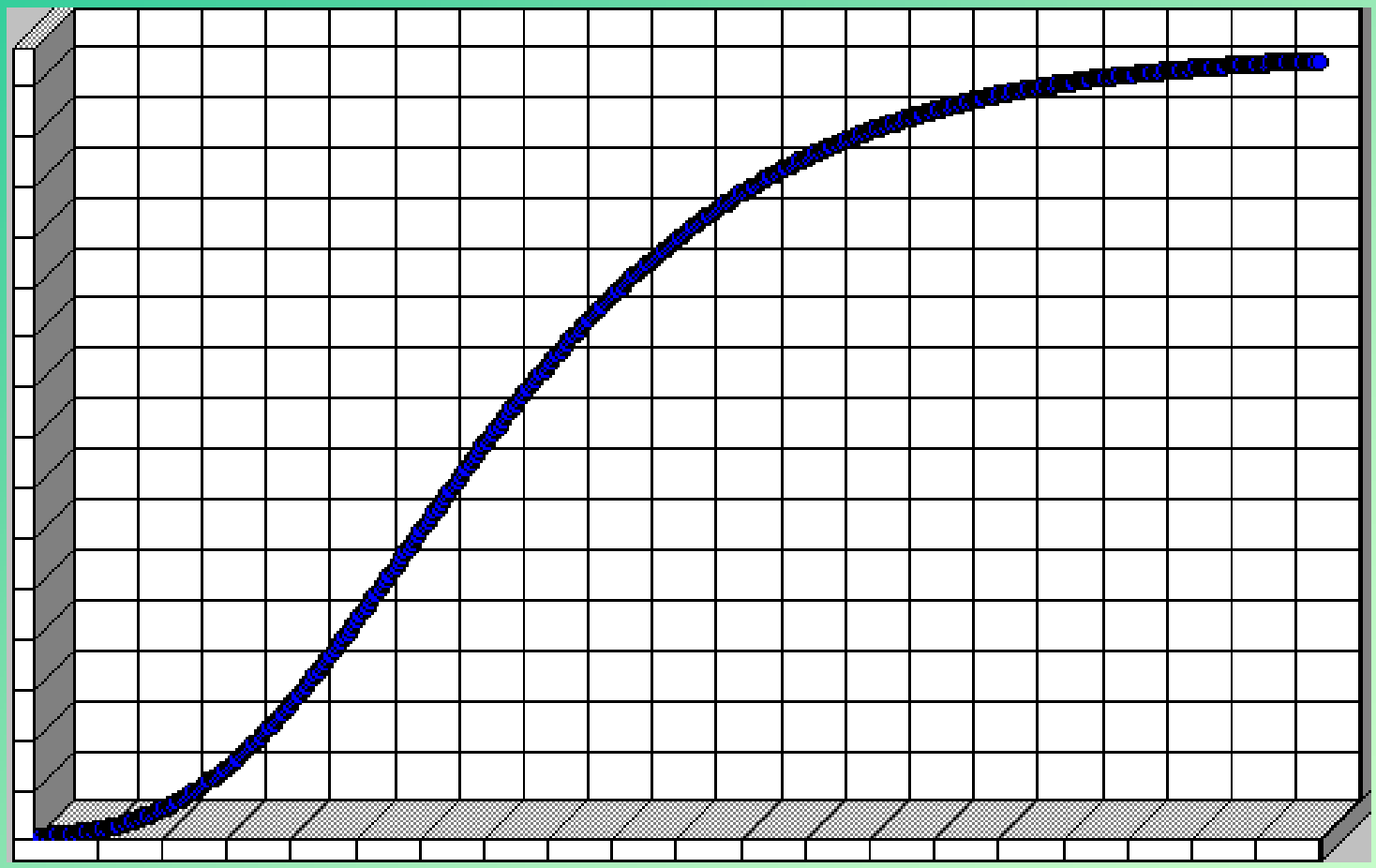
Relationship of Growth Rate of the Primary Tumor to that of the Metastases

- Key concept: in order to go back in time to see how fast the brain metastases were growing at their inception one needs to use a different mathematical model:
- GOMPERTZIAN KINETICS

Gompertzian Kinetics Elucidated

- Basic concept: cancers grow very rapidly when very small (a few cells) and slow down as they get larger, presumably because their nutritional demands cannot be met through inadequate blood supply and oxygen
- The growth curve therefore flattens out as the tumor gets bigger

The sigmoid growth curve of Gompertzian kinetics



Log Tumor volume

Time elapsed

From, Stark JJ *Defense Counsel Journal 65:*277-84, 1998

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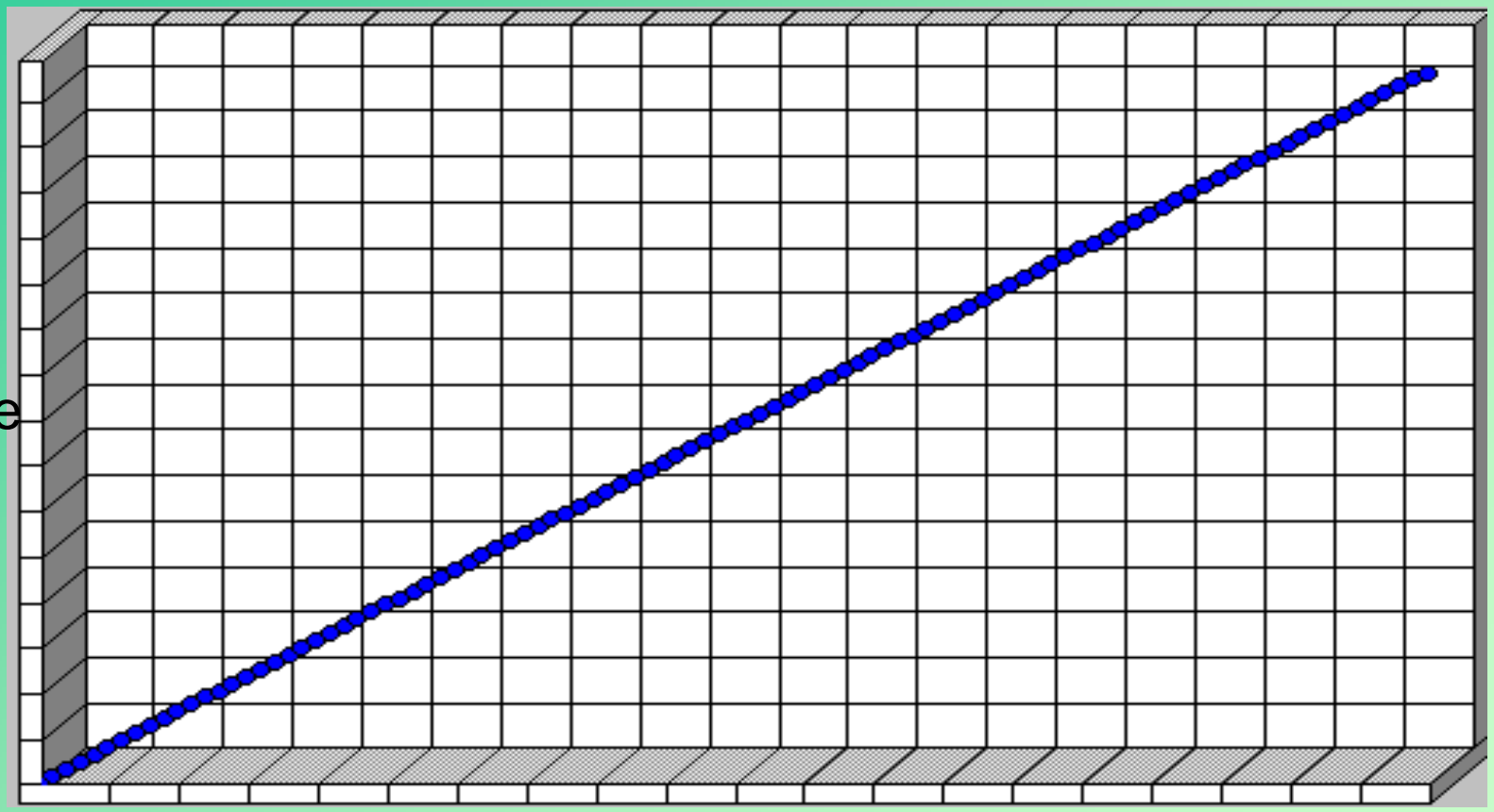
Exponential Kinetics



Log tumor volume

Time elapsed

What are the consequences of which growth model is used?

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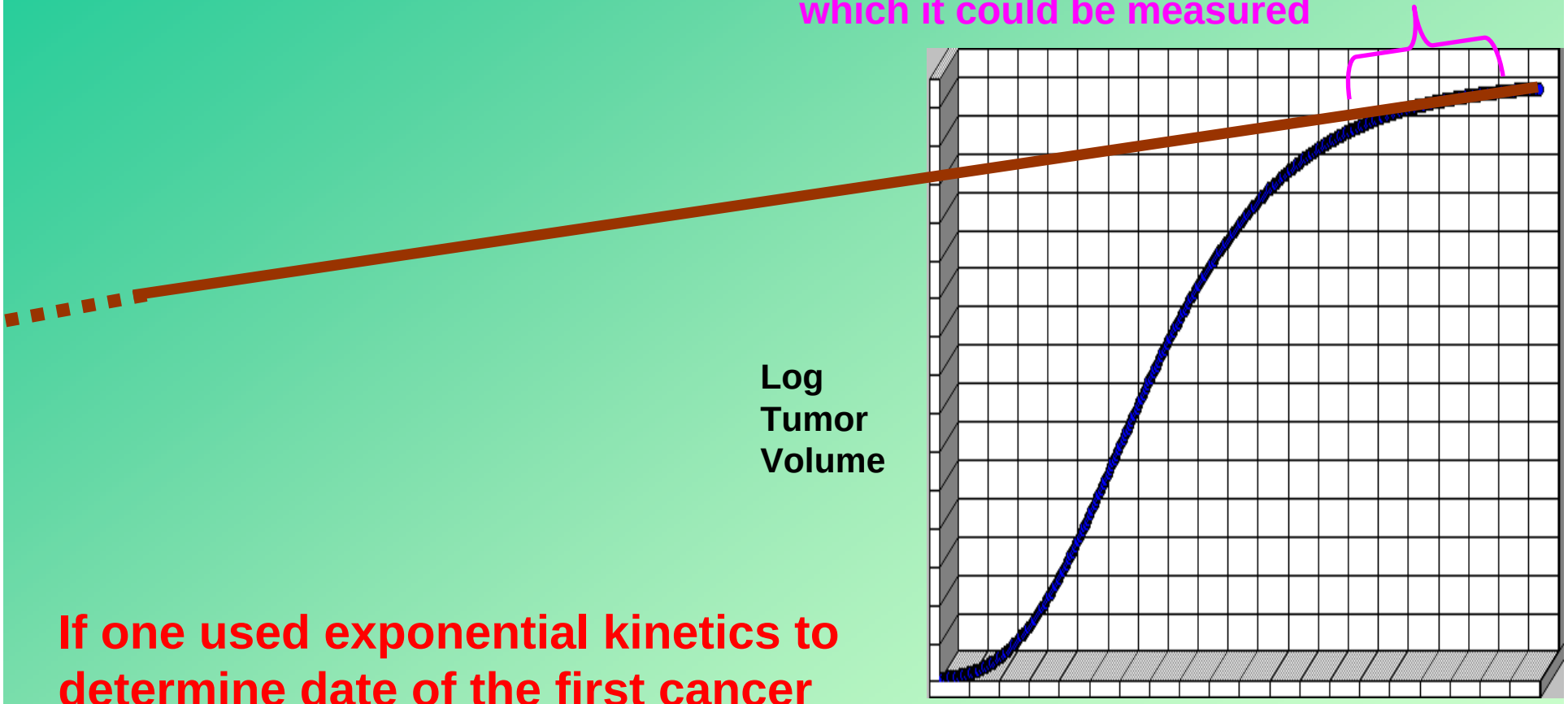
Gompertzian vs. Exponential Models, continued

- Substantial animal experimental and some human data support use of Gompertzian model to describe tumor growth from inception of cancer
- Hard to explain to juries..arguably the purview of the expert witness
- Use of exponential model to describe growth of metastases makes most cancers incurable no matter when diagnosed
  - Lopsided and inaccurate view of the real world

Comparison of Gompertzian and Exponential Kinetics

Growth of brain metastasis over time in which it could be measured



If one used exponential kinetics to determine date of the first cancer cell in the brain, the answer would be absurd…perhaps before the patient was born.

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Back to our case…

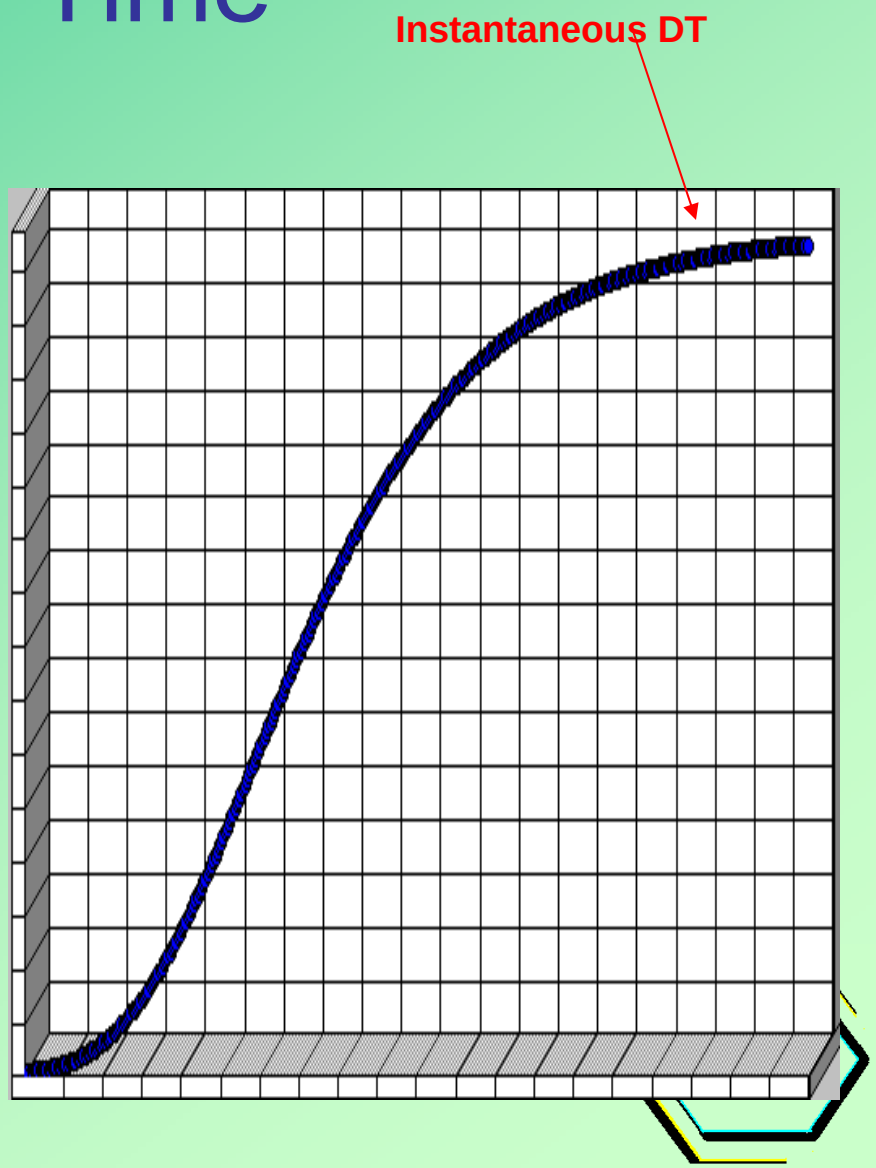
- Where we stand:
  - Slow growing asymptomatic lung cancer – good news for the plaintiff
  - Based on large published surgical series (not cited herein) a 3 cm lung cancer with negative lymph nodes at surgery is associated with a 55-60% cure rate
  - Brain metastasis diagnosed 26.5 months later; 0.8 cm in diameter

The Big Question

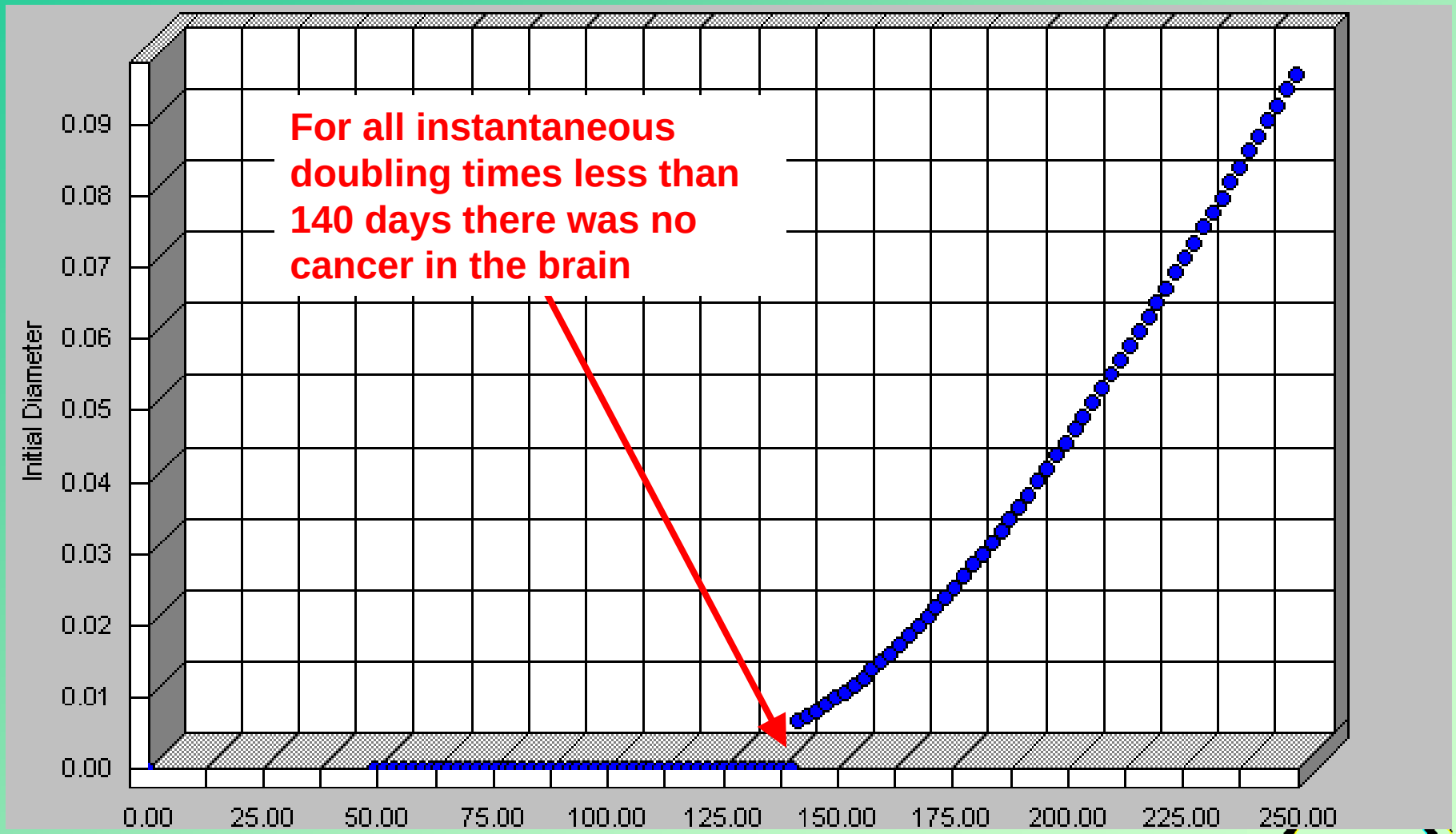
- Were there cancer cells in the brain at the time of the first X-ray?
- Using Gompertzian kinetics one can try to answer the question
- Solve the Gompertzian equation for the size of the brain lesion in January, 2005 using a range of possible doubling times knowing the growth rate of the primary…

The Concept of Instantaneous Doubling Time

- Doubling time using GK is constantly changing
- For purposes of calculations “DT” herein means instantaneous DT at time of discovery when growth has slowed down



Initial diameter vs. doubling time over the likely range of doubling times – Gompertzian kinetics



Actual calculations and graphics done with help of custom-designed software

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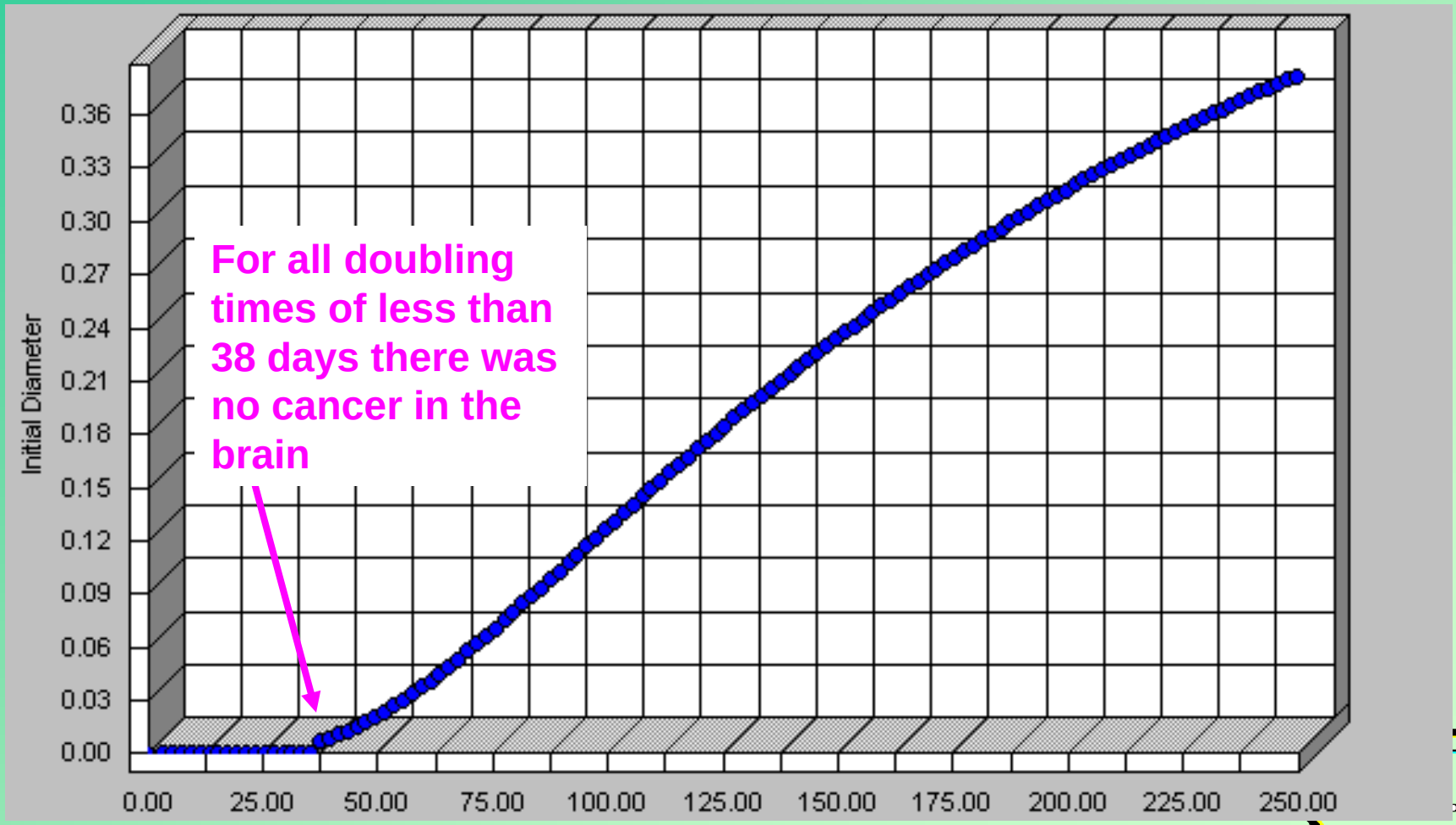
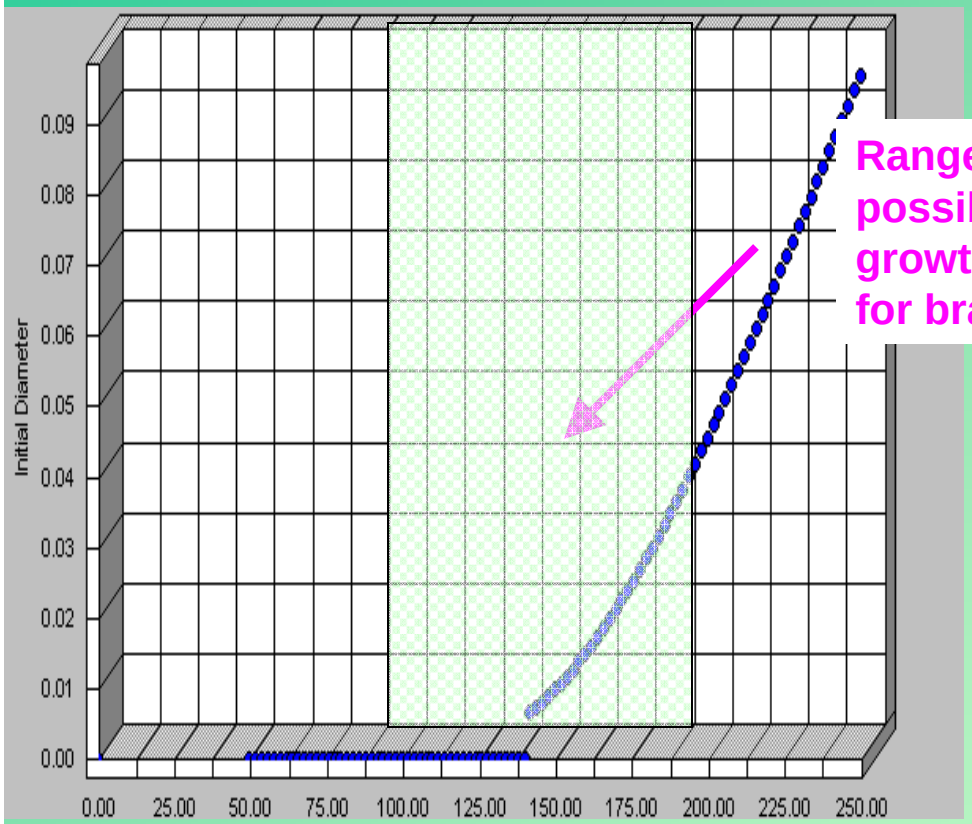
Initial diameter vs. doubling time over the likely range of doubling times – Exponential kinetics



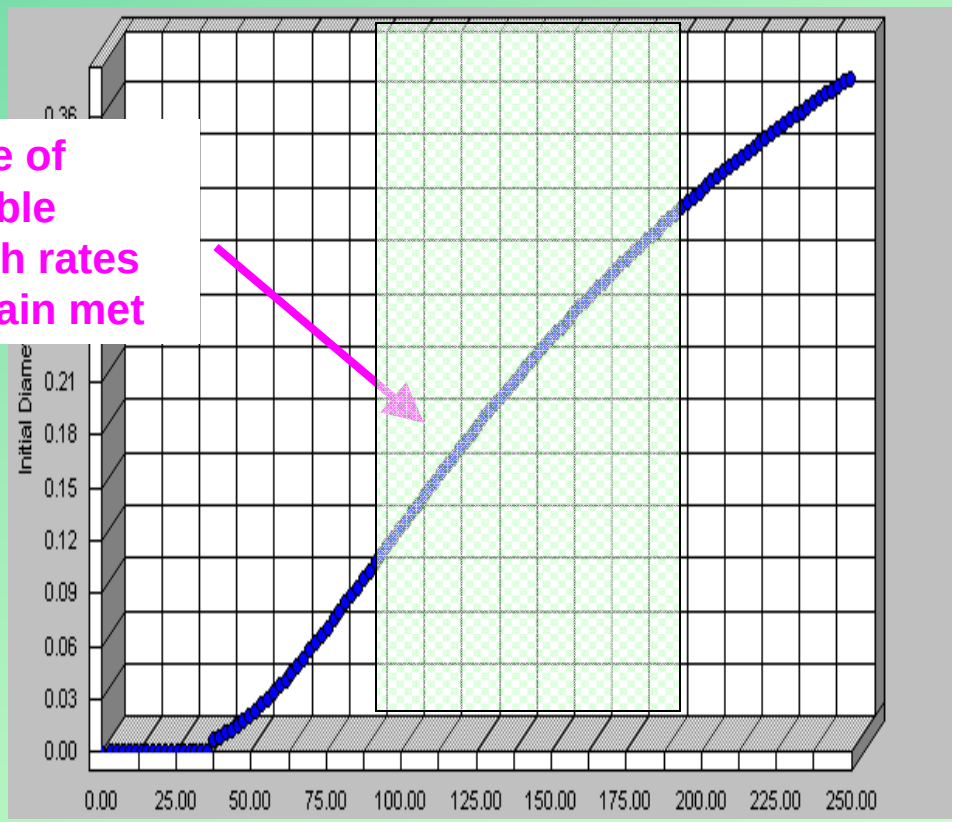
Continuing the analysis…

- Given the doubling time of the primary tumor (268 days) the likely doubling time of the metastatic lesion is 90 to 180 days
- Using Gompertzian kinetics it is reasonable to conclude that over most of the above range there was no tumor in the brain
- Using Exponential kinetics there was tumor in the brain over this entire range

Side-by-side comparison of both mathematical models



Range of possible growth rates for brain met



Gompertzian Kinetics

Exponential Kinetics

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Further Analysis

- If you are representing the injured party you could prevail in this argument, i.e., the brain was potentially cancer free at the time of the first X-ray
- If you use the Exponential model you lose the argument
- Based on existing human and animal experimental data the Gompertzian model is the proper one to use
- It is common, however, for defense attorneys to hire experts who use the Exponential model and try to argue using this reasoning that most cancers were never curable

Further refinement of discussion of this case

- Clearly for the Exponential model the defense wins the proximate cause argument
- For the Gompertzian model it may be important what local law says about burden of proof
- If in this case one has to show a >50% chance of survival it is a close call
- If all one has to show is a substantial possibility of survival (or similar language) the plaintiff wins

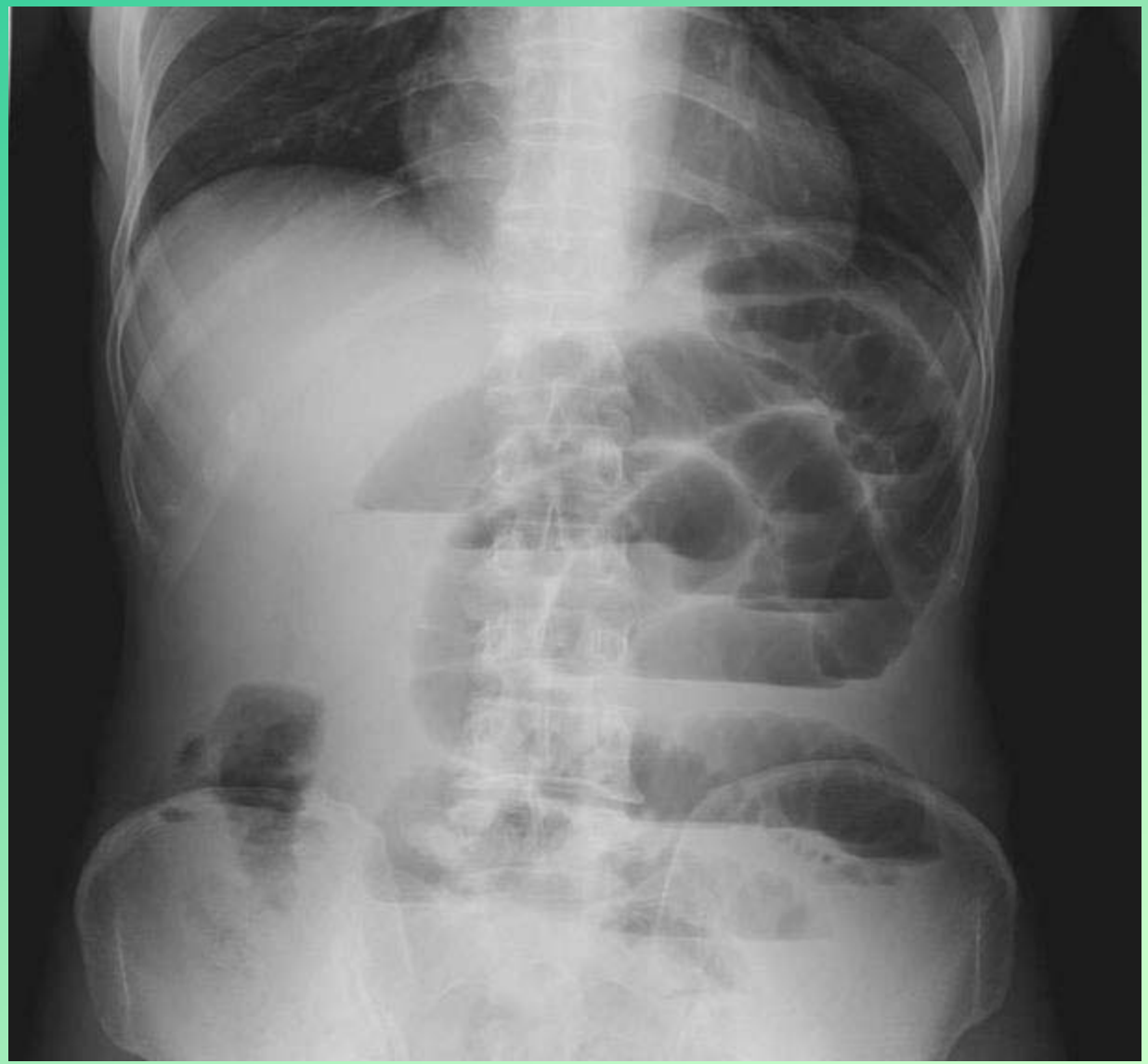
Refinements, continued

- Other cases with other numbers can yield a variety of results
- From my perspective as an expert the numbers are the numbers and I cannot always carve out a winning argument for the attorney I am advising
- When the numbers work, using appropriate visual aids I can make a powerful argument for presence or absence of metastatic disease for any moment in time

Failure to screen meets Gompertzian Kinetics: Case #2

- 58 y.o. man enters the hospital via the ED with crampy abdominal pain
- Anemic: H/H 8/30 MCV 72 platelets 585,000
  - Ferritin 8; Fe/TIBC 15/400
  - Stool hemoccult positive
- Picture of bowel obstruction on x-rays

Small Bowel Obstruction



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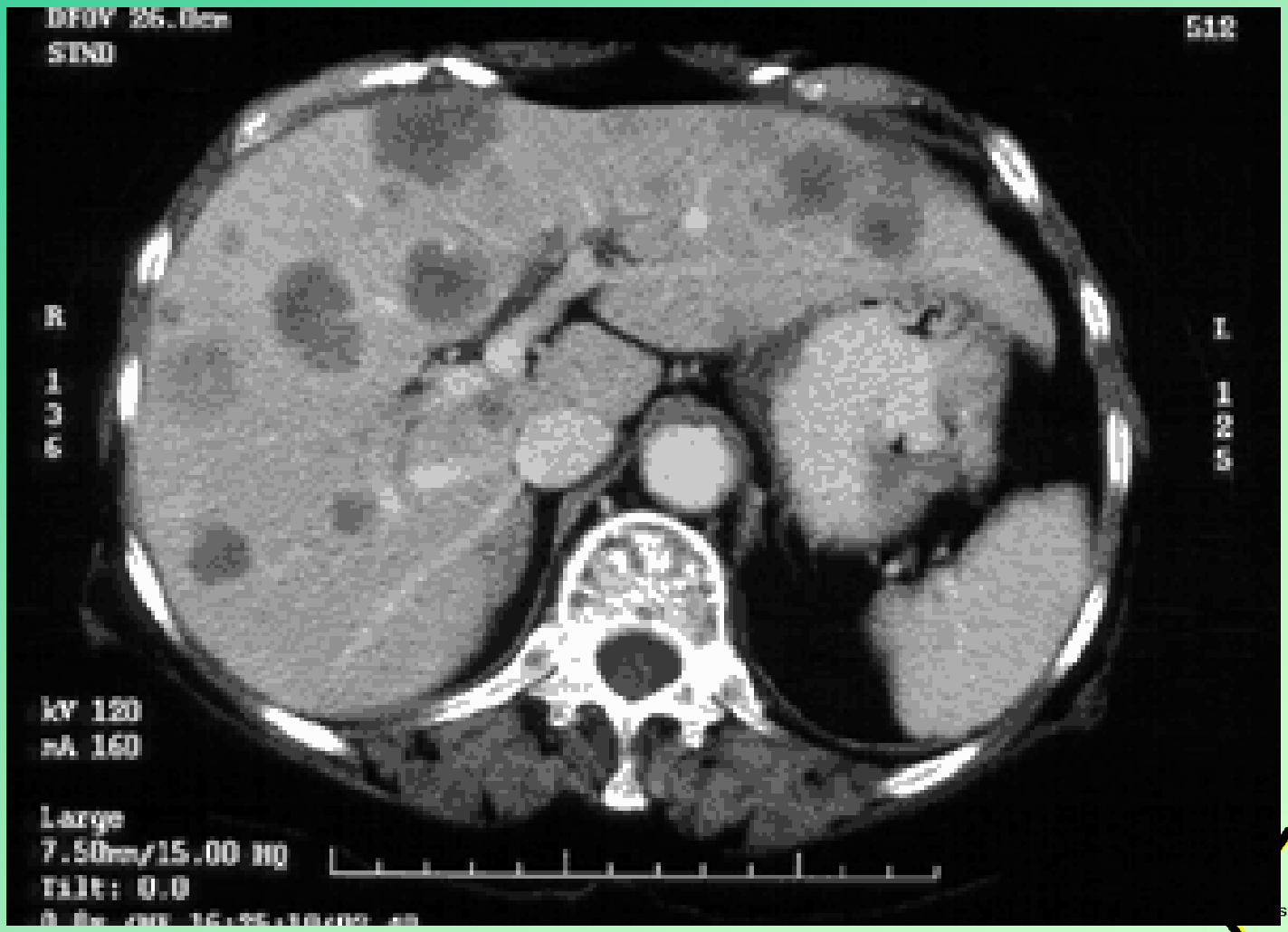
Failure to screen meets Gompertzian Kinetics: Case #2

- Further work-up reveals obstructing cancer of hepatic flexure
- Semi-urgent cecostomy performed to decompress bowel
- Several days later definitive surgery done…

Case #2, continued

- At laporotomy large cancer of hepatic flexure is encountered with impending perforation
- Numerous metastatic lesions in liver and omentum discovered; largest is 3 cm

Numerous Liver Metastases; largest 3 cm



Case #2, continued

- Palliative resection of primary tumor performed
- No resection of liver metastases feasible
- Post-operatively patient started on chemotherapy; lives for 22 months, dies of metastatic disease
- **Before death, patient sues PCP for failing to initiate colorectal screening at age 50; estate carries on with suit after his death**

The Lawsuit

- Claim states that if screening had been initiated at age 50, tumor would have been found while it was still polyp or at a stage when much smaller cancer and metastases would have been prevented
- Issues to discuss in analyzing physician's potential exposure is whether earlier diagnosis would have made a difference, and…
  - Frequency of screening of asymptomatic individuals in general population (i.e., does failure to screen constitute negligence?)
  - Likelihood of finding lesion even if appropriate guidelines had been followed
  - Value of the early detection of colorectal cancer in the prevention of excess mortality in this case and in general

Taking a Step Back: Basics of cancer screening

- Disease must be common
- Patient must be asymptomatic for disease being screened or event is not true “screening”
- Screening test must be safe, cost-effective (defined in societal terms: cost/life saved; what society will bear as burden) and have high sensitivity (few false negatives; false positive rate may increase with enhanced sensitivity)
- Outcome of disease screened must be altered by early detection

Screening basics, cont.

- Above considerations rule out screening for such things as cancer of pancreas, brain tumors and, probably, lung cancer
- With colon cancer, slow growth rate and long premalignant (i.e., adenomatous polyp) phase make argument for screening most compelling among all diseases commonly screened (along with cancer of cervix)

Fundamentals of Colorectal Screening (to be presented in detail later in morning)

- Everyone over the age of 50
- People at high risk should be started at earlier age (e.g., familial syndromes)
- Screening itself involves *at least*:
  - Episodic flexible sigmoidoscopy
  - Annual stool hemoccults X 3 on meat-free high residue diet
  - Guidelines do vary a bit among various bodies that set the standards (e.g., American College of Surgeons vs. American Cancer Society vs. American College of Physicians)

National Data on CRC Screening Compliance

- Year 2000 survey conducted by National Center for Health Statistics, branch of CDC
- Household response rate 72.1%
- Some of these people had no regular health care (percentage not specified in report)
- Database of 11,800 respondents
- Results….

Seeff et al *CANCER 100:*2093, 2004

Results of CRC Screening Survey

- Home FOBT screening: 36%
  - 88% were true screening events; rest for symptoms
- 38% for endoscopy
  - Only 61% were true screening events
- 54% for either one even though some of these people did not have a regular primary-care physician; not all were true screening events: some done for symptoms

Best recent data on compliance

- Very large study from 1340 PCP's in managed care plan in California
- Looked at practice patterns in 1999-2000
- Utilized detailed questionnaires in retrospective look at practice patterns among average risk patients > 50 y.o.
- High return rate on questionnaires
- Results…..

Dulai et al *CANCER 100:*1843,2004

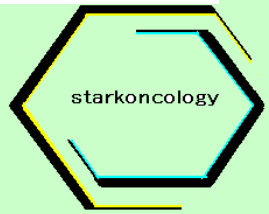
Compliance* for various colorectal screening tests
(based on physician's recall)

Test type	Median (IQR) % of patients to whom test was recommended	% of patients who followed screening recommendation	Most commonly recommended screening interval (yrs)
FOBT	90 (50–100)	70 (50–80)	1 (1–1)
FS	70 (30–90)	50 (30–75)	5 (3–5)
Barium enema	5 (0–20)	50 (10–80)	5 (5–5)
Colonoscopy	8 (0–30)	50 (10–90)	5 (5–10)

IQR: interquartile range; FOBT: fecal occult blood testing; FS: flexible sigmoidoscopy.

*i.e., 50th percentile physician recommended 90% of time

Therefore overall compliance is 63%



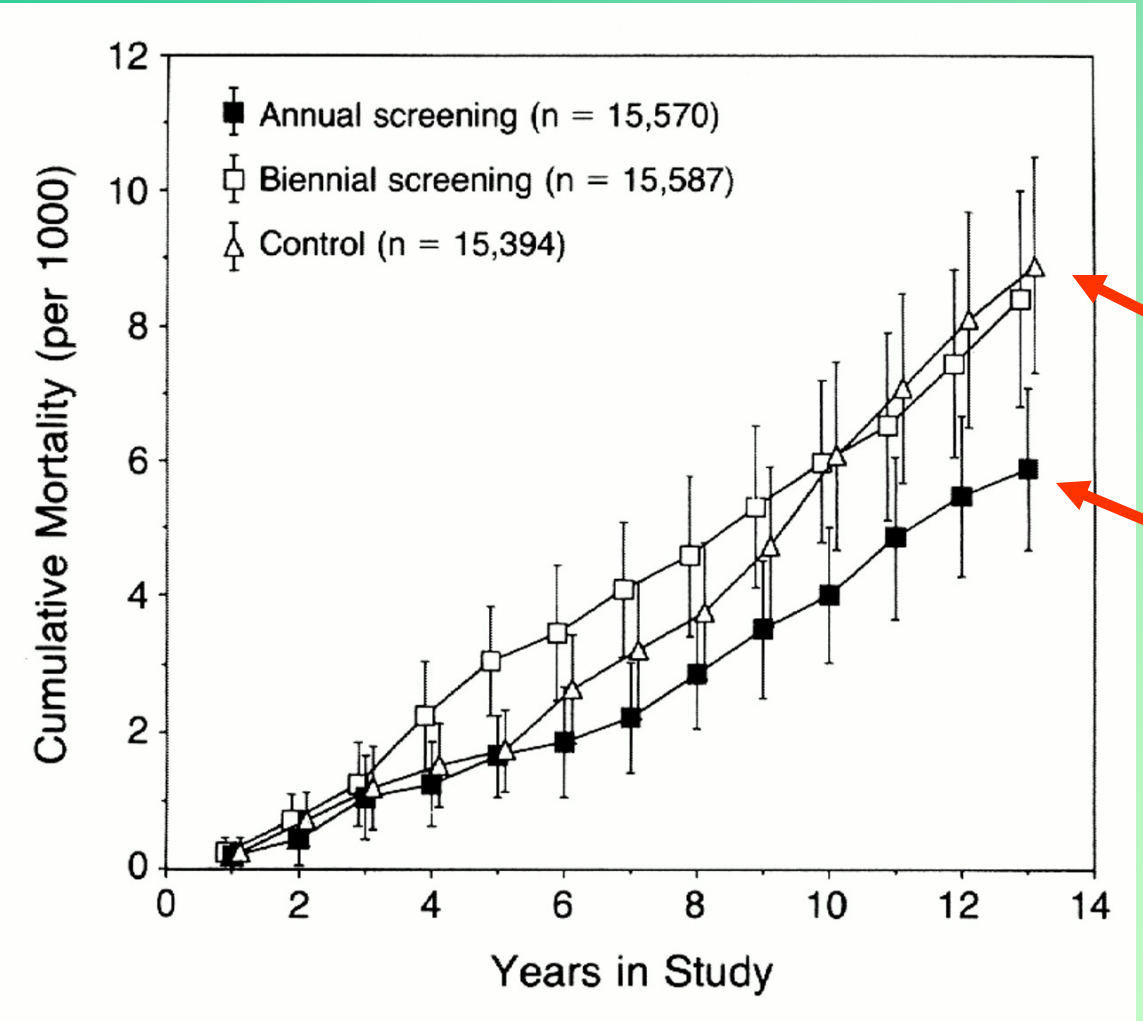
Evidence to Support CRC Screening

- Fecal occult blood testing: Three large studies show altered outcome for patients screened versus general population
  - The Göteborg Study
  - The English FOB trial
  - The Mandel US trial – best data, longest follow-up…

Mortality reduction from FOB screening

- Mandel study in *NEJM* shows dramatic reduction in mortality as a result of FOB testing
- 46,551 participants
- Screenings annual, or once every two years, or no screening
- Long follow-up…..

Cumulative Mortality from Colorectal Cancer, According to Study Group



Big difference between annual screening and none

Mandel, J. S. et. al. *N Engl J Med* 1993;328:1365-1371

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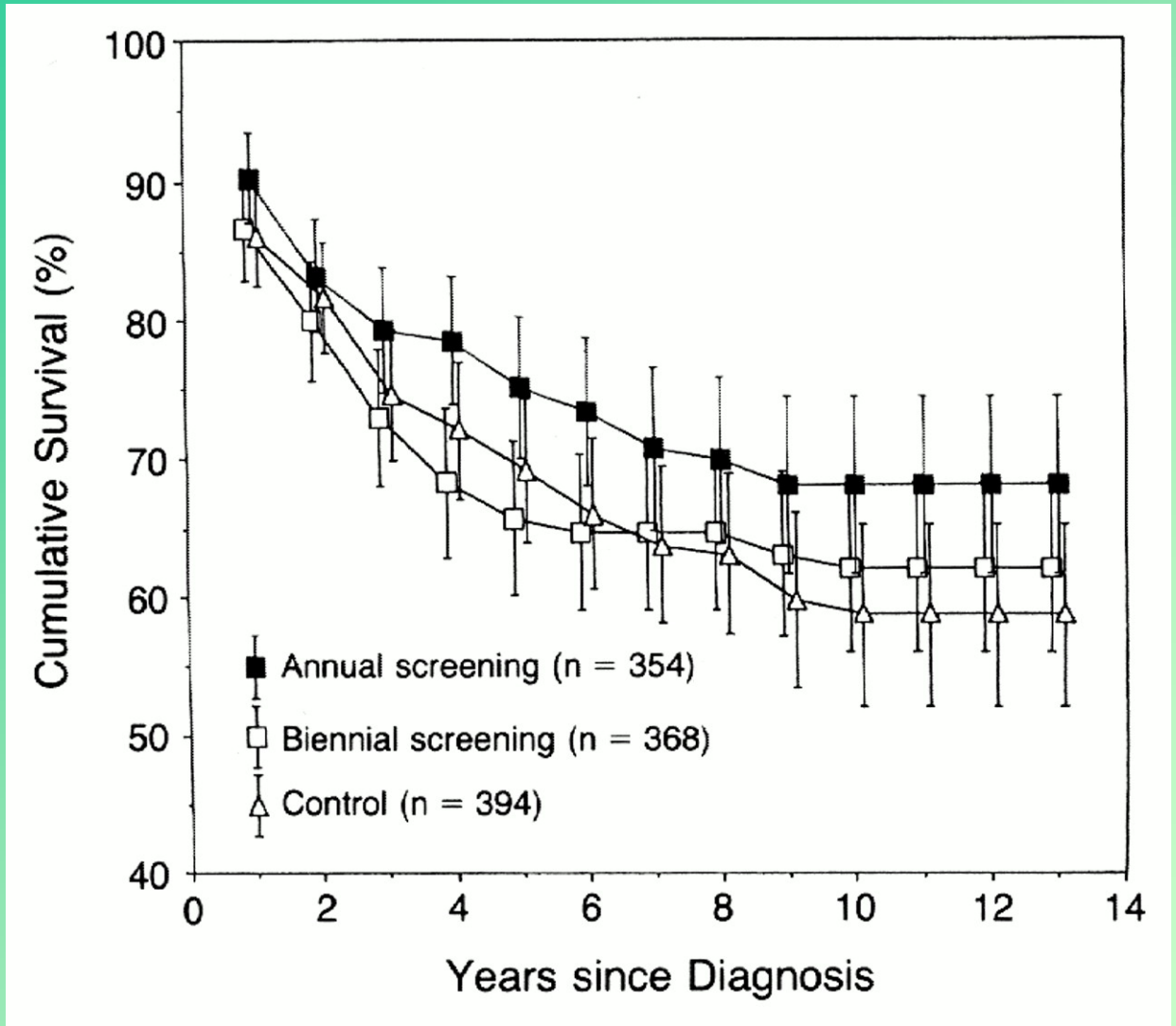
Cumulative Survival of Participants with Colorectal Cancer, According to Study Group



Mandel, J. S. et. al.

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CRC Screening: flexible sigmoidoscopy (SS)

- Best data from case-control study*
  - Not true randomization; compares screening in affected group vs. general population
- Looked at records of 261 Kaiser Permanente Medical Care Program enrollees in SF Bay area who died of colon cancer between 1971 and 1988
- 8.8% of the 261 had undergone SS in 10 years prior to diagnosis of cancer
- 868 age- and sex-matched non-cancer controls selected from their database (didn't use cancer survivors (!))
- 24.2% of Kaiser control enrollees had undergone SS in same period of time

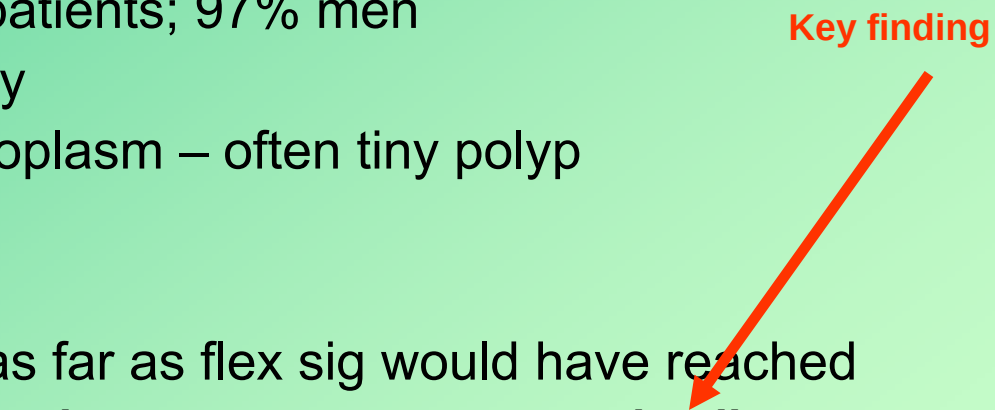
***Selby *NEJM 323*: 653, 1992**

Kaiser, continued

- Next looked at 268 patients dead of CRC with tumors beyond reach of SS
- Looked at 268 controls from Kaiser database
- No difference in frequency of SS between groups
- Conclusion: SS reduces mortality from CRC in that portion of colon seen with scope ($p<0.0001$); absence of change in mortality in proximal colon validates model

Role of Colonoscopy in CRC screening

- As screening test poorly defined; no randomized trials; theoretically should be best; question is how much gain of information versus cost/morbidity
- VA Study* studied 17,732 patients; 97% men
- 3121 agreed to colonoscopy
- 37.5% had some sort of neoplasm – often tiny polyp
- Significant polyps in 9.5%
- Invasive cancer in 1%
- 1765 had negative exams as far as flex sig would have reached
  - **2.7 % of these had large polyps or cancer more proximally**
  - **52% of patients with proximal lesions had no distal lesions**
- Authors concluded that colonoscopy added value above and beyond flexible sigmoidoscopy



*Lieberman *NEJM 343:*162, 2000

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The Imperiale Study

- Looked at value of adding colonoscopy to screening sigmoidoscopy
- Screened 1994 asymptomatic adults (>50 y.o.) 1995-98 as part of elective screening program offered by single employer
- 97% success rate in getting to cecum
- Detailed results….

Imperiale, T. F. et al. N Engl J Med 2000;343:169-174

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Prevalence of Advanced Proximal Neoplasms According to the Distal Findings

Distal Finding	Total	Advanced Proximal Neoplasm		Adjusted Relative Risk (95% CI)†
	no. of patients (%)	no. of patients	% (95% CI)	
No polyp	1564 (78.4)	23	1.5 (0.9–2.1)	1.0
Hyperplastic polyp	201 (10.1)	8	4.0 (1.3–6.7)	2.6 (1.1–5.9)
Tubular adenoma	168 (8.4)	12	7.1 (3.3–11.0)	4.0 (1.9–8.3)
Advanced neoplasm	61 (3.1)	7	11.5 (3.4–19.5)	6.7 (3.2–16.6)

*An advanced neoplasm was defined as a polyp or polypoid lesion with villous features, a polyp or polypoid lesion with high-grade dysplasia, or cancer. CI denotes confidence interval.

†The relative risk was adjusted for age and sex. The group of patients with no distal polyps was the reference group.

Imperiale, T. F. et al. N Engl J Med 2000;343:169-174

?Magnitude of benefit of adding colonoscopy to negative flex sig

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Accuracy of Colonoscopy

- Previously thought to be Gold Standard
- Latest studies show 4-10% chance of missing polyp ≥ 5 mm; higher for smaller lesions
- Sites most likely missed are on proximal side of colonic fold and in the distal rectum
- Renewed interest in so-called flat lesions – about 10% of polyps; ways to recognize them in evolution
- Virtual colonoscopy has given us new tool to analyze accuracy of traditional colonoscopy
  - Virtual and optical colonoscopy each miss up to 10% of polyps, but different polyps from each other
- "Gold Standard" called into question

Pickhardt *Ann. Int. Med 141:352-9, 2004*

Summary of Colonoscopy Studies

- Studies show a likelihood of <3% that a colonoscopy will show significant pathology in the face of a negative flexible sigmoidoscopy
- Colonoscopy is not the Gold Standard previously assumed; up to 10% error rate for small polyps surprising and disturbing
- Error rate creates some confusion about value of procedure
- Whether, all things considered, data are compelling enough to support colonoscopy as screening test is unclear
- Colonoscopy probably not yet “standard of care” for colorectal cancer screening in the average-risk adult

Colorectal screening: conclusions

- Recommendations still call for all patients over age 50 to be screened
  - Data strongly support role of FOB testing
  - Sigmoidoscopy data less compelling but still positive
  - Colonoscopy data in evolution; makes sense but little cost-benefit outcomes data to support routine use
  - “Gold Standard” only 90% accurate
  - Current guidelines support use of FOB plus endoscopy of some sort
- Absence of plan for screening for CRC is beneath the standard of care

What about our patient?

- Based on compliance data presented it is conceivable to construct a defense that screening is not the *de facto* standard of care but impossible to show that it does not affect the outcome
- Data on outcome with screening make argument for screening compelling
- Remaining questions for *this* malpractice claim: how long had cancer been present and diagnosable; did he have metastatic disease when cancer could have been found?

Growth Rate of Primary Colon Cancer: What is Known

- Slowest growing common adult malignancy
- Studies looking back at previous barium enemas (where cancer was missed!) suggest doubling in volume of tumor every one to two years
- Polyps probably present for many years before they undergo malignant degeneration and probably grow even more slowly than the tumor into which they evolve
- Therefore any cancer diagnosed by endoscopy or barium enema has probably been there and visible for many years, including period during which cancer was only a polyp

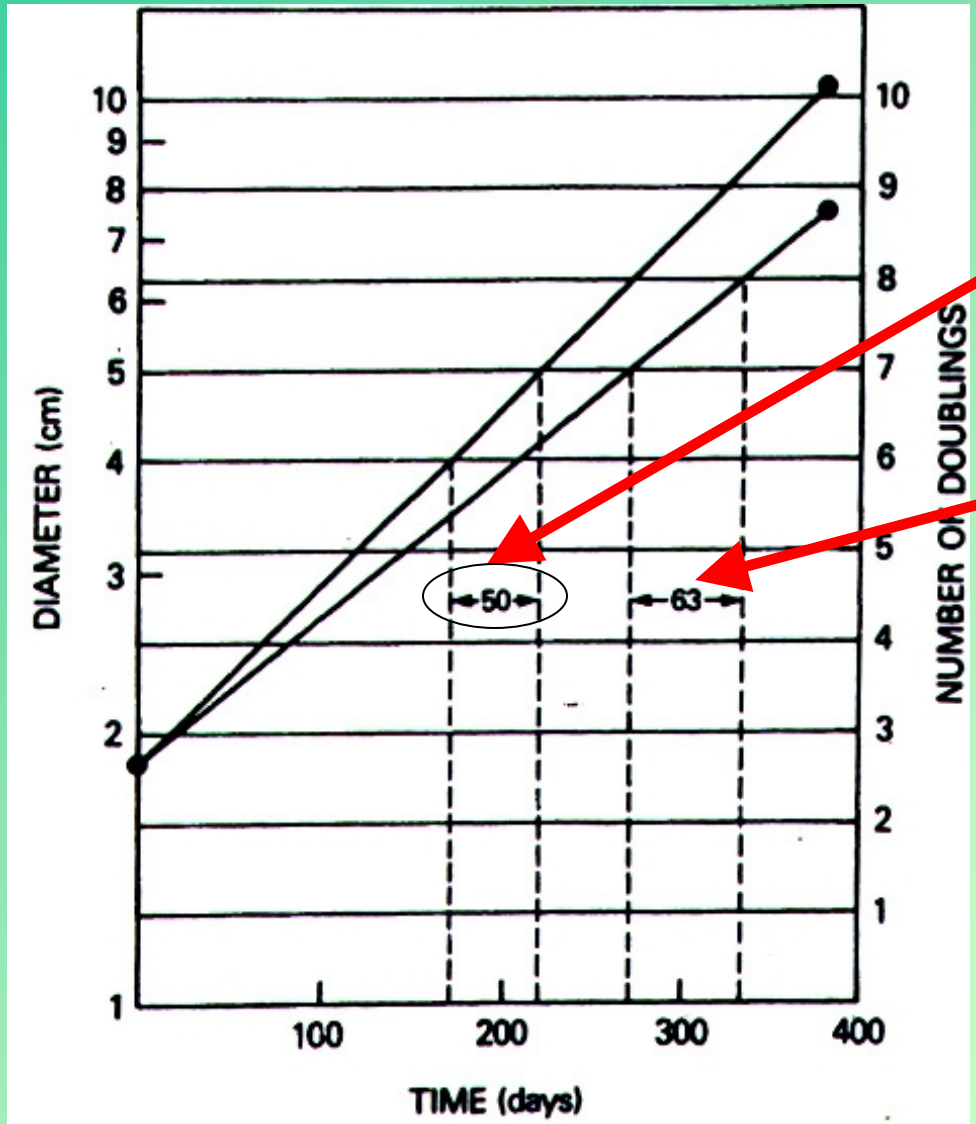
Growth Rate of Metastases: What is Known

- What is known: Havelaar and Finley studies
- At the time of diagnosis of metastasis instantaneous doubling time of metastases in untreated patients is between 40 and 150 days

Havelaar IJ et al *CANCER 54:* 163-171, 1984

Finley IG et al *Br. J. Surg 75:* 641-44, 1988

Calculation of doubling time of liver metastasis based on serial observations (exponential method) in untreated patients



Intervals of measurement prior to treatment

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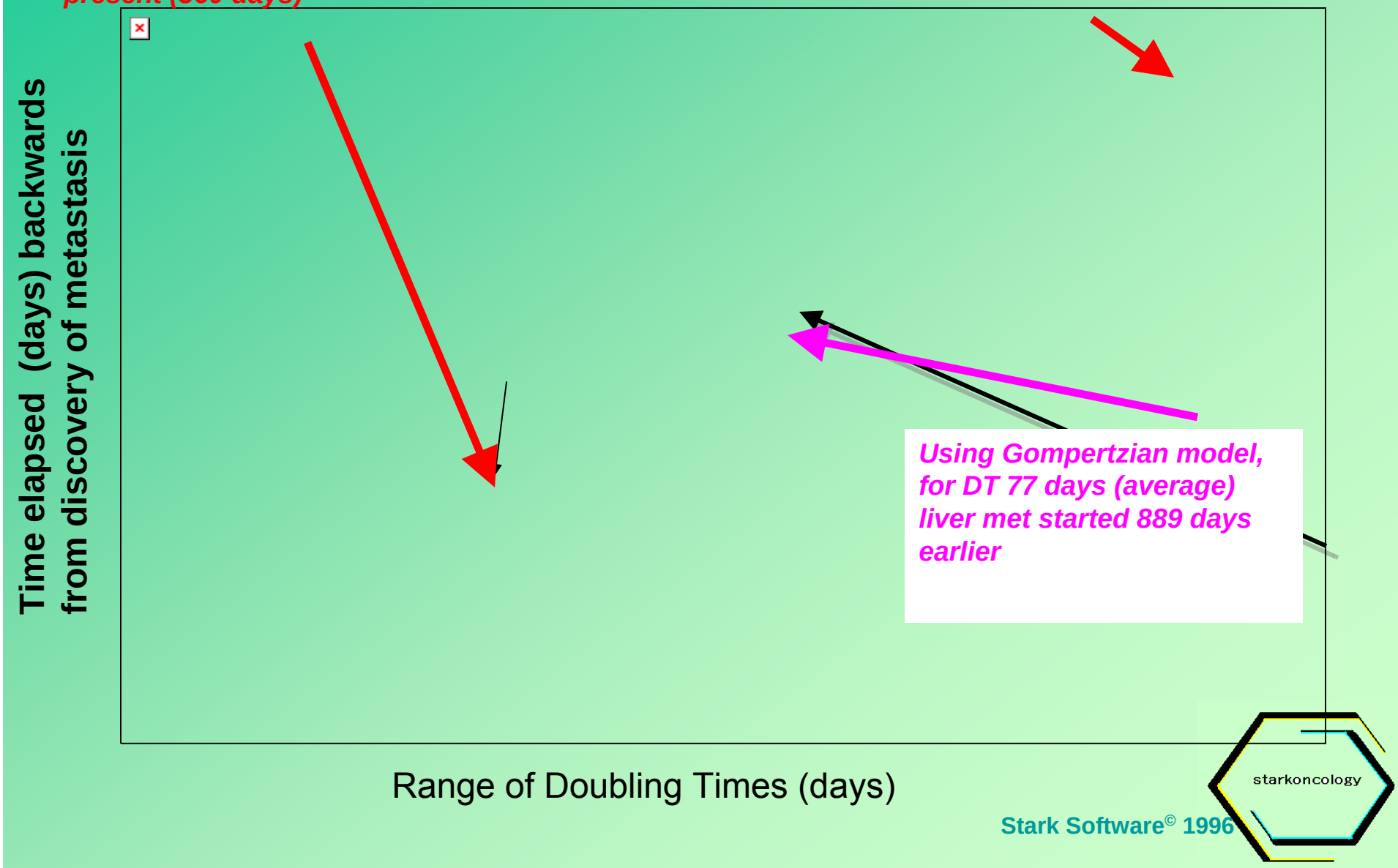
Havelaar IJ et al *CANCER 54: 163-171, 1984*

Start of 3 cm metastasis with Gompertzian model



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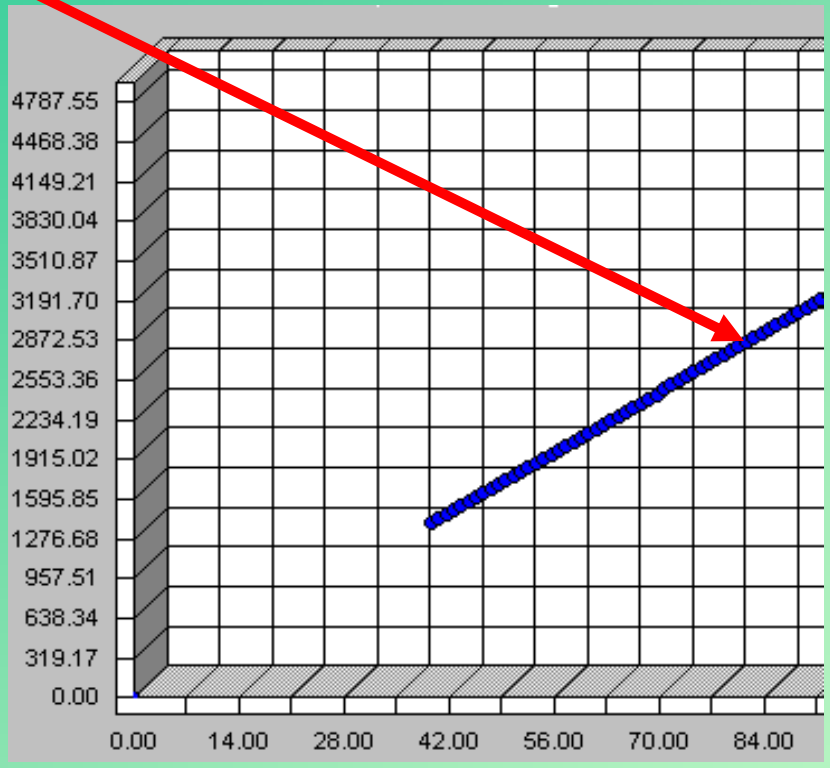
Comparison of two methods of calculating time backwards to initial cancer cell using DT of 77 days

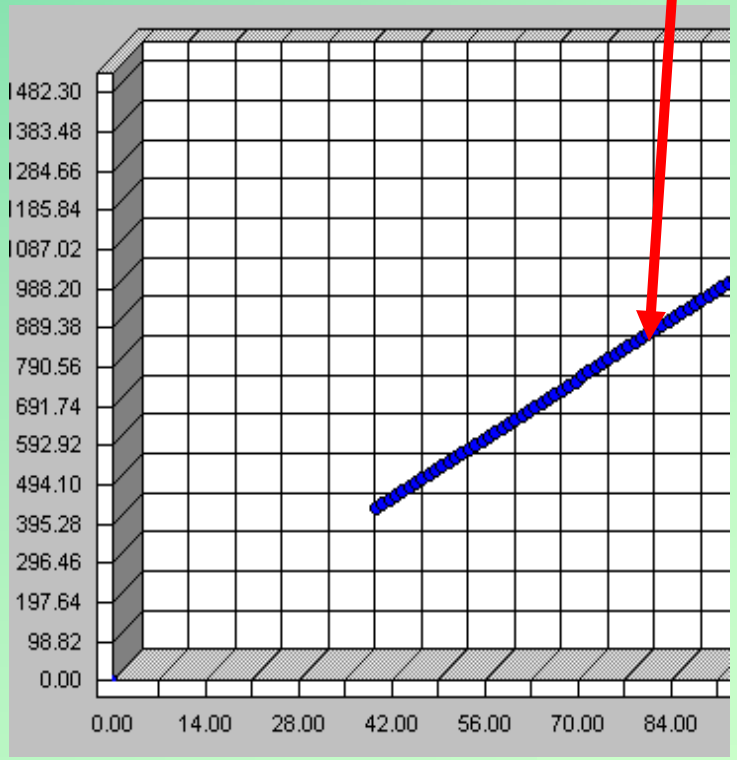
Metastasis started 2873 days earlier

Exponential



Metastasis started 889 days earlier

Gomptertzian



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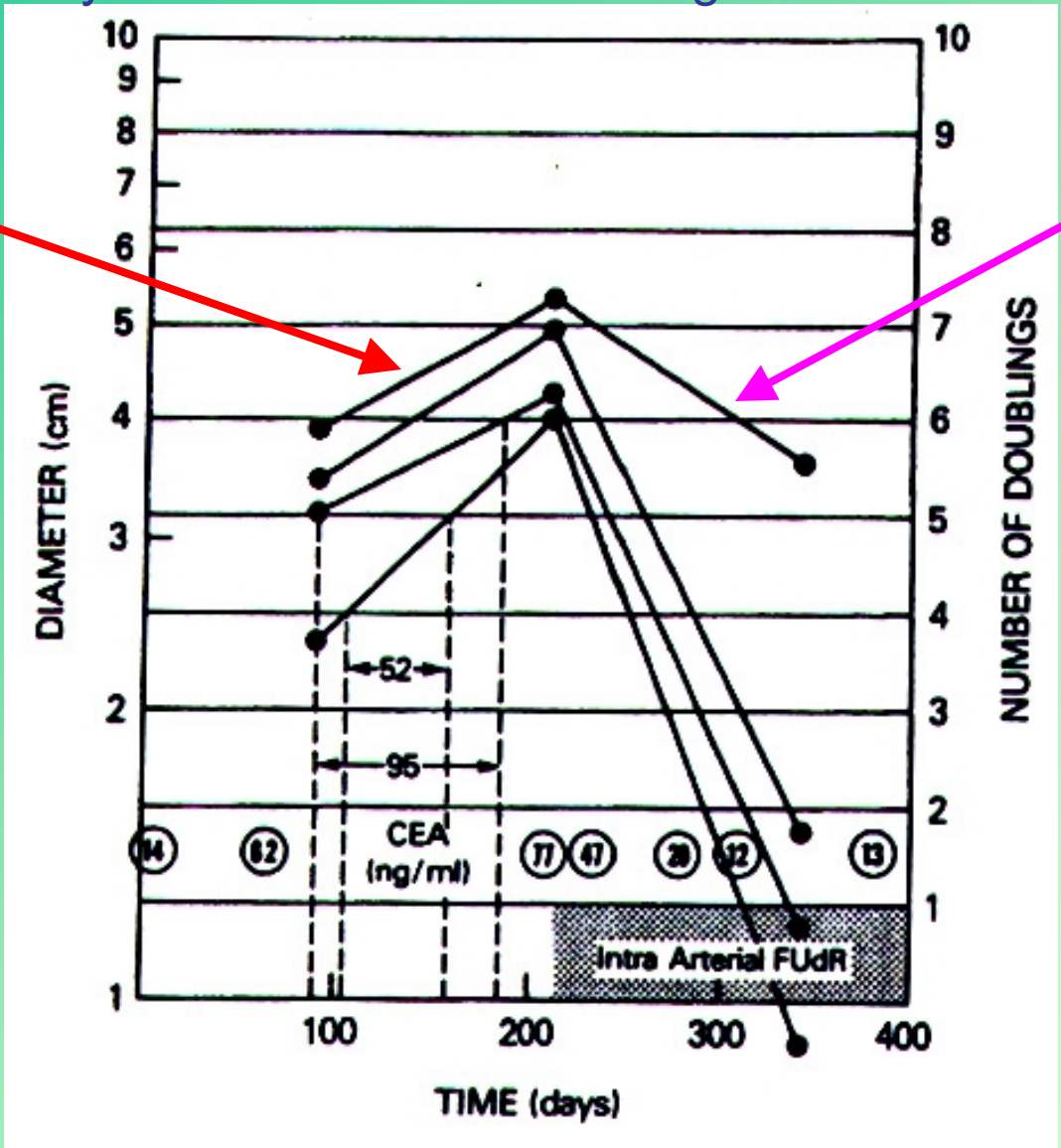
Conclusions regarding Case # 2

- Based on very slow growth rate of primary colon cancer and even slower growth rate of adenomatous polyp, diagnosable abnormality was likely present for many years
- Based on model of Gompertzian growth kinetics and literature on growth rate of metastases in colorectal cancer 3 cm (largest) metastasis had been present for between one and four years – probably not long enough for the defendant to prevail on argument of proximate cause

Impact of Chemotherapy on Growth of Intra-abdominal Metastases… or why these studies can no longer be carried out

Growth before chemotherapy (see also previous slide)

Growth after chemotherapy is started



Havelaar IJ et al *CANCER 54: 163-171, 1984*

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Conclusions

- Doubling time calculations of primary tumor and metastatic lesions can enable one to create a compelling argument for earlier curability if the numbers support the argument
- Doubling time can be used to confirm curability in situations where there was failure to screen for cancer