Evaluation of clinical studies when no reference arm exists

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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.
Evaluation of clinical studies, when reference arm doesn’t exist

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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

Main task of hyperthermia has to concentrate on these problems

Survival time and quality of life

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?

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The survival curve

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

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

All new cells meet the condition of the microenvironments produced by the cells in previous steps.

The self-similar development could be followed by the physiologic-psychologic 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.

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

Two parameters characterize the survival curve

The Weibull function has two parameters:

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

The \( n \) and \( t_0 \) parameters can be converted to mean and medium values.
The Weibull function

\[ t_0 = 1; \ n = 2 \]

- Inflection point \((0.707, 0.607)\)
- Median point \((0.833, 0.500)\)
- Mean point \((0.886, 0.456)\)
- Reference point \((1, 0.368)\)

The Weibull fit to the Kaplan-Meier plot

0.25% (p=99.975)
Two parameter conversion in the survival curve

Two parameters, mean and median could be transferred to \( n \) and \( t_0 \)

![Graph showing survival probability with time (months) and parameters](image)

Other, more exact methods also exist for the transformation

Calculating responding and non-responding patients

\[
W^{(KM)}(t) = c_{RP} e^{- \left( \frac{t}{\alpha^{(RP)}_0} \right)^n_{(RP)}} + (1 - c_{RP}) e^{- \left( \frac{t}{\alpha^{(NP)}_0} \right)^n_{(NP)}},
\]

![Graph illustrating survival probability with time (months) and parameters](image)

**RG is not assumed**

- Weibull n=1.34 t0=68.89 %0.526
- Weibull n=1.62 t0=20.02 %0.474
- Overall survival (N= 1180)
- SUM of Weibull functions
- Deviation \( r^2\)=0.99943

**NP = Non-responding Patients (47.4%)**

**RP = Responding Patients (52.6%)**
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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
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Study of inoperable advanced pancreas carcinoma


Number of patients
- active arm n=89 (73+26 two centers)
- control arm n=34 (historical control)

Decomposition to responding and non-responding groups

Overall survival with mEHT (censored patients with x)
Overall survival
Responding group (34.4%)
Sum of the two selected groups (r²=0.995)
without mEHT
Non-responding group

Survival probability

overall survival (m)
Study of advanced non-small-cell lung cancer


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

Decomposition to responding and non-responding groups

Overall survival showing the censored patients

Responding group (37.6%)
Non-responding group
Sum of the two selected groups (r²=0.995)
Median line with mEHT
without mEHT

Study of advanced glioblastoma multiform, monotherapy


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

Decomposition to responding and non-responding groups

Overall survival with mEHT (censored patients with x)

Responding group (16.1%)
Sum of the two selected groups (r²=0.995)
Median line measured with mEHT
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

![Graph showing survival probability over time with various lines and markers indicating different survival scenarios.]

- **General shift by the mean value**
- **HJP estimation of follow-up survival** $KM(t_{HJP})$
- **Median value**
- **Elapsed time to 1st mEHT (Survival in the curative period)**

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.

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

**Modified HJP estimation**

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

**Normal distribution curve** is assumed for expected survival time in palliation

- $(\sigma/2)$ is chosen as the percentage of the non-responding patients dividing the survival groups.
- Mean of elapsed time to first mEHT is at unity by HJP.
- $\mu = 0$ for monotony of the distribution

**Verification of modified HJP estimation**

![Graphic showing survival probability over time with lines and markers indicating different survival scenarios.]

- **Survival of the responding group (34.4%)**
- **Overall survival of the mEHT treated group**
- **Survival of the non-responding group of patients**
  - **Responding (34.4%)**
  - **Median line**
- **The expected overall survival by modified HJP**
- **Survival of the historical control group**

Quasi-control by modified HJP approximation

Overall survival

pancreas carcinoma

Measured single-arm Kaplan-Meier plot

Control arm by modified HJP approximation

non-small-cell lung cancer

Glioblastoma multiforme

The job is done

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Thank you very much for your attention

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