Kaplan–Meier Method in Tumor Size Doubling Time Estimation

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Abstract

The assessment of tumor response to treatment is a typical task of experimental cancer research. Usually tumor growth delay data *in vivo* consist of at least two groups of animals: control and treatment. Tumor Doubling Time (TDT) is widely used for quantification of tumor growth rate for prognostic purposes *in Vivo* study and can quantify therapeutic effects of different treatment modalities. Some studies assume that the growth of an unperturbed tumor follows the exponential distribution, and the TDT is determined from two volume estimations with measurement time intervals using the first derivative of the exponential model; others assume that tumor growth follows a Gompertz model and TDT is estimated with a nonlinear function. However, in the case of the Xenograft Tumor Model, neither models fit the tumor growth with different treatment strategy. Thus we investigate using model free Kaplan–Meier estimates in TDT estimation. The results show that the KM method in TDT estimation is more robust than other model based methods. The KM method can also provide a comparison between treatments in TDT simultaneously.

Key words: Tumor doubling time, Gompertz curve, exponential distribution, KM survival function, Log- rank test.

1. Introduction

The assessment of tumor response to treatment is a typical task of experimental cancer research. Usually tumor growth delay data *in Vivo* consist of at least two groups of animals: control and treatment. In pre-clinical study, it is often to randomize tumor-bearing animals into various treatment groups in order to assess the treatment effect. The resulting dataset consists of a series of volumes for each animal at different study days, which one analyzes to determine whether and how the treatment affects tumor growth. The treatment effect could be evaluated as tumor growth rate or tumor doubling time from the first day of treatment. Although there are many models used to fit animal growth to evaluate treatment effect using parametric methods include analysis of variance method with repeated measurement, mixed model, multivariate analysis (2), nonlinear regression (3), most of these parametric methods are sensitive to model assumption, a deviation from model assumption will lead a biased estimation. In another side,

investigator is interested not only in the treatment effect but the tumor growth rate or the tumor doubled time from the start of therapy as outcomes.

Tumor Doubling Time (TDT) is widely used for quantification of tumor growth rate for prognostic purposes *in vivo* study and can quantify therapeutic effects of different treatment modalities. Some studies assume that the growth of an unperturbed tumor follows the exponential distribution, and the TDT is determined from two volume estimations with measurement time intervals using the first derivative of the exponential model (4); Gompertz growth model is often used to model growth of solid tumors for which relative growth rate decreases with increasing tumor size (3, 5). However, in the case of the xenograft tumor model, neither models fit the tumor growth when anticancer treatment applied. Thus we investigated using model free Kaplan–Meier (KM) estimates in TDT estimation. KM method is a non-parametric estimate of the survival function. It is commonly used to describe survivorship of study population/s and compare two study populations along with intuitive graphical presentation. Although it has disadvantage in population study due to lack of controlling for covariates and can't accommodate time-dependent variables, it is not a question *in Vivo* animal model because all study environment is under controlled. Using KM method, we define the time of tumor doubly from the treatment therapy start as 'event' and animal will be treated as censored if the tumor does not reach doubled at the end of experiment. Thus the descriptive nature of the KM method is an appropriate option to estimate tumor doubling time when anticancer treatment applied, which account for right 'censor' when animal has not reached doubly size of the tumor when experiment expired.

2. Method

We compared different statistical models that often be used to estimate the time to tumor size doubled under experiment conditions in order to identify the most effective treatment that slow tumor growth in cancer research. Gompertz model is written as

$$V(t) = A \exp\{-b\exp(-ct)\}$$

Where V (t) is the tumor volume at time t and A, b and c are positive. Parameter A determines the limit of growth (the maximum tumor volume), parameter b determines the initial tumor volume and parameter c determines the rate of growth.

For an exponentially growing tumor, the growth rate is proportional to its volume (V).Tumor Doubling time (TDT) is the time period when $V2 = 2V1$, then

$$TDT = (t2 - t1) \ln2/ (\ln(V2/V1)$$

The Kaplan–Meier estimator (6, 7) also known as the product limit estimator, is an estimator for estimating the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment. In economics, it can be used to measure the length of time people remain unemployed after a job loss. In engineering, it can be used to measure the time until failure of machine parts. In ecology, it can be used to estimate how long fleshy fruits remain on plants before they are removed by frugivores. Here we are interested in how to estimate the time that a tumor's volume or size is doubled from initial treatment *in vivo* experiment. Assuming the survival function

$$S=\Pr\,(T>t)$$

The event is defined the time from entry into a study until a animal has a tumor doubled its size after different treatment strategies; Animals are censored if the study ends before their tumor size are doubled at study entry. The Log-Rank Test can be used to compare the TDT among treatment groups with log-rank statistic $\sim\chi2$ with $G-1$ df. An important advantage of the Kaplan–Meier curve is that the method can take into account some types of censored data, particularly *right-censoring*.

All analyses were carried out using SAS V.9.2 (SAS Institute, Cary, NC, USA).

3. Results

The Data came from a research laboratory to use chemo therapeutic drug in combination with an innovated antibody to evaluate the combination effect on treatment of breast cancer in animal model. Figure 1 presented tumor growth over experiment under different treatment plans. Group 1 is control, and other groups 2-6 represented as either single drug or combinations. The objective of this study is to estimate the time of tumor size doubled from initial experiment, and whether there are different between treatment groups.
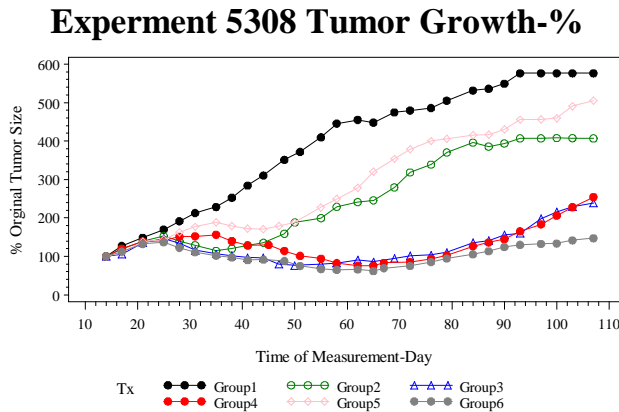
Experment 5308 Tumor Growth-%

Figure 1 Tumor Growth Curve from *in vivo* Experiment with different Treatments

Table 1 TDT Estimation from Three Methods

TX Group	Experiment data Median Min-max	Mean SD	Exponential Model Median Min-max	Mean SD	Mean diff (%)	Gompertz Model Median Min-max	Mean SD	Mean diff (%)	Kaplan-Meier Method* Median 95% CI	Mean SD	Mean diff (%)
1	30 23-45	32 6.8	28 19-38	29 6.1	-9.3	52 35-88	56 18.7	75	28 20-35	29 1.9	-9.3
2	57 37-107	68 27.8	51 33-58	49 8.2	-27.9	29 26-62	-322 854.5	-370.5	58 38-	54 2.2	-20.5
3	107 70-107	96 14.0	74 65-83	74 7.9	-22.9	2 -331-331	-31 191.5	-132	- 72-	87 2.0	-9.3
4	92 25-107	89 26.6	77 25-66	67 24.8	-24.7	-36 -124-84	-17 78.9	-119	93 25-	83 7.9	10.5
5	60 27-107	61 25.2	54 26-77	50 20.3	-18.0	53 30-128	55 28.0	-9.8	62 28-80	58 7.3	-4.9

6	107 66-107	100 13.7	76 59-84	73 12.9	-27.0	-13 -339-69	-51 115.1	-151	- 69-	90 3.1	-10

*median time represented 50% animal had their tumor size doubled from intial treatment.

We used *in vivo* animal experiment 5308 to simulate the 'mean' of the time to tumor doubling for each treatment group. From the selected animal tumor growth curves in Figure 2, we observed that the distribution of animal tumor growth was following exponential distribution only when there was no treatment, e.g. in group Tx1, and tumor growth were deviated from exponential as the effectiveness of the treatment increased, treatment effect (Tx 2, Tx5), and Tx 3 and Tx6. The estimation of TDT from above three methods was presented in Table 1 with mean, standard deviation, median and min and max for each method for each treatment group. Mean diff (%) represented the percentage difference between estimated TDT and the true TDT in experiment, which was calculated as 100*(estimated TDT-True TDT)/True TDT. Table 1 indicated that it was not appropriate to fit animal tumor growth to a parametric based model using nonlinear regression when anti-cancer treatment therapy applied, e.g. Gompertz model, which provided biased estimation of TDT, and had the great deviation from the true TDT; exponential distribution model could be used only if the treatment had less effect, e.g. Tx1, Tx2 and Tx5; In contrast, model free method with KM approach provided the best estimation of TDT regardless of the distribution of animal tumor growth after treatment therapy.
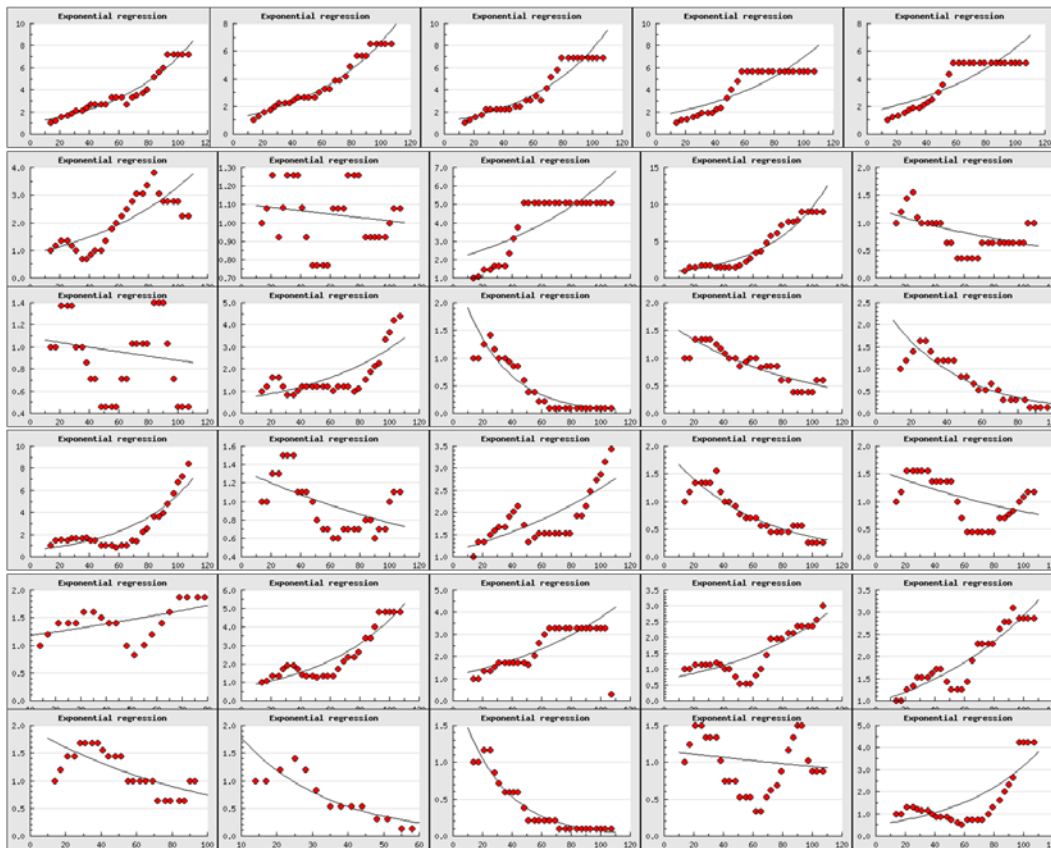

Figure 2 Selected Animal Tumor Growth from Animal Data 5308 Simulated by the Gompertzian model

In conclusion, *in vivo* tumor growth doesn't follow the same distribution after anti-cancer treatment applied; thus using parametric methods to fit animal tumor growth model will yield biased estimation of TDT. KM method provides not only accurate estimate, e.g. smaller mean diff %, it provides also the information how many animals have not reached the TDT when a study is completed. The KM method can also provide statistical a comparison in TDT between treatment simultaneously while other methods are not able to provide statistical comparison between treatment in TDT directly.

Acknowledgements

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