

Parametrization of Survival Measures (Part II): Single Arm Studies

Andras Szasz¹, Gyula P. Szigeti², Marcell A. Szasz³

¹Biotechnics Department, Faculty of Mechanical Engineering, St. Istvan University, Budaors, Hungary

²Innovation Center, Semmelweis University, Budapest, Hungary

³Cancer Center, Semmelweis University, Budapest, Hungary

Email: biotech@gek.szie.hu

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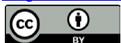
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Abstract

In some clinical applications in oncology randomized, double armed, and double-blind trials are not possible. In case of device applications, double-blinded conditions are nonrealistic, and with many times the randomization also has complications due to the high-line treatments where the reference cohort is not available; the active “arm” has mainly palliative initiative. Sometimes highly personalized therapies block the collection of the homogeneous group and limit its double-arm randomization. Our objective is to discuss the situations of the single arm evaluation and to give methods for the mining of information from this to increase the level of evidence of the measured dataset. The basic idea of the data-separation is the appropriate parameterization of the non-parametric Kaplan-Meier survival pattern by the poly-Weibull fit.

Keywords

Single-Arm Clinical Trial, Survival-Time, Decomposition of Survival Curves, Personalized Treatment, Observational Trial

1. Introduction

Survival studies most frequently use the Kaplan-Meier (*KM*) non-parametric estimate. The *KM* estimator is fixed by the duration of participation in the observation. Both the start of the observation time and the end of the observation of the individual by events (censored due to death or dropped out from the cohort) are not absolute and have inexplicit values. The precariousness flows from the differences between real lifetime to observational time. We summarize the characteristic points of the life of a cancer-patient in **Figure 1**. Periods out of observation

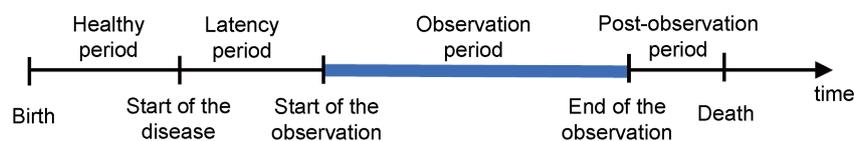


Figure 1. The time-scale of the individual participant's lifetime (Periods out of observation could be zero in any actual case, while the start of the observation could be a group of dates: the routine screening or the first symptoms and/or the first diagnosis).

could be zero in any actual case. One point (start of the disease) is elusive because the real symptoms of any disease could be later than the starting point of the disorder. This situation usually happens because the observation facilities of malignant diseases are technically limited. We could have only guessed the latency period, which starts with an avascular situation, forming a dormant microscopic cluster [1]. When the tumor leaves the dormant state by a scaling transformation [2], growth becomes traceable.

The real survival period in this content is blurry, so the definitions of the real survival points are the sum of the observation and the post-observation period. The evaluation may concentrate on disease-related death or any deaths in the observational period, irrespective of the cause. The observation period may only contain careful watch, then the treatment, and at the end, a long follow-up too. The observation period usually is evaluated statistically by the Kaplan-Meier non-parametric estimates (Figure 2). The end of observation could be decided by the endpoint of the study (e.g. 5 y survival), irrespective of the actual diagnosis of the patients at the end; or could be determined when all involved individuals have been censored or dead. In case of survival, the end could be determined when the patients of the studied group were cured and their state was declared NED (no evidence of disease). However, long (e.g. five years) survival does not necessarily mean a cured status [3]; a relapse of new metastases could happen in the post-observation period when in most of the cases new treatment starts.

The start of the observation could be after the routine screening when patients complain (about symptoms) and the statistically valuable period starts at the first diagnosis. The latent period can be long, even years before the discovery of cancer [4].

Measuring the effect of the treatment has various approaches, since having complications of the bio-variability and personal sensitivity of the treated individuals as well as the variation of the results depends on the social background and lifestyle of the patients. Randomized clinical trial (RCT) is a commonly used study design to measure lifetime. In an RCT, the active (investigated) arm can be statistically compared to the well-randomized control group in a carefully chosen, unified cohort. To evaluate a clinical intervention with the optimal possibility of RCT has ethical issues [5] [6], justification problems [7], and cohort-forming limitations. A crucial step of valid evaluation is, of course, selecting a group of patients who share common characteristics (cohort); otherwise, the variation of the results does not allow the estimation of the effect; discrepancies arise because of the patients' differences and not because of the therapy itself. Forming an

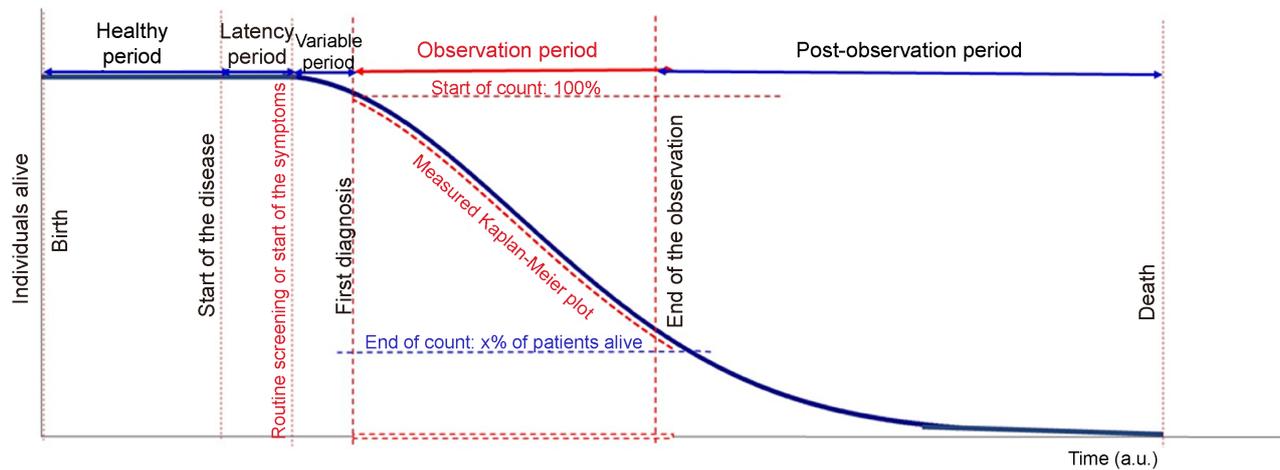


Figure 2. The time-scale of the group of participants' life-line (The lines for periods are naturally not definite; these are ranges of time-periods that could be overlapped too. The measured *KM* plot is the topic of interest for clinical trials).

appropriate cohort is a complex issue. Cohort forming sometimes uses forced conditions by reaching a definite toxicity predefined by the protocol (like in high-dose chemotherapy [8]), expecting the same (unified) reaction on the stage-selected patients. The RCT approach is devoted to the application of the most appropriate treatment update and for the reference control is used from the same cohort (called control-arm). The new therapy (active arm) must show its superiority over the control in comparison. The equipoise selection into both arms is mandatory, but the two treatments could be compared by not only their positive efficacy but their side effects as well, that may adversely affect the treatment [9].

Sometimes, in cancer treatment, a misleading (or at least not complete) evaluation is practiced by measuring the local control of the tumor, instead of the systemic development of the malignancy in the whole body. The problem of the overall control of the system is complicated and not even possible with imaging because of micro-metastases and such adverse effects which cause comorbidities for the patient. Therefore, parametrization would only be effective if the endpoint of the study is the overall survival and the quality of life combined.

Before deciding on the RCT, both sides of the balance of measured efficacy and the adverse effects must be taken into account. In case of serious diseases or terminal cases, no curative treatment is available, or further curative therapy is simply not possible because of comorbidities like organ-failure, low-blood-count, etc. Note that some conditions limit the RCT evaluation even in the double arm construction: the false inclusion and exclusion criteria (sometime “cherry picking”); the missing normal distributions; or the changing time series that have the same statistical momentums but their time-fluctuations differ. The data-set in the last case is out of the applicability of the usual analysis of variance (ANOVA). Furthermore, the ethical selection issues oppose the randomization, so the trial must be solved in a simple non-randomized design of single arm.

Due to the possible problems of RCT, some prospective clinical trials register

the data in the single arm only. The most frequent reason is the targeted far advanced disease where the conventional curative therapies have failed, and no other treatment is available except for the newly tried one. In these cases, the best supportive care (BSC) could be applied [10], like a control group when an active curative or palliative therapy is under investigation, and retrospectively, a historical control of the same hospital or large databases are also frequently compared to the historical data-set of the same hospital or compares to other large databases, retrospectively. There are some situations where no suitable historical control is available because of the completely new approach of the therapy [11], or the disease is so rare, that no comparison could be found [12]. Of course, we know that the single arm without a reference cannot give information about the changes that were achieved by the therapy involved. However, it is also obvious, that the data of the interesting changes are involved in the single arm spectrum as well but are well hidden without an orientation to measure the changes.

The single arm design is popular in the Phase I process when safety data is collected. The goal in this phase of the study is to determine the toxicity, the side effects and the dose with dose-escalation process. The investigation of efficacy is not included in Phase I trials. The Phase II studies concentrate on efficacy of the applied safe process [13]. When the hypothesis to be proved is clearly defined and the “null hypothesis” could be the zero response, the minimum of the clinically relevant response should define the size of the trial contrary to the simple design where the evaluation of the data can be rather complicated due to the difficulty of the missing reference for comparison, which is hard anyway because of the natural biological variability. The interpretation of the results of single arm distinguishes the placebo effect or the spontaneous natural history of the disease from the actual treatment efficacy. However, the single-arm trials may be the option when placebos are unethical, and opportunities of the controlled trial are limited, due to the vast variations of the patients. For example, the advanced diseases in oncology are frequent topics of single-arm trials, due to the massive, exhausting and mostly variant protocols of failed pretreatments. The reason of the failure is usually a progressive and refractory disease, or limitations in applying the conventionally proven methods due to organ-failure or a dangerous level of blood damages. In these cases, forming appropriate cohorts is very difficult or even not possible. When a single arm study is chosen due to the certain drawbacks of RCT, we mostly apply a palliative BSC additive to the active treatment. One of the most important condition of such single arm treatments is that it must not worsen the results of BSC, and its worst outcome must be the ineffectiveness. The best indicator of this condition is the combination of overall survival time and the quality of life.

2. Methods

Lifetime studies have a surprising universality by the self-organizing [14] [15]

and consequently by the self-similarity of the morphological structures and dynamic processes in living objects. Self-similarity has a morphological consequence, showing the spatiotemporal fractal structure in biological objects [16]; [17]. These ideas are forming the similarities of the species [18], which directly leads to the expected lifetime universality of well-selected cohorts. The general allometry is as wide as the cover of the mass, ranging from respiratory complexes, through the mitochondria, to the animals with the largest mass [19].

Due to the self-similarity, most of the biological structures and processes can be described by a simple-power function (like $P(x) = ax^\alpha$), where a and α are constants, and so the form of $P(x)$ remains only multiplied by the constant during any m magnification of x : $P(mx) = a(mx)^\alpha = m^\alpha ax^\alpha = m^\alpha P(x)$. This magnification process (scaling [20]), could be followed by a few orders of magnitudes (scale-free behavior) in biosystems.

In consequence of the widely applicable universality behavior, the general ontogenic growth [21] allows the deduction of the Weibull distribution [22], which can be used to analytically describe the non-parametric Kaplan-Meier estimate for tumors. Self-similarity drives the tumor-development, which shows the universal law of growth [23] [24]. This lays the foundation of our attempt to find the reason behind the universal parametric regression for the lifetime of the patients, which is supported by the universal law of growth of the solid tumors [25]. The extension of the Weibull model allows us to estimate the tumor-latency too [26]. We had shown the self-similarity of bioprocesses in general [27], leading us to some well-defined mathematical formulas like the Avrami equation, which has a complete formal correspondence with the function of the cumulative Weibull distribution (WF) [28]. The two-parameter cumulative Weibull distribution (WF) is a good candidate for the parametrization of the *KM*-plot [27]. It is both theoretically and practically established for clinical applications [29].

The real challenge is how we can reveal the hidden data in the single active arm in case of the missing randomization that forms reference in double arms. We have limited possibilities for mining the available information without a reference set, even though we know it well, that the information is in the data. The general self-similar behavior of the various tumors has different parametrization and so can be distinguished from each other. Consequently, the fitting to survival curves gives hints on how to extract information from the single arm alone.

Experimental data fit well to the empirical data in biology as well as it has been widely investigated and proven in solid-state reactions (precipitations, phase-transitions, aggregations, nucleation, growth, and others) [30] [31] [32] [33] [34]. Indeed, experimental data show that many biological reactions follow the Avrami equation. It is applied universally to different processes regardless of the structure and dynamics of the system. Avrami functions are self-similar, and various comparative functions characterize the exponents [35]. The considerations of Avrami function explain the parametric approximations of the non-parametric Kaplan-Meier survival distribution (*KM*) [27].

The mortality can be approached by the fitting of different distributions [36]

in epidemiologic modeling. The most popular descriptions are the Gompertz, Weibull and logistic distributions [37]. These methods are usually used for gerontologic, aging mortalities, modelling the statistics of the ages of death, do not consider any particular disease or clinical therapy involvements [38] [39] [40] [41]. A generalized Weibull-Gompertz distribution could derive various distributions [42]. In demographic aging, the Gompertz and Weibull functions describe different biological causes [39]. The Gompertz model involves a multiplicative aging mortality, while it is additive in Weibull description. The multiplicativity affects the extrinsic, while the additivity the intrinsic causes in older ages. Our present modeling does not deal with aging mortality and the connected epidemiologic consequences. Our considerations comprise the cancer-survival, which is strongly disease and therapy dependent, so it covers the intrinsic causes, on the actual parametrization of the probability of survival. This non-aging survival discussion prefers the Weibull distribution in comparison to Gompertz, describing the intrinsic self-organization behaviour of the human living organism.

In such advanced situations, when the malignancy is double refractory, the WF provides the best fit to the *KM* [11]. The cancer incidences significantly fit Weibull distribution in 18 types of malignancies [43], and so WF is justified to describe the driver events of the tumor-building process. Extending this idea, we expect that the best fit parametrization of the survival curve could lead to the information about the hidden facts in the actual non-parametric *KM* plot.

The approximation with a simple WF function in real cases of the *KM* non-parametric survival curve is not precise enough. The missing preciosity apparently contradicts the WF self-organized basis. When the survival is self-organized in the same way as we observed in all the biological processes, the fitting to the non-parametric *KM* has to show the self-similarity, because it is entirely rigorous due to the universality of the lifetime of the living systems and the growth dynamics of the tumors. The contradiction is due to the fact that the self-similar WF only fits to strictly homogeneous patients' cohorts. WF parameters characterize the group of generally equal participating individuals, which is of course not acceptable. The *KM* represents a cohort group of patients with the equipoise of individuals made as ideal as possible, choosing explicit inclusion and exclusion criteria. Nevertheless, the choosing criteria in the situation when we are not able to apply RCT cannot be fixed well. The only inclusion is the failure of conventional curative treatments and the only exclusion is when the patient is in such terminal stage when any extra intervention could be fatal.

Due to the enormous variability of the living conditions (like social, diet, habits, etc.) and bio-variability of the individuals (like genetic variability, immune-variability, sensing-variability, etc.), any chosen cohort has inhomogeneities. However, it is possible to divide the cohort into more homogeneous subgroups than the full set of individuals, expecting that the fitting of the self-similar WF will be better by the growing homogeneity of the subgroup to which it is applied.

Usually, the groups of local responses (complete response (*CR*), partial response (*PR*), no change (*NC*), or progression of the disease (*PD*)) come into the center of the attention automatically at the finishing of the study. We could make similar subgrouping in systemic (lifetime, survival) measurements, and WF fit them individually. The measured data is the summary of the complete cohort with overlapping data in the experimental non-parametric *KM* estimates, containing the data of all the subgroups. For simplicity, using the same subgrouping as in local response, the subgroup of those patients who could be regarded is introduced as “cured” (*CP*), the subgroup for those whom the treatments helped (they as responding patients (*RP*), and the patients who had no benefit from the therapy as non-responding patients (*NP*). The *KM* in the real experiment measures is only the sum of these (in the same way as in the analysis of the local response). Fit WF for subgroups and sum it for fitting to complete *KM*:

$$W^{(KM)}(t) = \frac{n_{CP}}{N} e^{-\left(\frac{t}{t_0^{(CP)}}\right)^{n^{(CP)}}} + \frac{n_{RP}}{N} e^{-\left(\frac{t}{t_0^{(RP)}}\right)^{n^{(RP)}}} + \frac{n_{NP}}{N} e^{-\left(\frac{t}{t_0^{(NP)}}\right)^{n^{(NP)}}} \quad (1)$$

and $n_{CP} + n_{RP} + n_{NP} = N$

where n_{CP}, n_{RP}, n_{NP} are the number of patients in *CP*, *RP* and *NP* groups, and N is the number of patients in the complete cohort. Note, that the difference between the *CP* and *RP* groups is only in the definition, just like in the local response between the *CR* and *PR* categories. Usually *CP* can be defined to the lifetime of the healthy group of patients in an age-normalized comparison. Consequently, for easy categorizing, usually the *CP* is the long, *RP* is the medium and *NP* is the short survival.

Simpler and more robust WF regression received, when the fitting is divided into only two different functions [44]. Here we define two sub-cohorts composed linearly [45] [46] [47], one that the treatment had no or minor influence on (*NP*) and one where the treatment was effective (*RP*):

$$W^{(KM)}(t) = c_{RP} e^{-\left(\frac{t}{t_0^{(RP)}}\right)^{n^{(RP)}}} + c_{NP} e^{-\left(\frac{t}{t_0^{(NP)}}\right)^{n^{(NP)}}} \quad (2)$$

where the Weibull parameters denoted by (*RP*) and (*NP*) superscripts, according to their sub-cohorts. Due to the complete set of patients, $c_{RP} + c_{NP} = 1$, so (2) is:

$$W^{(KM)}(t) = c_{RP} e^{-\left(\frac{t}{t_0^{(RP)}}\right)^{n^{(RP)}}} + (1 - c_{RP}) e^{-\left(\frac{t}{t_0^{(NP)}}\right)^{n^{(NP)}}} \quad (3)$$

Using the regression with division into only two subgroups by temperature development criteria was used by others [48] where the patients included in the hyperthermia cohort were divided into “heatable” and “non-heatable” sub-groups, where the end of the study was determined by the time when the last patient was proved to be unaffected by hyperthermia. Two (responding and non-responding) or more subgroups (including the stabilization, treating a chronic disease, or other), could be introduced this way as well.

The two-subgroup division has five parameters to fit. Looking for the only

concentration parameter ($c = c_{RP}$), some examples look like it is shown in **Figure 3**.

In that special case when the *RP* subgroup is cured, meaning no disease-specific death happen in the whole observation period (including the available follow-up time too), the $e^{-\left(\frac{t}{t_0^{(RP)}}\right)^{n^{(RP)}}} \cong 1$, so the WF-like curve will have the following form:

$$W^{(KM)}(t) = c_{cure} + (1 - c_{cure}) e^{-\left(\frac{t}{t_0}\right)^n} \tag{4}$$

According to our general knowledge in oncology, the size of the malignant tumor certainly affects the lifespan of the cancerous individuals. The ratio of the actual basal metabolic rate (basal energy consumption) of the malignant lesion $E(t)$ to the healthy one E_0 with the same volume modifies the survival distribution ($P_s(t)$) which modifies the simple Weibull-related distribution as follows [24]:

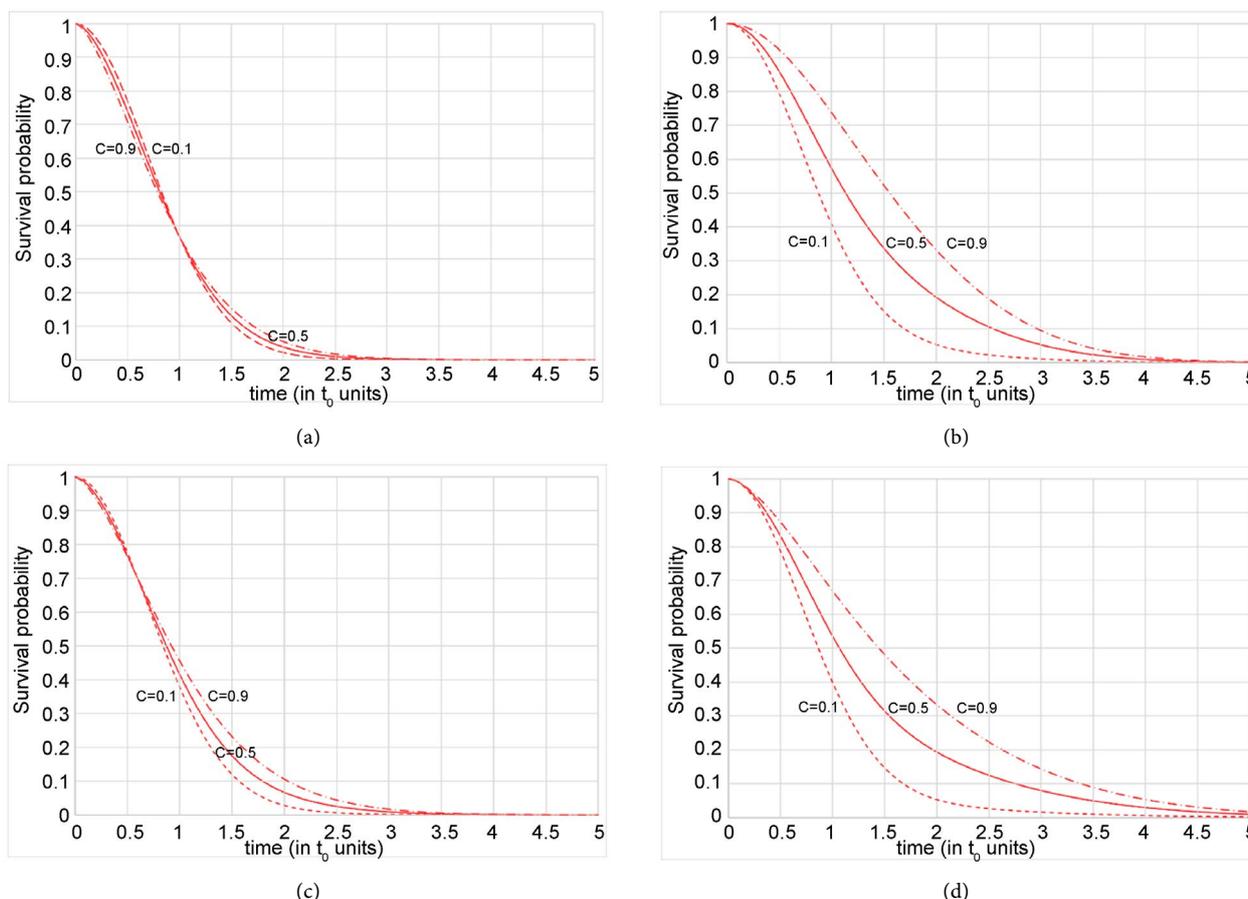


Figure 3. Examples of the fitting curves at various *c*-values, where (a) equal the time-factor: $n^{(NP)} = 2$, $t_0^{(NP)} = 1$, $n^{(RP)} = 1.5$, $t_0^{(RP)} = 1$; (b) equal the shape-factor: $n^{(NP)} = 2$, $t_0^{(NP)} = 1$, $n^{(RP)} = 2$, $t_0^{(RP)} = 2$; (c) changing by a 20% increase of the time-factor in real mix $n^{(NP)} = 2$, $t_0^{(NP)} = 1$, $n^{(RP)} = 1.5$, $t_0^{(RP)} = 1.2$; (d) changing 100% increase of time-factor: $n^{(NP)} = 2$, $t_0^{(NP)} = 1$, $n^{(RP)} = 1.5$, $t_0^{(RP)} = 2$.

$$W_s(t) = \exp\left(-\frac{E(t)}{E_0}\left(\frac{t}{t_0}\right)^n\right). \quad (5)$$

The modification of (5) can be interpreted as the change of the t_0 , and the scale factor of the Weibull function:

$$t'_0 = t_0 \left(\frac{E(t)}{E_0}\right)^{-1/n} \Rightarrow W'(t) = \exp\left(-\left(\frac{t}{t'_0}\right)^n\right) \quad (6)$$

Consequently, the scale-factor of WF (the time-factor of survival fit) contains the information about the tumor-growth in the way it was shown in (6). The original Weibull-based parametric approach of *KM* survival curve from the 0th stage gives a reference to the E_0 value.

On this basis we study the changes of the two Weibull-parameters by fitting the cumulative distribution curve to the hypothetical choice of the survival studies in different stages of the disease, which is directly connected to the inclusion criteria of the study. Also, we follow the change of parameters by the endpoint of the studies fitting to the finishing conditions. The mathematical fit of the curves uses the least square method by digital stepping of the functions in large number ($n > 1000$) steps and optimizing the square of Pearson parameter (maximize) and also the sum of squares of deviations (minimize). We used two software supports: the Excel (Microsoft 365) and the MathCad 15.

3. Results

Using the hypothesis, that the self-similar WF follows the real bioprocesses in survival, the effect of the malignancy staging at the first diagnosis could be followed with the Weibull fitting method, hypothesizing, that the staging strongly correlates with the time of the first actual diagnosis in the same cohort of patients. Diseases discovered earlier have lower stages than the ones diagnosed later. First, we are dealing with the survival curves of the patients in the control arm (reference arm, which in principle could be placebo as well), so the treatment modification will be considered later.

The start of the treatment is not immediate. Even the most accurate and modern detection methods do not allow the diagnosis in a latent state. The earliest time when the first diagnosis can be made is only after the dormant (untraceable) period of the disease. The traces of the disease cannot be detectable by imaging (due to its lower sensitivity), but some blood-test could detect the signal of disseminated circulation cancer cells or its parts. Overall Stage Grouping uses stages 0, I, II, III, and IV to characterize the progression of cancer [49]. Stage 0: when the cancerous cells are observed very locally without an observation anywhere else (carcinoma in situ); Stage I: cancers are well localized; Stage II: cancers are locally advanced and affect the sentinel lymph node or nodes only in one side of the tumor; Stage III: cancers are regionally advanced, the affected lymph-nodes are around the tumor; Stage IV: cancers have distant metastases. WF function could extrapolate the undetectable period from the fittings to the

actual clinical stage of the tumor [25]. The extrapolation of Weibull regression considers the time when the study starts, which is of course later (earliest detectable stage after dormancy) than the start of the tumor-process. The space-resolution of the most frequent imaging methods in clinical practice resolves the tumor in a 10^{-2} m range, which is about 1 cm^3 volume, having already billions of tumor-cells. Supposing a cluster contains 30 cells (~ 3 cells in a diameter) and supposing it takes 100 days to double its size, the tumor will be in the preclinical (latent) state for approx. 8 years, without the existing malignant tumor being observable, but we assume the self-organized growth during this time-period too.

Considering the basic survival curve from the start of the malignant behavior even from a single “renegade cell” [50], the WF describes the tumor development including the dormant period until all the patients deceased or censored, (we obtain (7):

$$W_b(t) = e^{-\left(\frac{t}{t_0^{(b)}}\right)^{n_b}} \quad (7)$$

Following the staging of the tumor status with WF when the diagnosis is based on the development of the malignant lesion related to (5):

$$W_S^{(i)}(t) = \exp\left(-\frac{E_i(t)}{E_0} \left(\frac{t}{t_0^{(i)}}\right)^{n_i}\right) \quad (i = \text{I, II, III, IV stages}) \quad (8)$$

Hence, according to (6), the measured $t_0^{(i)}$ in subsequent stages from

$$t_0^{(i)} = t_0 \left(\frac{E_i(t)}{E_0}\right)^{-1/n_i} \Rightarrow W_i(t) = \exp\left(-\left(\frac{t}{t_0^{(i)}}\right)^{n_i}\right) \quad (i = \text{I, II, III, IV stages}) \quad (9)$$

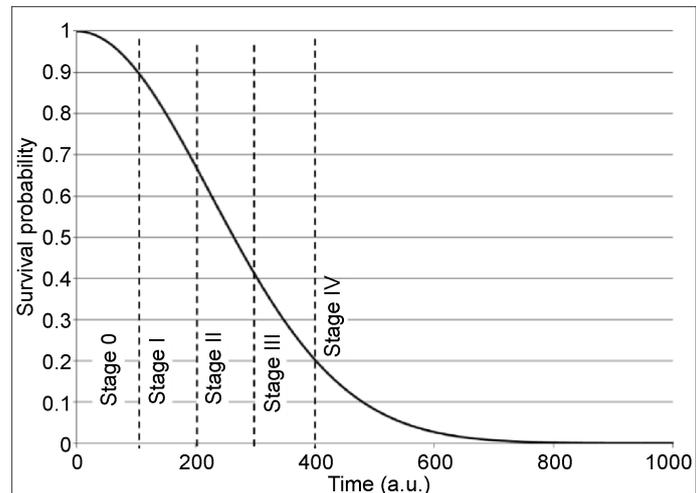
Let us denote the time when the tumor is observed like in carcinoma in situ, by T_0 . Due to the supposed continuity of the tumor-growth from the latent to the observable stage, the WF fit could follow triple parametrization to the KM non-parametric estimate. In this case a location parameter is added to the shape and scale parameters:

$$W_0(t) = e^{-\left(\frac{t+T_0}{t_0^{(0)}}\right)^{n_0}} \quad (10)$$

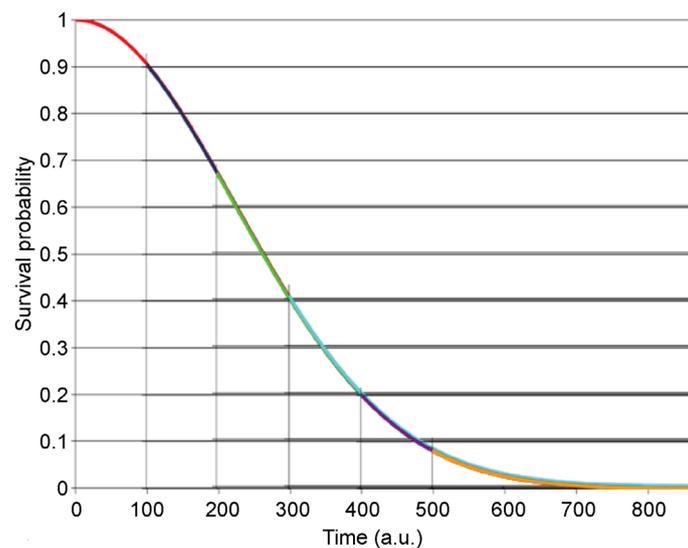
This gives a “truncation” possibility of this basic (Equation (7), hypothetical) overall survival plot (Figure 4).

Following the complete survival until the last event (or censoring) in the studied group of patients, the start of the study will be at the shifted time, which determines the truncations of the basic WF to its parts (Figure 5).

The survival studies of different stages could be regarded as studies in shifted time (T_i), starting the observation of the patients (first diagnosis) a certain time later than the guessed start (stage 0) of the malignant process. The new start is of course regarded as a new study, considering again 100% of the patients who are involved in this stage, with a probability of 1. The truncated curves (Figure 5) considered as the new studies, that could be WF fitted with modified parameters.



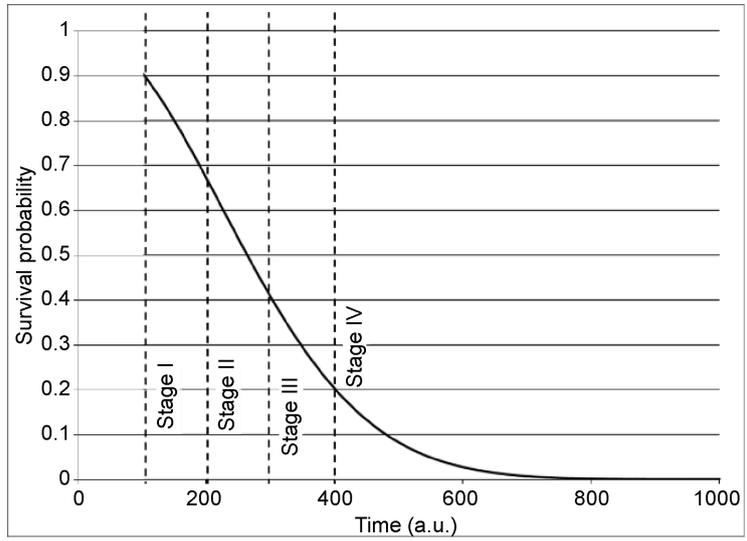
(a)



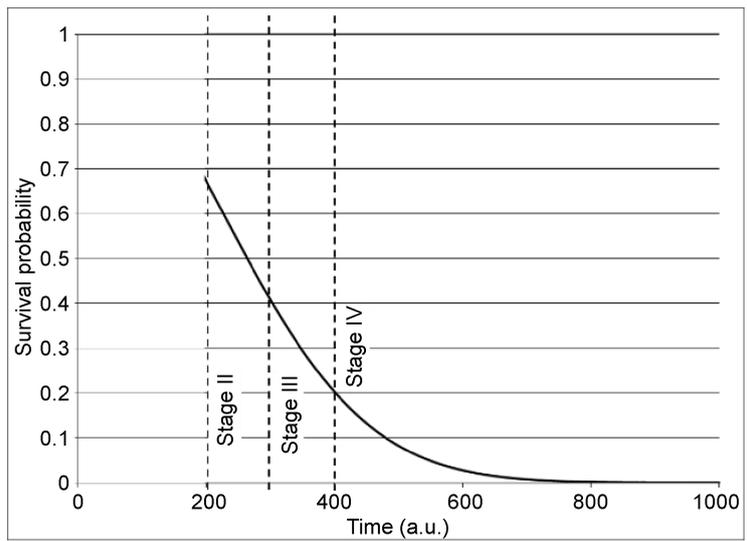
(b)

Figure 4. A hypothetical stage grouping of overall survival. 0: carcinoma in situ; I: well-localized lesions; II: locally advanced, affected the sentinel lymph-node; Stage III: regionally advanced, affected lymph-nodes; Stage IV: distant metastases. Parameters of the original WF are $n = 2$, $t_0 = 316$. (a) cut by stages, (b) various parts are colored.

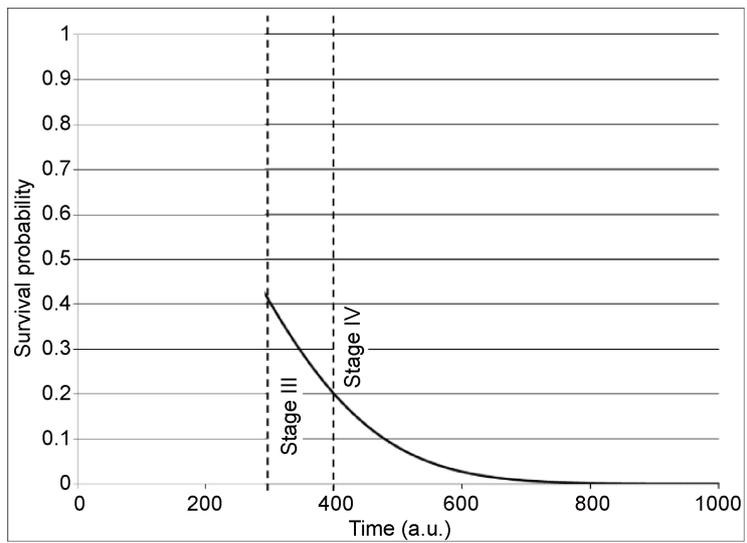
Screening could be misleading for survival evaluations because sometimes the elongation of overall survival with a certain time is an addition to the differences between the first diagnosis [51] and the overall survival. We expect that the earlier discovery of the tumor extends the survival by more than the time difference between the first diagnosis and the discovery of the symptoms. Consequently, a certain change of the scale factor (t_0) does not consider any treatment in the truncated periods due to the obvious shortening of the survival when we truncate the constant WF function. Of course, despite the unchanging type of the tumor, there is no guarantee for the constant shape-factor of survival in various stages. The change of the tumor-size changes the micro- and macroenvironment



(a)



(b)



(c)

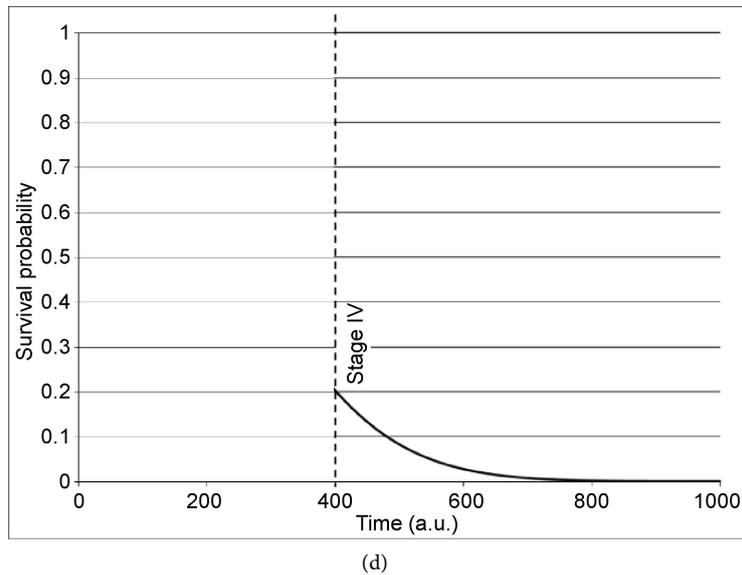


Figure 5. The remaining parts of the original (basic) WF truncated accordingly to the subsequent stages. (a) The tumor is diagnosed in stage I; (b) The tumor is diagnosed in stage II; (c) The tumor is diagnosed in stage III; (d) The tumor is diagnosed in stage IV.

of the tumor, reorganizes the complete structure in the lesion, so the shape parameter also changes. Note, that normally different tumors can be detected in different stages. For example, most of the breast and cervical cancers are detected in the stages 0 or I, while lung cancer is usually detected in stage III or IV, depending on the observed symptoms or the accident screening without indicated complaints of the patient. Due to the developing technical conditions, the complete process depends on the historical time of the screening.

Considering T_i , the shift for the studies in subsequent stages, we get:

$$W_i(t) = e^{-\left(\frac{t+T_i}{t_0}\right)^{\eta_i}} \tag{11}$$

The T_0 is the start of the observational period: optimally the immediate treatment, or at least the watchful waiting (watch and wait, WAW period); when the treatment cannot be decided yet. For simplicity we consider the studies as time-to-event (TTE) data, where time is denoted from a starting point to a certain event, such as death. When the end of the study fixed differently, we must use the fit shown in (2). All studies start as new one, of course, there is no knowledge about the unmeasured early treatments; consequently, survival probability at the start of the treatment is 1, irrespective of when it started. We show the later starting points in the time-line of the disease in **Figure 6**.

We start counting the elapsing time from T_i , by time-shift in (12). The complete time-scale is shifted by T_i value. The number of patients at the starting of the trial is considered 100% for *KM*, consequently, the truncated “remains” must be normalized to 1 to be able to fit with WF fitted. Usually the cancer in T_0 does not cause symptoms for the patients. When the symptoms appear, and a

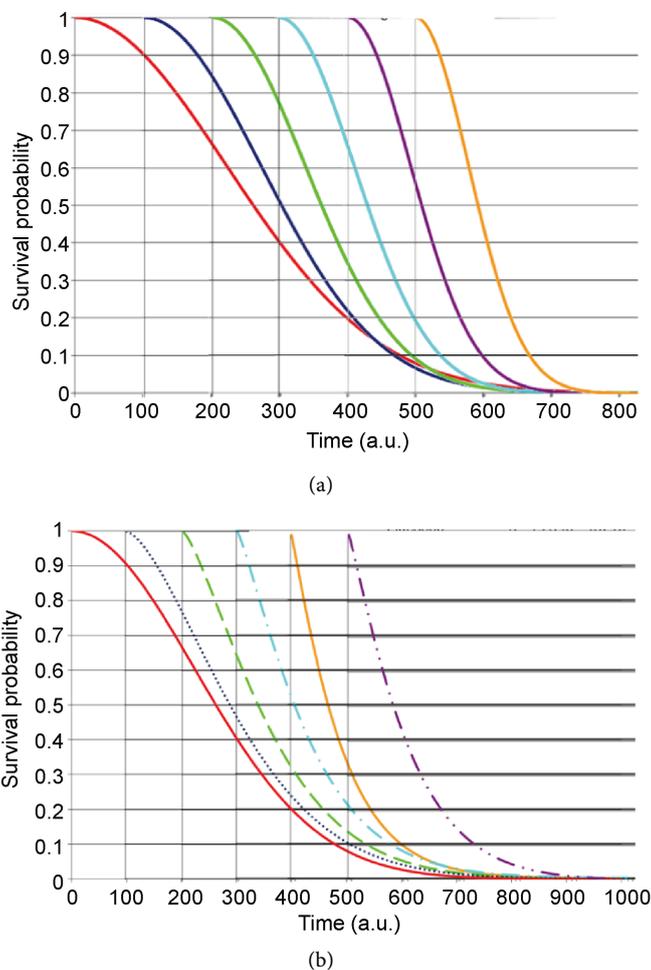


Figure 6. Late starts and WF-fits to the truncated curves that are shown in **Figure 5**. The original WF parameters: $n_b = 2$, $t_0^{(b)} = 316$, (solid line). (a) Curves have the same shape parameter as the original, but the treatment was started in one of the subsequent T_i time; $T_0 = 0$, $T_1 = 100$, $T_2 = 200$, $T_3 = 300$, $T_4 = 400$, $T_5 = 500$, the shape parameter is a fixed constant as the characteristic value of the actual disease. (b) is the same as (a), but WF is optimally fitted to the new conditions, therefore the shape parameter decreases.

patient recognizes the problem, it is usually in a later stage, when a higher number of cancer cells are already present, or even when they have already been disseminated from the local site. The WF fittings to the truncated “remains” (not showing the carcinoma in situ 0th stage), are shown in **Figure 7**. Calculation of the shape scale factors was made when the shape kept being constant (meaning the disease is the same in all the studies, irrespective of its starting time). Another calculation showed an optimal Weibull fit, when both the scale and shape factors changed. The idea is that in spite of the same disease, the late start met different conditions of the disease from the in-time beginning.

The curves in **Figure 7** could be considered as the start of the treatment in various stages (or TNM state) of the disease. The n_i and $t_0^{(i)}$ parameters have

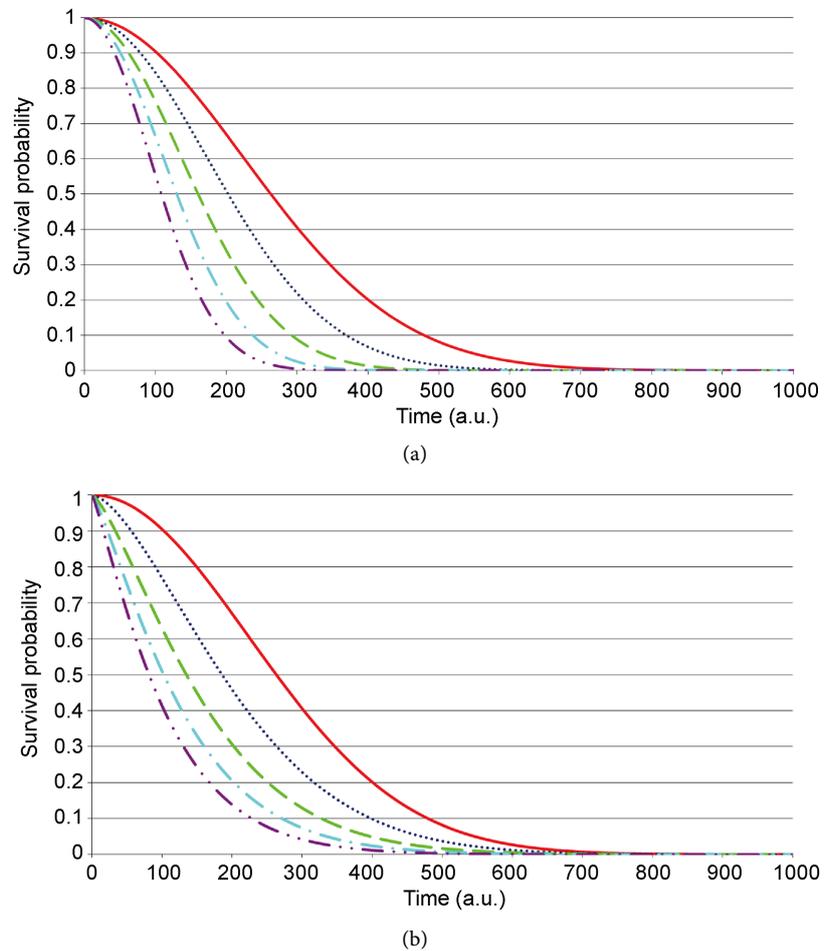


Figure 7. WF fits of late starts on truncations which are shown in **Figure 5**. The original WF parameters: $n_b = 2$, $t_0^{(b)} = 316$, (solid line). (a) Curves have the same shape parameter as the original. Other parameters are: $T_1 = 100$, $t_0^{(1)} = 234.6$, (dotted line); $T_2 = 200$, $t_0^{(2)} = 192.8$, (dashed line); $T_3 = 300$, $t_0^{(3)} = 156.6$, (dashed-dotted line); $T_4 = 400$, $t_0^{(4)} = 130.5$ (dashed-double-dotted line); (b) Curves are modified by shape for best fit. The parameters: $T_1 = 100$, $n_1 = 1.57$, $t_0^{(1)} = 234.3$, (dotted line); $T_2 = 200$, $n_2 = 1.35$, $t_0^{(2)} = 176.7$, (dashed line); $T_3 = 300$, $n_3 = 1.23$, $t_0^{(3)} = 137.9$ (dashed-dotted line); $T_4 = 400$, $n_4 = 1.16$, $t_0^{(4)} = 111.3$ (dashed-double-dotted line).

logarithmic dependence on the T_i late start time in **Figure 8**.

In reality, the real *KM* curve could be decomposed to at least two components like it is shown in (2). An example is shown in **Figure 9**, where the disease is characterized by the same shape factor, only the scale factor changes from 1 y (non-responding) to 10 y (responding) situations. When the later start of the study is linearly changed we assume linearity of the decomposition factor too.

The form of **Figure 9** shows the general figures of the comparison of studies started in different stages of the same malignant disease well.

The late (at a more serious stage) start of the treatment is not the only challenge in the evaluation. Another common challenge at the *KM* evaluation is the

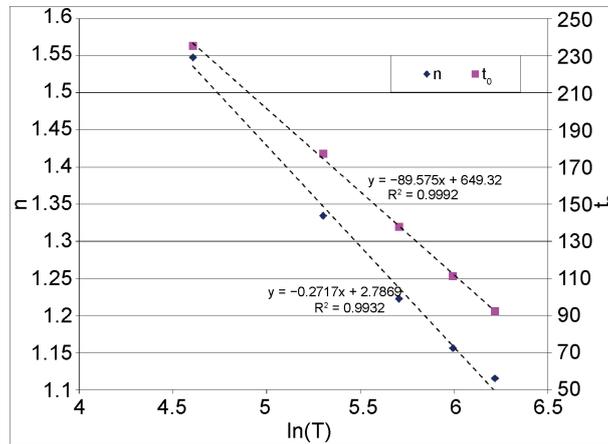


Figure 8. Fits n_i and $t_0^{(i)}$ vs. $\ln(T_i)$ when the original WF ($n_0 = 2$, $t_0^{(b)} = 316$) had been truncated [$n(T) = -0.27\ln(T) + 2.79$, ($r^2 = 0.993$) and $t_0(T) = -89.58\ln(T) + 649.3$, ($r^2 = 0.999$)] (data are from **Figure 7(b)**).

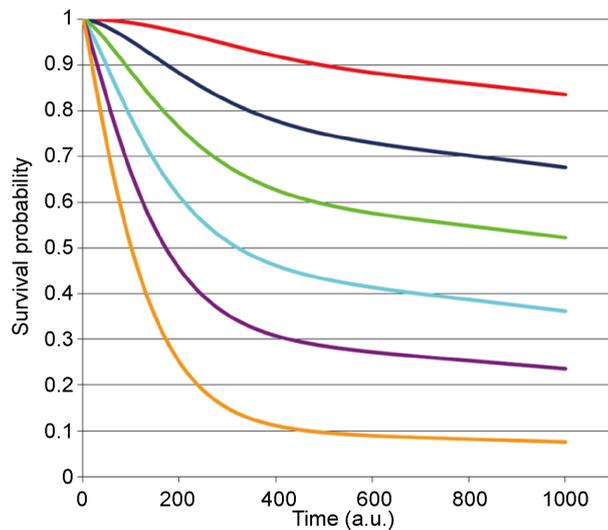


Figure 9. The KM curves for different stages (the study started at different times), where the KM is decomposed from two WFs. Original WFs for responding and non-responding patients have: $t_0^{(RP)} = 3650(10 \text{ y})$, $t_0^{(NP)} = 365(1 \text{ y})$; $n^{(RP)} = n^{(NP)} = 2$. The actual decomposition factors from up to down are $c_0^{(RP)} = 0.9$, $c_1^{(RP)} = 0.75$, $c_2^{(RP)} = 0.6$, $c_3^{(RP)} = 0.45$, $c_4^{(RP)} = 0.3$, $c_5^{(RP)} = 0.1$ to the late-start times $T_0 = 0$, $T_1 = 100$, $T_2 = 200$, $T_3 = 300$, $T_4 = 400$, $T_5 = 500$, respectively.

end-time of the study. Most of the clinical studies have limited time for follow-up, so they are usually finished before all involved patients are deceased or censored, and they do not force the TTE condition. At the end of the study, a certain group of patients remains (patients at further risk, *PFR*), or patients are completely cured (PCC). Identifying the PCC group in the practical applications is very unprecise, and by definition, the *PFR* at five years point regarded as PCC. However, there are doubts about this strict limit [3], so we use the *PFR* only, without declaring the PCC. The end-time-point of the study is the preplanned

goal, and the patients in the *PFR* group are censored at this point. This time-limit causes a certain early truncation of the hypothetical overall-survival curve. The hypothetical curve fit to *KM* is WF when the study goal is TTE; so it would be continued to the complete end (all patients deceased or censored, no patients are at risk). The finish-times (F_i) define the *PFRs* in actual points, when N patients were involved in the study:

$$\frac{PFR_i}{N} = \exp\left(-\left(\frac{F_i}{t_0}\right)^n\right) \tag{12}$$

where the PFR_i values are patients that are alive (they are at risk, belonging to the actual *PFR*) at the early finish time when the actual study ends. When the study finishes before all events happen at F_i , the patients at risk is PFR_i , and the number of events (loss of patients due to death or censored) until this point will be: $(N - PFR_i)$. The finish of the study (F_{last}) is when a single patient remains at risk ($PFR = 1$), and censored from the initial set of N individuals,

$$F_{last} = t_0 \left(-\ln\left(\frac{1}{N}\right)\right)^{\frac{1}{n}} \tag{13}$$

According to the Hardin-Jones-Pauling's (HJP) biostatistical theory [52] [53], we expect the death of the last patient by the time of the average survival of the actual study is after the trial is closed. Consequently, the hypothetical complete length of the study would be

$$F_{end} = t_0 \left[\left(-\ln\left(\frac{1}{N}\right)\right)^{\frac{1}{n}} + \Gamma\left(1 + \frac{1}{n}\right) \right] \tag{14}$$

The early finished studies, when a certain number of patients remain in risk are shown by an example in **Figure 10**.

The studies finishing early have a slight shift in t_0 when elongating them and the number of patients at risk decrease (**Figure 11**).

4. Discussion

Both the two independent Weibull parameters change by inclusion criterial of staging. Both the shape and the scale factors are decreased when treatment starts later, which is natural. In case of an unchanged n shape-character, the decrease of the scale factor is less than in case of a changing n .

Using (9) we get:

$$t_0^{(i)} = t_0 \left(\frac{E_i(t)}{E_0}\right)^{-1/n_i} \Rightarrow E_i(t) = E_0 \left(\frac{t_0^{(i)}}{t_0}\right)^{-n_i} \quad (i = I, II, III, IV \text{ stages}) \tag{15}$$

Expression (16) allows an approximating of the metabolic rate from the change of $t_0^{(i)}$ by WF fit to various *KM* non-parametric estimates. Metabolic activity could be measured approximately by positron emission tomography (PET), evaluating the standardized uptake value (*SUV*) of the radiolabeled tracer

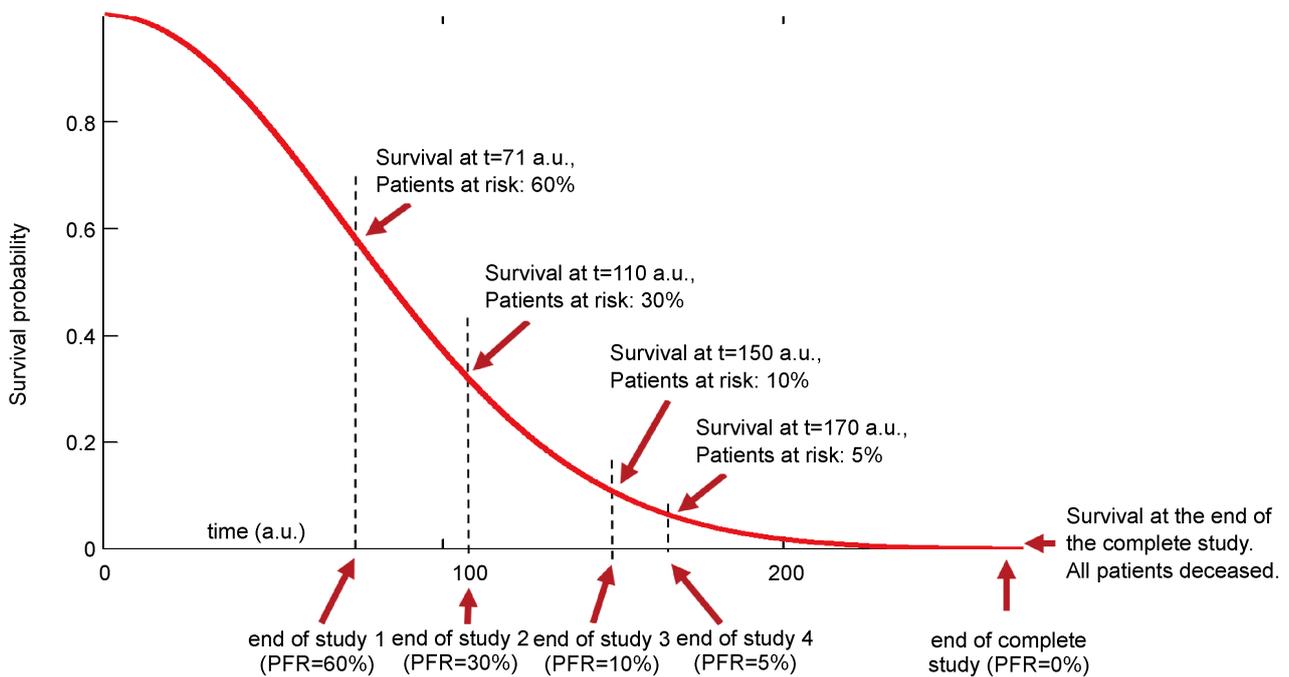


Figure 10. The hypothetical variation of the finishing of a study when a certain number of patients remain at risk (The parameters of basic WF are $n = 2$; $t_0 = 100$, $N = 100$).

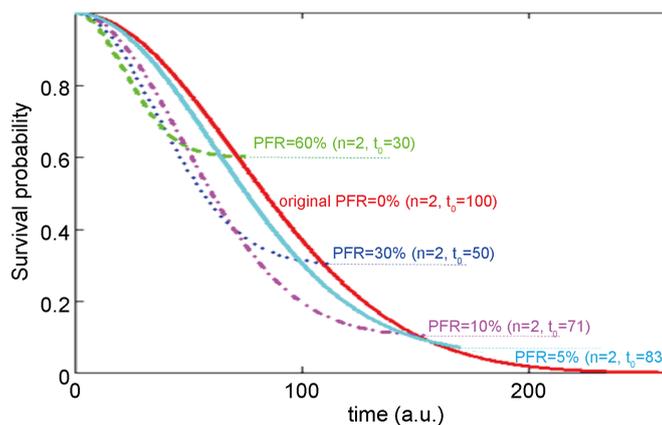


Figure 11. The different studies finished before all events happen ($PFR = 5, 10, 30, 60$ percentages). Note the changes of the t_0 value. The parameters are 83, 71, 50, 30 time units, respectively. The parameters of the complete *KM* are $n = 2$; $t_0 = 100$, $N = 100$.

2-deoxy-2-[18F] fluoro-D-glucose (FDG) uptake in tumors in various stages at the start of the trial (SUV_i), so:

$$\left(\frac{E_i(t)}{E_0}\right) = \left(\frac{t_0^{(i)}}{t_0}\right)^{-n_i} \Rightarrow \left(\frac{SUV_i(t)}{SUV_0}\right) \approx \left(\frac{t_0^{(i)}}{t_0}\right)^{-n_i} \quad (i = I, II, III, IV \text{ stages}) \quad (16)$$

where SUV_0 is the FDG uptake of the neighboring healthy tissue. The metabolic ratio, calculated by $\left(\frac{t_0^{(i)}}{t_0}\right)^{n_i}$ at the late start process above gives a quite

accurate linear dependence from the T_i late start time (Figure 12).

In this way we could also approximate the basic survival curve, when the PET is actually sensitive enough to measure cancer in situ lesions, supposing the time when the tumor starts to form in a microscopical region and its clusters are still undetectable with our present diagnostic methods.

The treatment of the chosen patient cohort is expected to change the KM of the active arm compared to the control arm, which is untreated with the same protocol, and formed from the same cohort. The changes of KM in active arm will modify the WF fit, too. The measured change of metabolic rate by SUV indicates the effect of the actual treatment. When the malignant tissue shows a lower metabolic rate (lower SUV ratio) the treatment regarded effective. The lower SUV has a longer scale parameter (t_0) according to (17). In case of a successful treatment, the shape-parameter (n) decreases, “smooths” the probability of event with a longer, heavier tail.

The question is: how the situation changes by treatments in the study? The WF changes of course and the evaluation use this change to compare it to the reference (control arm) WF. There are different parametric estimations for the result. The first attempt is always the median survival, which looks undecided about the efficacy of the treatment in the measuring process. However, this single parameter is not nearly enough to see the complete picture. It is possible that the treatment is effective without the change of the median of the KM , while the distribution has a long tail; patients over the median lifetime live longer. for example Figure 13. It can happen when the mortality of the disease is very rapid, and the development of the resistance made by the treatment needs a longer time compared to the median survival.

For the decision of the efficacy we must use an information parameter from the WF, an important parameter of a probability distribution: the Shannon-entropy (S_{Sh}) [54], as it is discussed in the first part of this series [27]. The SE parameter measures the diversity of probability density function (pdf), which is in the case of Weibull distribution:

$$S_{Sh}(n, t_0) = \gamma \left(1 - \frac{1}{n} \right) + \ln \left(\frac{t_0}{n} \right) + 1 = S_{Sh1}(n) + S_{Sh2}(t_0) \quad (17)$$

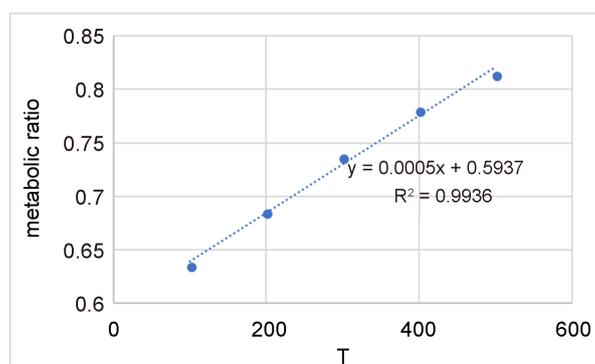


Figure 12. The metabolic ratio (approximate SUV ratio) vs. T is late start time.

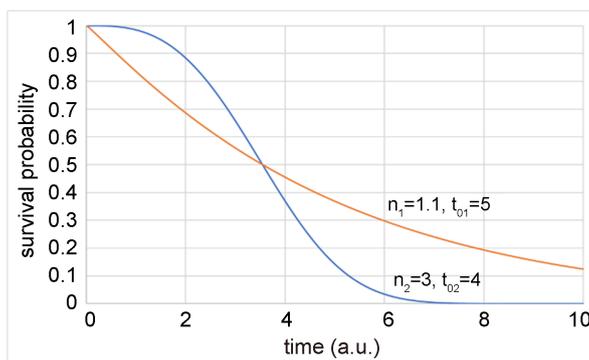


Figure 13. The two-survival function has the same median ($=3.54$). However, the survival curves are very different ($n_1 = 1.1$, $t_{01} = 5$; $n_2 = 3$, $t_{02} = 4$), which treatment is more effective? Shannon entropy decides.

where γ is the Euler-Mascheroni constant: $\gamma \cong 0.5772$, and

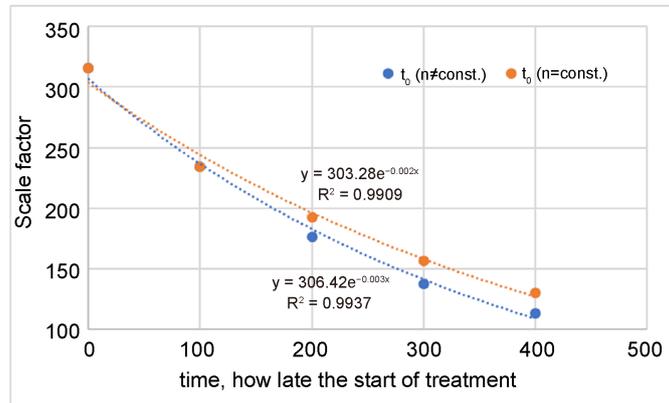
$$S_{Sh1}(n) = \gamma \left(1 - \frac{1}{n} \right) - \ln(n) + 1; \quad S_{Sh2}(t_0) = \ln(t_0) \quad (18)$$

The information source of S_{Sh} is produced by a stochastic data-source, like the probability distribution of the survival time. In the simple formulation, it refers to the amount of uncertainty about an event associated with a given probability distribution. At the probability of the survival, this directly means, that the decreasing entropy shows the increasing probability of death. The easiest way to decide the advantage of a treatment which changes the parameters of the WF, is with this parameter, because the survival is better when S_{Sh} is higher. It is due to the meaning of the entropy: a larger entropy means less information and a higher uncertainty of death. Visualizing it on the image of the pdf, it has more located peak when n grows, and its width is shrinking by t_0 , therefore both make death more definite. The growing n and decreasing t_0 both decrease the entropy, making the certainty of death higher. In the case of **Figure 13**, the entropies are $S_{Sh1} = 1.67$ and $S_{Sh2} = 2.58$, consequently the survival with $n_2 = 3, t_{02} = 4$ parameters is worse than the survival characterized by $n_1 = 1.1, t_{01} = 5$.

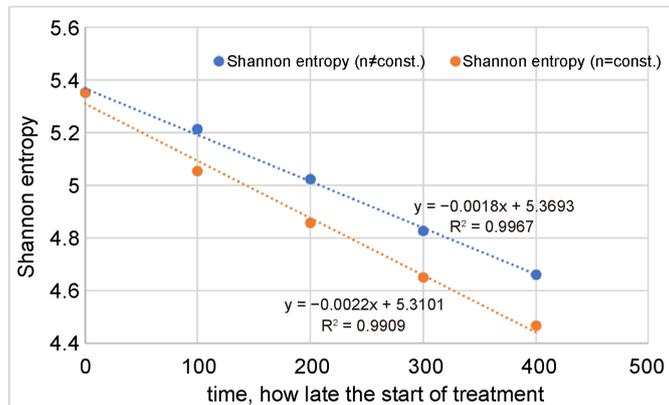
The entropy evaluation in the case shown in **Figure 7** is presented in **Figure 14**. The lower chance of survival is shown well by the decrease of the entropy with the late start times (T_i). This is complete correspondence with the expectations: the later cancer diagnosis decreases the prognosed survival.

Interestingly, despite the more moderate decrease of the scale factor when the shape factor decreases in optimal fit, the Shannon entropy shows an advantage for these optimal WF sets, compared to the constantly fixed shape. The reason is that the patients with longer survival time are fit for the later start of the treatment and were selected by their other, less hazardous conditions than the others.

The Shannon entropy can be evaluated for late-start treatments (treatments in various stages of the tumor) like that it is shown in **Figure 9**. The Shannon entropy



(a)



(b)

Figure 14. The scale factor and the Shannon entropy in the stages of late treatment time shown in **Figure 7**. (a) The scale factors, (b) Shannon entropy values.

for non-responding patients (group A), and for responding ones (group B) is shown in **Figure 15**. The decrease of the entropy well shows the increasing certainty for events.

The Shannon-entropy decreases the number of patients at risk linearly, due to the increasing certainty of death (**Figure 16**).

We assume, that no extra comorbidity developed (or at least it is controlled) over the elapsed time, consequently, we kept the original two parameters (shape and scale) unchanged, regarding the same cohort of patients participated; only their study started in different F_i times. When we calculate with the developing comorbidities, then both parameters of WF will be changed in a direction that S_{Sh} decreases, indicating a higher certainty of the event.

5. Conclusion

We discussed a method of data mining from the single-arm clinical study without a reference group. We studied the possibility to open the hidden information in the measured Kaplan-Meier non-parametric estimate by the composition of proper parametrization of cumulative Weibull functions. We had shown the

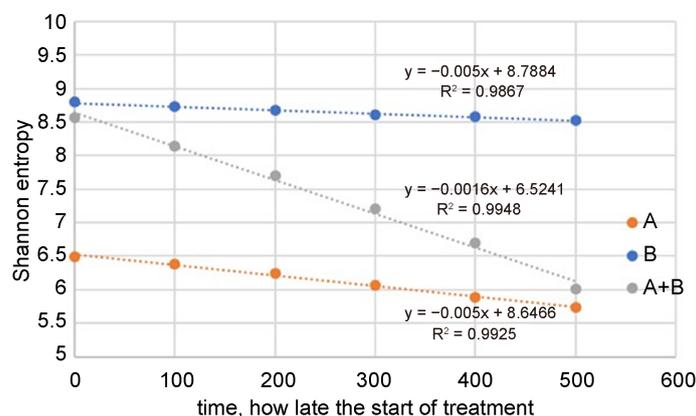


Figure 15. Shannon-entropy decreases in both the non-responding (A) and responding (B) groups of the patients. The change is 10 times more rapid for non-responding group. The composite of the real overall survival (measured KM) from these components shows the entropy-change more characteristically (The evaluation is made for the KM curves in **Figure 9**).

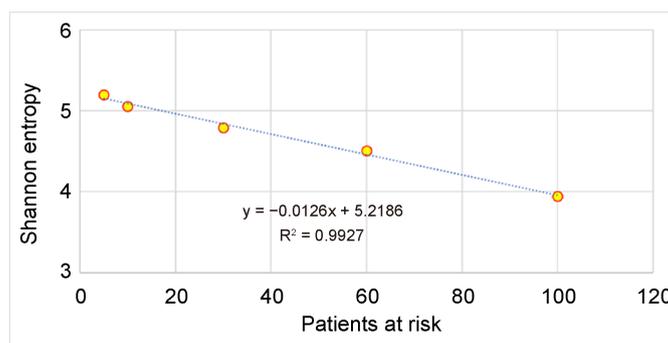


Figure 16. Shannon-entropy decreases by the number of patients at risk (Original WF: $n = 2$; $t_0 = 100$, $N = 100$).

changes of the two independent parameters of the Weibull cumulative distribution by the study design, namely their dependence on the inclusion criteria (staging) and the intended end-point (finishing). We had shown that the various studies with different inclusion and exclusion criteria and different endpoints could be well described by the decomposition method. The fit of these results to real studies in clinical applications will be shown in the next part of this series of articles.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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