Evaluation of single-arm studies of oncothermia

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Background: 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. 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.

Methods: 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. 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.

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.

Conclusions: 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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