Evaluation of single-arm studies of oncothermia

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Objective

Oncothermia survival studies are problematic due to the missing control arm This is a problem is general, when the treatment targets advanced, mostly refractory, relapsed malignancies in high treatment lines, when the only way is the sequential treatment Usually the care in high line treatment (or in terminal phase) has very limited evidence based possibilities, its medical decision making processes are usually well tailored to the individual patients [18], [19] In these cases evidences have to be shown when randomized controlled trials are not possible, [20] The sequential trial [1], [2], [3], is well known, and applied frequently in the case of small trials [4] The sequential trial (like the oncothermia) is applied for the same patient in sequences, In this approach the development of the patient is measured and documented Our objective to show how the evaluation of the single arm study could be realistic enough to be evidence based

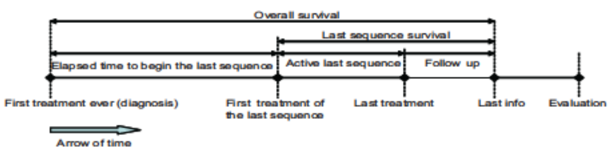
Method

The basic of the idea of the data separation is the appropriate parameterization of the non parametric Kaplan Meier survival pattern by poly Weibull fit However we have some qualitative assumptions
- Patient starts the new sequence when the previous had not (or had not satisfactory) result
- The new sequence gives positive addition (no worsening of the patient's stage due to the applied therapy in the actual sequence)
- The new sequence does not block the possibility of subsequent sequences, the patients will not be excluded from the possible other therapies by the actual one
- The effect of the new sequence affects the survival curve, so the studied Kaplan Meier plot includes the information
- The sequence is medically controlled at least on the same way, as were done in pervious therapies No uncontrolled "side therapies" are in use

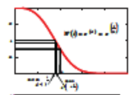
Studying the median of a survival curve alone disregards the real success measurable at the end of the study Correcting this "mistake" the average (mean) of the distribution is considered
The mean is more affected by the "tail" of the distribution, so it gives more accurate idea on the cure rate The median is more responsible for the information how quick the loss of the patients, while the mean has more part on the information how long the effect of the high success patients Both are important for characterization, the time scale and the shape of the distribution are independent parameters The distribution curve must be characterized at least by two parameters These two parameters are the mean and the median, supposing to characterize the non parametric distribution, and so in fact this is a hidden parameterization of the Kaplan Meier plot Best mining of the data would be when the non parametric Kaplan Meier survival plot could be parameterized Description of survival curves by parametric distribution function was a long time effort, could be approached by fitting the parametric Weibull (Avram) curves [21], [22], [23], [24], [25], on the actual probability function The universal applicability of the Avrami function was recognizes much earlier, [26], [27], [28]
Using the Weibull distribution function to approach the survival curve parametrically is theoretically and practically established for clinical applications, [25] Fitting the measured Kaplan Meier survival curve (*KM(t)*) by a function *S(t)* composed by two Weibull functions (with parameters denoted by superscripts *(R)* and *(NR)*), describing the responders and non responders by a composite ratio *C*, respectively Application the parametric Weibull distribution function approaching the survival curve for clinical applications is established theoretically and practically, [5], [6], [7], [8] It is used for a long time for survival description in gerontology [9], [10] and in oncology [11] as well

$$KM(t) \approx S(t) = (1-C)e^{-\left(\frac{t}{t_0^{(R)}}\right)^{n^{(R)}}} + Ce^{-\left(\frac{t}{t_0^{(NR)}}\right)^{n^{(NR)}}}$$

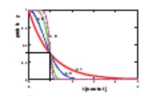
Sequenced trial is well known and applied frequently in the case of small trials [29]
However we have some qualitative assumptions:
1 Patient starts the new sequence when the previous had not (or had not satisfactory) result This condition is generally valid no reason start new therapy when it works satisfactory (In some cases due to psychology or other factors anyway could be abandoned a successful therapy but we assume it is less than 5% of all the treatments)
2 The effect of the new sequence affects the survival curve so the studied Kaplan Meier plot includes the information (Example: when the effect is improving the quality of life but does not affect the survival the sequence cannot be studied by survival curves)
3 The sequence is medically controlled at least on the same way as were done in pervious therapies No uncontrolled "side therapies" are in use

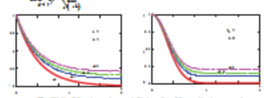


The time sequences of oncothermia studies The time between the first ever treatment and the first oncothermia is complex having numerous pre treatments It is regarded here as one step

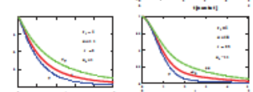


The special points of the Weibull function the median, the mean and the value, where t t0 (1/e=0 37)





The Weibull function when a definite ratio of the patients is cured



The fitting curves at various c values

By these assumptions we study a split of the original cohort distribution splitting it to two groups: responding and non responding patients The Weibull approach [15] is divided it into two different distributions [16] [17] composed linearly one whom the treatment had no or minor influence and one where the treatment was effective The weighted addition of the curves reconstructs the original The "inclusion criteria" for the patients to oncothermia treatment is when the "gold standards" are not eligible These criteria could be checked by study the elapsed time to the first oncothermia from the first diagnosis The time from the first diagnosis to the first oncothermia has to be a cohort (when the inclusion of the patients to oncothermia had identical criteria) consequently it has to be characterized by single Weibull parametric formulation
The process is performed at oncothermia survival first (five parameters is considered to the best fit: the two Weibull curves t_0 and n for each and their composite ratio C (ratio of the non responders) which fixes the patients by their numbers into two groups (equation 45) The residual will be automatically obtained from this fit which is nothing else only the value of the survival fit at the maximal survival time [$S^{(OT)}(t_{max})$]

The same composite ratio is applied for overall survival also

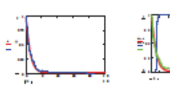
$$S^{(OT)}(t) = (1-C)\exp\left[-\left(\frac{t}{t_0^{(r)}}\right)^{n^{(r)}}\right] + C\exp\left[-\left(\frac{t}{t_0^{(nr)}}\right)^{n^{(nr)}}\right] \qquad S^{(OS)}(t) = (1-C)\exp\left[-\left(\frac{t}{t_0^{(r)}}\right)^{n^{(r)}}\right] + C\exp\left[-\left(\frac{t}{t_0^{(nr)}}\right)^{n^{(nr)}}\right]$$

Results

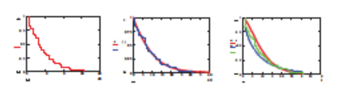
The evaluation of the Kaplan Meier plot by parametric distribution works well in the practice Patients responding to the treatment are well distinguishable from the responders, and on this basic the overall survival benefit can be evaluated The significance level depends on the number of patients, but over 25 patients it usually fits better than 95% confidence We evaluated numerous single arm clinical trials, showing the efficacy of the study The evaluation was well correlated with the independently measured other parameters as well as the criteria of start of oncothermia also shows stable reference distribution

$$S^{(start)}(t) = \left(1 - C^{(start)}\right)\exp\left[-\left(\frac{t}{t_0^{(1)}}\right)^{n^{(1)}}\right] + C^{(start)}\exp\left[-\left(\frac{t}{t_0^{(2)}}\right)^{n^{(2)}}\right]$$

Further control could be given by study the historical control of the pancreas treatment from the same investigator (n=34) who did the oncothermia treatments The Weibull decomposition fit produces statistically identical curves no possibility to detect any significant differences in decomposition It is a cohort Comparison of the non responders in overall survival and the control group shows remarkable correspondence this supports again the validity of the decomposition

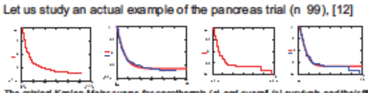


Full fit of the curve by parameters: $n^{(1)}$=1 17, $t_0^{(1)}$=5 51, $n^{(2)}$= 14 02, $t_0^{(2)}$= 6 00, C=0 021 The decomposition curves show the absolute dominance of a single Weibull distribution, (its modification is 2 1%)



The Kaplan Meier survival curve of the historical control and its fit by two Weibull functions Parameters: $n^{(1)}$=1 47, $t_0^{(1)}$=10 76, $n^{(2)}$= 0 83, $t_0^{(2)}$= 7 19, C=0 50 The decomposition curves are statistically identical

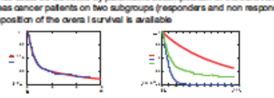
Let us study an actual example of the pancreas trial (n 99), [12]



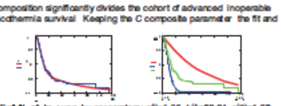
$$W^{(cure)}(t) = c + (1-c)e^{-\left(\frac{t}{t_0^{(cure)}}\right)^{n^{(cure)}}}$$

The original Kaplan Meier curves for oncothermia (a) and overall (c) survivals and their fits The parameters are n=1 14, t_0=6 34, c=0 18 and n=1 38, t_0=13 74, c=0 17 for oncothermia and overall survivals, respectively

Better fits could be achieved by parametric decomposition of the survivals The decomposition significantly divides the cohort of advanced inoperable pancreas cancer patients on two subgroups (responders and non responders) in oncothermia survival Keeping the C composite parameter the fit and decomposition of the overall survival is available

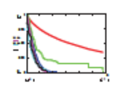


Full fit (a) of the curve by parameters by (45): $n^{(r)}$=0 95, $t_0^{(r)}$=43 13, $n^{(nr)}$=1 34, $t_0^{(nr)}$=4 75, C=0 61 The decomposition curves show the significant difference of responders (39%) and non responders (61%)



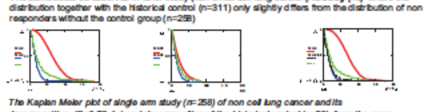
Full fit of the curve by parameters: $n^{(r)}$=1 06, $t_0^{(r)}$=59 94, $n^{(nr)}$=1 67, $t_0^{(nr)}$=11 00, C=0 61 The decomposition curves show the significant difference of responders (39%) and non responders (61%) [Applied the same ratio as in oncothermia survival]

The "inclusion criteria" for the patients to oncothermia treatment is when the "gold standards" are not eligible These criteria could be checked by study the elapsed time to the first oncothermia from the first diagnosis The time from the first diagnosis to the first oncothermia has to be a cohort (when the inclusion of the patients to oncothermia had identical criteria) consequently it has to be characterized by Weibull parametric formulation where the two distributions are close or $C^{(start)}$ is small Indeed fit and decompose) the curve of elapsed time from the first diagnosis to the start of oncothermia the definite dominance of one single curve This shows our "inclusion criteria" is really valid cohort forming condition



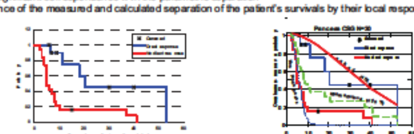
Comparison with the historical control

The same could be observed in other study (non small cell lung cancer [NSCLC]) [13] where the distribution together with the historical control (n=311) only slightly differs from the distribution of non responders without the control group (n=258)



The Kaplan Meier plot of single arm study (n=258) of non cell lung cancer and its decomposition, (C=0 79 4,) and decomposition of the historical control (n=53), from the same investigator (C=0 55,) and their comparison

Other prospective study [14],had measured the local cinical response and the survival time in the same trial The direct response (CR+PR) shows good, significant correspondence with the parametric separation
Significant correspondence of the measured and calculated separation of the patient's survivals by their local response



Conclusion

Parametric evaluation of Kaplan Meier non parametric distribution works well for single arm studies The single parameter reference of the Kaplan Meier (median survival) is unsatisfactory; the two parametric Weibull distributions describe the situation much more exactly

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