Evaluation of clinical studies when no reference arm exists

Andras Szasz

St. Istvan University, Dept. Biotechnics, Hungary

E-mail: biotech@gek.szie.hu

Presented at the 37th ICHS, Thessaloniki

Cite this article as:
Szasz A. (2019): Evaluation of clinical studies when no reference arm exists, Oncothermia Journal 27: 174- 187
www.oncotherm.com/sites/oncotherm/files/2019-10/Evaluation_of_clinical_studies.pdf

In the advanced metastatic stages of the malignant diseases the standard curative therapies usually fail, and the patient receive palliative care only. In the case of modulated electro-hyperthermia (mEHT, tradename oncothermia) this situation is common. The patients come to mEHT when no other curative therapy is available, and mEHT tries to turn the simple palliation to the curative therapeutic approach again. This could be with resensitization of the standard conventional therapies or applied mEHT in monotherapy regime together with the best supportive care. The treatment setup in these cases is very individual, it depends on the previous treatments and their results, the reason of the inapplicability of conventional methods (like organ failure, hemato-complications, refractory status, intolerable side effects, comorbidities, etc.). Due to the broad spectra of the patients and the missing availability of other active treatment for comparison form randomized, the double arm is impossible.

Furthermore, sometimes highly personalized therapies combined with mEHT block the collection of the homogeneous group and limit its double-arm randomization. Due to the above problems, many clinical trials have prospective or retrospective datasets without comparison to the control-group formed by the same cohort as the active one. The measured single arm naturally contains the relevant information; however, in most of the cases, it is impossible to obtain it from the complex survival curve without a reference. Our objective is to discuss the situations of the single arm evaluation. We give a method for the mining of information from single arm study 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 psychometric poly-Weibull fit. With the Weibull decomposition of the survival curve, we can fit at least two subgroups of patients. The weighted sum of the decomposed fractions could be optimized analytically and determining the best parameters of the components and the best composition ratio of the weighted sum is also possible. We will show how the method works in a real clinical environment through mEHT as a complementary method, applied curatively when no other conventional curative therapies are available. The decomposed function of the non-responding group provides an excellent agreement with the historical controls in the investigated group of patients with pancreatic cancer and non-small-cell-lung-cancer studies.

37th Conference of
International Clinical Hyperthermia Society
Thessaloniki Greece, September 19-21, 2019

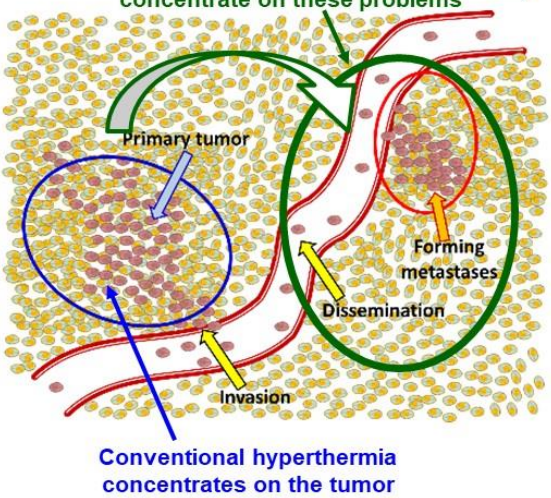
Evaluation of clinical studies, when reference arm doesn't exist

Andras Szasz, Ph.D.
Professor, St. Istvan University
CSO of Oncotherm Group

Outline

- ❑ The problem of the evidences in advanced diseases
- ❑ The general behaviour of the survival curves
- ❑ The strategies of studies
- ❑ Evaluation examples: pancreas, lung, glioblastoma

Challenge of hyperthermia in oncology



The challenge of evidence based statistical evaluation:

patients are **heavily pretreated**, having large variety of advanced stages with metastases, relapses

⇩

they are in fact in the **palliative** phase only

⇩

no cohort can be collected

⇩

prospective or retrospective single arm study can be only constructed

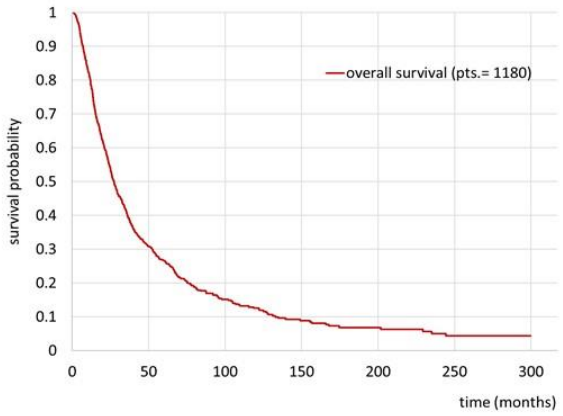
How to deal with this challenge?

Outline

- ☑ The problem of the evidences in advanced diseases
- ❑ The general behaviour of the survival curves
- ❑ The strategies of studies
- ❑ Evaluation examples: pancreas, lung, glioblastoma

The survival curve

Well-known **Kaplan-Meier** non-parametric estimation shows survival probability by time



Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and practices. Springer Science, Heidelberg

The Kaplan-Meier estimate contains **all relevant information,** only we are **not able to filter it** (missing reference)

The survival has special self-similar behavior, because the **step-wise** growing of the tumor.

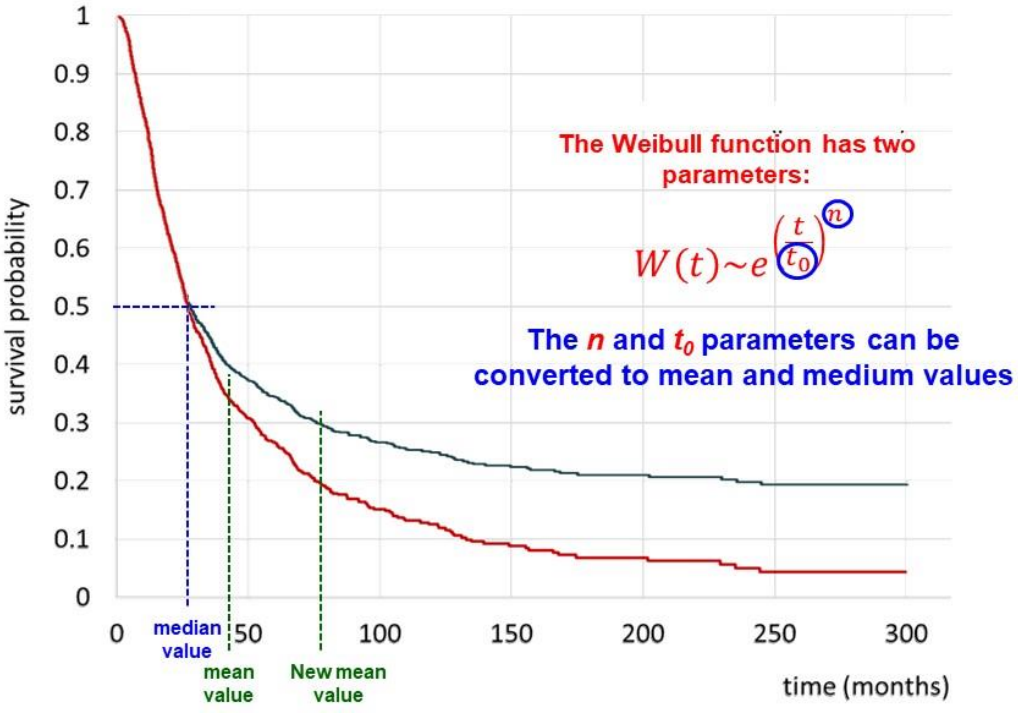
All new cells met the condition of the **microenvironments** produced by the cells in previous steps

The **self-similar** development could be followed by the physiologic-psychologic function:
Weibull-function

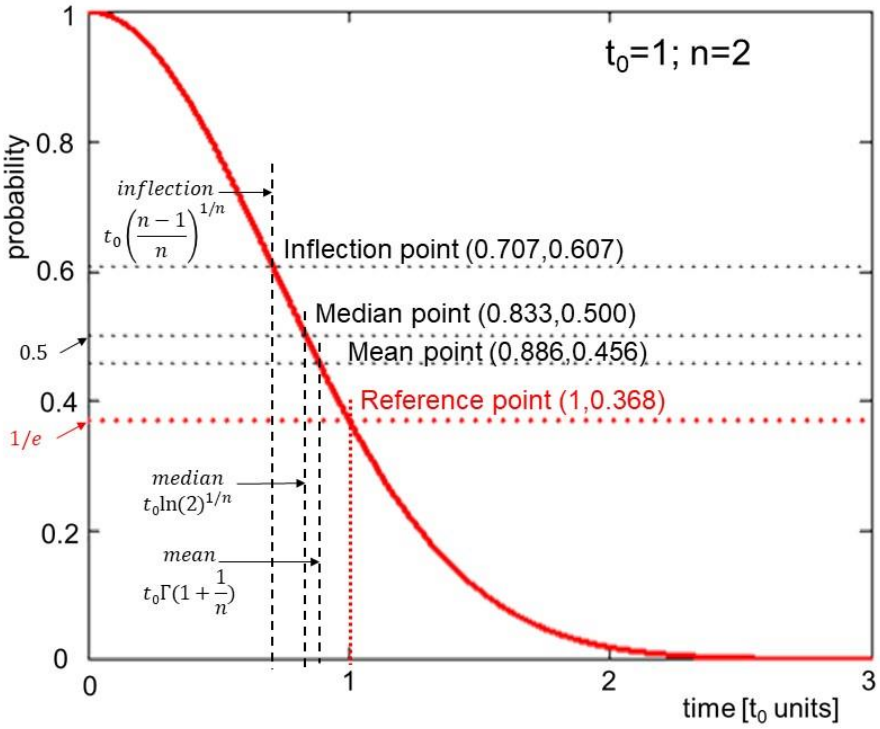
$$W(t) \sim e^{\left(\frac{t}{t_0}\right)^n}$$

where t is the time, t_0 is a scale factor and n is a form factor

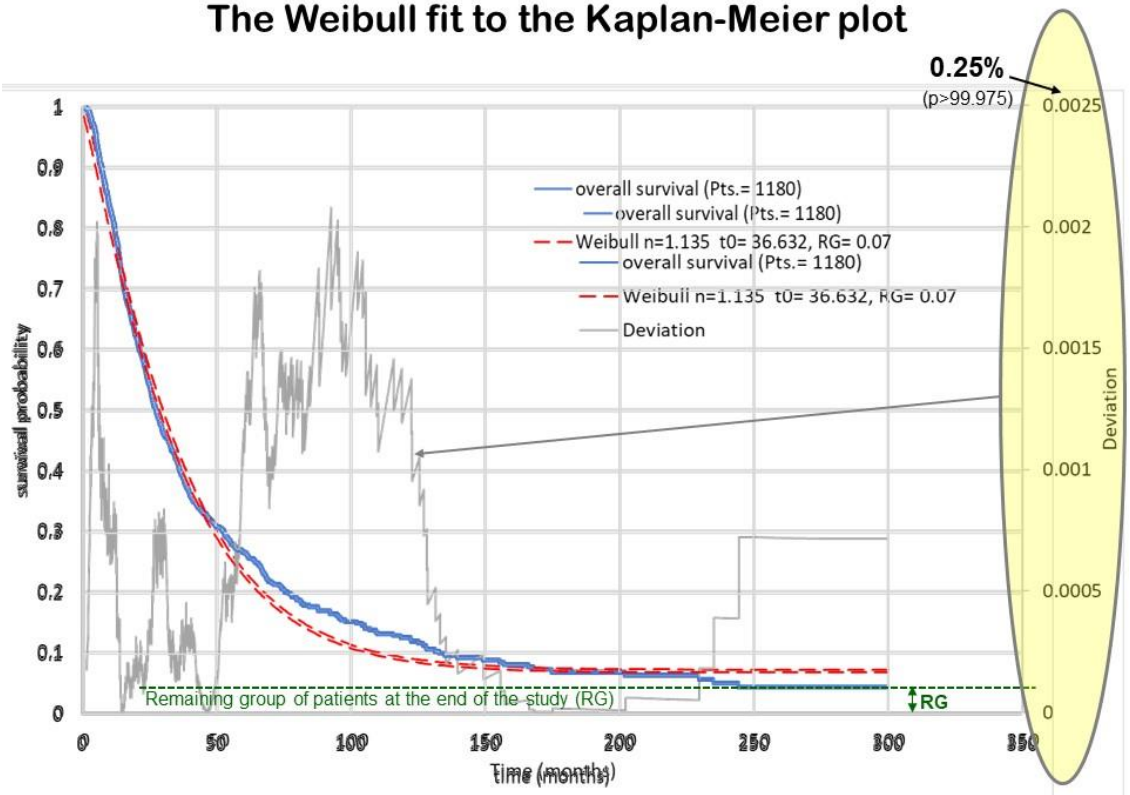
Two parameters characterize the survival curve



The Weibull function

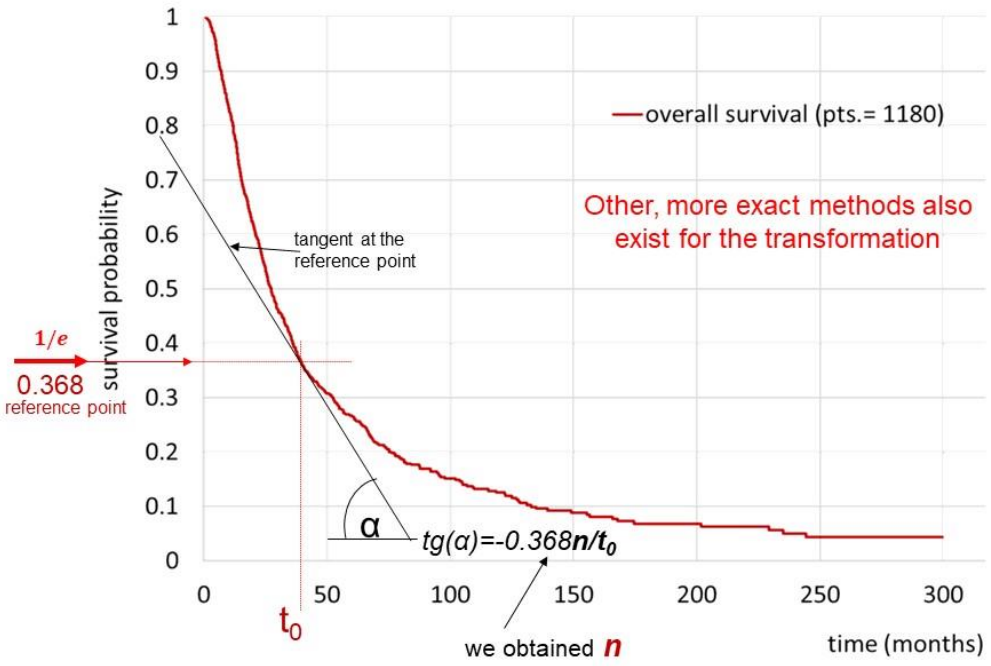


The Weibull fit to the Kaplan-Meier plot



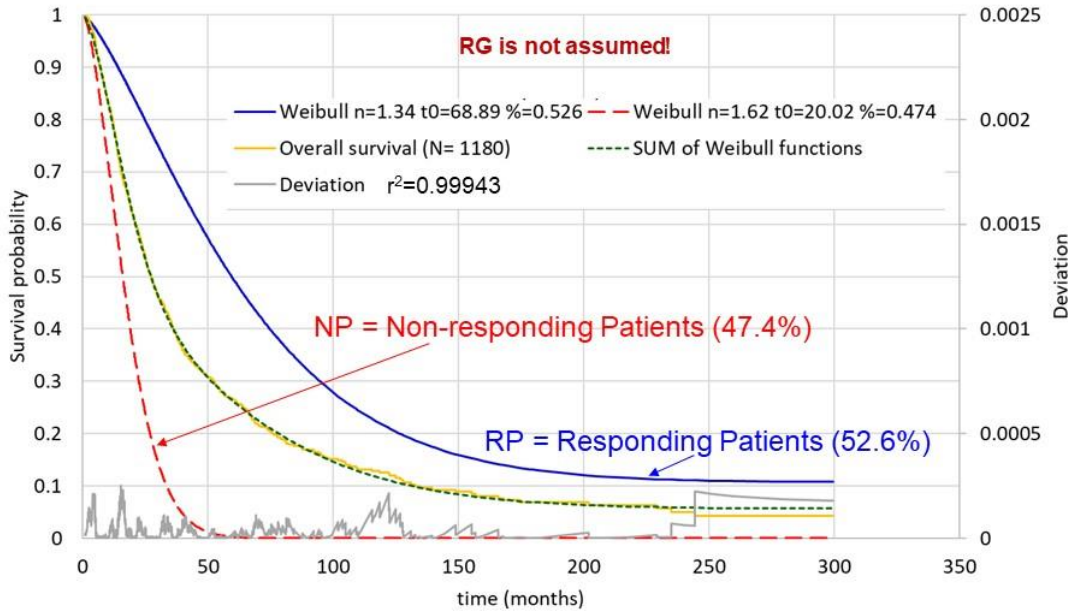
Two parameter conversion in the survival curve

Two parameters, mean and median could be transferred to ***n*** and t_0



Calculating responding and non-responding patients

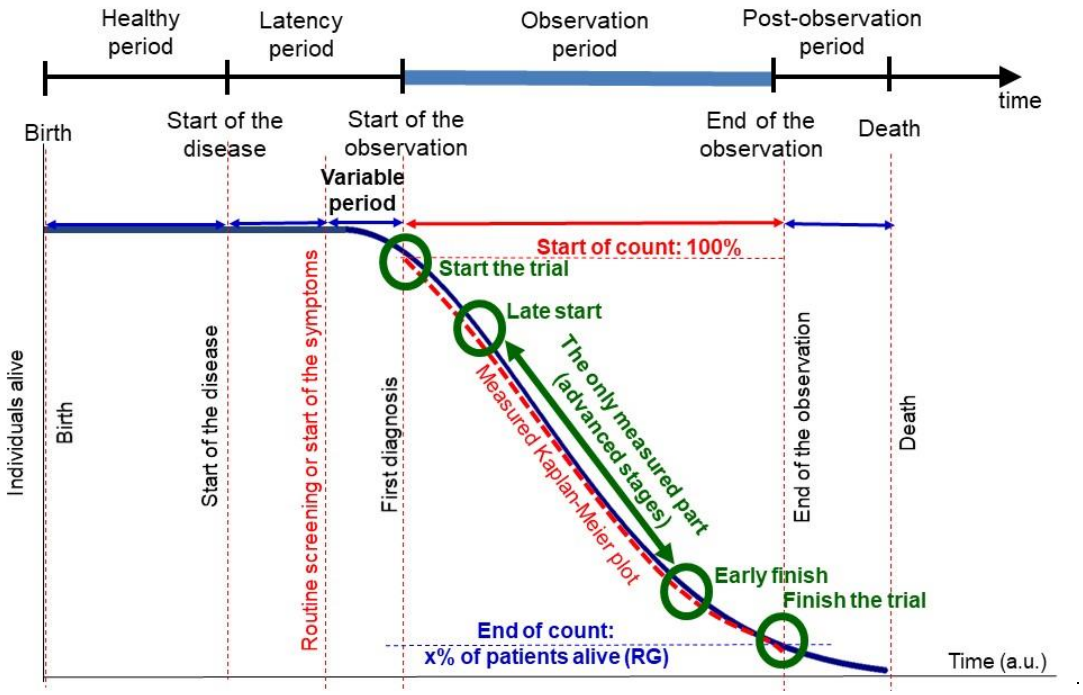
$$W^{(KM)}(t) = c_{RP}e^{-\left(\frac{t}{t_0^{(RP)}}\right)^{n^{(RP)}}} + (1-c_{RP})e^{-\left(\frac{t}{t_0^{(NP)}}\right)^{n^{(NP)}}}$$



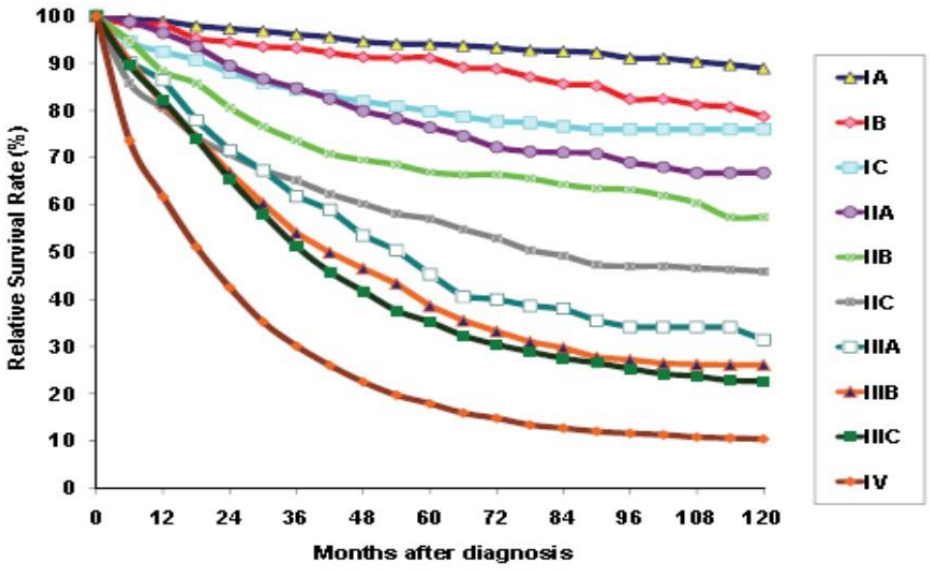
Outline

- ☑ The problem of the evidences in advanced diseases
- ☑ The general behaviour of the survival curves
- ❑ The strategies of studies
- ❑ Evaluation examples: pancreas, lung, glioblastoma

Complete life-span of the patient

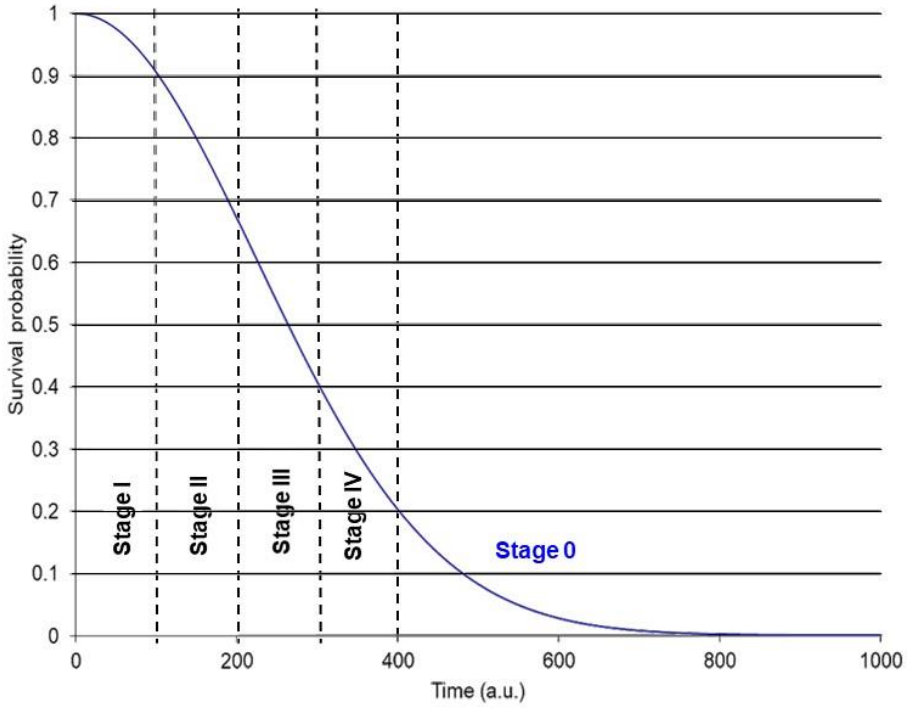


Trials for advanced stages (NSCLC)

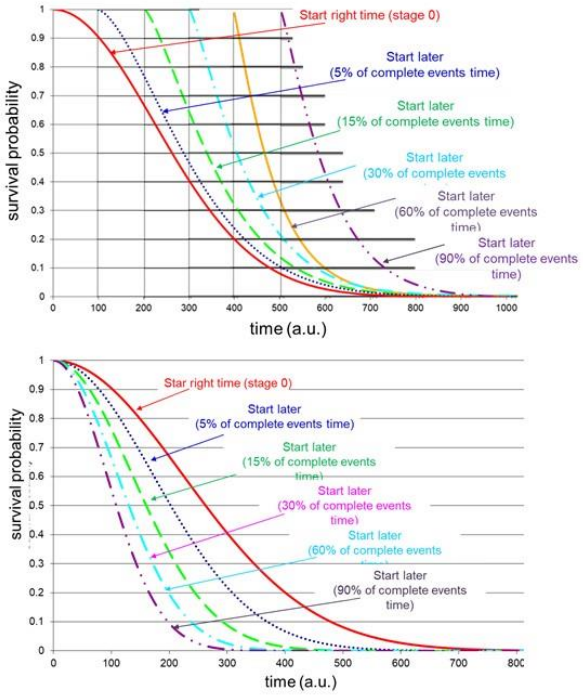


Late start challenge

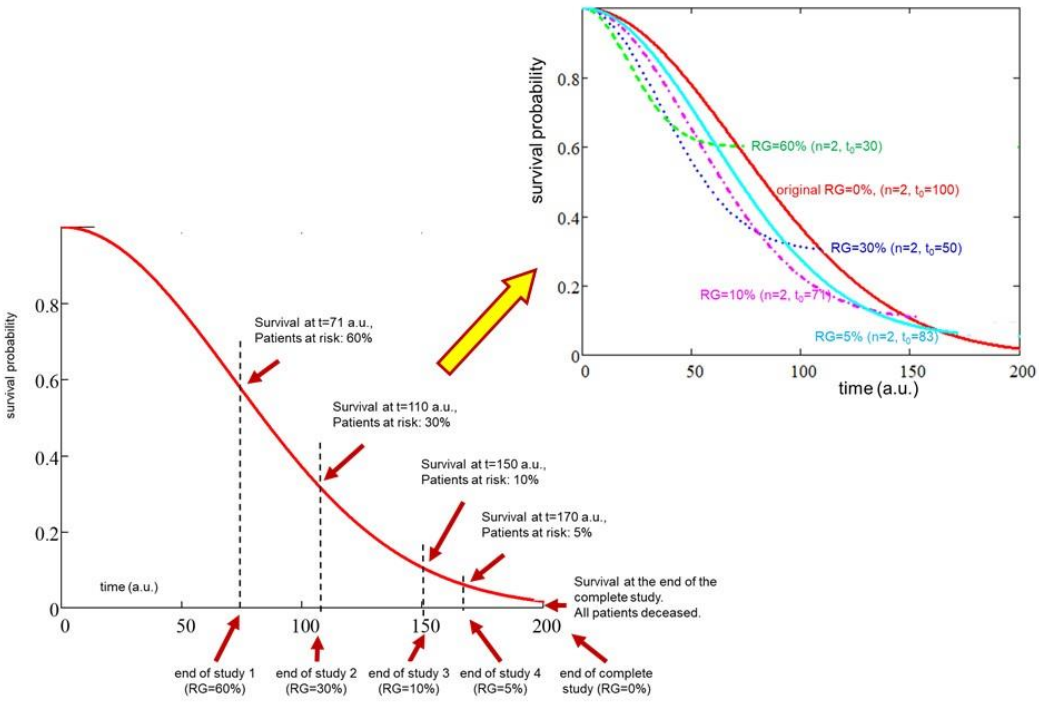
All late starts consider their start point as 100%, and starts at zero time



Consider every late start as 100%



The early end situation truncates the original plot



Outline

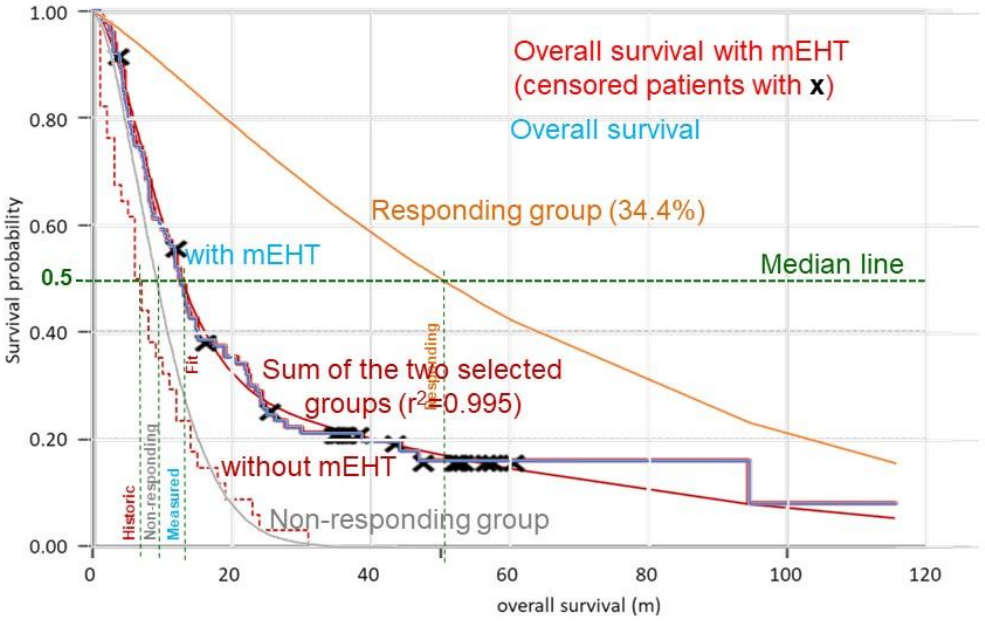
- ☑ The problem of the evidences in advanced diseases
- ☑ The general behaviour of the survival curves
- ☑ The strategies of studies
- ❑ Evaluation examples: pancreas, lung, glioblastoma

Study of inoperable advanced pancreas carcinoma

Dani A, et al. (2008) Clinical study for advanced pancreas cancer treated by oncothermia. Forum Hyperthermie 1:13–20

Number of patients
- active arm n=99 (73+26 two centers)
- control arm n=34 (historical control)

Decomposition to responding and non-responding groups

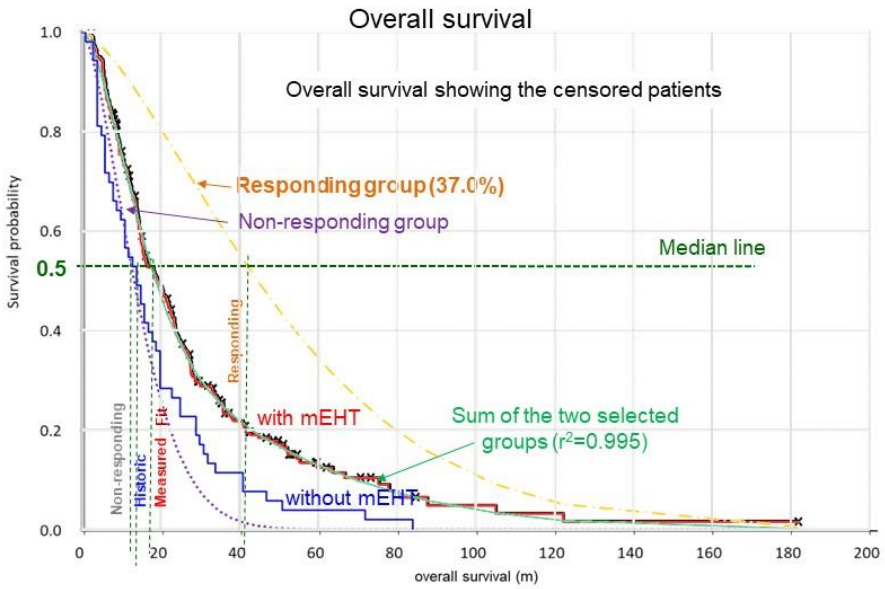


Study of advanced non-small-cell lung cancer

Szasz A (2014) Current status of oncothermia therapy for lung cancer. Korean J Thorac Cardiovasc Surg 47:77-93

Number of patients
- active arm n=258 (197+61 two centers)
- control arm n=53 (historical control)

Decomposition to responding and non-responding groups

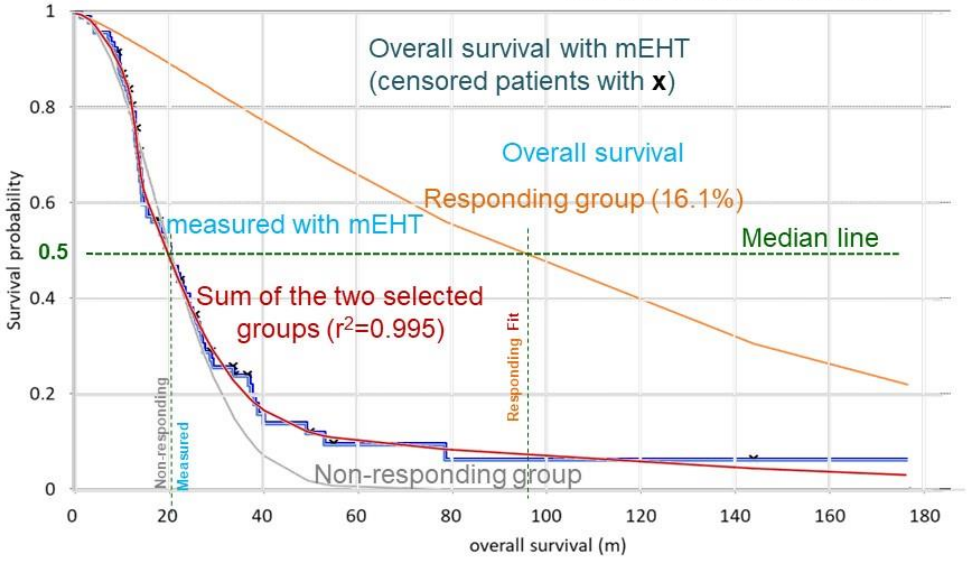


Study of advanced glioblastoma multiform, monotherapy

Sahinbas H, et al.(2007) Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas. Deutsche Zeitschrift fuer Onkologie 39:154–160

Number of patients
- active arm n=94 (single institution)

Decomposition to responding and non-responding groups



Modified Hardin-Jones-Pauling (HJP) method

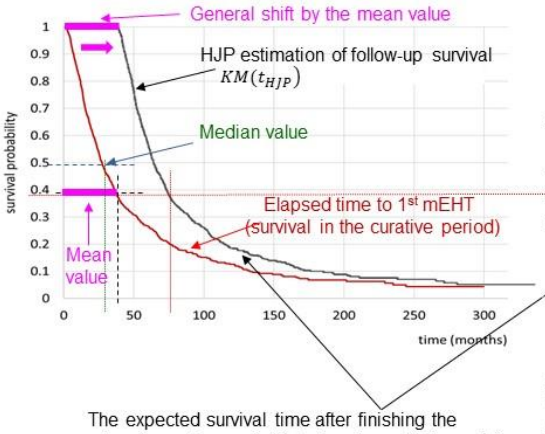
HJP argument: the expected survival of the patients in a follow-up time of a study is the average time involved in the study added to the final time of the observation.

Our assumption: the expected survival in palliative period can be calculated from its elapsed time

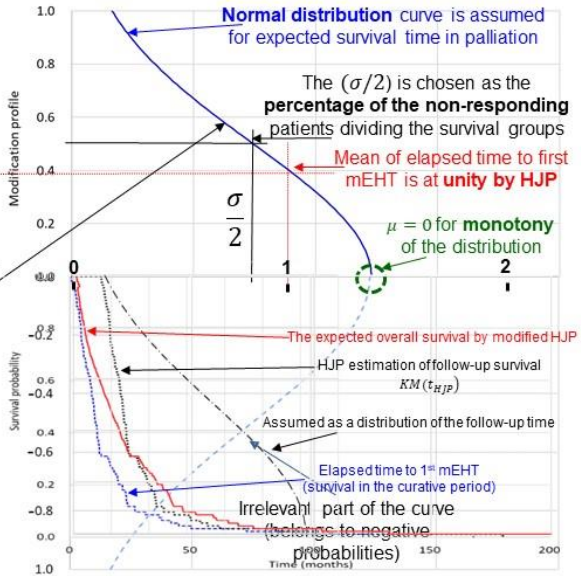
Challenge: Patient who had entered in palliative phase early has less probability to survive longer.

Modified HJP estimation

$$KMm(t_{HJP}) = \frac{KM(t_{HJP})}{\alpha\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(KM(t_e)-\mu)^2}{2\sigma^2}\right)$$

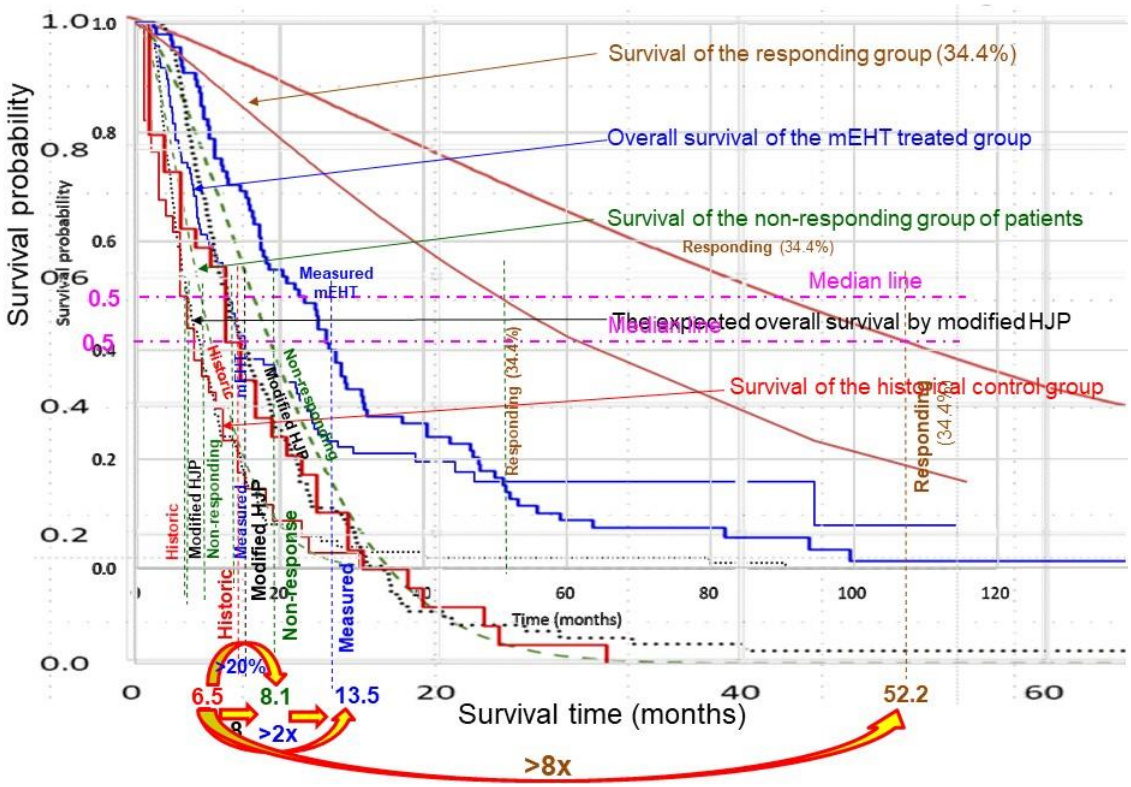


The expected survival time after finishing the conventional curative period (starting the palliative only) is the convolution of the HSP estimation and the normal distribution fit to the KM curve.



Pauling L, Herman ZS; (1989) Criteria for the validity of clinical trials of treatments of cohorts of cancer patients based on the Hardin Jones principle. Proc. Natl. Acad. Sci. USA, 86:6835-6837

Verification of modified HJP estimation



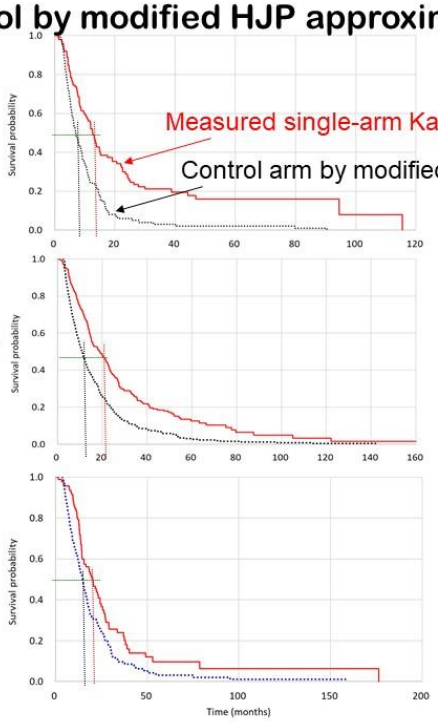
Quasi-control by modified HJP approximation

Overall survival

pancreas carcinoma

non-small-cell lung cancer

Glioblastoma multiform



The job is done

- ☑ The problem of the evidences in advanced diseases
- ☑ The general behaviour of the survival curves
- ☑ The strategies of studies
- ☑ Evaluation examples: pancreas, lung, glioblastoma

Thank you very much for your attention

Grant support: NVKP_16-1-2016-0042

PROGRAM FINANCED FROM THE NRDI FUND