Logistically Modelling The Growth Rates of Different Cancer Types and Tumors

Meer Al-mufti

Abstract:

The unpredictability and eccentricity of cancer growth are issues that have not yet been resolved. With cancer being a personalized disease that stems from unique cell mutations, there are multiple types, and some grow faster than others. The purpose of this research project is to discover the most efficient way to track tumor growth using coded simulations and to discover how the growth trajectory can affect the course of treatment. A model was developed (ChatGPT only contributed to coding it) that compiles research from a variety of online medical resources and articles to project the likely growth trajectories for 10 different types of malignant tumors. This paper will discuss how and why the code works and what resources were used to develop accurate results.

Unpredictability and difficulty of treating cancer:

Since cancer is caused by a gene mutation, the ways that it chooses to present itself in patients in the form of growth rates may vary from person to person. Specifically, a mutation causes a growth advantage in cells, causing them to grow rapidly past cell checkpoints that maintain a cell's normal life cycle. Tumors are variable and can be affected by many implicit influences. This causes there to be multiple classifications of the disease based on location and cell type; however, quantitative factors like growth rate are still difficult to measure due to the biological variety of human bodies. Some bodies may be extremely susceptible to the disease due to age and health, while others may be aptly armed against it. However, all cancers follow the same steps. It all begins with cell mutations that cause a small tumor to appear. This small tumor, which has already grown past cell checkpoints, may use the nearby blood supply to grow further, possibly using the arteries as a passageway to metastasize to other locations. The immune system, being the body's natural defense force, fights back against the tumor, but without external aid eventually ceases to protect the body. The growth is sometimes extremely quick, and the immune system might fail to counteract its growth because some cancers can hide from the immune system due to various causes. This causes a necessity of therapy; however, targeting these cells is also difficult due to the fact that they have a similar biological makeup to healthy body cells, making it so healthy tissues get caught in the crossfire. Multiple different therapies exist, including chemotherapy, radiation treatment, hormonal treatment, and most recently, "cancer vaccines". Although there seem to be multiple different ways to treat tumors, a lot of them have crippling side effects, including heavy damage to the immune system and further cell mutation. In some cases, a tumor may gain an early beneficial mutation that

allows it to harness the body's hormones to boost its development. It may increase its blood supply by growing blood vessels, or remain undetected by immune defenses one way or another. Using hormone therapy to counteract this might also prove futile, as it can quickly abandon the need to be stimulated by hormones and grow through ongoing therapy. Overall, the mortality and rate of growth of the disease are unpredictable and affected by numerous factors, such as randomness and demographic differences

Mathematical overview of the model:

Tumor growth is defined by a period of swift replication followed by a plateau when blood flow to the tumor is insufficient to cause forward growth. However, during the first period, the growth is exponential as the rate of growth is determined by the amount of already existing tumors and is directly proportional to it. Mathematically, this growth rate can be represented as

$$\frac{DV}{dt} = kV$$

However, for large values of t, this formula fails to project a plateau period; thus, correction factors must be added to ensure it does. In the end, we get

$$\frac{DV}{dt} = kV(1 - \frac{V}{k})$$

Where K is the carrying capacity. solving the above differential equation with initial condition V(0)=O, we derive

$$V(t) = \frac{K}{1 + \left(\frac{K - O}{O}\right)e^{-kt}}$$

The model takes this function and scales the non-spatial variables k, O, and K to fit real-world growth trajectories of multiple cancers seen in various studies in different conditions.

Non-spatial variable determination:

The non-spatial variables determine how different cancer trajectories are made different. K represents the carrying capacity or maximum volume, O represents the original measured amount, and k represents the rate of growth. The variable K faces the most discrepancy with real life data, as the plateau volume for any one cancer is entirely dependant on multiple factors

that are too difficult to measure, hence average data from multiple studies is used to deduce K and each cancer type has its own value of K. O is an input variable, meaning that the user should measure the volume of the specified tumor and insert the measurement in place of O. And finally, k is the variable that is dependant on the most initial conditions. Due to the fact that the program maps multiple different functions with different values of k, the chance of k being large or small is dependent on provided variables such as age and hormone count.

Effects of testosterone and estrogen on K:

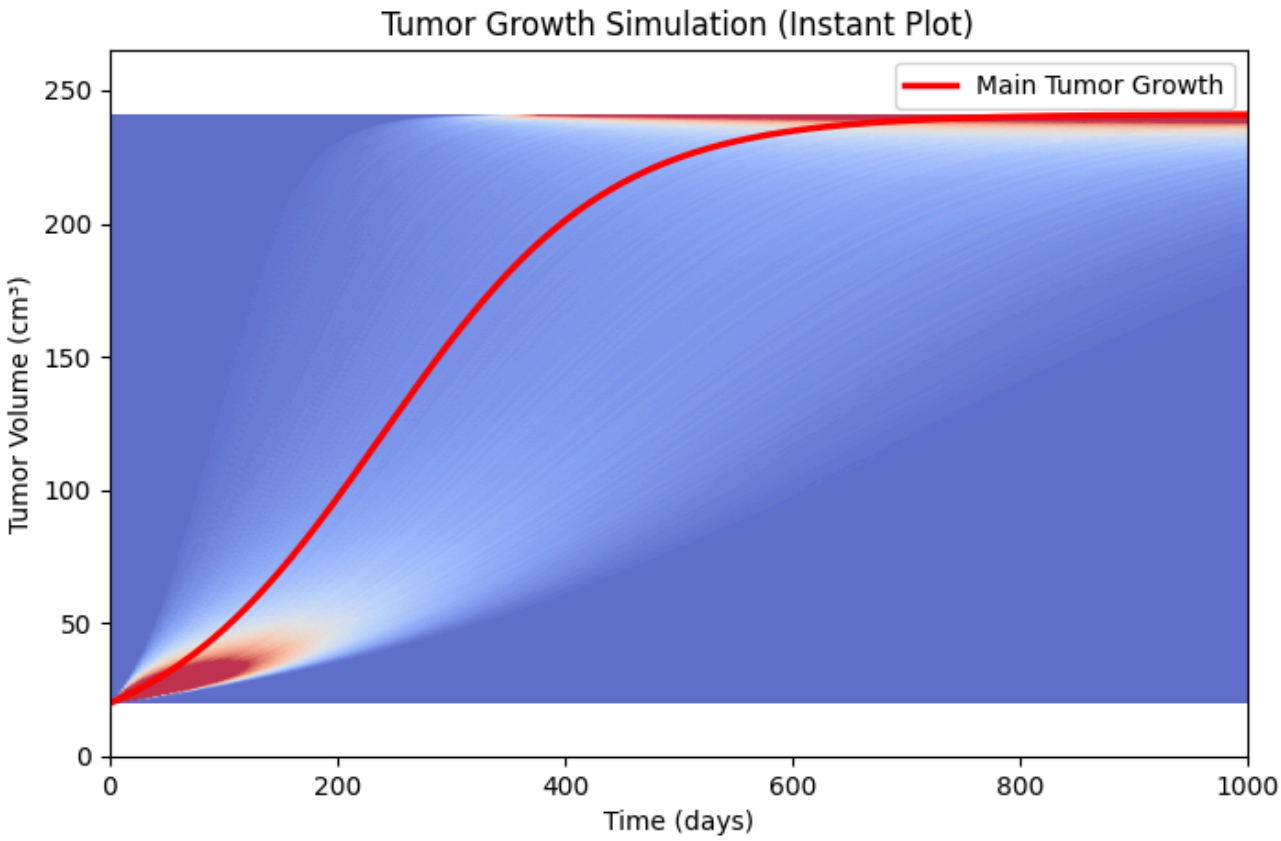
While in some cases testosterone may be used to treat or inhibit prostate cancer rates, it may very slightly contribute to the value of K, either causing an increase based on the cancer type. A study done by D D Ørsted found that high levels of plasma testosterone was associated with a 30-80 percent early death in cancer patients[9]. However, it only increases the rate of early death, not the likelihood of it presenting. It is well known that the level of estrogen can increase the growth rate of ER-positive breast cancer, and it does so more clearly than testosterone does with prostate cancer and other cancer types [10]. Therefore, the value of K is expected to take elevated values when testosterone is high and increase when estrogen is high, depending on the cancer type.

Effects of age on tumor development:

Age has a somewhat paradoxical relationship with tumor development. In mice, it has been reported that while older mice are more likely to fall ill to cancer, cancer grows faster in younger mice, probably due to the higher availability of resources in younger bodies. However, this only applies to some cancers, as other cancers grow faster in older bodies. Alternatively, an argument can be made that mutations in younger bodies are more severe as they cause advanced growth in a cell that isn't as damaged by mutations as cells in older people. Therefore, age should cause the value of K to tend towards more extreme values [1].

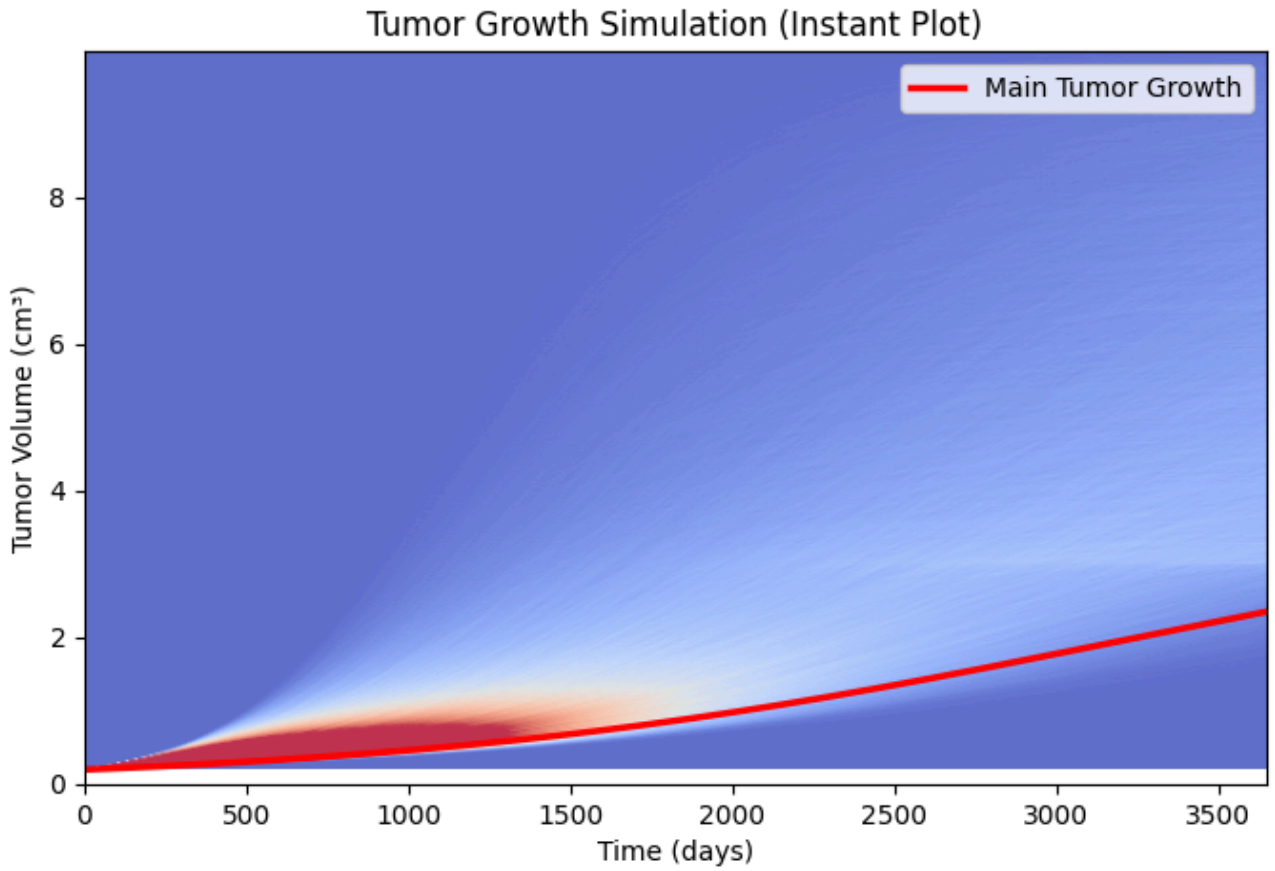
small cell lung cancer:

Grambow-Veilla et al. reported a tumor volume of 241 cm^3 in patients undergoing chemo-immunotherapy in progression-free survival [11]. K should also take values on the higher end, as SCLC progresses extremely quickly. It should also remain unaffected under varying estrogen and minimally change under testosterone, as it is unaffected and unresponsive to these hormones. The following figure and the rest have a set age of 45.



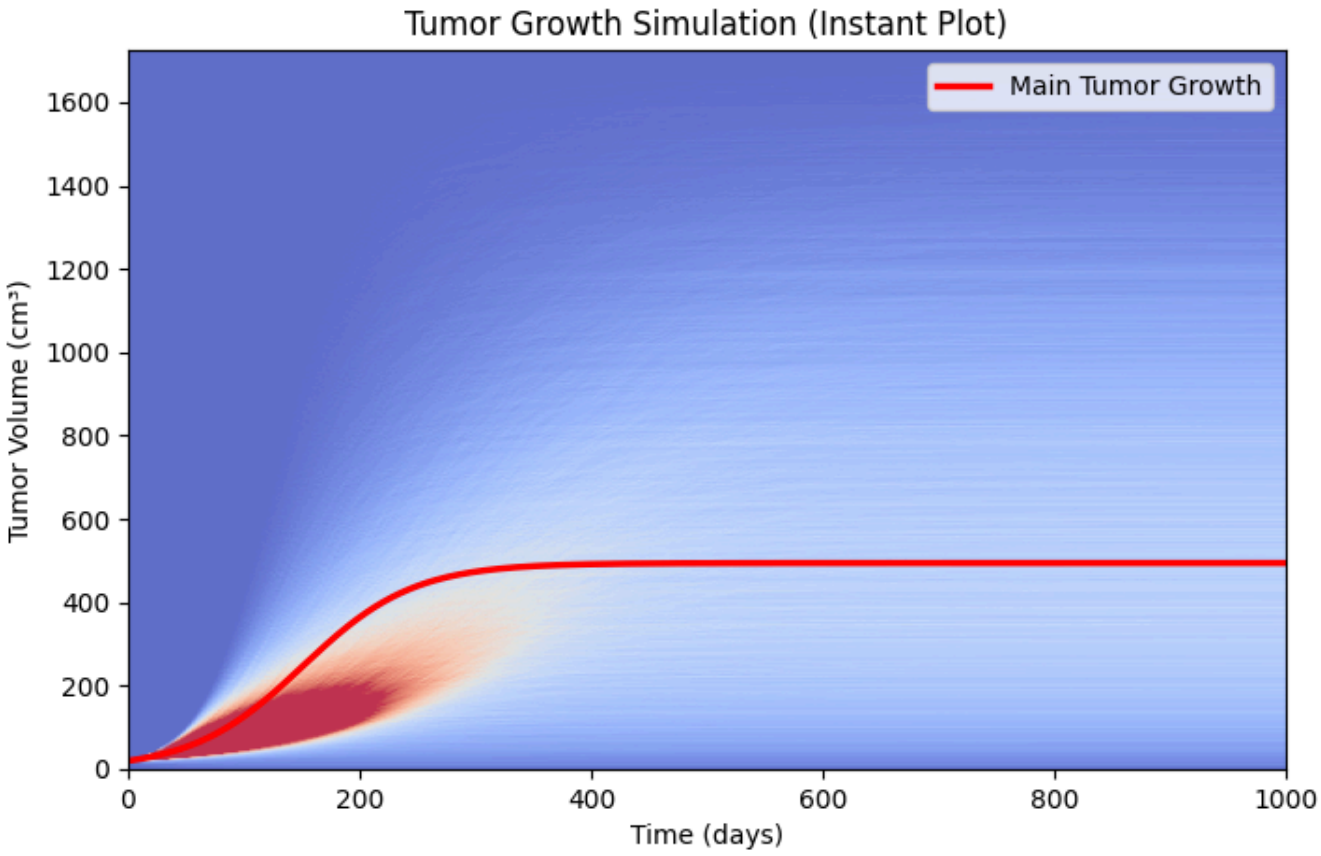
Meningiomas:

A study done by Nakamura et al. reported a mean tumor growth rate of 0.8 cm^3/year, and a mean doubling time of 21.6 years [12]. Using this information, over 10-20 years of non-treatment, it may reach a size of 10 cm^3. Due to this, low values of k are expected, and it may also follow that estrogen and testosterone minimally affect the tumor growth.



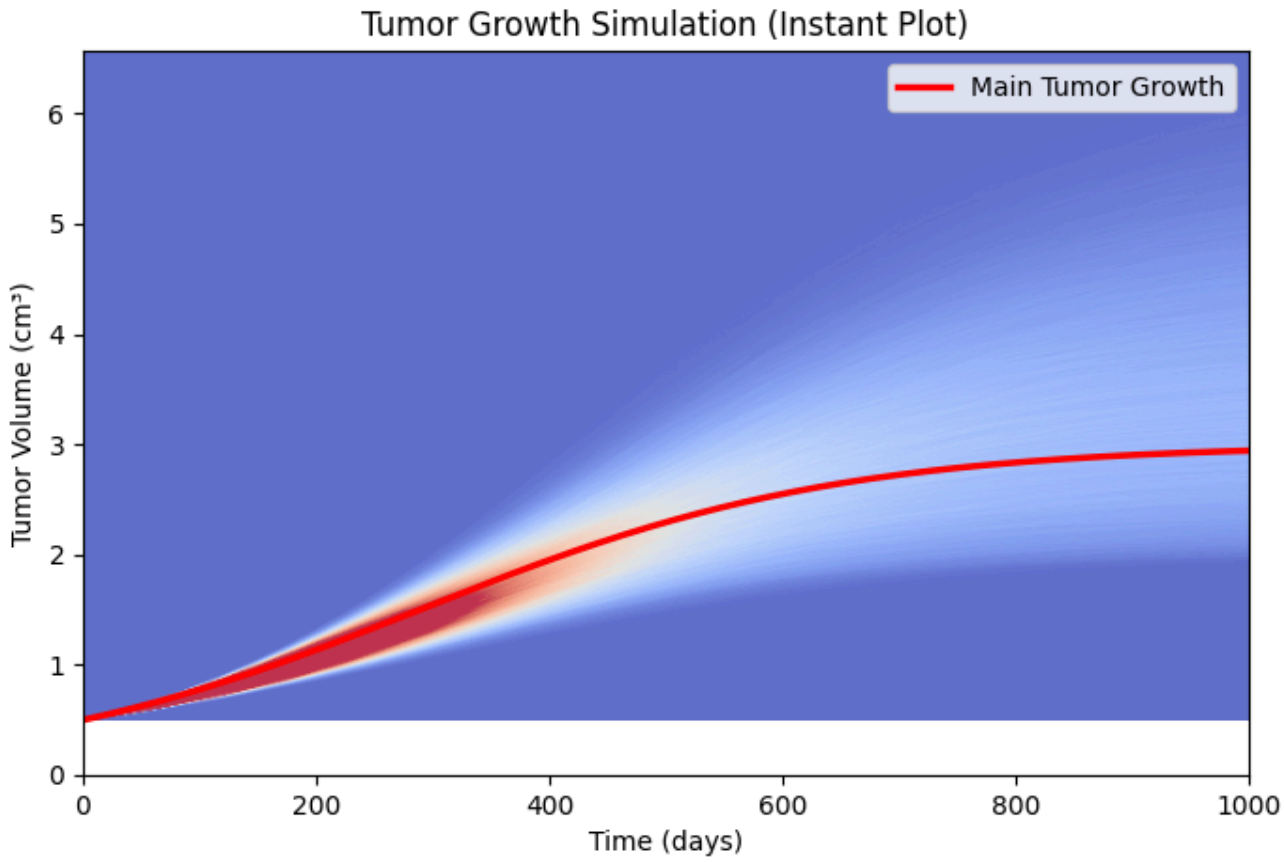
Melanomas:

Melanomas, which usually have the most space to grow, as they grow directly on the skin, have been shown to have unbounded growth in multiple case studies. A case study by G kim et al. reported a man who grew a tumor of 260 cm^3 with no signs of future boundedness [2]. Due to this, we set a max volume of 260-2000 cm^3 as the default to represent this unbounded growth but randomness. Cutaneous melanomas also show a somewhat rapid and radial growth rate, leading to relatively high values of k. Estrogen and testosterone are not expected to affect its growth rate



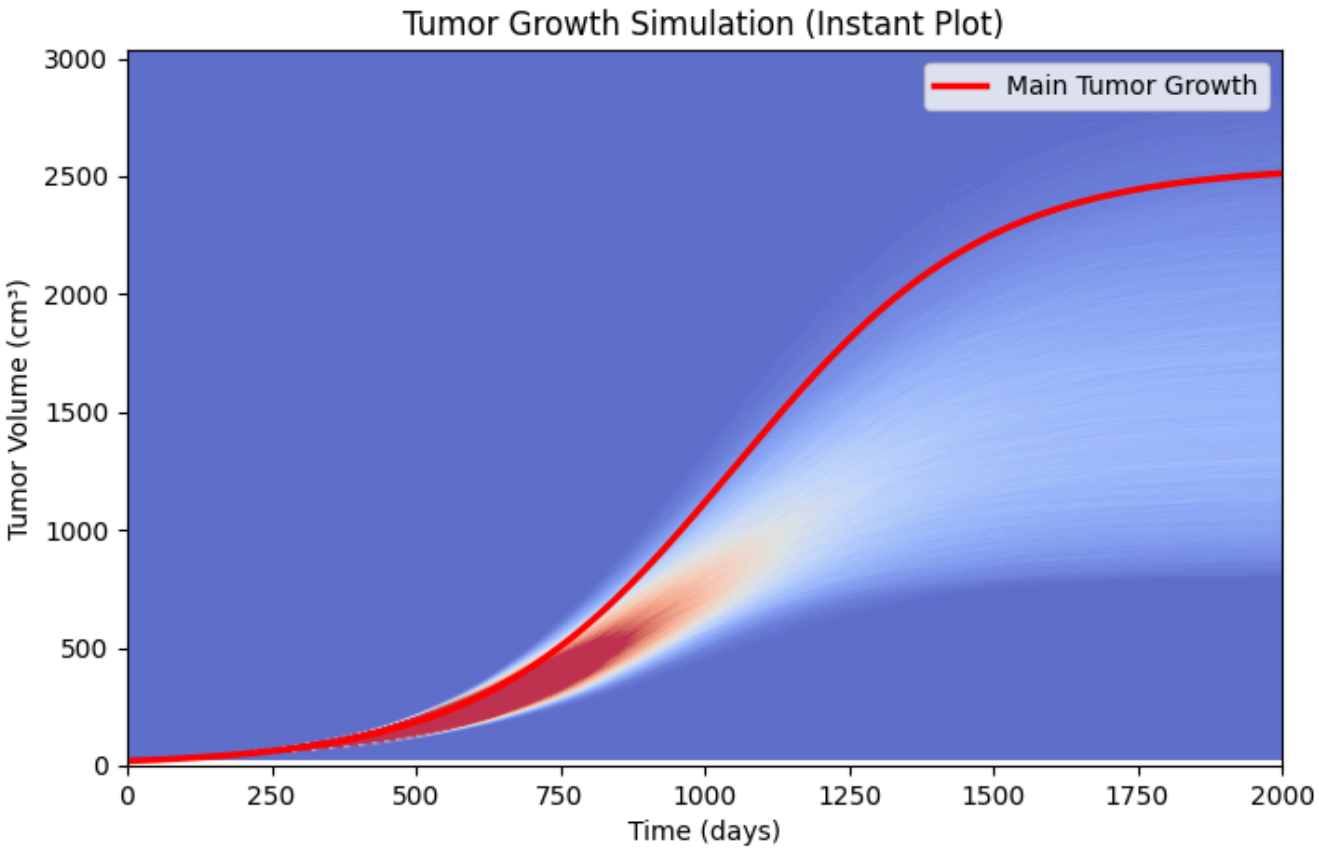
Pancreatic cancer:

Given the fact that pancreatic cancer is relatively common, a lot of research exists that can be used to help pinpoint its growth trajectory in future cases, according to a study done by H Furukawa et al. Their study on pancreatic adenocarcinomas presented a median doubling time of 144 days [3]. This can be used to deduce a specific spectrum of values of k. Another study done by D. Choung et al. reported final volumes of post-therapy pancreatic tumors to lie between values of 2-7 cm^3 [4]. Estrogen and testosterone are not expected to affect its growth rate.



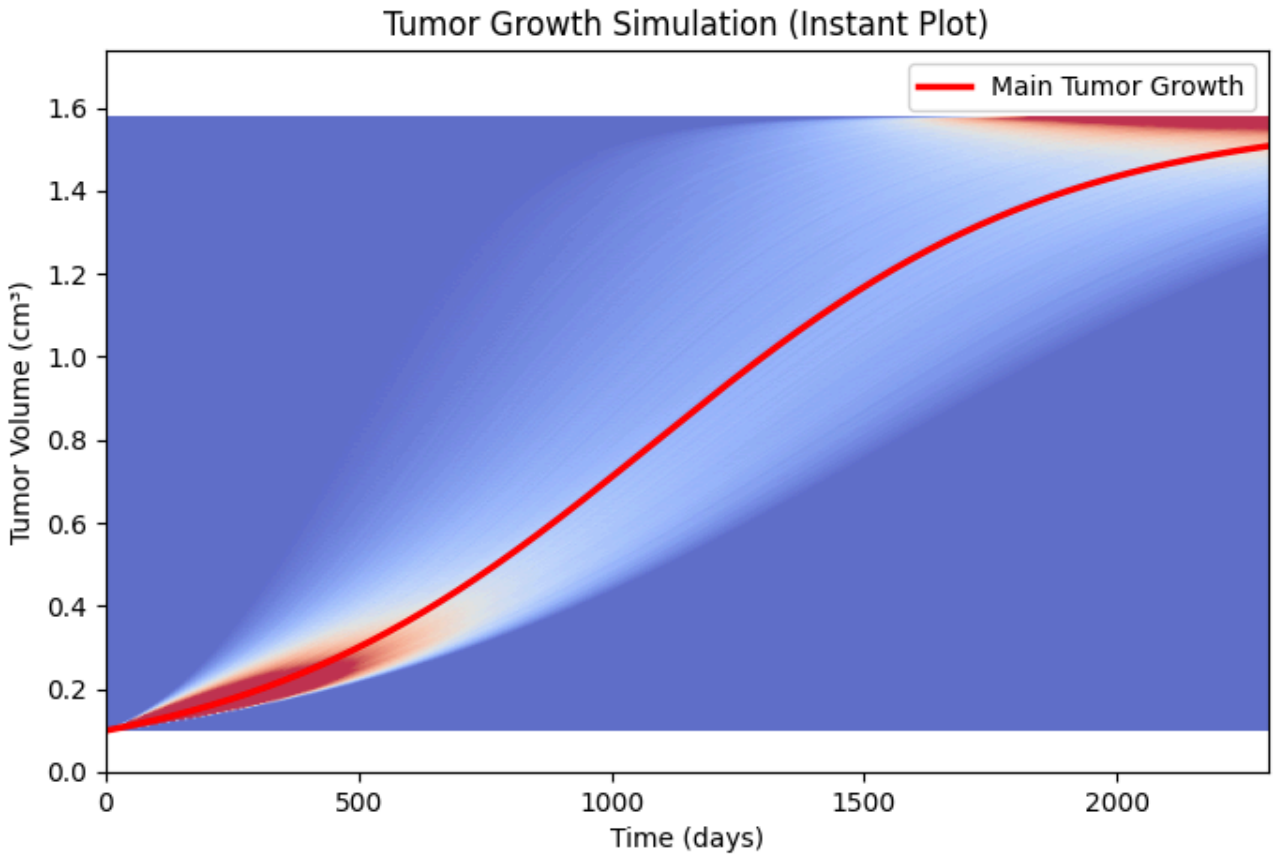
Breast cancer:

Due to breast cancer being directly linked to how fast the breasts themselves grow, it can be found that high estrogen may be a risk factor in rapid cancer growth. A paper written by D Hart et al. found that models predict breast cancer growth to halt at 3100 cm^3 [5], while a case study by Xiaoyin Mao et al. found that the growth of a particular woman's breast cancer halted at 800 cm^3 [6], being an extremely low bound, but is likely to be replicated in other growth patterns. According to another study done by Shuyin Zhang et al. Found that the doubling time of breast cancer seemed to be close to 164 days [8].



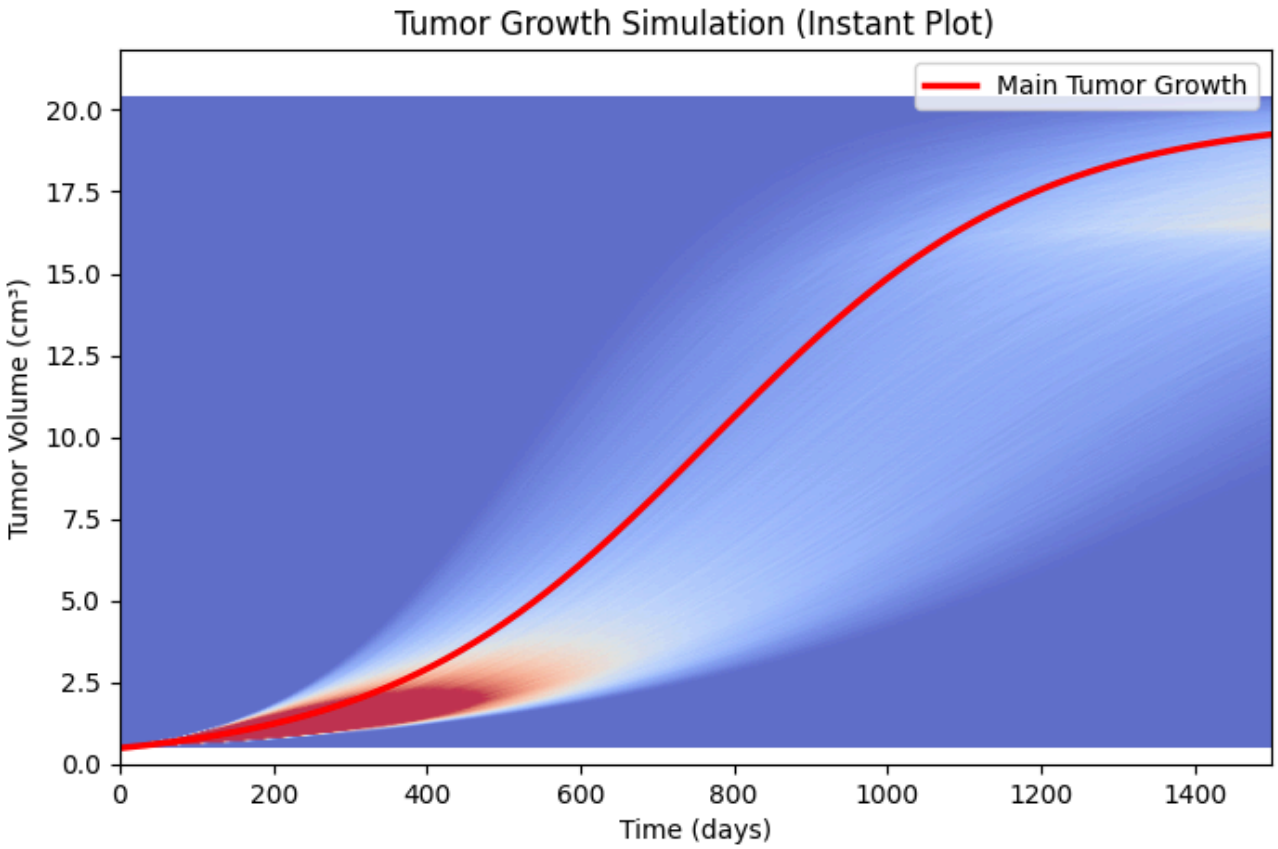
Prostate cancer:

There isn't a lot of research that provides a window into where a plateau border can be placed. However, clinically insignificant (Gleason 6) prostate tumors show depressed growth past 0.5-2.0 cm^3, showing no risk of future growth or metastasis into dangerous territory [7]. High testosterone can also pose as a factor of advanced growth.



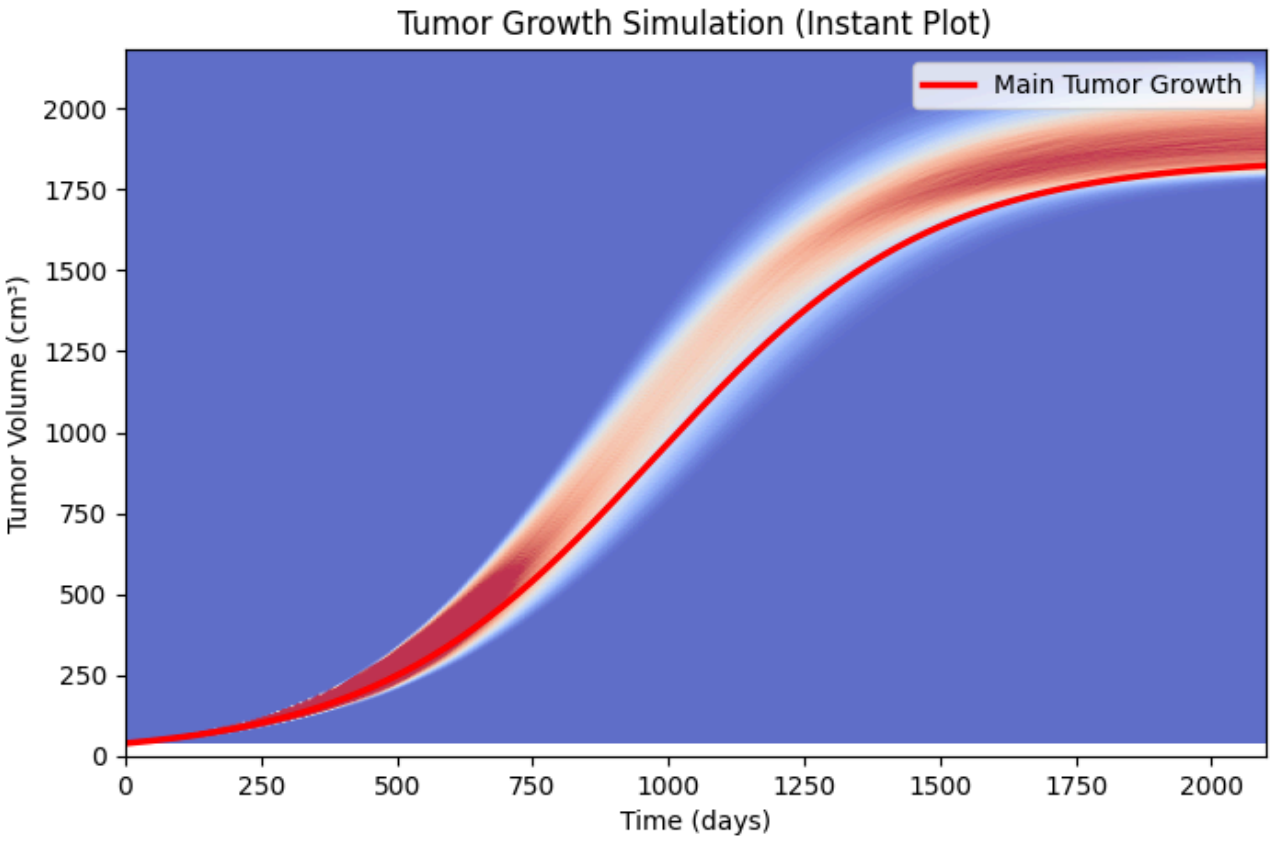
Colon cancer:

Jorge Arredondo et al. Found that colon cancer undergoes a median volume change of 51.0-18.4 cm^3 under chemotherapy in 44 participants [13]. Cancers of smaller volumes may achieve this bound but fail to grow under harsh conditions, such as those provided by chemotherapy; therefore, an upper bound of 18.4 cm^3 is provided for colon cancer with an uncertainty of ~2 cm^3 due to varying conditions. It is also not expected to be affected by either testosterone or estrogen.



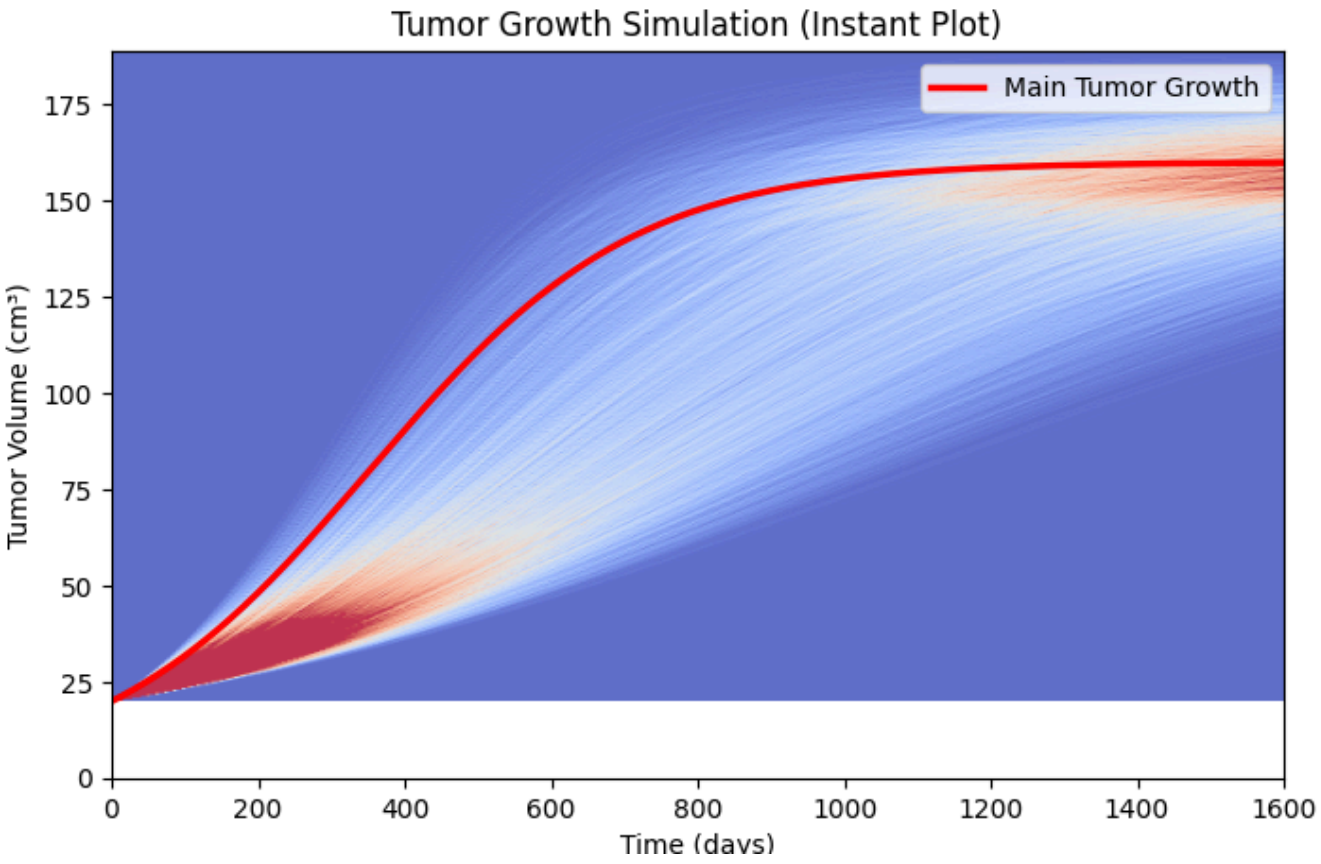
Hepatocellular carcinoma:

Although being extremely common, HHC studies don't state any plateau volume that could be used as a replacement for k, so we set a max default volume of 2000 cm^3 to account for some uncertainty. However, there is a given doubling median time of 164 days we can use, provided by Meng-Chen Ba et al. [14]. HHC is not expected to have its growth rate influenced by either estrogen or testosterone.



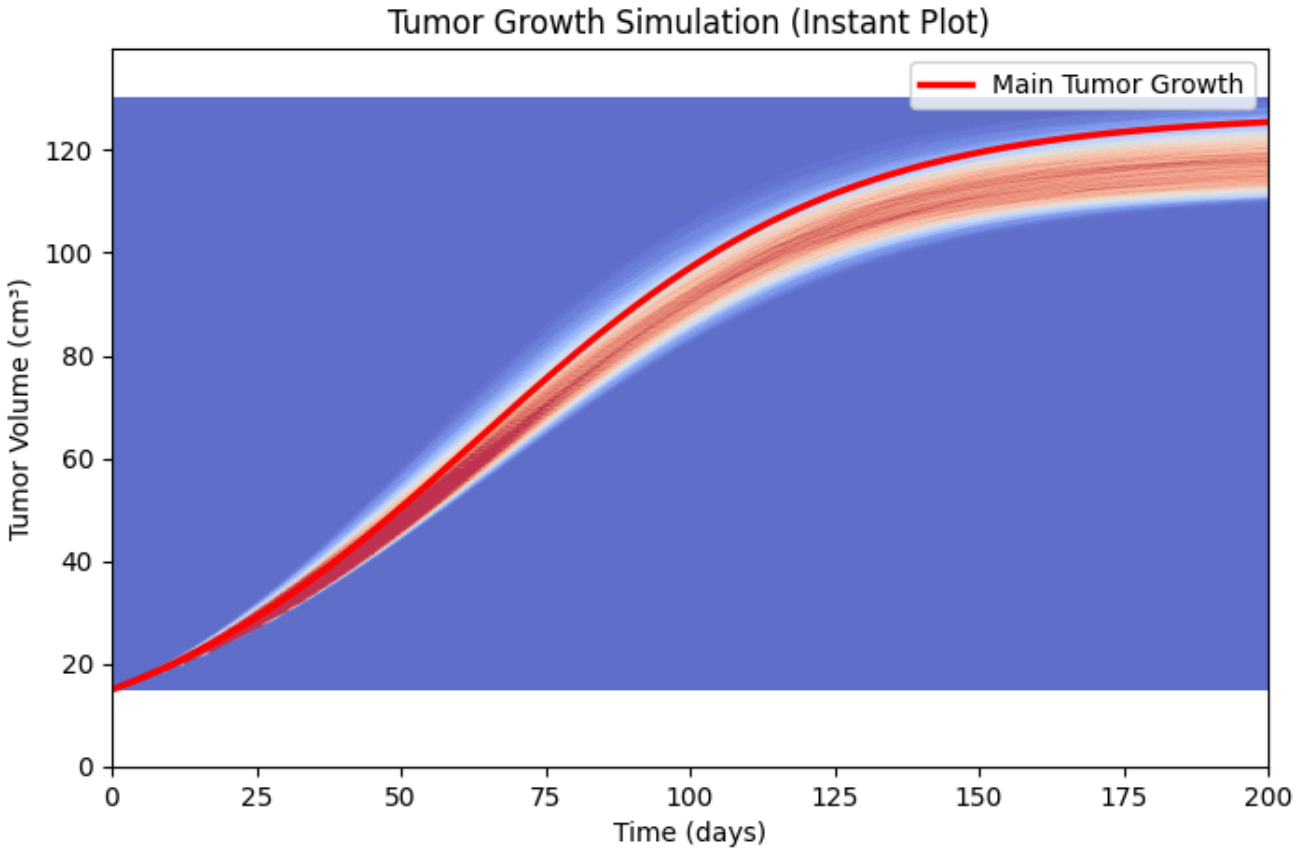
Non-small cell lung cancer:

A study done by Xiaxia Chen et al. Found that almost 40 percent of patients had NSCLC of a size below 150 cm^3, while the median size of 180 cm^3 [15]. By setting the plateau volume or carrying capacity between these two sizes, we can maintain that it's highly likely that at least 50 percent of cases can be predicted by the program. NSCLC is not expected to be affected by testosterone or estrogen.



untreated glioblastoma:

Although there is a lack of research on the growth of gliomas under chemotherapy, a direct study exists that describes the properties of untreated gliomas when predicted under stochastic growth conditions. According to a study done by Ziwei Ma et al. [16], their model predicted a plateau of 121.6 cm^3, while another study done by Benjamin M Ellingson et al. reported a doubling time of 21.1 days [17]. Gliomas aren't expected to be affected by testosterone or estrogen.



code installation:

The link to the code is available in this GitHub link (https://github.com/meerzozik/cancer-tracker). To use the code, you run it in Python after installing the necessary libraries and fill in the necessary parameters in the menu box. After filling them in, you click on the run button, and the graph should be generated, adjusted to follow the given parameters

References:

[1]Oh J, Magnuson A, Benoist C, Pittet MJ, Weissleder R. Age-related tumor growth in mice is related to integrin α4 in CD8+ T cells. *JCI Insight.* 2018 Nov 2;3(21):e122961. doi: 10.1172/jci.insight.122961. PMID: 30385729; PMCID: PMC6238736.

https://pubmed.ncbi.nlm.nih.gov/30385729/

[2]Khim OG, Leong JF, Sani MH, Mohamed Haflah NH. Unusual Presentation of Giant Upper Limb Malignant Melanoma. *Cureus.* 2021 Aug 8;13(8):e16996. doi: 10.7759/cureus.16996. PMID: 34540398; PMCID: PMC8423318.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8423318/

[3]Furukawa H, Iwata R, Moriyama N. Growth rate of pancreatic adenocarcinoma: initial clinical experience. *Pancreas.* 2001 May;22(4):366-9. doi: 10.1097/00006676-200105000-00005. PMID: 11345136.
https://pubmed.ncbi.nlm.nih.gov/11345136/

[4]Chuong MD, Hayman TJ, Patel MR, Russell MS, Malafa MP, Hodul PJ, Springett GM, Choi J, Shridhar R, Hoffe SE. Comparison of 1-, 2-, and 3-Dimensional Tumor Response Assessment After Neoadjuvant GTX-RT in Borderline-Resectable Pancreatic Cancer. *Gastrointest Cancer Res.* 2011 Jul;4(4):128-34. PMID: 22368736; PMCID: PMC3283109.
https://pubmed.ncbi.nlm.nih.gov/22368736/

[5]Hart D, Shochat E, Agur Z. The growth law of primary breast cancer as inferred from mammography screening trials data. *Br J Cancer.* 1998 Aug;78(3):382-7. doi: 10.1038/bjc.1998.503. PMID: 9703287; PMCID: PMC2063020.
https://pubmed.ncbi.nlm.nih.gov/9703287/

[6]Mao X, Zhou M, Fan C, Chen B, Jin F. Timescale of tumor volume of a young breast cancer patient with luminal B subtype: A case report. *Medicine (Baltimore).* 2019 Oct;98(43):e17659. doi: 10.1097/MD.0000000000017659. PMID: 31651890; PMCID: PMC6824670.
https://pubmed.ncbi.nlm.nih.gov/31651890/

[7]Kryvenko ON, Epstein JI. Definition of Insignificant Tumor Volume of Gleason Score 3 + 3 = 6 (Grade Group 1) Prostate Cancer at Radical Prostatectomy—Is it Time to Increase the Threshold? *J Urol.* 2016 Dec;196(6):1664-1669. doi: 10.1016/j.juro.2016.06.013. Epub 2016 Jun 9. PMID: 27291653.
https://pubmed.ncbi.nlm.nih.gov/27291653/

[8]Zhang S, Ding Y, Zhou Q, Wang C, Wu P, Dong J. Correlation Factors Analysis of Breast Cancer Tumor Volume Doubling Time Measured by 3D-Ultrasound. *Med Sci Monit.* 2017 Jun 27;23:3147-3153. doi: 10.12659/msm.901566. PMID: 28652562; PMCID: PMC5498121.
https://pubmed.ncbi.nlm.nih.gov/28652562/

[9]Ørsted DD, Nordestgaard BG, Bojesen SE. Plasma testosterone in the general population, cancer prognosis and cancer risk: a prospective cohort study. *Ann Oncol.* 2014

Mar;25(3):712-718. doi: 10.1093/annonc/mdt590. PMID: 24567517; PMCID: PMC4433522. https://pubmed.ncbi.nlm.nih.gov/24567517/

[10]Yue W, Wang JP, Li Y, Fan P, Liu G, Zhang N, Conaway M, Wang H, Korach KS, Bocchinfuso W, Santen R. Effects of estrogen on breast cancer development: Role of estrogen receptor independent mechanisms. *Int J Cancer.* 2010 Oct 15;127(8):1748-57. doi: 10.1002/ijc.25207. PMID: 20104523; PMCID: PMC4775086. https://pubmed.ncbi.nlm.nih.gov/20104523/

[11]Grambow-Velilla J, Seban RD, Chouahnia K, Assié JB, Champion L, Girard N, Bonardel G, Matton L, Soussan M, Chouaïd C, Duchemann B. Total Metabolic Tumor Volume on 18F-FDG PET/CT Is a Useful Prognostic Biomarker for Patients with Extensive Small-Cell Lung Cancer Undergoing First-Line Chemo-Immunotherapy. *Cancers (Basel).* 2023 Apr 10;15(8):2223. doi: 10.3390/cancers15082223. PMID: 37190152; PMCID: PMC10136504. https://pubmed.ncbi.nlm.nih.gov/37190152/

[12]Nakamura M, Roser F, Michel J, Jacobs C, Samii M. The natural history of incidental meningiomas. *Neurosurgery.* 2003 Jul;53(1):62-70; discussion 70-1. doi: 10.1227/01.neu.0000068730.76856.58. PMID: 12823874. https://pubmed.ncbi.nlm.nih.gov/12823874/

[13]Arredondo J, González I, Baixauli J, Martínez P, Rodríguez J, Pastor C, Ribelles MJ, Sola JJ, Hernández-Lizoain JL. Tumor response assessment in locally advanced colon cancer after neoadjuvant chemotherapy. *J Gastrointest Oncol.* 2014 Apr;5(2):104-11. doi: 10.3978/j.issn.2078-6891.2014.006. PMID: 24772338; PMCID: PMC3999636. https://pubmed.ncbi.nlm.nih.gov/24772338/

[14]Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, Rigamonti A, Barbara C, Grigioni W, Mazziotti A, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. *Hepatology.* 1992 Jul;16(1):132-7. doi: 10.1002/hep.1840160122. PMID: 1352268. https://pubmed.ncbi.nlm.nih.gov/1352268/

[15]Chen X, Zhang W, Luo L, Fu S, Cao D, Su S, Li Q, Yang W, Geng Y, Lu B, Ouyang W. Effect of primary tumor volume on survival of concurrent chemoradiotherapy in stage IV non-small cell lung cancer. *Cancer Med.* 2024 Sep;13(17):e70221. doi: 10.1002/cam4.70221. PMID: 39279741; PMCID: PMC11403300. https://pubmed.ncbi.nlm.nih.gov/39279741/

[16]Ma Z, Niu B, Phan TA, Stensjøen AL, Ene C, Woodiwiss T, Wang T, Maini PK, Holland EC, Tian JP. Stochastic growth pattern of untreated human glioblastomas predicts the survival time for patients. *Sci Rep.* 2020 Apr 20;10(1):6642. doi: 10.1038/s41598-020-63394-w. PMID:

32313150; PMCID: PMC7171128.
https://pubmed.ncbi.nlm.nih.gov/32313150/

[17]Ellingson BM, Nguyen HN, Lai A, Nechifor RE, Zaw O, Pope WB, Yong WH, Nghiemphu PL, Liau LM, Cloughesy TF. Contrast-enhancing tumor growth dynamics of preoperative, treatment-naive human glioblastoma. *Cancer.* 2016 Jun 1;122(11):1718-27. doi: 10.1002/cncr.29957. Epub 2016 Mar 21. PMID: 26998740.

https://pubmed.ncbi.nlm.nih.gov/26998740/