

A retrospective study of 1180 cancer patients treated by oncothermia

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Abstract

Oncothermia is a local-regional hyperthermia treatment devoted to oncological applications. In our present series of studies we show the retrospective results obtained by two cooperating Hungarian Institutions (HTT-Med Day-Clinic and Peterfy Hospital). Generally heavily pre-treated patients in advanced stages were studied in various localizations. Cohorts could be studied for non-small-cell lung cancer (n=258), for pancreas (n=99), for stomach (n=68) for colon (n=114) for rectum (n=89), for breast (n=103) for cervix uteri (n=38), for kidney (n=35) for brain (n=24) and for ovary (n=27). In the first part of the series we present the overall data and their conclusive summary, and in the next parts we will present the cohort studies in details. Results show the advantage of the oncothermia treatment for the entire studied population as well as for all of the cohorts. The present study indicates the feasibility of the oncothermia treatment for advance cases and points up the necessity of the prospective clinical trials.

Keywords: clinical-hyperthermia, oncology, oncothermia

Introduction

Heat therapy (hyperthermia) is an aboriginal, traditional healing method. Even the first known, more than 5000 years old, written medical report from the ancient Egypt mentions the hyperthermia [1]. The use of hyperthermia for cancer therapy was first documented by Hypocrites for the treatment of breast tumor [2]. His approach of course mainly was supported by the Greek philosophy, where the fire (heat) had the highest level of abilities and freedom. Hyperthermia was also mentioned throughout the Middle Ages [3], but due to the strict Galenus' school and the inadequate heating techniques, the treatment never became a standard in the oncology practice.

Among the first modern curative applications in oncology, Busch [4] and Coley [5] were successful at the end of the 19th century with artificial fever generated by infection and toxins, respectively. These systemic applications soon were followed by local and regional heating by Westermarck F. [6], by Westermarck N. [7], and by Overgaard K. [8]. The leading German surgeon in that time, Bauer KH opinion in his monograph "Das Krebsproblem" about the oncological hyperthermia is typical: "All of these methods impress the patient very much, they do not impress their cancer at all." However, very early, in 1912, a controlled Phase II clinical study was published on 100 patients showing the benefit of the thermo-radiation therapy [9].

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At the end of the last century, energy delivery by electromagnetic fields became possible; nevertheless, its use for hyperthermia only began about 30 years ago. The first symposium on oncological hyperthermia was held in Washington DC, USA in 1975 and the second one in Essen, Germany in 1977. Both conferences were supported by the local scientific communities. From this time we may count the born of the modern oncological hyperthermia as a strong candidate becoming a member of the conventional tumor-therapies. Very soon the European Society of Hyperthermic Oncology (ESHO) and International Clinical Hyperthermia Society (ICHS, had its last conference in Mumbai [10]) were established, and high-level respected periodicals, the International Journal of Hyperthermia, were published. National and regional scientific societies have been founded in more and more countries and regions of the Globe.

The mechanisms of oncological hyperthermia have since been debated [11], leading to an increasing number of books [2], [12], [13], [14], and journals [15]. Publications and an increasing number of clinical trials also appear in highly prestigious medical and scientific journals [16], [17], [18]. The request of the reliable clinical data in prospective, randomized, controlled clinical trials is formulated clearly in the last conference of the International Clinical Hyperthermia Society in Mumbai [19].

Hyperthermia today, like many early-stage therapies, lacks adequate treatment experience and long-range, comprehensive statistics that could help us optimize its use for all indications. Nevertheless, we will present a wealth of information about the clinical results of a special kind of hyperthermia devoted to oncological use (oncothermia), proving oncothermia's worth for further research. In our present study a large number, (N=1180), well documented electro-hyperthermia treated oncological patients from Hungarian hospitals (HTT, PTF) [20] are summarized. These were presented in conferences [21], [22]; but were not published yet.

Objective of the present clinical study is to test the method to a very wide range of tumor-lesions and different tumor-types and show that the oncothermia is a feasible option for the treatment of malignant tumors. In this present starting part of the series, we would like to focus on the general conditions and having some general conclusions on the oncothermia treatment modality. The cohort studies will be published in the subsequent parts of the series.

Method

The present study is retrospective, single-arm, open-label, double-centric clinical trial on intention-to-treat population [ITT], (in agreement with the actual oncologist). Study time was from 1997 to 2003 (recruiting 1997-2002). Generally heavily pretreated patients, in various localizations, mostly in late stages, were studied. Some localizations (non-small-cell lung cancer [n=258], for pancreas [n=99], for stomach [n=68] for colon [n=114] for rectum [n=92], for breast [n=103] for cervix uteri [n=38], for kidney [n=39] for brain [n=24] and for ovary [n=27]) are large enough to have conclusions of these actual cohorts. All together in our study presents the data of 1180 patients. Two cohort studies (brain and pancreas) were reproduced as a control in two independent German hospitals [23], [24]; showing good reproducibility, indicating reliability of the present data.

The endpoint was the survival time as a primary check of the efficacy of a curative method in such a lethal disease. The date of death (or alive) were checked by the Hungarian National Death Register, so the actual and accurate data were collected. The final check of the deaths was December of 2003.

Inclusion criteria were: patients are inoperable and/or have progression after radio- or chemotherapy. Exclusion criteria were only the well-known contraindications of the oncothermia method (metallic implants or replacements in the treated area, missing heat-sense in the treated area, pacemaker or other field-sensitive implants in the patient).

The evaluation methods were: descriptive biostatistics, log-rank survival tests (Kaplan-Meier

plot), and comparison with large studies and databases and/or local historical data.

Patients were dominantly in late/advanced stages, where the traditional oncotherapies were unsuccessful.

The study had a couple of possible negative biases: (1) the treatment is paid or co-paid by the patients, who do it on voluntary basis (ITT) in strict control by the oncologist who was responsible for the patient treatment till that time; (2) no randomized control arm exists, the trial is compared to the historical control or to the available literature.

However, the present study had a few possible positive biases as well: (1) patients are treated in their advanced stages, when other treatments failed and/or not possible; (2) the involved clinics are not equipped so well than the special institutes/universities; (3) the involved patients had no extra “trial-attention”.

The safety of the method is proven. It has been applied over 15 years in clinical practices. Presently, yearly more than 100.000 treatments are performed. No any serious safety problem has been reported about the oncothermia treatments. The devices are approved according to the European Medical Device Directive (CE/MDD) and those are under permanent vigilance system. The treatment dose is personalized, fitted for the actual status of the given patient.

The used device was EHY2000 (OncoTherm), capacitively coupled, working on 13.56 MHz, time-domain (fractal) modulated, with 30-150 W power absorbed by the tumor. The treatment control was made by the absorbed energy [kJ], which was converted to the equivalent temperature [T]. The equivalent temperature is higher than the actual temperature value, calculated by the assumption that the energy makes only a temperature increase. The reality, that the energy together with the increase of the temperature is basically used for the distortion of the structures, change of the chemical bonds and compensate of the physiological regulations, [25], [26]. The equivalent temperature is in average higher about 10 °C than the measurable in the actual conditions, however it is always the function of the given conditions and mechanisms.

Results

The age-distribution of patients follows well the normal distribution, (Fig. 1. and Fig. 2.) average/median ages of the patients were 54.1/56 (1-87) years, the standard error of mean is 0.41, the standard deviation 14.2, and kurtosis/skewness is 1.88/-0.96. No outliers present.

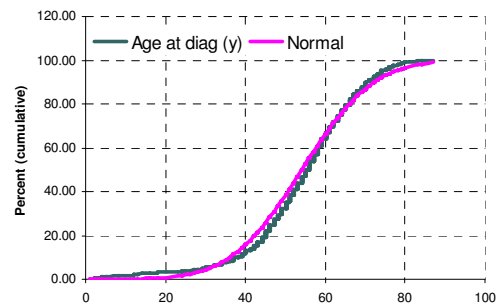
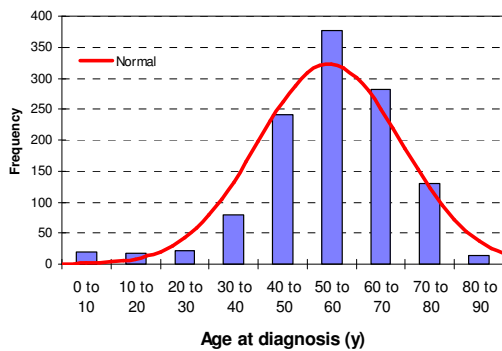


Fig. 1. Distribution of patients in the study

Fig. 2. Cumulative age distribution

The male/female ratio is 612/568, their median ages are 57/54, (mean 55.2/52.9), respectively. 928 patients were treated in HTT, while 252 in PFY center. The groups of

patients not less than 10 is shown in Table 1.

Disease	ICD	Number of cases [pts.]
Head&Neck	C00-C14	64
Esophagus	C15	12
Stomach	C16	68
Colon	C18	114
Rectosigmoid junction	C19	12
Rectum	C20-C21	92
Liver	C22	25
Other biliary	C24	14
Pancreas	C25	99
Larynx	C32	10
Lung and bronchus	C34	258
Skin	C43-C44	32
Soft tissue	C49	16
Breast	C50	103
Cervix	C53	38
Ovary	C56	27
Prostate	C61	18
Kidney	C64-C65	39
Urinary bladder	C67	18
Brain	C71-C72	29

Table 1. Main localizations investigated in the present study. (Localizations having less than 10 cases are not listed.)

Patients were heavily pretreated, (2.62 pretreatments for one patient in average), Fig. 3. show the advanced cases in the study. (The combinations of the pretreatments is also shown.)

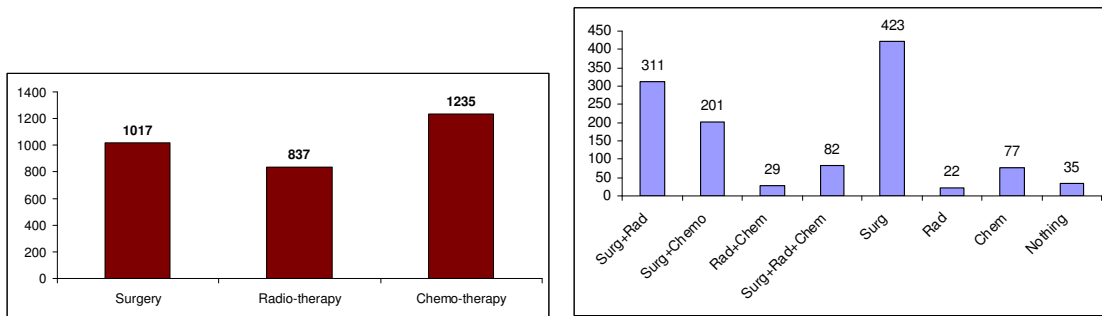


Fig. 3. Pretreatment statistics of the 1180 patients. The right panel shows the combination of the therapies.

Number of metastases also was high, (Fig. 4), about a quarter of patient had no metastasis, and also about the quarter had more than one. The ICD codes of metastases per patients are shown on Fig. 5.

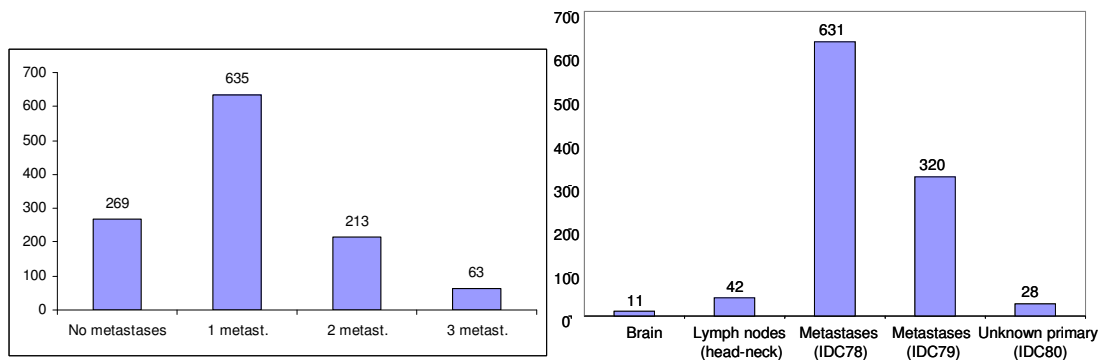


Fig. 4. Distribution of metastases

Fig. 5. The ICD codes of metastases

The average/median oncothermia treatment-time was 68.8/60.0 min (30-180), the average/median equivalent temperature 50.9/52 C (37.4-59.9) the applied average/median treatment number 8/6 (1-69). Patients tolerate the treatment very well, the pain-relief was obviously presented, they subjective and objective quality of life was increased. No any

serious toxicity was observed.

The overall survival (median 25.20 months, [0.87-299.6] and the mean: 35.24 months, [std.err.:1.06]), and the survival from the first oncothermia treatment (median 7.67 months, [0.03-75.3] and the mean: 14.29 months, [std.err.:0.45]).

Survival times are of course depends on the metastases. Generally the patients with metastases have much worse life-expectancy than without. The difference (considering all the studied localizations) is statistically massively significant. (for overall survival $p < 0.00004$, and for survival from the first oncothermia treatment $p < 0.000002$; Fig. 6.)

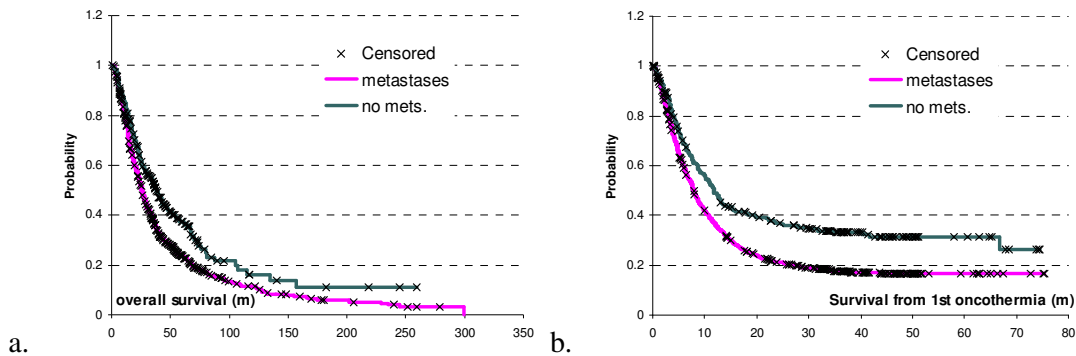


Fig. 6. The survival dependence of the metastatic diseases: a.) overall survival from the first diagnosis of the disease, b.) survival from the first oncothermia treatment.

The pretreatment efficacy in the surviving fraction of the oncothermia treated patients has been also checked. While the surgery ($p < 0.002$) and radiotherapy ($p < 0.004$) have significant effect, the chemotherapy ($p > 0.17$) was not significant in the overall survival rate and none of those was significantly changed the survival from the first oncothermia.

The average oncothermia treatment parameters (number of treatments, average treatment time and the equivalent temperature of the treatment) were also studied, having no significant change on survivals (except the naturally different treatment number), (Figs. 7., 8).

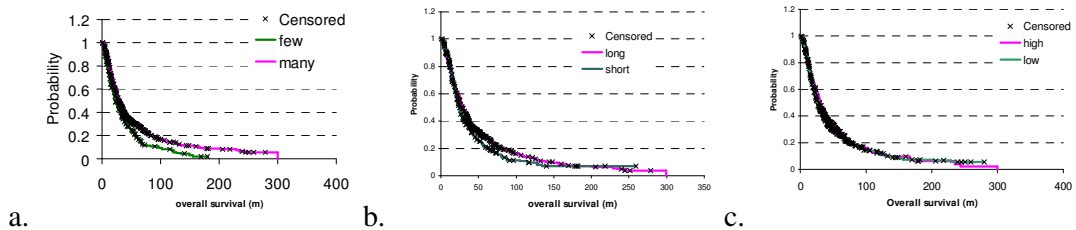


Fig. 7. Effect of the average treatment parameters on the overall survival: a.) number of treatments ($p < 0.00015$), b.) treatment time ($p > 0.14$), and equivalent temperature ($p > 0.42$). The two-two quantities are divided by the median value (below or above) of the given parameter.

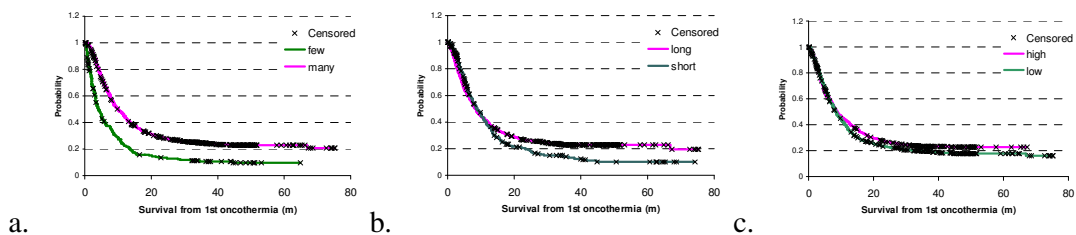


Fig. 8. Effect of the average treatment parameters on the overall survival: a.) number of treatments ($p < 10^{-17}$), b.) treatment time ($p < 0.17$), and equivalent temperature ($p < 0.17$). The

two-two quantities are divided by the median value (below or above) of the given parameter.

Average/median time from the 1st diagnosis to the first oncothermia treatment was 20.9/10.6 (0-265.7) months, which compared to the average/median overall survival [35.2/25.2 (0.9-300)], shows, that the patients were treated only in the second-half of they survival time, (median of the ration of elapsed time to overall survival is 57.14 [0.0-99.8]) and the confidence intervals show the very hectic practice to include the hyperthermia in the applied treatment protocol. However, the survival time of the patients from the first oncothermia treatment is generally longer, if the elapsed time till start the EHY is smaller.

The elapsed time from the diagnosis to the first oncothermia trivially affects the overall survival significantly, but the effect on oncothermia survival is not significant, (Fig. 9.)

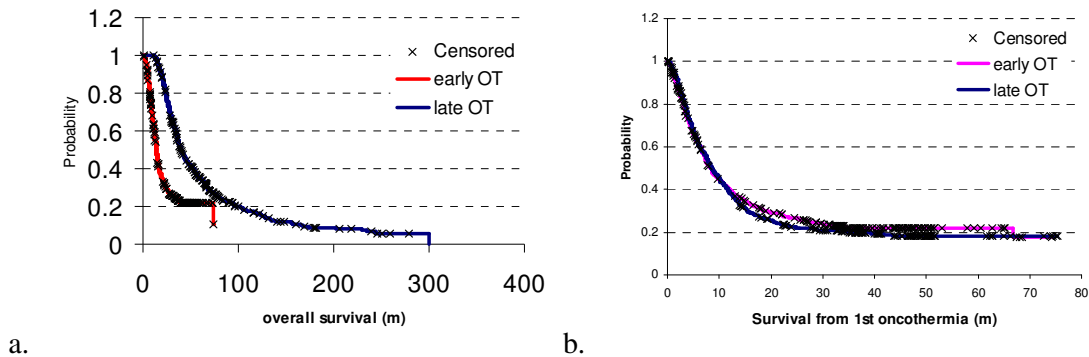


Fig. 9. The effect of the elapsed time to the first oncothermia on the (a) overall ($p < 10^{-44}$) and (b) oncothermia ($p > 0.47$) survivals. (The two-two quantities are divided by the median value (below or above) of the given parameter.)

Age dependence of the results was also considered. The elderly (>68) and the young (<18) groups were independently studied and the differences were measured (see Figs. 10., 11.).

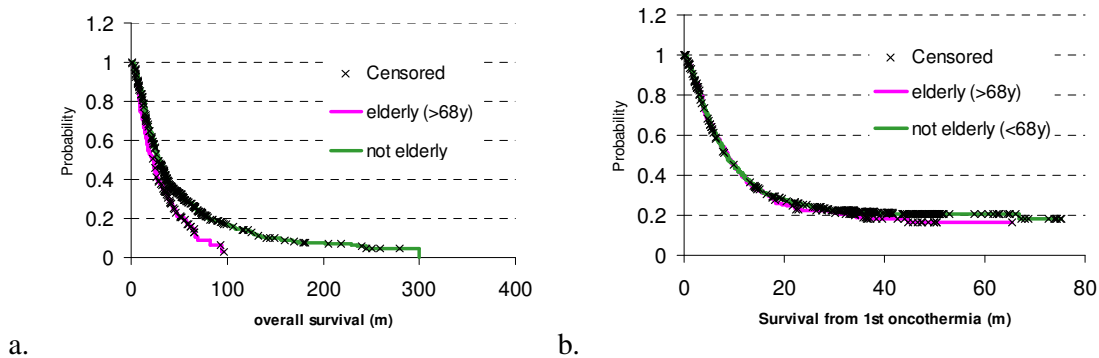


Fig. 10. The age dependence of the results in gerontology point of view: a.) overall survival ($p < 0.00016$) and b.) survival from the first oncothermia ($p > 0.63$).

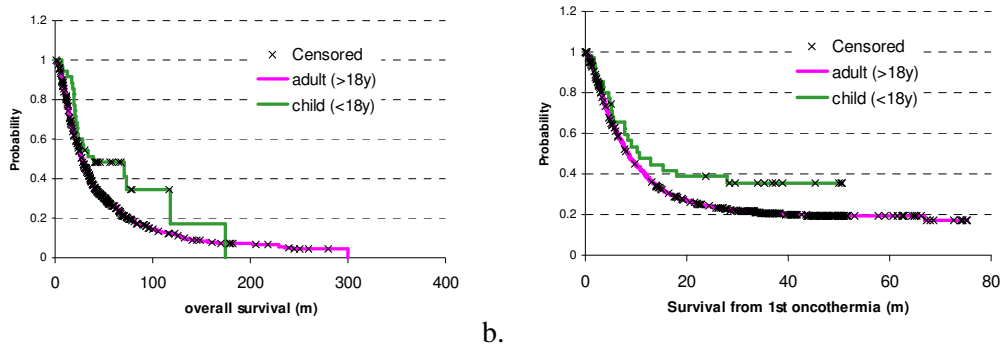


Fig. 11. The age dependence of the results in pediatric point of view: a.) overall survival ($p < 0.038$) and b.) survival from the first oncothermia ($p = 0.09$).

No serious toxicity/burn was reported during the full study. The low forwarded energy was well focused on the actual tissue; the energy loss was not mentionable to cause surface burn.

Patients reported subjective improvements in their quality of life.

Discussion

Results are shown the general behaviours of the oncothermia treatments and of course are not satisfactory to make any final conclusions on the actual cancer cure. The huge number of patients are satisfactorily normally distributed to make some general arguments about the oncothermia method. The cohort studies in details will be shown in the next parts of this series.

However in general we may state: the heavily pre-treated, advanced cases of the patients had in median survival after the first oncothermia almost one third of their overall survival, which is in the case of such a group (over the limit of the traditional treatments) is a remarkable result. It is a necessity that the patients with one of multiple metastases have less survival than their non-metastatic counterparts, and of course this difference is larger in the last third of their survival. About the pre-treatment efficacy we are not able to make any remarks, because it is very much localization (and specific protocol) dependent.

To evaluate the treatment parameters, naturally the larger number of treatments is connected to the longer survival. However, the data shows the after oncothermia survival is significantly longer ($p < 10^{-15}$) in the more treatment numbers than in the fewer ones. This surprisingly shows: the survival after first oncothermia is not fulfilled by the only permanent treatment time, the follow-up (after oncothermia) is considerable in most of the cases, and the survival gives a real dependence of the oncothermia frequency.

However, a question remains: has role when oncothermia starts? The analysis of the ratio the elapsed time to the survival from the first oncothermia shows difference between the early- and late-started oncothermia (Fig. 12.).

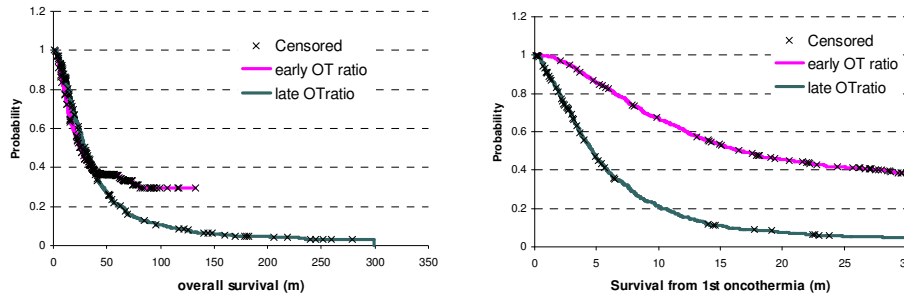


Fig. 12. The ratio of the elapsed time from the first diagnosis till the first oncothermia treatment to the survival from the first oncothermia makes the difference. The earlier oncothermia is significantly better in both the survivals (a. overall survival [$p=0.07$], b. oncothermia survival[$p<10^{-74}$]). (The two-two quantities are divided by the median value (below or above) of the given parameter.)

Also it could be a great influence of the experience of the treating staff on the results. Data analysis shows that the oncothermia training and experiences of use have been well handled since the very beginning of the applications. To compare the early experience (first half of the study-time) and the late experience (second half of the study time) has almost significant difference ($p=0.052$) in the oncothermia survival, but no any significance could be observed in the elapsed time to the first oncothermia and in the overall survival, Fig. 13.

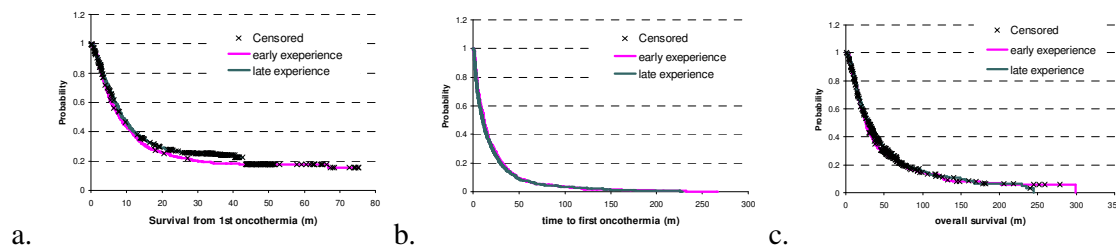


Fig. 13. Differences by the experience of the treatment procedure during the trial, dividing the results for two groups: obtained in the first or in the second half of the study-time. a.) Survival from the first oncothermia ($p=0.052$), b.) elapsed time to the first oncothermia ($p>0.44$) and c.) overall survival ($p>0.29$).

The retrospective analyses in independent clinics show coherence in the success, and definitely and significantly higher survival time than the large databases (SEER (Surveillance, Epidemiology, and End Results; published by the National Cancer Institute USA, April 2000) [27], Eurocare [28]). These databases contain all the cancer patients registered in USA and Europe respectively. Due to the Oncothermia is applied mostly in very advanced cases, the direct comparison with any overall databases is incorrect. The results of advanced stages only can not be realistically compared to the overall results. The real comparison however could be with the short survivals with the patients, whom disease is rapid, and so their oncothermia treatment has more weight in their overall treatments than for the others. The long survival patients (because of the oncothermia is applied only, when the traditional methods are fallen) have only a little modification on their overall survival from the oncothermia, but the short living ones could have significant modification. The aggressive disease with short survival is a chance to indicate the efficacy. This is the point, why the full yearly comparison with the large databases are misleading, and the most useful comparison could be done only on the first year survival. In this meaning oncothermia indicates good benefits shown on Table 2. In this sense oncothermia is indicated as a feasible, effective method [29]; [30], [31], [32]; (see Fig. 14.).

Databases	Number of patients	1st year survival (%)
SEER	1,812,783	68.9
Eurocare-3	908,286	62.8
present oncothermia	1,180	77.2

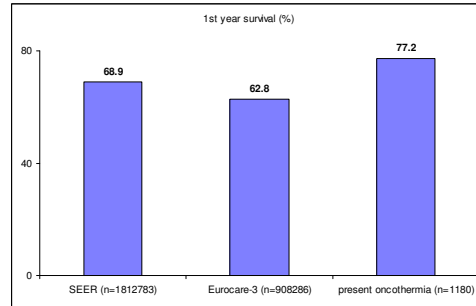


Table 2. Comparison of the large number of cancer patients from available databases. The gain of oncothermia to the weighted average is 15.5%.

The main efficacy factor is the effect of the modulated electric field, which has three times more cellular killing than the temperature based hyperthermia methods on the same 42 C temperature, [33].

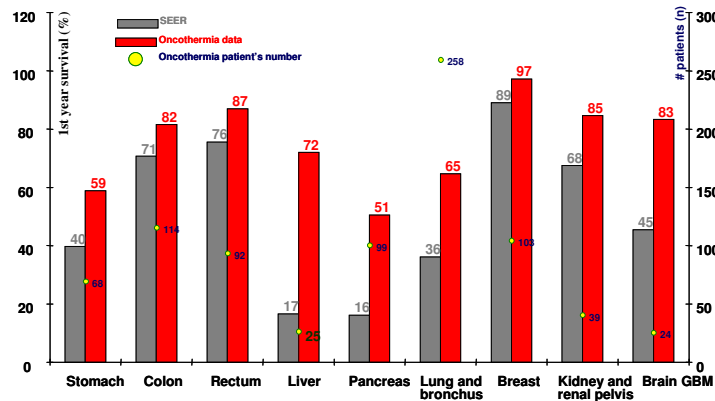


Fig. 14. Comparison of the first-year survival rates of various cancers with the large SEER database

One of the further advantages of the oncothermia is its effect on the quality of life and suppressing the side effects of the complementary applied conventional methods. This effect is not measured in objective basis, only subjective reports are collected.

Summary, conclusion

We indicated above the feasibility of oncothermia method as a promising new modality of cancer treatments. It is indicated to fulfill numerous demands: non-toxic, excellent in any combinations with other treatments, with minor contraindications.

However, we have to fix about the present study:

1. The present study was not concentrating on the specific cancer localizations or stages, only devoted to see some overall properties of the oncothermia treatment, irrespective its actual application.
2. The present study is an indication of the feasibility and not a proof on the evidence based meaning.

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