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Clinical studies made by Oncothermia

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Desription of the studies

Oncothermia has a long-time history with large number of documented case reports and clinical trials [1]. During more than 20 years 43 studies were performed involving more than 2000 patients all together from 14 clinics in 4 countries (see Table 1.) Details of the clinical effects is summarized in the publications as well as in the specialized monograph [1].
The clinical trials of oncothermia are dominantly retrospective. To develop randomized clinical trials has a challenge for patients. Patients do not agree to be in the control-arm at any case. In most of the cases they are registered for oncothermia because the other (conventional gold standards) are fallen. This case could be progression anyway, resistance, organ-overload (kidney, liver, etc.), relapses, sometimes psycho-resistance, etc.
The advanced cases at the conditions described above, emphasize not only the complexity of the individual situation of patients, but also underlines the fact that oncothermia is applied as the facility of the "no other is possible" many time hopeless cases providing over 3rd line treatment approach. This high-line treatment process is in general palliation (the first goal is to provide acceptable quality of life), which is an important factor for oncothermia as well. However oncothermia even in these advanced situations has curative value, and makes curative therapy in 3rd-line or over. The professional literature shows well the rare facility of the evidence-based clinical trials for these high-line treatments. Other evidences have to be shown when randomized controlled trials are not possible, [2]. The challenges of evaluation appears specifically strongly in the care of patients with advanced stages, having inoperable (or partly resected), relapsed, resistant on gold-standards patients, and this is the challenge facing oncothermia as well.

We have to make especial attention evaluating of the clinical results performed by oncothermia. The complications make definite challenges to objective evaluation. The main challenges are:

- Oncothermia is applied in higher (usually third and subsequent) treatment-lines, boosting or resensitizing the effect of the conventional therapies. Oncothermia is mostly applied in the cases when the conventional therapies fall. The most probable reasons when the cases are inoperable, radio-resistant, chemo-resistant, low-blood-counts, liver-failure, kidney-failure and sometimes psycho-resistance alone or in their combination. Due to these conditions, oncothermia is applied in higher line of the therapies. This sequence of the treatments is mostly determined by the individual decisions of the physicians [3], usually without having help from any evidence based statistical approvals.
- Usually it is applied in palliative care; many patients are in terminal phase. This patient care has very limited statistical evidence based trials; the medical decision-making processes are usually well tailored to the individual patients [4], [5].
- Only few controlled randomized clinical trials are available for oncothermia. The results have to be concluded from observational studies and from the historical and data-base comparisons. Mostly used the USA- and EU-databases (SEER [6], Eurocare [7]).Due to the not solved problematic between the hypothesis check confidence of evidence based medicine and the observational studies [8], [9], this data-comparison is acceptable. Make the result as objective as could be, we compared the collected results of the same localizations and same protocols from various clinics. They common significant difference from the databases could be accepted as evidence.
- In the case of long-survivals, we have to consider, that oncothermia is taken only in a small fraction of the overall survival. The patients are treated by oncothermia in their definite late stages, after prognosis "no curative help" by continuing of gold-standards alone. In consequence the long overall survival generally is not the result of the oncothermia, but the selection of the patients in their end. Oncothermia effect in these cases could be negligible, irrespective of its real efficacy. The chance to measure the efficacy is the first year survival

rate (%), when the patients with most aggressive kind of the given cancer do not survive the send year after the diagnosis. If they start the oncothermia in the first year, the survival-rate result could have objective sign of the efficacy.

- Special cases are treated on Intend-to-Treat population. This makes the patient selection not objective enough, but the dominantly metastatic patient's spectrum compensates this lack of selection. In this case we have an automatic selection of advanced (many times terminal) cases.
- Due to the generally low quality of life (QoL) of most of the patients, a combination with supportive therapies, this again weakens the measurability of oncothermia alone. However, due to oncothermia is not proposed as monotherapy, the combination objectively measures the benefit, if the supportive therapies alone would not be successful at all.
- The patients are treated with oncothermia in their very advanced, metastatic states. The local oncothermia treatment of course concentrates on definite localizations, (primary or metastatic) which again lowers the full measurability of the oncothermia in the development of the cancer. This is the main reason, why oncothermia measures first of all the overall survival rates, which are good objective parameters of the treatment efficacy in general.
- The quality of life (QoL) of the patients is an important characteristic of such a method which is oncothermia. In a general controlled randomized studies trial effect exists [10], which is not the case in oncothermia applications. However, it could be negative outcome, that in a strict competitive market the opinions are not independent and objective [11] and of course the conflict of interest could make considerable bias [12], [13].

On the above bias structure the characteristics of the clinical studies could be described as – Single arm, open label, observational for intention-to-treat (ITT) population, dominantly for the patients in late/advanced stages, where the conventional methods have failed. Mostly the survival rate was the studied endpoint. The inclusion criteria was the inoperable and in progression after chemo- and/or radio-therapy. Exclusions were only the well-known, above described contraindications of oncothermia.

The oncothermia challenge is its use when the conventional treatments are unsuccessful. In consequence its effect could be active only in a small (last) fraction of the overall survival. Patients with long overall survival could have dominantly enjoy the conventional treatments, without applying oncothermia, and the last stage oncothermia application could be not observable on life-elongation, even if oncothermia was effective.

To make objective evaluation we have special considerations how get the evidences from the available information pool and find the objective evidences. It is a complex challenge, having four basic approaches. These methods highlight the objective information and their parallel results make the obtained data evidence-based. The five legs are:

1. Fast course case comparison. Use the survival of the rapid, fast course cases (most advanced, drastically quickly developing cases) as comparison with large databases. (Only the survival is considered as relevant parameter, the clinical outcomes (responses) are not studied as evidences.)
2. Comparison of clinics. Compare the obtained data of the independent clinics, using the same protocol for the same cohort.
3. Quality of life comparison. Collect the quality of life data and the adverse effects limiting the application of oncothermia.
4. Create a quasi-control arm. Patients having no benefit from oncothermia could form a quasi-arm for control. The "no benefit" category could be defined when the patient survival is short from the time of the first oncothermia treatment.
5. Parametric evaluation. Use the available latest statistical knowledge to find the relevant parameters of the survivals and use the best fit of the parametric distribution for evaluation.

Evaluation of Oncothermia Studies

The clinical trials of oncothermia are dominantly retrospective. Prospective trials are in progress. To develop randomized clinical trials involves a challenge for patients. Patients do not agree to be in the control arm under any circumstances. In most cases they are registered for oncothermia because other conventional gold standards have failed. This could in any case involve progression, resistance, organ-overload (kidney, liver, etc.), relapses, sometimes psycho-resistance, etc.
The advanced cases under the conditions described above, emphasize not only the complexity of the individual situation of patients, but also underlines the fact that oncothermia is applied as a facility for the "no other treatment is possible" often hopeless cases providing an over 3rd line treatment approach. This high-line treatment process is in general palliation (the first goal is to provide acceptable QoL), which is an important factor for oncothermia as well. However, oncothermia even in these advanced situations has curative value, and provides curative therapy at 3rd-line or over. The professional litereature shows well the rarity of evidence-based clinical trials for these high-line treatments. Other evidences have to be shown when randomized controlled trials are not possible [14]. The challenge of evaluation appears specifically strongly in the case of patients in advanced stages, in inoperable (or partly resected), relapsed or patients resistant to gold standards, and this is a challenge facing oncothermia as well.

Evaluation Conditions

We have to give special attention to the evaluation of the clinical results of oncothermia. The complications mean definite challenges for objective evaluation. The main challenges are:

- Oncothermia is applied in higher (usually third subsequent) treatment lines, boosting or resensitizing the effect of the conventional therapies. Oncothermia is mostly applied in cases where the conventional therapies fall away. The most probable reasons include when the cases are inoperable, radio-resistant, chemo-resistant, have low blood counts, liver failure, kidney failure, and sometimes psycho-resistance alone or in combination. Because of these conditions, oncothermia is applied in a higher line of the therapies. This sequence of treatments is mostly determined by individual decisions of the physicians **[3]**, usually without the help of any evidence-based statistical approvals.
- Usually it is applied in palliative care; many patients are in the terminal phase. This type of patient care has very limited statistical evidence-based trials; the medical decision-making processes are usually well tailored to the individual patients **[4], [5]**.
- Only a few controlled randomized clinical trials are available for oncothermia. The results have to be concluded from observational studies and from historical and database comparisons. Mostly used are the USA- and EU-databases (SEER [**6**], Eurocare **[7]**). Because of the unsolved problematic between the hypothesis check confidence of evidence-based medicine and observational studies **[8]**, **[9]** this data comparison is acceptable. To make the result as objective as it could be, we compared the collected results for the same localizations and same protocols form various clinics. The common significant difference from the databases could be accepted as evidence.
- In the case of long survivals, we have to consider, that oncothermia forms only a small fraction of the overall survival. The patients are treated with oncothermia in their definite late stages, after prognosis of "no curative help" by continuation of gold standards alone. The long overall survival generally is not the result of the oncothermia, because patients start oncothermia in their advanced stage only. The survival effect of oncothermia in the very late, hopeless cases could be negligible, irrespective of its real efficacy. An opportunity to measure the efficacy is the first-year survival rate (%), when the patients with the most aggressive kind of the given

cancer do not survive the second year after the diagnosis. If they start the oncothermia in the first year, the survival-rate result could form an objective sing of the survival efficacy.

- Special cases are treated on Intend-to-Treat population, where in many cases patient chooses the treatment. This makes the selection not objective enough, but the advanced, dominantly metastatic patient's spectrum compensates of this lack of selection. We have an automatic selection of advanced (often terminal) cases.
- Because of the generally low QoL of most of the patients, and a combination of supportive therapies, this again weakens the measurability of oncothermia alone. However, as oncothermia is not proposed as monotherapy, the combination objectively measures the benefit, if the supportive therapies alone would not be successful at all.
- The patients are treated with oncothermia in their very advanced, metastatic states. The local oncothermia treatment of course concentrates on definite localizations (primary or metastatic), which again lowers the full measurability of oncothermia in the development of the cancer. This is the main reason, why oncothermia measures first of all the overall survival rates, which are good objective parameters of the treatment efficacy in general.
- The QoL of the patients is an important characteristic of oncothermia. In general a trial effect exist in controlled randomized studies **[10]**. It could be a negative outcome, as in a strict competitive market opinions are not independent and objective **[11]**, and also a conflict of interest could cause considerable bias **[12]**, **[13]**. These are not characteristic in oncothermia applications. In summary: there are some recognized negative biases in the retrospective data:
- Reimbursement bias: The treatment is paid for by private insurance or by the patient. This is an additional factor to the inclusion criteria in selecting patients eligible for treatment.
- Voluntary bias: Treatment is on a voluntary basis (intention to treat [ITT] population), which selects patients on the basis of their own decisions.
- Historical bias: Controls are from the historical arm or from the large databases. This makes the comparison statistically not exact.
- Clinical bias: The protocols are identical, but the selection of patients and practice of cure (mainly the supportive therapies) could differ.
- Personalization bias: Oncothermia is a personalized treatment, no definite overall dose or other overall valid parameters could be applied.

There are however some positive biases which could underestimate the results:

- Late-stage bias: Oncothermia is applied when conventional treatments fall aside. Results of this kind are not comparable with the regular curative processes.
- High-line bias: Oncothermia is applied in high lines of the treatment process, in which states evidence-based trials rarely have been performed. The falling-away of conventional therapies takes oncothermia out of the evidence based line, and makes it palliative in most cases.
- Private clinic bias: Private clinics dominate in terms of number, taking care of patients in advanced or even in the last stage. Oncothermia is applied mostly by these medical units. Private clinics usually lack the high-tech set of diagnostic and treatment equipments of non-private centers. To achieve and control the same results is sometimes difficult.
- Lack of "trial-bias": No extra trial attention is taken on the patients, who makes the results more objective.

On the basis of the above bias structure the characteristics of the clinical studies could be described as – single arm, open label, observational for (ITT) population, dominantly for patients in late/advanced stages, where the conventional methods have failed. Mostly the survival rate was the studied endpoint. The inclusion criteria was inoperable and in progression after chemo- and/or radiotherapy. Exclusions were only the well known, above-described contraindications of oncothermia.

The temperature during the oncothermia treatment is calculated from the absorbed energy, which is provided, and it is displayed in real-time. This parameter allows a "classical" orientation of the physician in terms of the safety of the actual process. However, in the tumor considerably higher temperature than the average has to be considered. The temperature calculation is based on solid measured data of absorbed energy (not on forwarded alone). The approach is the socalled "equivalent-temperature" idea. The equivalent temperature is the equivalent distortion ability of the cells with static overheating. Oncothermia heats up the tissue by a dynamic, gradient method, using the field effects at the cellular membranes. So the distortion is more efficient by oncothermia than by simple heating. To reach the same efficacy as oncothermia does, considerably higher temperature (equivalent temperature) has to be managed than the actual temperature in the oncothermia process. However, this approach of "equivalent temperature" is widely applied for temperature measurements by MRI as well. The MRI signals (T1 and T2 relaxation times) are temperature sensitive, but without calibration to a realistic system it is inapplicable. The calibration of the T1 and T2 time-shifts are made on phantoms, which are static (no physiology effects are included), and the MRI measures the phantom-equivalent, static temperature as well.

Note, the patient's ability to sense is the best safety alarm for any unwanted, unexpected events. Do not ignore it, react immediately. Oncothermia is a highly effective power transfer, its mismanagement by ignoring the patients sensing (or suppressing it by any analgesic medication) could be unsafe.

Evaluation Methods

The challenge of oncothermia is its use when conventional treatments are unsuccessful. In consequence its effect could be active only in a small (last) fraction of the overall survival. Patients with long overall survival have already benefitted from a long period of conventional treatments, without the application of oncothermia, and the last stage oncothermia application may not be observable in terms of life-elongation, even if the oncothermia was effective.

To make an objective evaluation we have developed methods to obtain the evidences from the available information pool and determine the objective evidences. These methods highlight the objective information and their parallel results make the obtained data evidence-based. It is a complex challenge, having five basic approaches:

1. Fast course case comparison. Use the survival of the rapid, fast course cases (most advanced, drastic quickly developing cases) as a comparison with large databases. (Only the survival is considered as a relevant parameter, the clinical outcomes (responses) are not studied as evidences.)
2. Comparison of clinics. Compare the retrospective data of the independent clinics, using the same protocol for the same cohort.
3. Quality-of-life comparison. Collect the QoL data and the adverse effects limiting the application of oncothermia.
4. Create a quasi-control arm. Patients having no benefit from oncothermia could form a quasi-arm for control. The "no benefit" category could be defined when the patient survival is short from the time of the first oncothermia treatment.
5. Parametric evaluation. Use the available latest statistical knowledge to find the relevant parameters of the survivals and use the best fit of the parametric distribution for evaluation.

The details of the approaches are complex.
Fast course case comparison. Compare the first-year survival rates (percentages of the surviving cases in the first year), to the large national and international databases. The comparison is realistically unfavorable for oncothermia, because it is generally applied in late stages, but the

databases consider all the available cases of the given disease. Consequently if oncothermia shows any benefit in this com- parison, it is a strong probability that it is reliable evidence. However this is only indicative, qualitative information, no quantitative conclusion could be made. The overall survival rate of the patients treated by oncothermia is mostly dominated by the non-oncothermia therapies, as oncothermia began only when the expectations from the gold standard therapies were weak. In consequence, to make any conclusion about the overall survival time is very complicated, it could even not be done without definite extra information and solid extra facts. However, the first-year survival ratio shows the most aggressive cases only, so the applied oncothermia could have a considerable effect in these aggressive cases. When the first-year survival is significantly increased by oncothermia, this should give a certain indication of the success of the oncothermia. The evaluation was made by regular descriptive biostatistics and a logrank survival test. Comparison to large studies and databases (SEER [**6**] and Eurocare-3 **[7]**) as well as local historical data was made.

Comparison of clinics. The survival rates can be collected from various clinics practicing oncothermia. These clinics when applying the same oncothermia pro- tocol in the same patient groups (cohorts), are ready to compare. The data could be analyzed by their coherence. When clinics using oncothermia have statistically significant congruence with each other that could be regarded as evidence. When these data are comparable within a statistically acceptable level (confidence inter- val) the objectivity of the data would be statistically proven. The weighted average of the results of these clinics could be compared to the large national and inter- national databases too. The possible difference between the database data and the statistical average of independent oncothermia applications from independent resources could provide evidence-based data to support or disprove the oncother- mia benefit. Both the first-year survival and the median survival could be chosen for comparison.

Quality-of-life comparison. The collection of data of QoL could show two differ- ent aspects of oncothermia: QoL during the curative process and also in the palliative actions. Because of late-stage applications, oncothermia is a palliative approach in most cases. In this stage the QoL has extreme importance. Also the connected adverse and side effects have to be evaluated for correct evidences. This is manda- tory for a treatment like oncothermia, where an evidence-based clinical study is not a real option for the high-line curative and/or palliative actions.

Create a quasi-control arm. Because of the single-arm data collection, the information of the oncothermia effect is hidden in the available set of data. A realistic control would be in a prospective, randomized trial, but as was discussed above, it has certain complications. The other possibility (less strong evidence) is to have historical control from the same clinic/hospital. However, the locations are highly specialized for very advanced patients, and their oncothermia treatment is overall routine, having no cohort patient group without oncothermia treatment. This method has an old history starting with Pauling's proposal [15]. However, Pauling's math- ematical construction has no realistic application in our case, where the patients have successive sequences of treatments, and oncothermia is applied only at the end. The method of propensity scores [16], [17] has also numerous problems.

Because of the very advanced and heavily pretreated cohort it is complicated (or impossible) to choose correctly the confounding variables and the proper cohort for control. The treated patients are in a hopeless, mostly untreatable state, which has to be treated by oncothermia as the last chance. The approach is the sequenced trial [18], [19], which is inherently applied in most cases, however the proper documentation of the data is not always satisfactory enough to derive strong conclusions from the dataset.

It is appropriate in our case for the choice of control group to select patients in whom the oncothermia was ineffective. This selection considers the method oncothermia has no harm for the patients (no adherent effects to cause tumor progress by the treatment alone), so the results have

two categories only: effective or ineffective in terms of the applied treatment. The patients are involved in the treatment in the stage after which the gold standards have failed, so if they die soon after the first oncothermia, we may assume, that oncothermia was ineffective in their case. The inefficiency in no-benefit is that oncothermia is not able to change their stage and should they die shortly after therapy begins, they would have received only a few oncothermia treatments. The choice of this group as a control does not mean the group is identical with the group of patients having short overall survival. The patients overall survival is dominantly determined by the elapsed time and the type of pretreatments before starting the oncothermia.

Parametric evaluation. This method evaluates the available data by parametric statistical methods. The right information is hidden in the overall survival due to the single-arm data, but it could be mined from that. The basis of the mining is the fact that oncothermia is only a fraction of the applied treatments, and the patient is included when the gold standard treatments fail.

Evaluating clinical trials we determined the empirical distribution function of survival probability. The description of survival curves [20], [21], [22], **[3]**, [Kaplan–Meier (KM), log-rank test (Cox-Mantel)], could be approached by fitting the parametric Weibull (Avrami) curves [23], [24], [25], [26], on the actual probability function. Using the Weibull distribution function to approach the survival curve parametrically is theoretically and practically established for clinical applications [27]. Fitting the distributions on the real survival curves divides the distribution in to two subgroups of the patients in the cohort. The originally homogeneous cohort is divided by this fit into subgroups of eligible and not eligible oncothermia effects for patients. (Anyway this approach used temperature development criteria, and the patients who were not "heatable," were declared as resistant to hyperthermia and were excluded from the trial (exclusion criteria) [28].

In this way we study a split of the original cohort distribution into two different groups **[27]** having Weibull approach **[27]**. Patients in the first group are for whom the treatment had no or minor influence, while the cases where the treatment was effective are in the second group. The "inclusion criteria" for the patients to oncothermia treatment is when they are no longer eligible for the "gold standards." These criteria could be checked by studying 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 a single-Weibull parametric formulation.

The fit of parametric curves splits both the survival plots (the overall and the oncothermia) into two subgroups. The split of the Weibull distribution can be used as a statistical formulation of the two arms. The quasi- arm is determined by the short-living subgroup surviving oncothermia treatments, very similarly (but parametrically expressed) to the quasi-control arm method. The responding and non-responding patients can be measured by their ratio as well. The two arms in overall survival, however, will slightly differ from those of the oncothermia survival. The latter shows clearly the eligibility of oncothermia, while the split in overall survival has numerous interacting factors due to taking into account the long time of the previous treatments. The patients ratio, however, has to be identical in the two survivals, so the best fit ratio obtained from oncothermia is fixed in the overall survival as well. In this way the control arm in the overall survival could be obtained from the best fit, and the evaluation of oncothermia would be possible

General Overview on a Large Patient's Pool

Numerous clinical studies have been performed on a huge number of patients. Presently (2009) there are more than 150 active oncothermia devices working intensively all over the word, providing more than 100,000 treatments in 2009. This huge number of treatments indicates the

usefulness of oncothermia, and the unharmed patients (no reported safety problems occurred) show the extreme safety of the method.

A remarkable amount of retrospective clinical studies are available to indicate the oncothermia effect in humans. It is commonly used for such complex and very frequent tumors like lung, liver, pancreas, brain, gastrointestinal, gynecological, etc. Only a few prospective evidence based clinical trials have been performed till now on oncothermia. The reasons for the predominance of observable trials are:

- Oncothermia is applied over the second/third line of treatments (in far more advanced cases). No evidence-based trials exists in this treatment line for pharmaceutical products also.
- The evidence-based studies are too expensive for the companies involved.
- Most of the users run a private clinic, with no interest in performing such studies.

Studies on a huge number of patients in any case show amazingly good results in all the registered localizations. One of the largest coherent databases (n = 1180) was retrospectively collected by Hungarian hospitals (HTT, PTF) [29], and presented at conferences [30], [31]. The study time was from 1997 to 2003 (recruiting 1997–2002). Generally heavily pretreated patients, with various localizations, mostly in late stages, were studied. Some localizations (non-small-cell lung cancer [n = 258], pancreas [n = 99], stomach [n = 68] colon [n = 114], rectum [n = 92], breast [n = 103], cervix uteri [n = 38], kidney [n = 39], brain [n = 24], and ovary [n = 27]) are large enough to derive some sort of conclusions. 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 of being alive) was checked in the Hungarian National Death Register, so actual and accurate data were collected. The final check of the deaths was December of 2003.

The age distribution of patients follows well the normal distribution, (see Figure 1.) 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 were present.
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 (HTT-Med Polyclinic, Budapest, Hungary), while 252 were treated in the PFY (Peterfy Hospital, Budapest, Hungary) center. The groups of patients not less than 10 is shown in Table 3.

Patients were heavily pretreated (2.62 pretreatments for one patient on average); see Figure 2. shows the advanced cases in the study. (The pretreatment combinations are also shown).
The number of metastases also was high (see Figure 3.), about a quarter of the patients had no metastasis, and also about a quarter had more than one. The topographical ICD (ICD-02) codes of metastases per patients are shown in Figure 4.

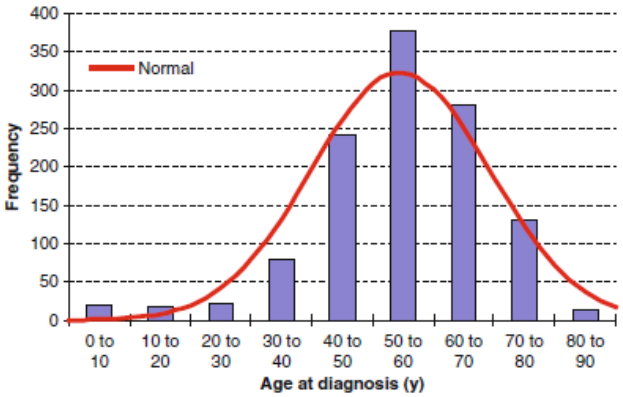


Figure 1. Distribution of patients in the study

Disease	ICD	Number of cases (pts.)
Head and 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 ten cases are not listed)

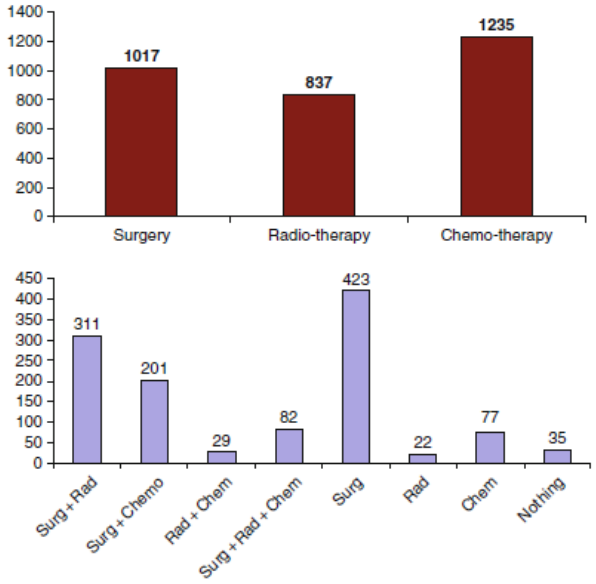


Figure 2. Pretreatment statistics of the 1,180 patients. The right panel shows the therapy combinations

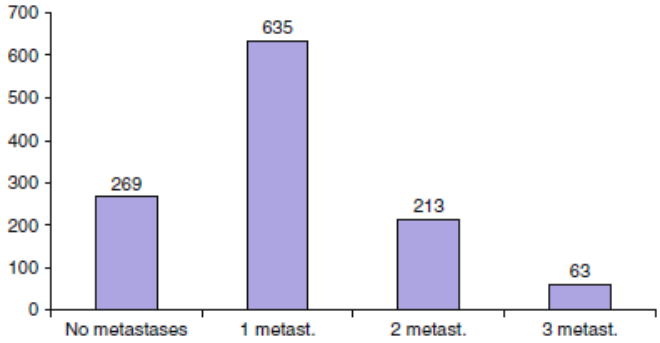


Figure 3. Distribution of metastases

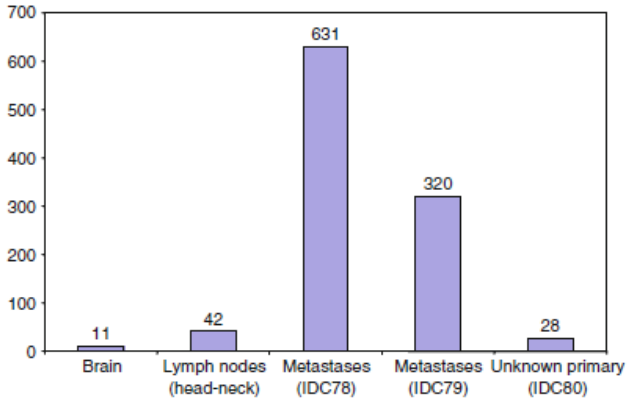


Figure 4. The ICD codes of metastases

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 aver- age/median treatment number 8/6 (1–69). Patients tolerate the treatment very well, the pain relief was obviously presented, the subjective and objective QoL was increased. No 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 dependent on the metastases. Generally, patients with metastases have much worse life expectancy than those 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 $p < 0.000002$; see Figure 5.)

The pre-treatment efficacy in the surviving fraction of the oncothermia-treated patients has also been checked. While surgery ($p < 0.002$) and radiotherapy ($p < 0.004$) have significant effect, chemotherapy ($p > 0.17$) was not significant in the overall survival rate and none of those 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) (see Figs. 6., 7.).

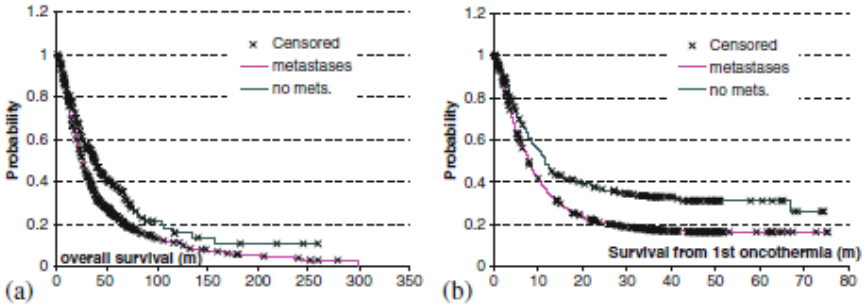


Figure 5. The survival dependence of the metastatic diseases: (a) overall survival from the first diagnosis of the disease, (b) survival from the first oncothermia treatment

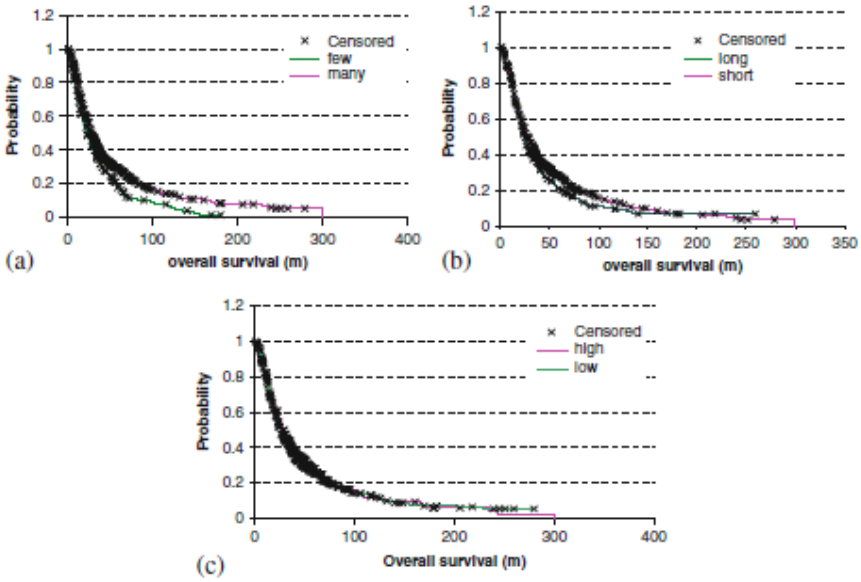


*Figure 6. Effect of the average treatment parameters on the overall survival: (**a**) number of treatments (p<0.00015), (**b**) treatment time (p>0.14), and equivalent temperature (p>0.42). The two-two quantities are divided by the median value (below or above) of the given parameter*

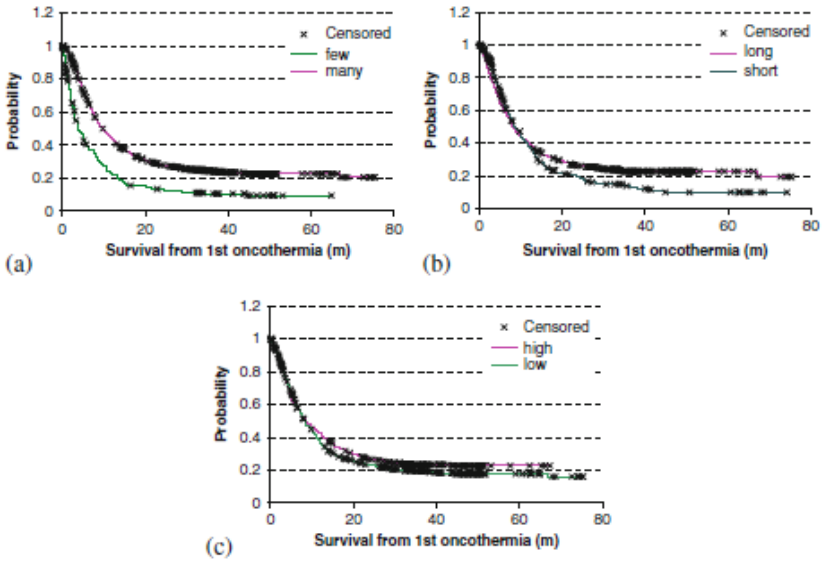


*Figure 7. Effect of the average treatment parameters on the survival from the first oncothermia treatment: (**a**) number of treatmetns (p<10-17), (**b**) treatment time (p<0.17), and equivalent temperature (p<0.17). The two-two quantities are divided by the median value (below or above) of the given 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 their second-half of their survival time, [median of the ratio of elapsed time to overall survival is 57.14 (0.0–99.8)] and the confidence intervals show hectic practice to include hyperthermia in the applied treatment protocol. However, the survival time of the patients from the first oncothermia treatment is generally longer, when the elapsed time to first oncothermia is smaller.

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 Figures 8., 9.).

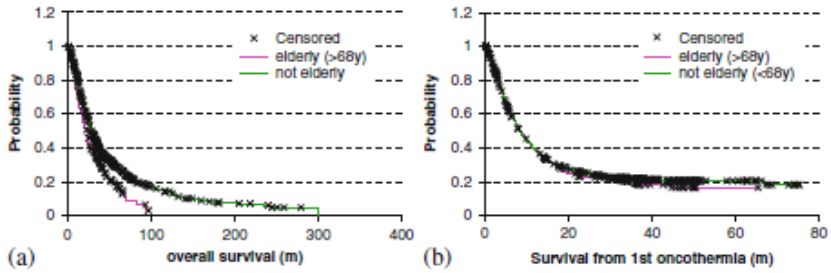


*Figure 9. The age dependence of the results from the gerontology point of view: (**a**) overall survival (p<0.00016) and (**b**) survival from the first oncothermia (p>0.63)*

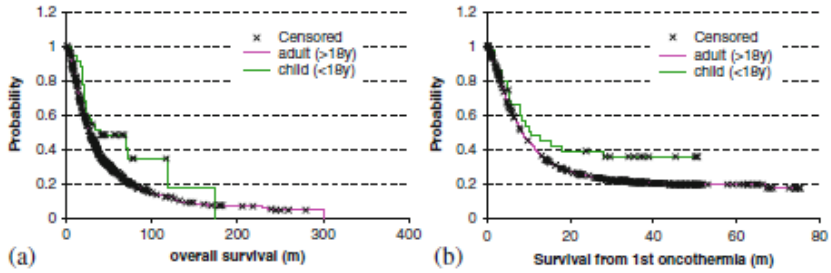


Figure 9. The age dependence of the results from the pediatric point of viw: (a) overall survival (p<0.038) and (b) survival from the first oncothermia (p=0.09)

No serious toxicity/burn was reported during the full study. The low forwarded energy was well focused on the actual tissue; there was not enough energy loss to cause surface burn.
Patients reported subjective improvements in their QoL.

Results show the general behaviors of the oncothermia treatments and are not of course satisfactory enough to derive any final conclusions on the actual cancer cure. The huge number of patients is adequately normally distributed to make some general arguments about the oncothermia method. The cohort studies in detail 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 in the case of such a group (beyond the limit of the traditional treatments) is a remarkable result. It is a fact that patients with one or multiple metastases have less survival than their non-metastatic counterparts, and of course this difference is larger in the last third of their survival. In terms of 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 ($p < 10^{-5}$) in the higher treatment numbers than in the fewer ones. This is natural: the longer survival has more possibilities to treat. However the longer survival in most of the cases was measured with a long follow- up period after finishing oncothermia.

However, a question remains: does the time of the start of oncothermia have a role? The analysis of the ratio of the elapsed time to the survival from the first oncothermia shows the difference between the early- and late-beginning oncothermia (see Figure 10.).

Also there could be significant influence on the results dependent on the experience of the treating staff. Data analysis shows there has been increasing beneficial effect from the ongoing oncothermia training and increasing experience of the users since the very beginning of its application. In comparison between the early experience (first half of the study time) and the late experience (second half of the study time) there is almost a significant difference (p = 0.052) in the

oncothermia survival, but no significance could be observed in the elapsed time to the first oncothermia and in the overall survival, see Figure 11.

One of the further advantages of oncothermia is its effect on the QoL and in suppressing the side effects of the complementarily applied conventional methods. The QoL was measured on anecdotal, subjective reports only. The dominant opinion (>70%) is the pain reduction and improved well-being leads to a better QoL.

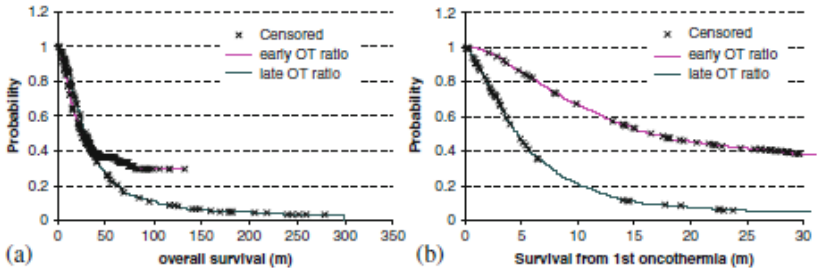


Figure 10. The ratio of the elapsed time from the first diagnosis till the first oncothermia treatment to the survival from the first oncohtermia shows a difference. The earlier oncothermia is significantly better in both the survivals (a) overall survival (p=0.07), (b) oncothermia survival (p<10-74) (The two-two quantities are divided by the median value (below and above) of the given parameter)

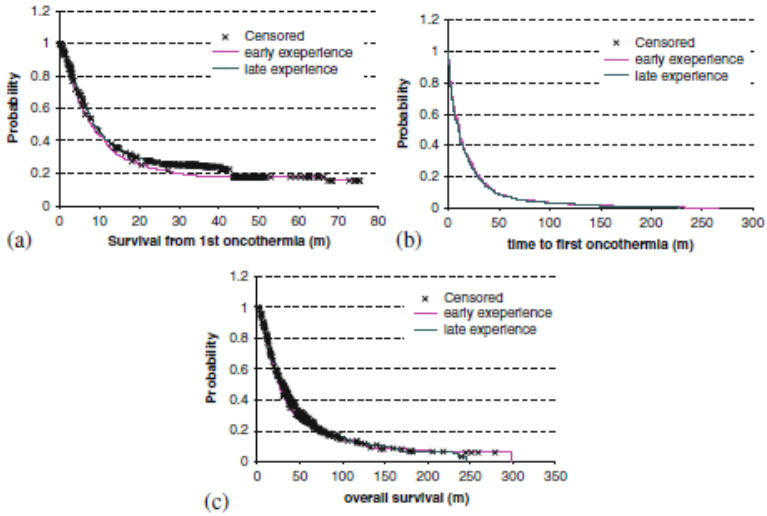


*Figure 11. Differences by the experience of the treatment procedure dugiint the trial, dividing the results into two groups: obtained in the first or in the second half of the study time. (**a**) Survival from the first oncothermia (p=0.052), (**b**) elapsed time to the first oncothermia (p>0.44), and (**c**) overall survival (p>0.29)*

Summary of the studies

There are 62 studies were performed withal together 3790 patients, from six countries (Hungary, Germany, Korea, China, Italy, Austria). The collection outlook is shown in Tables 4. and 5.

Study	Number of studies	Number of patients (n)	1st year survival (%)	Median overall survival (m)	Resposnding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of non-responding patients (m)
Brain studies	10	521	73.99	22.19	44.09	51.31	15.88
Pancresa studies	6	184	47.04	11.02	53.05	28.09	7.58
Lung studies	5	636	64.76	15.79	25.73		
Bone	3	79		40.10	90.90		
Liver metastasis	7	267	86.00	18.06	80.00		
Colorectal	7	447			63.18	109.80	23.20
Gynecology (pelvic)	5	100	93.22	33.25	44.82	89.36	21.70
Breast	1	103	97.10	52.10	45.00	274.80	10.90
Esophagus	2	19	41.70	55.64	35.00	29.40	8.50
Somach study	1	68	58.90	14.40			
Kidney cancer	1	39	84.60	35.90	48.00	78.40	33.70
Urinary bladder cancer	1	18	85.00	36.50	73.00	42.00	22.60
Head and neck	1	64	92.20	26.10			
Soft tissue sarcoma	1	16	100.00	35.90	31.00	115.30	31.30
Prostate	3	135	88.90	38.80	72.00	53.40	7.60
SUM	**54**	**2796**			**51.63**		

Table 4. Collection of the studies (Phase II) made by oncothermia in combinations with various conventional oncotherapies. (Data are weighted averages of the study-results)

Miscelleonous Study	Number of patients (n)
Borreliosis	12
General oncology	277
TCM general oncology	306
Abdominal effusion	49
Peyronie's disease	25
Chronic pelvic inflammation	283
Asthma	7
Chronic bronhitis	35
SUM patients	**994**

Table 5. Collection of the miscellenaous studies made by oncothermia in combinations with various other therapies

The survival time connected data, response rate connected data, the quality of life connected data, and tumor-market connected data are collected in Tables 6., 7., 8. and 9., respectively.

Study	Number of patients	1st year survival (%)	Median overall survival (m)	Resposnding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of non-responding patients (m)	Reference
Brain gliomas	27	86.2	23.6	43	66.2	18.2	[32], **[30]**
Brain-glioma study Phase II,	140	71.7					
Astrocytoma	40		25.8	80	40.2	20.2	[33],
Glioblastoma	92		16	73	21.*9	13.1	[34]
Diffuse astrocytoma	8		52.9				
Glioma (WHO IV) Study, Phase II, prospective, two arms	45		15				
Passive arm	36	40	11				
Active arm	9	65	14.5	43	66.2	18.2	**[1]**, [35]
Recurrent glioblastoma study, Phase II,	19	68.0	21.8	59	32.6	12.4	[36]
Glioma study, Phase II,.	36	60.0					
Astrocytoma	9		106				
Glioblastoma	27		20				[37]
Glioma study, Phase II,.	179						[38]
Astrocytoma	53	100	103				
Glioblastoma	126	76	16				
Advanced, relapsed brain gliomas, Phase II, .	12		10	25			[39]
Advanced, relapsed brain gliomas, Phase II,	24	55	12	25			[40]
Brain glioma WHO III-IV, Phase I, safety prospective	24						[41],[42, [43], **[44]**
Metastatic brain tumors study, Phase II	15	90.0	46.2	73	48.2	16.1	**[39]**
Head and neck study, Phase II. e	64	92.2	26.1				**[1]**, [45]
Bone-metastases, monotherapy, Phase II,	6	100	40.1				**[1], [45]**
Refractory bone-metastases study, Phase II,	11			90.9			[46]
Kidney cancer study, Phase II,	39	84.6	35.9	48	78.4	33.7	**[1], [45]**
Urinary bladder cancer study, Phase II,	18	85.0	36.5	73	42.0	22.6	**[1]**
Non-small cell lung cancer meta-analysis.	311						
Passive arm	53	26.5	14				[47]
Active arm	258	67.0	15.8	21	53.4	18.1	
Non-advanced (WHO<III)	77		11	17			
Advanced (WHO≥III)	140		14.7	88			

Small-cell lung cancer	28						
Passive arm	9	29					[48]
Active arm	19	58					
Lung carcinoma study, Phase II,	61	67.2	16.4				**[1]**, **[45]**
Breast cancers	103	97.1	52.1	45	274.8	10.9	**[1]**, **[45]**
Soft tissue sarcoma study, Phase II	16	100	35.9	31	115.3	31.3	**[1]**
Esophagus study, Phase II	12	41.7	28.5	35	29.4	8.5	**[31], [1]**
Esophagus study, Phase II,	7		6.8	100			[49]
Liver metastases from various origin, Phase II	25		20.5				[50]
Liver metastases from various origin, Comparative study, Phase II,	28						**[46]**
With radiotherapy	16			81			
With chemotherapy	8			38			
Monotherapy	4			25			
Liver metastasis form colorectal origin, Phase II,	80	86.0	24.1				
Passive arm		53	11				[51]
Active arm	80	91	24.1				
With chemotherapy	30	80	21.5				
Monotherapy	50	92	24.4				
Liver metastasis form colorectal origin, Phase II	15		23	80			[52]
Liver metastasis form colorectal origin, Phase II	22		28				[53]
Liver metastasis	29			86			
Liver metastasis form colorectal origin, Phase II,	30		22				[54]
Pancreas tumor study, Phase II,	26	46.2	11.6				[55]
Pancreas tumor study, Phase II,	107						**[31]**
Passive arm	34		6.5				
Active arm	73	52.1	9.93	58	25.5	8.4	
Pancreas tumor study, Phase II,	30	31.0		41	34.4	5.6	[56], [57]
Pancreas tumor study, Phase II,	42	52.4	12.3				[58]
Pancreas tumor study, Phase II,	13	40.0	11.9				[59]
Stomach cancer study, Phase II,	68	58.9	14.4				**[1]**
Colorectal cancer ()	218	84.9	28.5				**[1]**, **[45]**
sigma	12			34.1			
rectum	92			57.1	58	21	
colon	114			44.2	109.8	23.2	
Colon cancer study, Phase II, prospective, three arms, randomized	154						[60] [61]

Clifford TCM	53			75			
Monotherapy	50			81			
Combined therapy	51			91			
Rectum cancer study, Inoperable→operable, Phase II,	7			71			**[49]**
Rectal cancer, non-operable, Phase II,	65			96			[62]
Pelvic gynecological cancer studies, Phase II	74						
Cervix	38	86.8	27.6	25	63.5	20.9	[63]
Ovary	27	100	37.8	67	132.7	19.4	
Uterus	9	100	61.5	62	68.5	32.0	
Ovary, advanced, relapsed	26						[64]
Heavily pretreated	13		14.3				
Not heavily pretreated	13		27				
Prostate cancer study, Phase II,	18	88.9	38.8	72	53.4	7.6	**[31]**

Table 6. Summary of the studies made by oncothermia treatment (End-points are survival connected)

Study	**Number of patients**	**Complete remission (CR) [%]**	**Partial remission (PR) [%]**	**No change (NC) Stable disease (SD) [%]**	**Overall response rate (CR+PR+SD) [%]**	**Reference**
Colorectal inoperable, liver metastasis	60					
CDDP	28	0	3.57	3.57	7.14	[65]
OXALI	32	0	15.63	15.63	31.25	
Ovary (relapsed, advanced epithelial	26					**[64]**
Heavily pretreated	13	0.00	23.08	38.46	61.54	
Not heavily pretreated	13	30.77	23.08	38.46	92.31	
General oncology	277		21.50	37.00	58.50	[66]
TCM general oncology	306					
Oncothermia + TCM	75	6.67	57.33	26.67	90.67	[67]
Oncothermia+TCM+i.v.CTx	65					
Passive arm	51	7.84	60.78	15.69	84.31	**[67]**
Active arm	14	14.29	64.28	21.43	100.00	
Oncothermia+TCM+abdominal perfusion	87				0.00	
Passive arm	45	2.22	40	24.44	66.66	**[67]**
Active arm	42	7.14	54.76	26.19	88.09	
Oncothermia+TCM+bladder perfusion	37					
Passive arm	24	0	50	12.5	62.50	**[67]**
Active arm	13	7.69	53.85	30.77	92.31	
Oncothermia+TCM+RTx	42					
Passive arm	30	3.33	50	16.67	70.00	**[67]**
Active arm	12	8.33	66.67	16.67	91.67	
Abdominal effusion +oncothermia	49	4.08	53.06	16.38	73.52	**[67]**
Chronic pelvic inflammation	283					[68]
Passive arm	143					

Active arm	140	46.10	29.40	19.60	95.10	
Chronic bronhitis, TCM + oncothermia	35	30.00	24.30	25.70	80.00	**[68]**
Colon cancer study, , Phase II, prospective, three arms, randomized	154					**[67]**
Clifford TCM	53	5.7	28.3	18.9	52.90	
Monotherapy	50	10	26	26	62.00	
Combined therapy	51	13.7	45.1	23.5	82.30	
Colon operability	7	71			71.00	**[49]**
Prostatitis	72					**[68]**
Passive arm	36	16.70	27.80	19.40	63.90	
Active arm	36	41.70	36.10	22.20	100.00	
Prostate study	184	49.5	15.2	15.8	80.50	[69]
Prostate cancer (Kleef) (Gleason Score 2-6	16					[70]
Oncothermia +hormone therapy	8				50	
Oncothermia monotherapy	8				37.5	
Prostate cancer (Kleef) (Gleason Score 7-9	17					**[70]**
Oncothermia +hormone therapy	11				81.82	
Oncothermia monotherapy	6				33.33	
Peyronie's disease	25				100	
Pancreas	42		23.8	31	54.80	**[58]**
Pancreas	30	3.3	33.3	40	76.60	**[56], [57]**
Esophagus		8	50	42	100.00	**[49]**
CRC - liver	22	5		23	28	**[53]**
CRC liver	15		20	60	80.00	**[52]**
CRC liver Oxalyplatin	12				8.3	**[54]**
CRC liver cisplatin	18				27.8	
Advancer liver	28					**[46]**
Oncothermia + RTx	16		31	50	81	
Oncothermia + CTx	8		13	25	38	
Oncothermia monotherapy	4			25	25	
Brain	19		11	32	43	**[36]**
Asthma	7		75	10	85	[71]
Small-cell lung cancer (SCLC)	38		44.7	15.8	60.5	[72]
Benign tumors oncothermia + TCM	35	54.3	25.7		80.00	**[68]**

Table 7. Summary of the studies made by oncothermia treatment (End-points are response connected)

Study	**Number of patients**	**Pain-reduction [%]**	**increasing performances [%]**	**better overal QoL [%]**	**Reference**
Colorectal inoperable, liver metastasis	60				
CDDP	28	17.86	39.29	57.14	**[65]**
OXALI	32	46.88	7.86	100.00	
Borreliosis	12		100.00	100.00	[73]
Abdominal effusion +oncothermia	49	88.88	73.91	85.70	**[67]**

Colon cancer study, Phase II, prospective, three arms, randomized	154				**[67]**
Clifford TCM	53	37.7	13.73	58.49	
Monotherapy	50	36	23.53	60	
Combined therapy	51	58.8	62.75	86.28	
Prostate study	184				**[69]**
Prostate study	115		76.2	94.1	[74]
Colon operability	7		86	43	**[49]]**
CRC liver	15				**[52]**
CRC liver Oxalyplatin	12	66.7		83.3	**[54]**
CRC liver cisplatin	18	11.1		27.8	

Table 8. Summary of the studies made by oncothermia treatment (End-points are quality of life connected)

Study	**Number of patients**	**Tumor-market decrease [%]**	**References**
Colorectal inoperable, liver metastasis	60		**[65]**
CDDP	28	14.29	
OXALI	32	37.50	
CRC liver Oxalyplatin	12	58.30	**[54]**
CRC liver cisplatin	18	5.60	

Table 9. Summary of the studies made by oncothermia treatment (End-points are tumor-marker connected)

Studies connected to Quality of life are collected in Table 10.

Study	Number of patients	Pain-reduction [%]	increasing performances [%]	better overal QoL [%]	
Colorectal inoperable, liver metastasis	60				**[65]**
CDDP	28	17.86	39.29	57.14	
OXALI	32	46.88	34.38	100.00	
Borreliosis	12		100.00	100.00	**[73]**
Abdominal effusion +oncothermia	49	88.88	73.91	85.70	**[67]**
Colon cancer study, Phase II, prospective, the e arms, randomized	154				**[60], [61],**
Clifford TCM	53	37.7	13.73	58.49	
Monotherapy	50	36	23.53	60	
Combined therapy	51	58.8	62.75	86.28	
Prostate study	184				**[69]**
Prostate study	115		76.2	94.1	**[74]**
Brain study					
Colon operability	7		86	43	**[49]**

CRC liver	15				**[52]**
CRC liver Oxalyplatin	12	66.7		83.3	**[54]**
CRC liver cisplatin	18	11.1		27.8	

Table 10. Studies connected to quality of life of the patients

There are numerous studies continuing and planned. The most important activities are collected in Table 11.

#	Study	Investigation center
6	**Continued studies**	
1	MammaTherm	LM University Munich, Germany
2	OvaTherm	National Cancer Institute, Korea
3	CervoTherm	Johannesburg University, S. Africa
4	TCM + Oncothermia	Clifford Hospital, China
5	AndroTherm-Peyronie disease	Italian Andrology Institute, Italy
6	EsoTherm	Chiba University, Japan
2	**Non-oncology studies**	
1	Borrelia – lyme disease	Clinic Zais, Germany
2	Benign tumors and others	Clifford Hospital, China
16	**Experimental/Preclinical studies**	
1	Immunoeffects (in vivo)	Semmelweis University, Hungary
2	Bystander effects (in vivo)	St. Istvan University (Veterinarian), Hungary
3	Dendritic cell effects	Chiba University, Japan
4	RF-vaccinantion study	St. Istvan University, Hungary
5	Veterinarian studies (dogs, cats)	Tottori University, Japan
6	Selective cell-distortion mechanisms (in vitro)	Semmelweis University, Hungary
7	Electromagnetic effects (in vitro)	St. Istvan University (Veterinarian), Hungary
8	Correlation (entropy) effects (in silico)	Oncotherm laboratory, Hungary
9	Electric field distribution effects (in silico)	Pazmany P. Catholic University, Hungary
10	Viral effects (in vivo)	Oncotherm laboratory, Hungary
11	Ecciniococcus study (in vivo)	Dusseldorf University, Germany
12	Ecciniococcus study (in vivo)	Tottori University, Japan
13	Temperature distribution phantom models	Oncotherm laboratory, Hungary
14	TCM synergy with oncothermia	Oncotherm laboratory
15	Ultrasound apoptotic measurements	Pazmany P. Chatolic University
16	Fractal-template research	Oncotherm laboratory, Hungary
4	**Planned experimental/preclinical studies**	
1	Repetition programs,	Peince of Wales Hospital, Australia
2	Repetition programs,	Maryland University, USA
3	In vivo ovarian experiments	Yonsei University, Korea
4	Stem cell research	Toyama University, Japan
2	**Case studies**	
1	Blood effects (case-studies)	Arkadia Praxis, Germany
2	Systemic effects (case studies)	Samsung Hospital, Korea
32	**SUM of projected studies**	

Table 11. The projected studies (continued and planned) for oncothermia research

In the followings we show some of the clinical studies in details.

Brain studies

Brain safety study 1. (Phase I)

Gliomas are one of the most common primary brain-tumors. Despite surgery and radiotherapy (RT) with or without adjuvant chemotherapy, malignant glioma remains an almost uniformly fatal disease characterized by a rapid and devastating clinical course. Oncologic hyperthermia (oncothermia or modulated electro-hyperthermia) applied either alone or in combination with chemo- and/or radio-therapy is a new modality of brain-glioma (BG) treatments.
A monocentric prospective single-arm Phase I/II study (n=24) was performed by Neurology Clinic, Regensburg University, Germany (Investigators: Prof. U. Bogdahn & Prof. P. Hau) **[41], [43]**. Main inclusion criteria were recurrent high-grade glioma WHO Grade III or IV, age 18 to 70 and Karnowsky Performance Score ≥70. Primary endpoints were dose limiting toxicities (DLT) and maximum tolerated dose (MTD) with the combined treatment, (see Table 12.). Alkylation chemotherapy (ACNU, Nimustin) was administered in a dose of 90 mg/m^2 on day 1 of 42 days for up to 6 cycles or until tumor progression (PD) or DLT occurred. Relevant toxicities were local pain and increased focal neurological signs or intracranial pressure. No DLT occurred in the trial. In some patients, the administration of Mannitol during oncothermia or long-term use of corticosteroids was necessary to resolve symptoms. (The observed adverse effects are originated from ACNU which was ciombined by oncothermia.) Note, the curative dose is used two/three times a week, avoid any involvement of unsafe processes, and optimize the stress-protein reaction in the tumor.

Group	Number of Patients	Chemotherapy (single close of a 6 week cycle)	Oncothermia (4 of 6 week cycle)
1	3 (6)	ACNU 90 mg/m^2	Oncothermia 2x/week
2	3 (6)	ACNU 90 mg/m^2	Oncothermia 3x/week
3	3 (6)	ACNU 90 mg/m^2	Oncothermia 4x/week
4	3 (6)	ACNU 90 mg/m^2	Oncothermia 5x/week

Table 12. Dose-escalation in the safety study

Brain glioma study (Phase II)

The study is an open-label, single arm, monocentric, sequential Phase II study was finished in March 2006 **[33]**. The involved patients are being analyzed according to an intention-to-treat (ITT). Recruiting time was 56 months. The primary endpoints of the study were the overall survival time (OST) and the survival time from the first oncothermia treatment (TST). The applied test was Kaplan-Meier log-rank. Inclusion criteria were: (1) Inoperable or sub-totally resected or recurrent BG, (2) progression after radio- and/or chemo-therapy, (3) Karnowsky Performance Score (KPS) ≥ 30%.
Oncothermia was applied by power ranged between 40-150 watts and the calculated average equivalent temperature in the tumors was above 40 ^{o}C more than 90% of the treatment time. The applied bolus fixed the skin surface on 20 ^{o}C. The targeted area self-selectively was treated form the well covering electrode system. Oncothermia was performed in two/three sessions per week. Treatment time and power range per session were started with 40 W by 20 minutes, and (step by step) gradually and linearly raised up to 60 minutes, 150 W in two weeks.
Distribution of the BG patients by their WHO-grade show mostly advanced cases: diffuse astrocytoma, (DA): 8, (5.7 %); anaplastic astrocytoma, (AA): 40, (28.6 %); glioblastoma multiform, (GBM): 92, (65.7 %); (see Figure 12.). Most of the patients were failed responding on the applied traditional therapies.

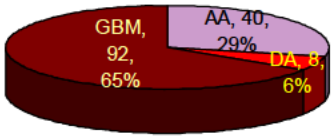


Figure 12. Distribution of the 140 patients involved in the study

The age-distribution shows near to normal (p<0.001 by Chi-square test for discrete variables), and no outliers (p<0.05) were present. The median age was 43.5 y (3-73), the mean-age was 43.2 y (Std.err=1.42), 15 (10.7 %) patients were below 18 y, and 8 (5.7 %) were over 68 y. The gender distribution was 50/90 female/male. The epidemiologically shown [75] more frequent BG in elderly population (in Japan BG-incident is 2.40/100000/y over 70 y, while under is only 1.42/100000/y [76]) is not appeared in our case. A slight increase from the normal distribution could be observed in the range of 50-70 year ages.

Pre-treatments were applied in 364 cases (~2.6/patient). The chemo therapies were: in 117 cases (84 %), the radiation was in 129 (92 %) and 117 cases surgery (84 %). (Two patients have no any pre-treatments due to individual reasons.) In mean, 69% of all patients had all tree therapy modalities.

OT was applied adjuvant in most of the cases. The chemo therapies (in most of the cases TMZ) were: in 102 (73 %) cases and the radiation was in 5 (3.6 %) cases, the supportive therapy was 105 (75 %) cases. Characterization of the applied supportive therapy is shown in Table 13. This therapy was started together with OT, and was applied for 3 months. Application of oncothermia as mono-therapy (2 cases (7 %)) and only combined with supportive therapies (27 cases, (19 %)) were applied if no other modality was possible.

Supportive drug	Dose
Boswelia carterii (Weihrauch)	6 g/d, (3x/d)
Mistletoe (Mistel, Lectinol)	15 ng, (3x/w), subcutan
Selenium	300 µg/d

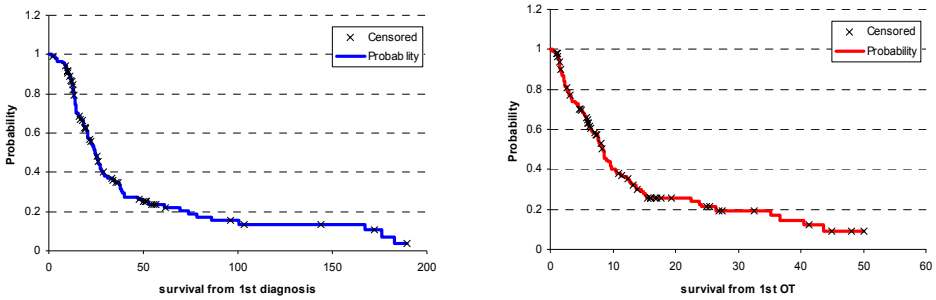
Table 13. The applied supportive therapy

The oncothermia treatment cycles were in average 1.8 (1-9) while the treatment number average was 21.5 (2-108). The median oncothermia treatment number was 15. The applied dose of oncothermia was regarded as low if did not exceed the 8-times 60 min load, (dose-threshold, DT). Such low dose was provided for 28 patients. The median time of total duration of the oncothermia treatment period was 1.7 m (1 d-36.4 m) in average 3.3 m (Std.err=0.4).

The median time elapsed to first oncothermia was 10.8 m (0.2-181) 21.7 m (std.err.=2.5) in average. The median follow-up time after the last oncothermia was 3.4 m (1day-49.1 months) in average 6.6 m (Std.err=0.8).

No toxicity or other problems were observed during the treatment, only 10-15 times we observed headache, no increased edema, but all the points were clinically controllable. In most of the cases the edema was decreased and the intracranial pressure also was decreasing. No any surgical or other intervention was necessary during or after the oncothermia treatments for anyone of the patients. All the patients had tolerated very well the treatment, and subjectively they reported better quality of life, but this was not objectively evaluated.

The MST of overall survival and TST for all of the patients were 19.8 m (1.4-190) and 6.7 m (0.3-50), respectively. The average (mean) survival time (AST) of overall survival and TST were 31.7 (std.err=3.0) and 10.0 (std.err=0.9), respectively. The corresponding Kaplan-Meier (KM) plots are shown in Figure 13. The same survivals categorized by their WHO-grade are shown in Table 14. and Figure 14.

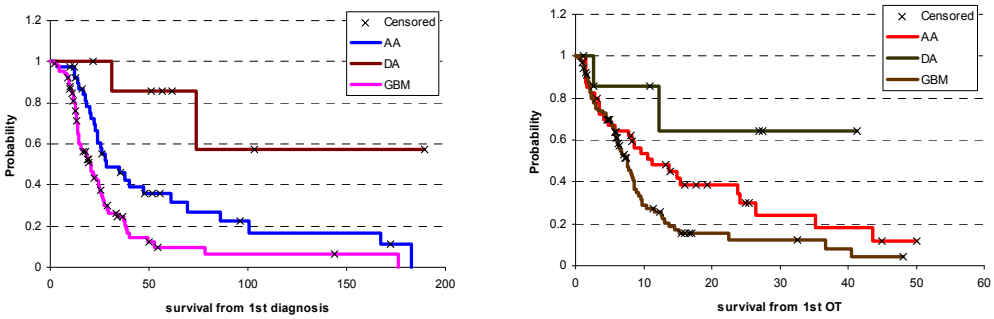


a) b)

Figure 13. a) overall survival and b) TST KM-survival plots for all of the treated patients

WHO grade	#Pts.	MST OST [m]	(min.-max.) [m]	MST TST [m]	(min.-max.) [m]	AST OST [m]	(Std.err.) [m]	AST TST [m]	(STD.err.) [m]
DA	8	59.2	22-190	11.6	1.1-41	73.6	18.8	15.6	5.2
AA	40	25.8	3.6-183	9.1	1.4-50	43.3	7.0	13.4	2.0
GBM	92	16.0	1.4-176	6.1	0.3-48	23.0	2.5	8.0	0.9

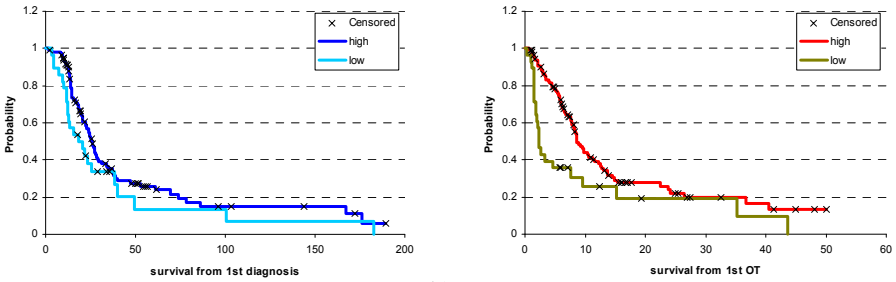
Table 14. Median and mean data of the survivals



a) b)

Figure 14. a) overall survival and b) TST KM-survivals for patients with DA, AA and GBM

The dose analysis shows (see Figure 15.) the relative dependence to DT not significant for overall survival (p=0.129) and significant for TST (p<0.01).



a) b)

Figure 15. a) Dose dependence to DT for overall survival (p=0.129) and b) for TST (p=0.003) survivals (KM survival plots)

The age-categories by young (<18 y, n=15) adult (between 18 y and 68 y) and elderly (>68 y, n=10), have no remarkable differences (see Figure 16.). The significance in the overall survival (at KM plot, Figure 16/b.) for elderly patients could be from natural reasons, which assumption is supported by the no-difference results in TST KM-plot (see Figure 16/d.).

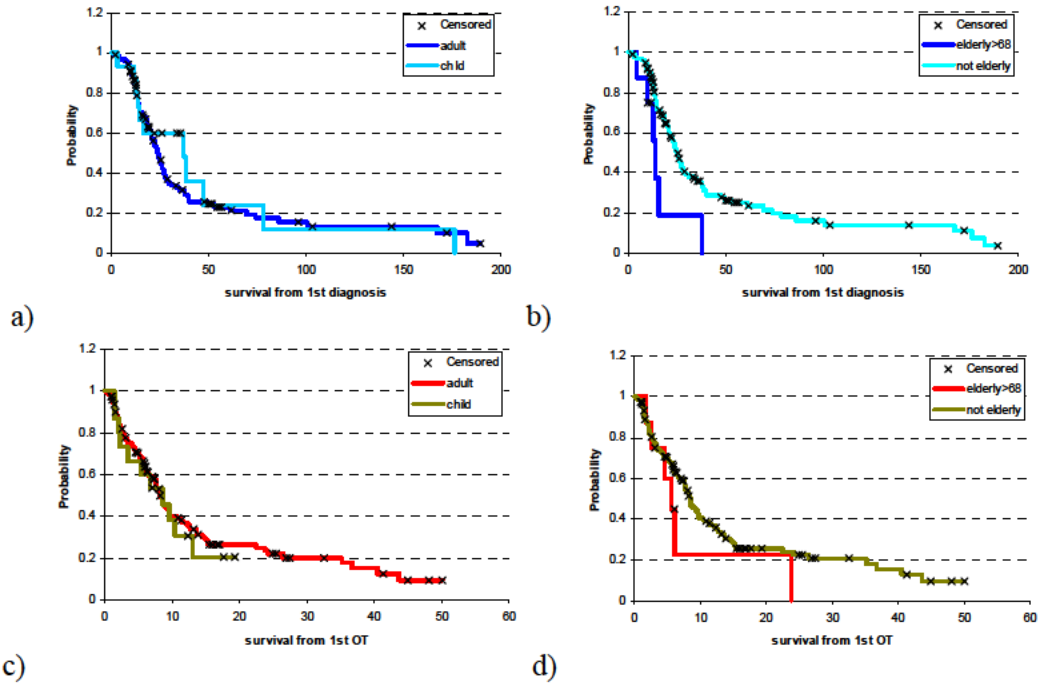


Figure 16. Comparison of adults with young (<18 y) and elderly (>68 y) patients. a) overall survival for youngsters (p=0.65), b) overall survival for elderly (p=0.016), c) TST for youngsters (p=0.66), d) TST for elderly (p=0.24)

No serious side effects were observed. Patients tolerated the treatments well during the whole treatment period. Most of the patients were well relaxed, some even felt asleep during the treatment. Patients reported better quality of life, but this information was not objectively measured.

The expected MST for BG patients is over all 11.3 m, which is well behind the actual 19.8 m (gained by 75.2 %). According to the RTOG classifications [77], we divided the patients to two groups: age under- and over-50 years. The obtained patient's distribution is shown in Figure 17. pie-diagram.

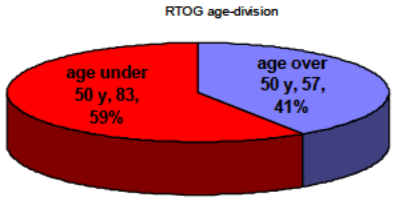


Figure 17. Distribution of patients by 50 years age-threshold

The overall survival and of TST in general definitely with high significance differs by these categories, as the KM-plots show, see Figure 18.

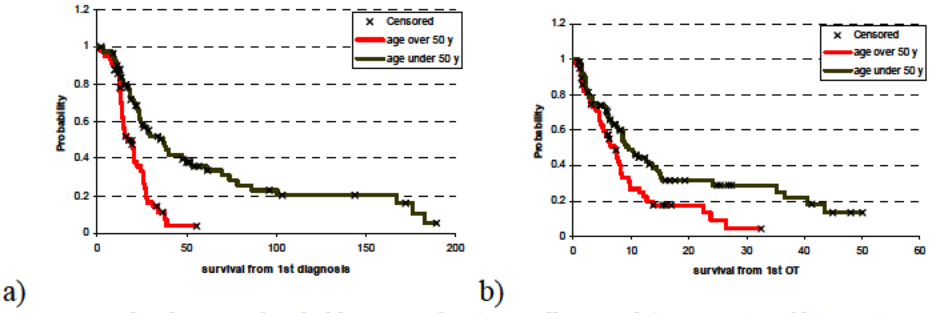


Figure 18. KM plots by years threshold 50 year: for a) overall survival (p<0.0003) and b) TST (p<0.009)

By categories the MST of overall survival was (except one category) systematically significantly well higher (see Table 15. than the expected ones for corresponding stage BG patients: the under and over fifty-years patients median gains are -28.5%, 24.0% for DA+AA and 39.4%, 46.4% for GBM, respectively. The KM-plots show well the significant differences (see Figure 19.). The gain is obviously large except the DA+AA patients under 50 year age. The reason of this discrepancy is not known. The next trial has to decide on this issue as well.

WHO grade	Patients no. (n)	MST OST [m]	(min.-max.) [m]	AST OST [m]	(Std.err.) [m]	MST RTOG [m]
DA+AA (<50y)	36	37.7	3.6-190	56.7	8.5	49.4
DA+AA (>50y)	12	18.4	9.9-56	23.3	3.8	21.7
GBM (<50y)	47	19.0	2.4-176	28.7	4.7	13.7
GBM (>50y)	45	14.4	1.4-39	17.1	1.3	9.7

Table 15. The main statistical characters by the RTOG division

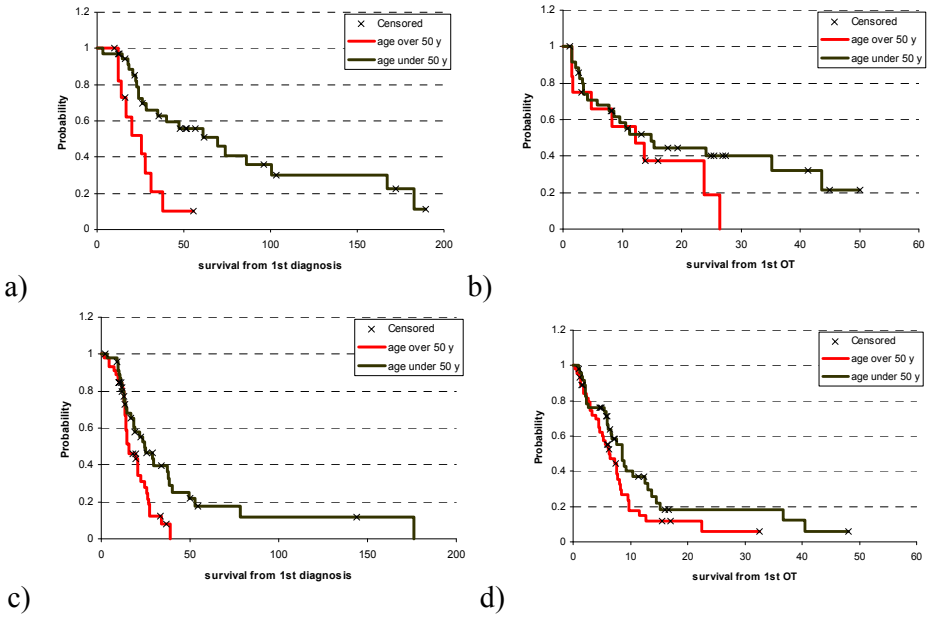


Figure 19. The KM-plots of patients by RTOG categories. For AA+DA a) overall survival (p<0.003) and b) TST (p=0.22), as well as for GBM c) overall survival (p<0.009) and d) TST (p<0.08)

The results could be well compared to the available SEER [**6**] data. Comparison of the overall survival of our retrospective 140 patients and SEER retrospective 28.970 patients is shown in Table 16., selected by the grade categories, The gain of the MST overall survival in various categories is 38,6 %, 146% and 57.0 % for DA, AA and GBM patients, respectively.

WHO grade	Patient number (n) (present)	MST OST (present) [m]	MST OST (min.-max.) [m]	Patient number (n) (SEER)	MST OST (SEER) [m]
DA	8	59.2	22-190	2749	42.7
AA	40	25.8	3.6-183	3273	10.5
GBM	92	16.0	1.4-176	5801	10.2

Table 16. Comparison of the data of SEER and our present study

The parametric evaluation shows definite benefit of oncothermia. The overall survival shows significant curative benefit, the slope of survival modified from 1.8 to 0.85 (gain: 53%) and from 1.95 to 1.42 (gain: 27.5%), for AA and GBM, respectively; see Figure 20.

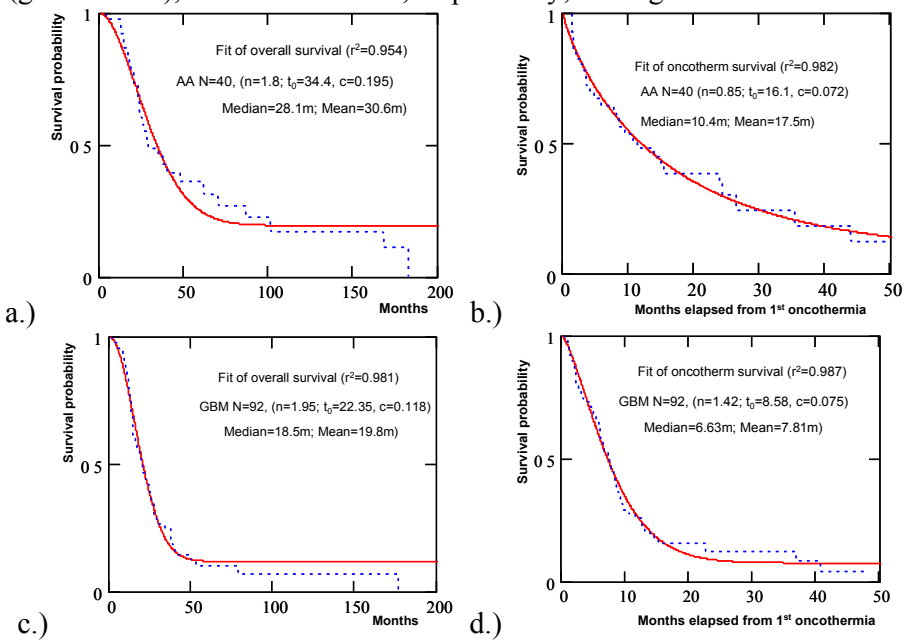
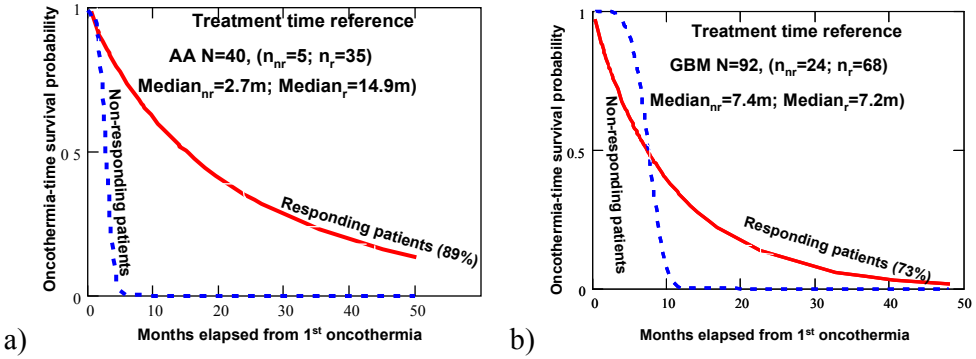


Figure 20. The accurate Weibull fit (solid lines) to the survival plots [AA in (a) and (b), GBM in (c) and (d), while the overall survivals respectively are on (a) and (c) as well as the survivals from the first oncothermia treatment are on (b) and (d) panels]

This general gain could be studied further, by separating the responders and non-responders. The parametric fit of the survival plots shows high response for treatment (responders are 89% and 73% for AA and GBM, respectively), see Figure 21. The relative large significant difference between the non-responding-arm and the actively responding one is the consequence of the inclusion criteria. When the patients are included in their last phase of treatments, than usually only a short time remains from their lifetime. Oncothermia in its active long treatment period is a considerable elongation of the lifetime. However it could be also explained from the side of efficacy. The oncothermia was effective for the patients who were in the active arm of the oncothermia, while the control arm collects the patients whom the oncothermia (and the concomitant other treatment with that) was not effective at all. Their percentage is rather large, so it shows a more complicated picture as it looks from the only probability comparison.



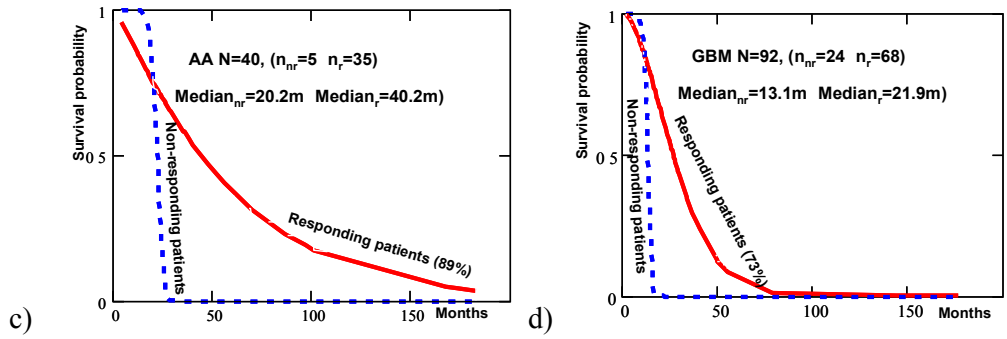


Figure 21. The parametric fit (method is described in Appendix 35.) of responders of Anaplastic astrocytoma cases (a & c) and glioblastoma multiform (b & d). The treatment reference (choosing the non-responding patients as control arm) (a & b) and the overall survival (c & d) shown independently. Both fits for AA and GBM show highly significant benefit of oncothermia to those patients who responds. (The subscripts nr and r denotes the non-responding and responding patient's data respectively.)

In one of a recent publication [78], the 1 and 2 year survivals with TMZ shows 58% and 31%, respectively. Compare these results with ours, the gain is also remarkable. 71.7 % (66/92) and 30.4 % (28/92) for 1 and 2 years survival, respectively. (The two-year survival for GBM by RTOG study (no TMZ application) is only 17%, [**77**].) The most recent TMZ randomized clinical trial for GBM [79], summarizing the results of 573 patients from 85 cooperating centers shows a gain of MST from 12.1 m (without TMZ) to 14.6 m (with TMZ). A former TMZ results [80] were similar, having MST in only RT group (n=24) 11.2 m, RT+CT (not TMZ) group (n=32) 12.7 m and for RT+TMZ group (n=23) 14.9 m. The two-year survival in the new study **[78]** increased form 10.4% (without TMZ) to 26.5% (with TMZ). Our present results were even better than the presently published best TMZ applications.

The long term survival of GBM is very rare, about over three years is only 1.8% is a 279 patients trial [81]. In our case from 92 GBM patient 13 (14.1 %) had longer overall survival than 3 years, which is a remarkable gain.

Studying the MRI images we have some indicative hints to suppose an extended apoptosis initialized by the oncothermia. This could be in good correspondence with some theoretical considerations [82], as well as with some experimental facts [83], [84], [85]. More considerable investigations on this line are in progress.

The results of this study well indicate the feasibility and the benefit of the oncothermia treatment, so the present study was sequentially continued with further observations. The data were published elsewhere, [86], and also extended with additional data from other clinic **[38]** (bicentral trial).

Quality of life of anyone of the oncothermia treated patients was not worsening. According to their subjective reports, the quality of life was considerable increasing in most of the cases. (No objective evaluation was done yet.)

Brain glioma study 2.

One of the first preliminary oncothermia results of primary brain gliomas (n=27), were published in Hungary **[32],** [**88**] (HTT-Med Polyclinic; Budapest, Hungary. Investigator: A. Varkonyi). In this study the stages were not distinguished. Overall survival median was 23.6m, while the overall average 46.7m. Survival times from 1st oncothermia are: median 6.4m, average 14.8m; see Figure 22. The parametric evaluation of responders shows 43% only (see Figure 23.).

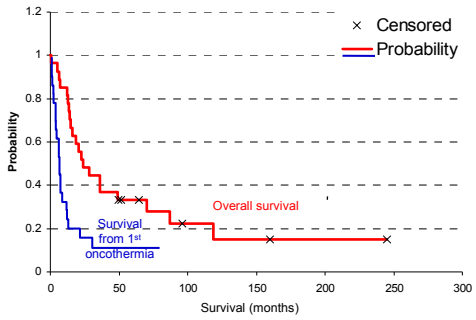


Figure 22. The overall survival (median 23.6m) and the survival from the first oncothermia (median 6.4m) are shown in Kaplan-Meier plot

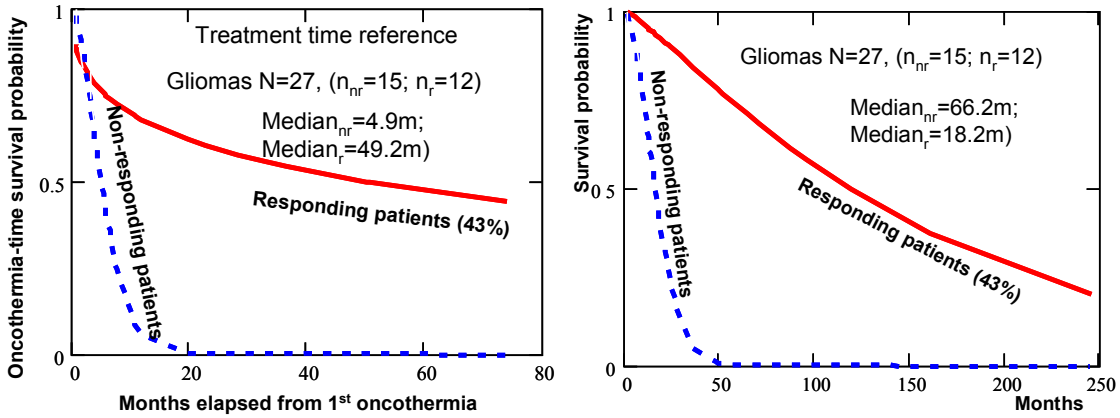


Figure 23. Responders are well distinguishable from the non-responders, but only less than half (43%) of the patients were responding in this very first study

Prospective, double arm brain glioma study

A small prospective double arm (control arm n=36, active arm n=9) study for advanced primary brain tumors (gliomas WHO IV.) was done in Nurnberg (Praxis Klinikum Nord, Nürnberg, Germany, Investigator: Prof. Dr. H. Renner). Trimodal therapy was applied: radiotherapy (50-60 Gy), chemotherapy (Temodal) and oncothermia (6-12x; 60 min) **[35]**. The median survival was measured on control-arm as 9m, while in the active oncothermia arm it was 15m (see Figure 24.).

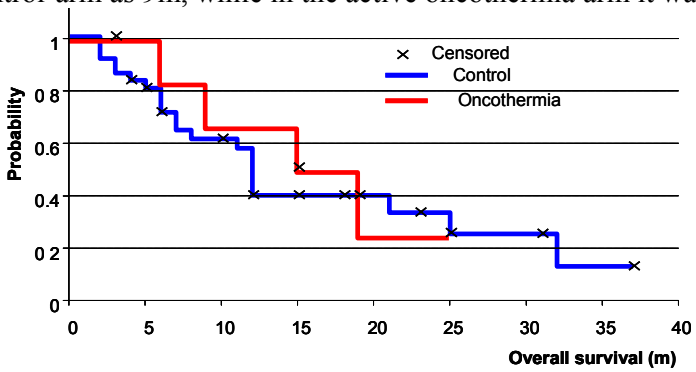


Figure 24. The double arm study shows remarkable improvement of advanced glioblastoma multiform patients (WHO IV.), but the change is not significant, due to the now number of patients (n=9 in the active arm)

Study of brain gliomas with local clinical responses

The same ACNU combination (60 mg/m^2), which was used for safety (Phase I; dose escalation) trial had bee used in Phase II as well for recurrent glioblastoma (n=19). (Clinic St. Georg, Bad Aibling, Germany, Investigator: Dr. F. Douwes, [87]). The quality of life of patients was measured

by standard Karnowsky Performance Score (index), (KPS) (see Figure 25.). The obtained median of overall survival was 21.8m (average survival 25.5m); while the median survival from first oncothermia was 8.8m (average survival 13.5m), Figure 26. The local clinical response had no complete remission, and 58% of the patients were in progressive disease (looks not responding on oncothermia, see Figure 27.). However, the responding patient's ration is 59% (falling 41%) calculated by the parametric selection (see Figure 28.). This difference could be caused by the relatively short follow-up in the trial.

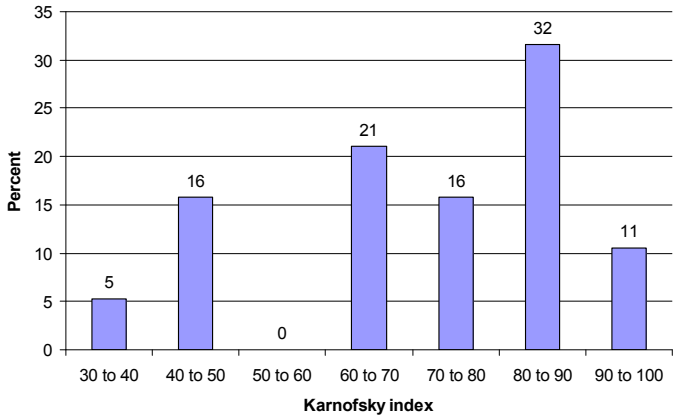


Figure 25. Distribution of KPS for the patients involved in the study, (percentages)

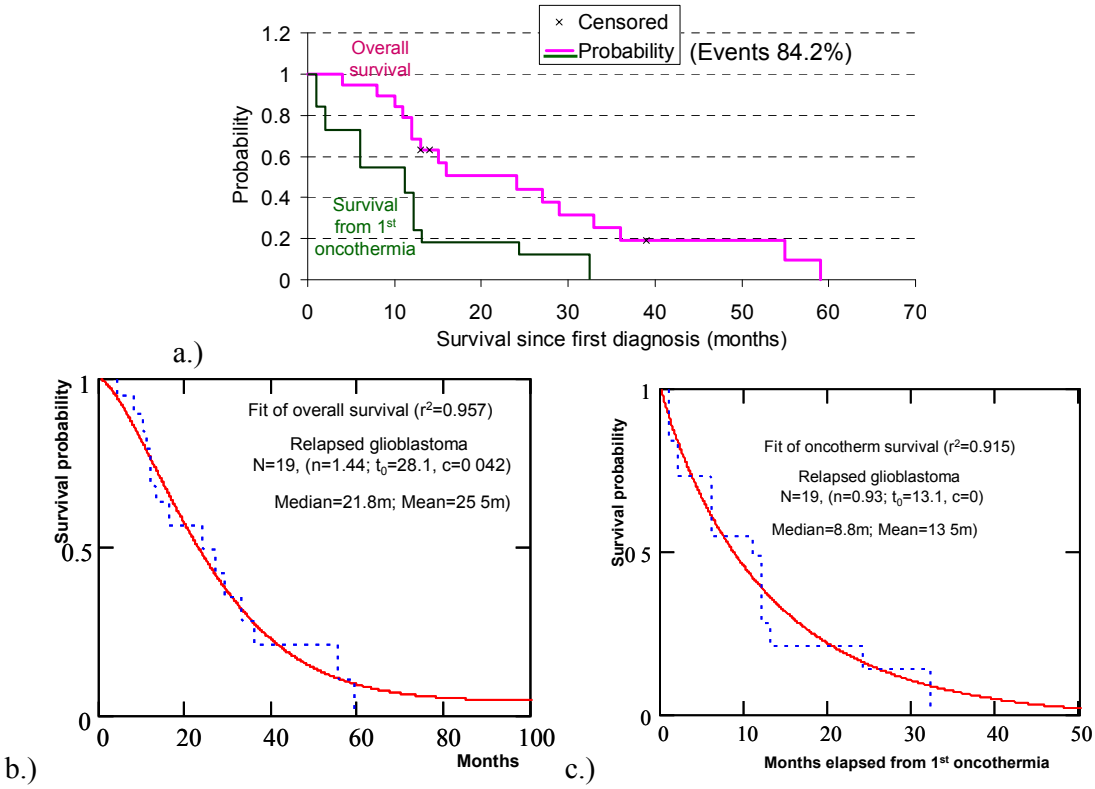


Figure 26. Kaplan-Meier survival plot for recurrent glioblastoma multiform. The median of overall survival is 21.8m. The parametric fit shows 35.8% gain by oncothermia

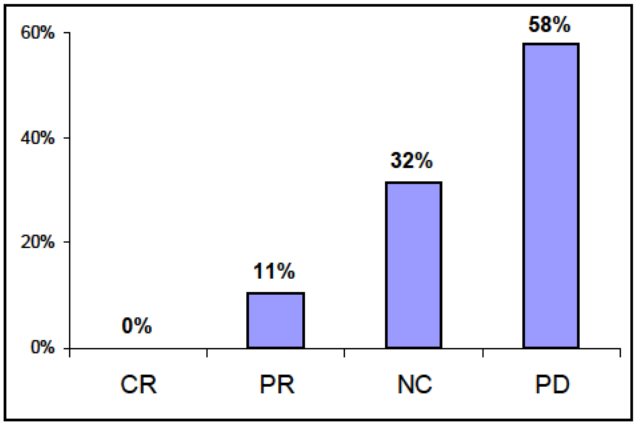


Figure 27. Local response was falling fro 58% of the patients

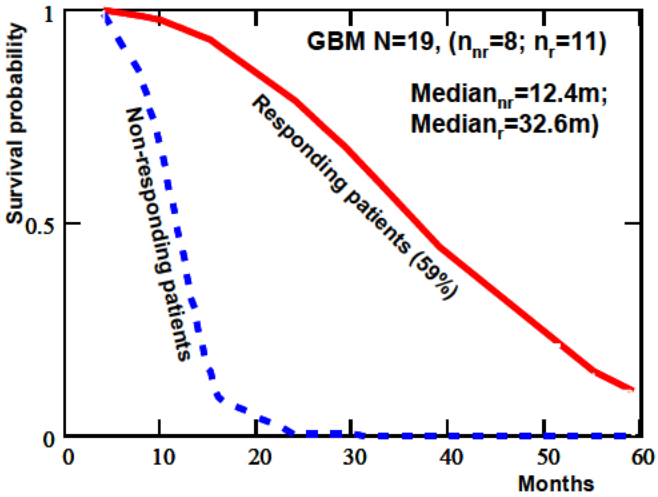


Figure 28. The parametric selection significantly divides the pool of cohort to two subgroups: responding (subscript "r") and non-responding (subscript "nr") patients

The local clinical response categorizing by KPS, shows interesting distribution, the local response was more dominant in the relatively low KPS, see Figure 29. This fact has explanation by the number of treatments, which shows better results when the treatments are more frequent, see Figure 30.

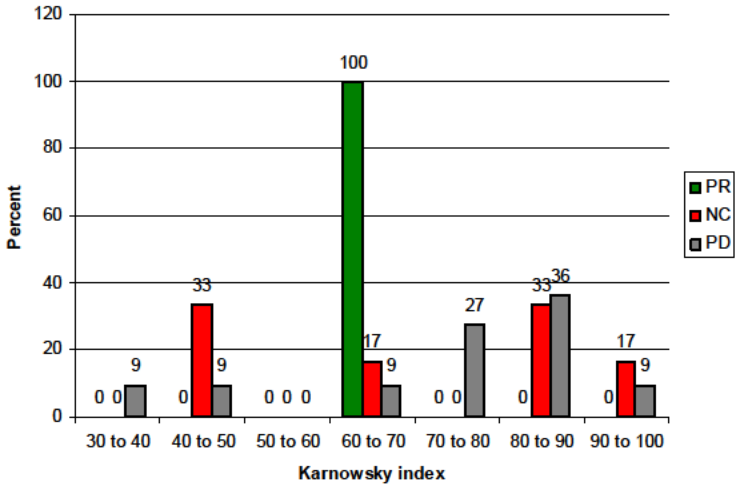


Figure 29. The clinical response was in case of 60≤KPS≤70

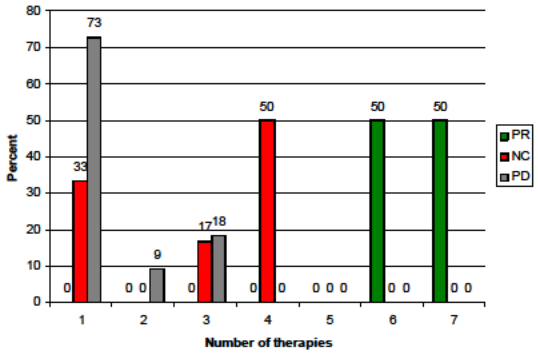


Figure 30. The number of treatments significantly drives the local clinical response

Brain glioma study with relapses

Treatments of brain tumors are actively used by oncothermia, due to its non-invasive transcranial effect and its safety. The first ASCO presentation of primary brain tumors treated by oncothermia was made in 2003 **[37]**. Results show the feasibility and efficacy of oncothermia: median survivals were measured as 106 m (n=9) and 20 m (n=27) for AA and GBM, respectively; see Figure 31.

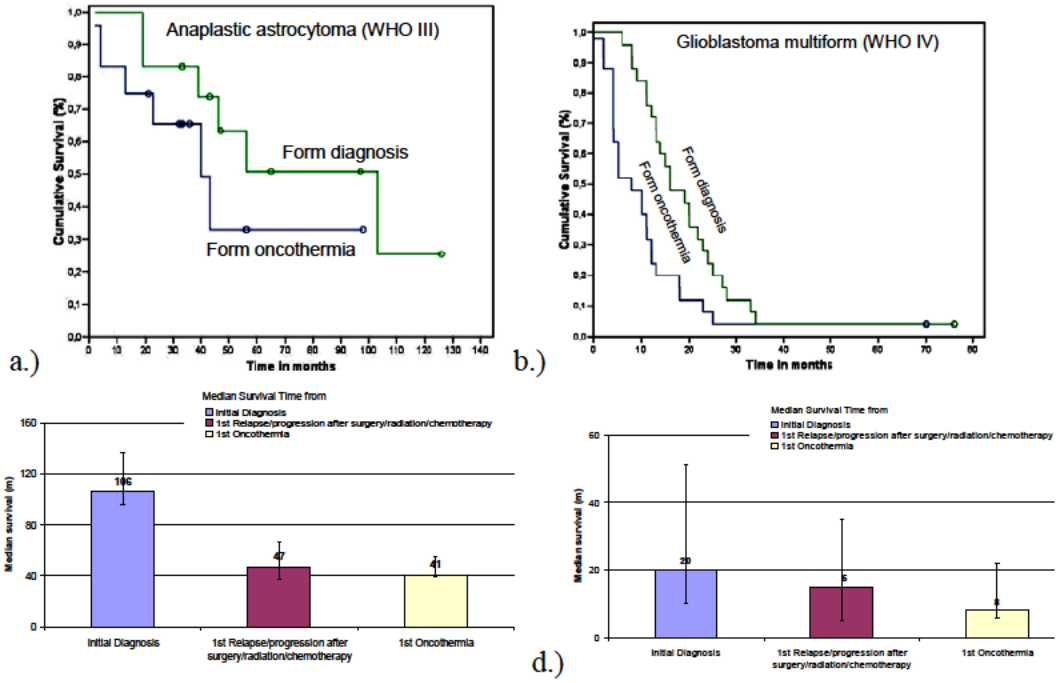


Figure 31. The cumulative survival (Kaplan-Meier plot) of overall survival and survival of oncothermia is shown for AA and GBM, on panels (a) and (b), respectively. The medians of overall survival, of the first relapse progression time after the conventional therapies and of the oncothermia treatment time are 106m, 47m, 41m and 20m, 15m, 8m for AA and GBM, respectively. (Biomed Clinic, Bad Bergzabern, Germany. Investigator: Dr. Dr. D.Hager.)

Bicentral brain glioma study

Further investigation was made by reuniting the cohort patient bases using the common treatment protocol was applied, **[37]**. The local complete response (CR) was more than 16% for AA (n=53) but CR was not obtained for GBM (n=126). Contrary, the progressive disease (PD) local response was pointed for GBM (64%), see Figure 32. The Kaplan-Meier survival plot (see Figure 33.) and the details of survivals were similar as before: the medians of overall survival, of the first relapse progression time after the conventional therapies and of the oncothermia treatment time are 103m, 10.6m and 20.6m, 7.6m for AA and GBM, respectively.

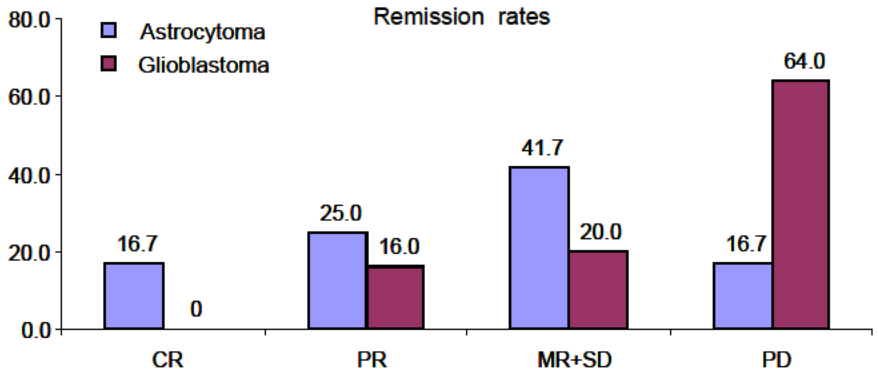


Figure 32. Local responses for AA (n=53) and GBM (n=126) in the study [38]

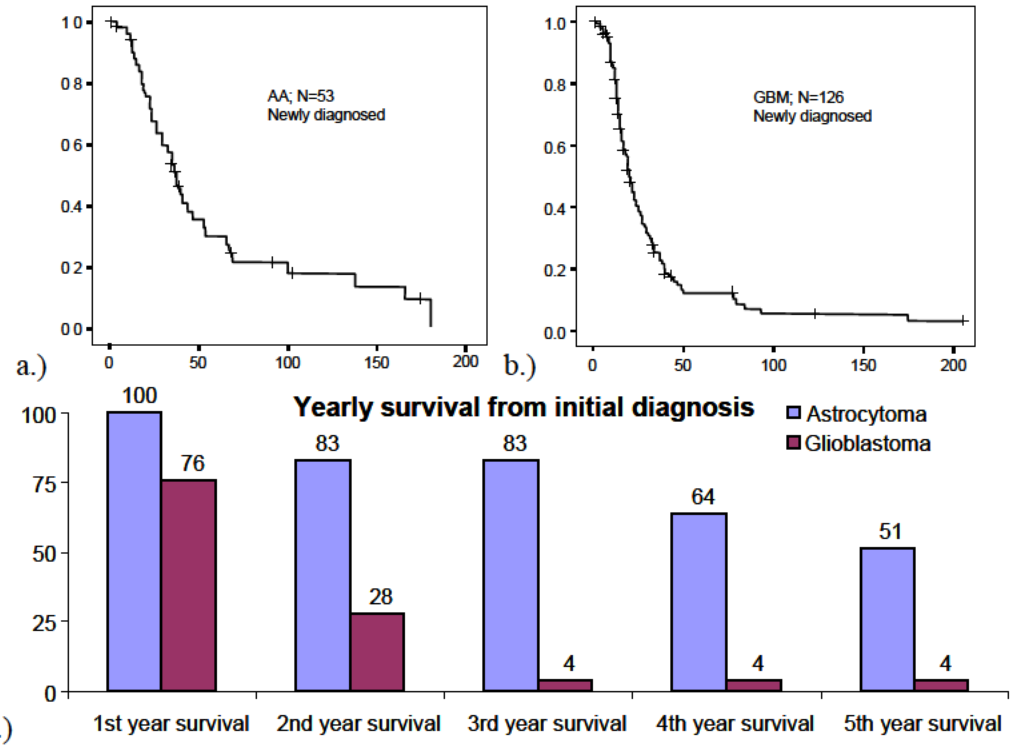


Figure 33. The cumulative survival (Kaplan-Meier plot) of overall survival and survival of oncothermia is shown for AA (n=53) and GBM (n=126), on panels (a) and (b), respectively. The yearly survival rate is shown in panel (c)

Oncothermia for heavy pre-treated & relapsed brain gliomas

Other Phase II trial (n=12) was made on very advanced glioblastoma cases **[39]**. All patients were heavily pre-treated (chemotherapy [temozolomide-based], radiotherapy) and relapsed. The median duration of response in this was 10m (4-32), and the survival from the fist oncothermia treatment was 9m, with 25% survival rate. One complete remission and two partial remissions were achieved in local clinical response.

Study of metastatic brain tumors

Various metastatic brain tumors were treated by oncothermia **[88]**, (n=15). Despite of the various primary origin of the tumors, the parametric evaluation of overall survival shows significant curative benefit: the slope of survival modified from 1.3 to 0.65 (gain: 50%); see Figure 34.

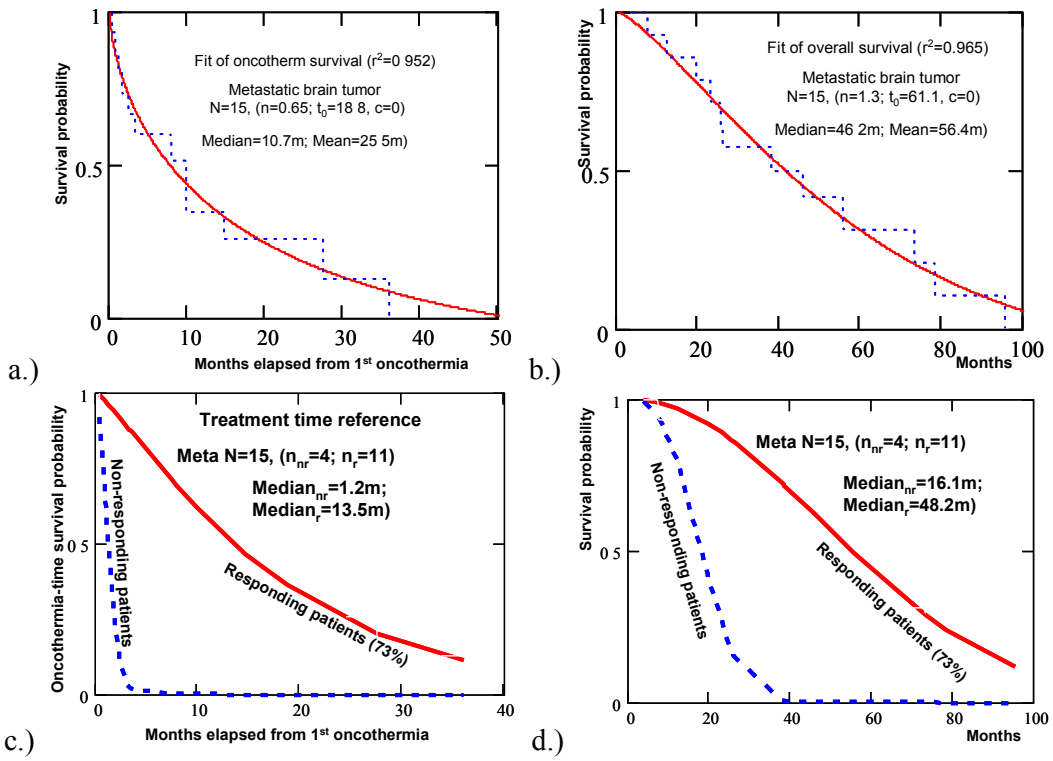


Figure 34. Results of metastatic brain tumors (n=15). The ration of responding patients were 73%. (The subscripts nr and r denotes the non-responding and responding patient's data respectively.)

Comparison of oncothermia brain studies

Some more open-label, single arm, monocentric, retrospective, intention-to-treat frame oncothermia studies had been published in professional conferences, [88], [89], [90], [91], [92] also.

Comparison of the median survivals for anaplastic astrocytoma and for glioblastoma multiform is shown on Figure 35. and Figure 36., respectively.

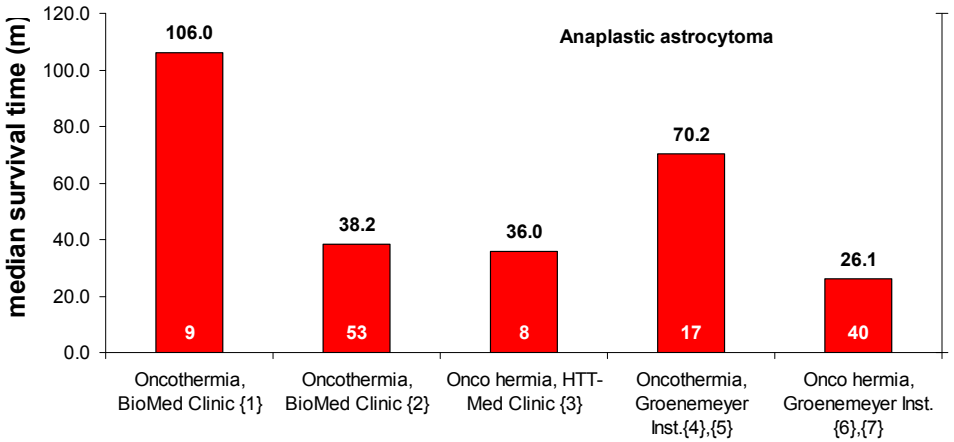


*Figure 35. Results of median survival time for advanced anaplastic astrocytoma in different, independent clinics using the same oncothermia protocol. ({1}=**[37]**; {2}=**[37]**; {3}=**[32]**; {4}=**[88]**; {5}=**[89]**; {6}=**[34]**; {7}=**[34]**.) (The number of the patients involved in the study is shown at the bottom of columns.)*

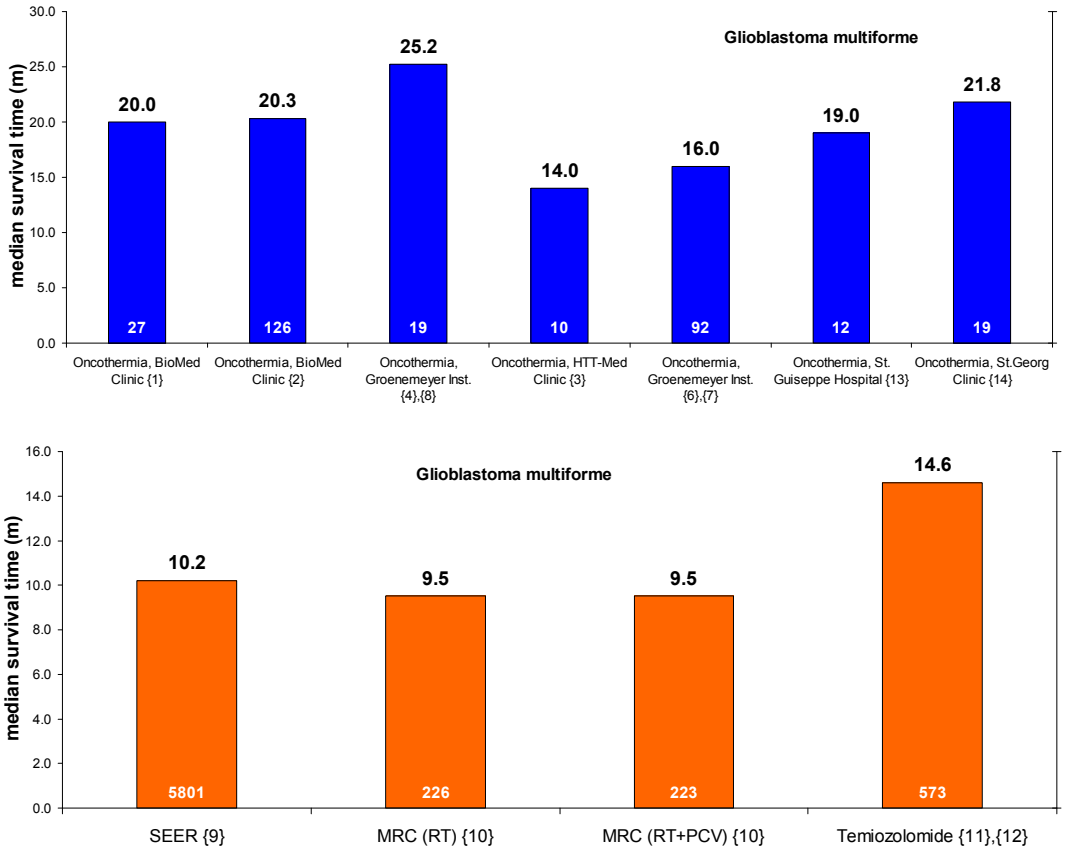


*Figure 36. Results of median survival time for advanced glioblastoma multiform in different, independent clinics used the same oncothermia protocol. Data from large database (SEER USA) and from other treatment results are shown for comparison. ({1}=**[37]**; {2}=**[37]**; {3}=**32]**; {4}=[**88**]; {6}=[**34**]; {7}=[**34**]; {8}=[**92**]; {9}=[**6**]; {10}=[93]; {11}=[**78**]; {12}=[**79**]; {13}=**[39];** {14}=[**87**]. (The number of the patients involved in the study is shown at the bottom of columns.)*

According to the RTOG classifications [**77**], we divided the patients to two groups: age under- and over-50 years. In this division oncothermia is also better, (see Figure 37.). The method shows successful applications in pediatric cases as well, [94].

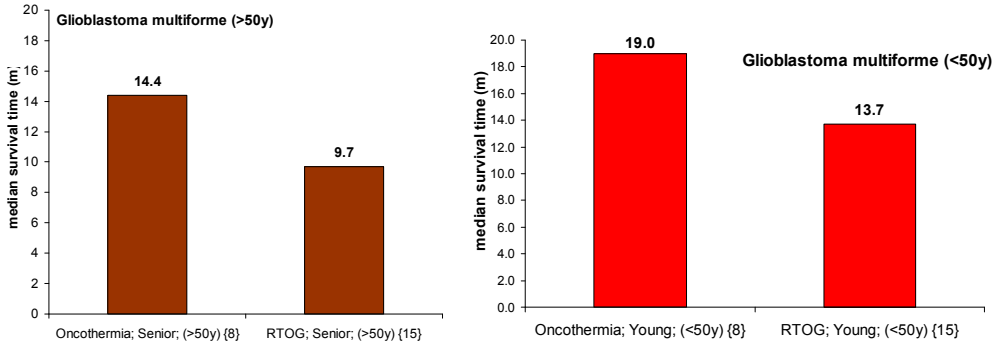


*Figure 37. Data from Radiation Therapy Oncology Group (RTOG) compared to the data of treatments made by oncothermia in age groups under and above 50 years. ({8}=[**92**]; {15}=[**77**].)*

The results are pretty coherently above the statistical values of the large databases SEER [**6**] and the gold-standard radiotherapy (RT) and RT+PCV [**93**]. The results of oncothermia show advantages in comparison with the recent publications on Temozolomide [**78**], [**79**], too.
The first-year survival rates compared to SEER [**6**] and EUROCARE **[7]** databases as well as to the recent chemotherapy of Temozolomide shows also significant advantages (more than 25% increase) of oncothermia (see Figure 38.).

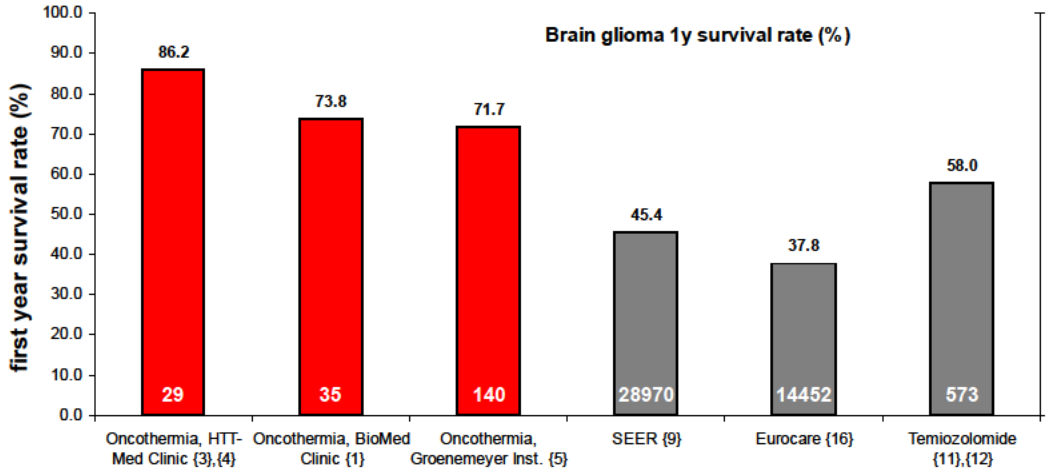


Figure 38. First year survival ratio (%) for advanced brain gliomas treated in different, independent clinics used the same oncothermia protocol. Data from large databases (SEER USA; Eurocare, EU) and from recent temozolomide treatment results are shown for comparison. ({1}=[37]; {3}=[32];; {4}=[88]; {5}=[89]; {9}=[6]; {11}=[78]; {12}=[79]; {16}=[7].). (The number of the patients involved in the study is shown at the bottom of columns.)

No serious side effects were observed **[34]**. Patients tolerated the treatments well during the whole treatment period. Most of the patients were well relaxed, some even felt asleep during the treatment. Patients reported better quality of life, but this information was not objectively measured.

Results are well indicating the feasibility and the benefit of the oncothermia showing a valid treatment potential and safe application. Oncothermia is a potential way to escape from the present impasse situation and treat brain gliomas successfully. Oncothermia is a potential way to escape from the present impasse situation and treat brain gliomas successfully. Question of Editorial of JAMA "Where to go from here?" [95] could be answered by oncothermia way.

Bone studies

Refractory bone metastases complementary to radiotherapy

This small study (n=11) was made in Clinic & Institute of Radio-Oncology, Zentralkrankenhaus Reinkenheide, Bremerhaven, Germany. (Investigator: Prof. H. Aydin.) Oncothermia was applied complementary to radiotherapy. Radiotherapy was 10MV, 1.5-1.8 Gy fractional radiation 5x /week, overall dose: 21-24 Gy and oncothermia was given 2x / week **[46]**. The subjective opinions of patients and the objective measurements of their status were identical: 9% (1/11) of the patients (see Figure 39.).

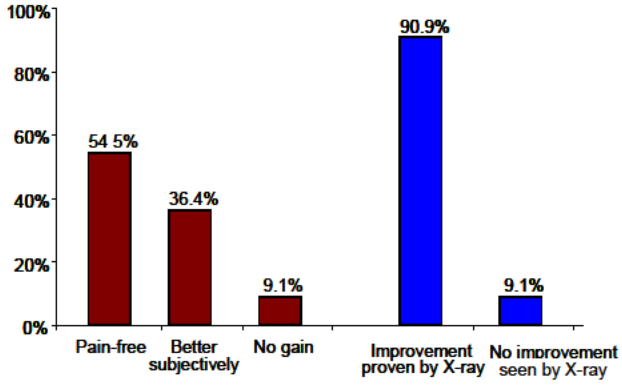
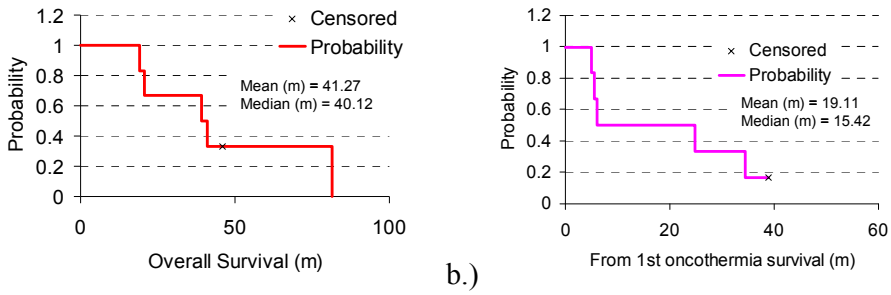


Figure 39. The subjective and objective evaluation of the patients. 10 of 11 patients involved in the study had benefit from oncothermia

Advanced bone metastases monotherapy

Advanced bone metastatic tumor was studied (n=6) **[45]**. (HTT-Med Clinic, Budapest, Hungary; Dr. A. Varkonyi & Dr. A. Dani.) The medians are 40.1m and 15.4m (mean 41.3m and 19.1m) for overall and oncothermia survivals, see Figure 40. Oncothermia was applied weekly 2-3 times 10-12 treatments with 10cm and 20 cm diameter electrodes.
First year survival rate for oncothermia was 100%, (In comparison the SEER and Eurocare data are 72.0% and 68.9%, respectively.)

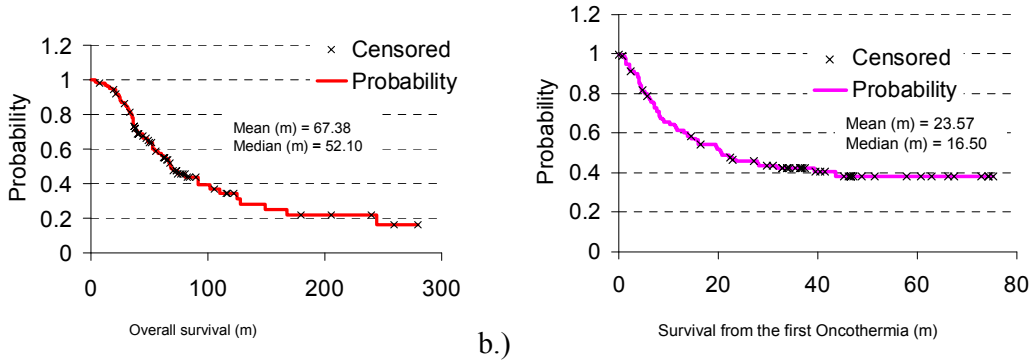


a.) b.)

Figure 40. Survival plots for overall (a) and oncothermia (b) times

Breast study

Hyperthermia is feasible for refractory, far advanced breast tumors, however it is limited by inflammatory lesions [96]. Oncothermia (with lower temperature increase as usual) is able to treat the inflammatory mamma-carcinoma
Advanced breast cancer was studied (n=103). (HTT-Med Clinic, Budapest. Investigator: Dr. A. Dani.) The medians are 52.1m and 16.5m (mean 67.4m and 23.6m) for overall and oncothermia survivals, see Figure 41. Oncothermia was applied weekly 2-3 times 8-10 treatments with standard (20cm diameter) electrode.
The parametric decomposition shows medians 274.8m and 10.9m for responders and for non-responders, respectively, see Figure 42. The responders by the parametric decomposition were less than the half, 45% (n_r=46) of the total treated patients (n=103). This large difference well focus our attention on the anyway high survival probability of breast cancers (median registered in SEER is 120m, (n=278784)) These patients are in fact completely cured (over 10 years survival), which is shown also in the decomposition of the oncothermia study results. The large cure-rate is indicated by the 25y follow up possibility in overall survival, and by the high value of the survival probability (~0.4) on Kaplan-Meier plot of oncothermia after five years follow-up, (see Figure 41/b.).
First year survival rate for oncothermia was 97.1%, (In comparison the SEER and Eurocare data are 89.0% and 91.7%, respectively.)



a.) b.)

Figure 41. The measured survival plot for overall (a) and for oncothermia (b) times

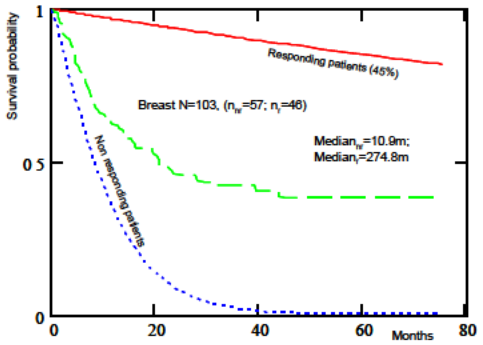


Figure 42. Parametric decomposition of the oncothermia breast study. (The measured plot is dash-line.)

Colo-rectal studies

Preoperative oncothermia for rectum carcinoma

This study was devoted to see the preoperative application of oncothermia for liver metastases from rectum carcinoma **[49]** (Klinikum Nord, Nürnberg, Germany. Investigator: Prof. H. Renner.). The studied primer-tumors were inoperable (R2) rectum carcinoma, (n=7). A trimodal therapy was applied: radiotherapy: 45+5 Gy, (fractional), chemotherapy: 5-FU/Mitomicine-C (2x), Oncothermia: 60 min, diam.30 cm (8-10x), Result: after oncothermia all patients become eligible for operation. The results of operation (Figure 43.) was excellent: 71% of patients were in condition for complete resection (R0) while one was partially resected (R1) and one was not successfully operated, (remained R2).

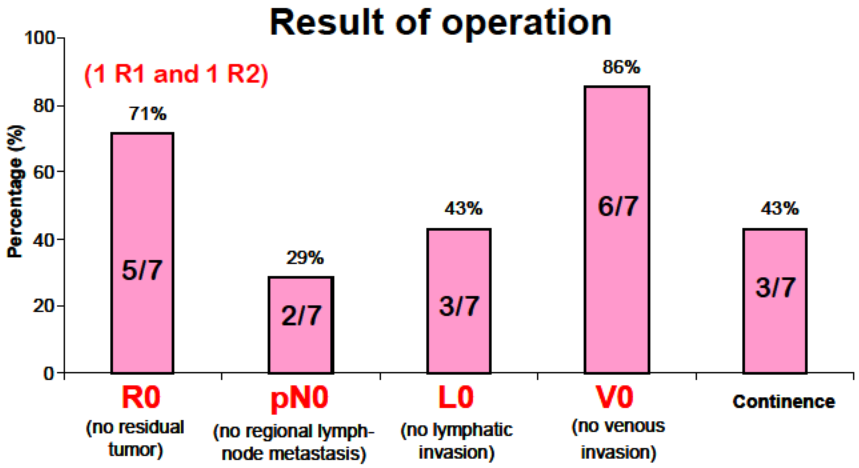


Figure 43. The result of the operations made post oncothermia on the patients were inoperable before

Colorectal carcinoma study

Advanced, heavily pre-treated (failed pre-treatments), colorectal cancer (n=218) was studied in bicentral study (HTT-Med Clinic & Peterfy Hospital, Budapest. Investigators: Dr. T. Magyar, Dr. A. Varkonyi & Dr. A .Dani.) **[45]**. Patients were categorized for rectum (n=92) for colon (n=114) and for rectosigmoid junction (sigma, n=12) carcinomas.
The median survival time is 28.5m (mean 34.4m), while the median time from the start of oncothermia therapy was 8.6m (mean: 14.8m), see Figure 44. Oncothermia was applied weekly 2-3 times 6-12 treatments with 20 cm diameter electrodes.

First year survival rate for oncothermia was 84.9%, (In comparison the SEER and Eurocare data are 72.0% and 68.9%, respectively.) The first year survival in the two institutions are comparable (87.5m (n=178) and 81.4m (n=40) for HTT and PFY, respectively, see Fig 45.

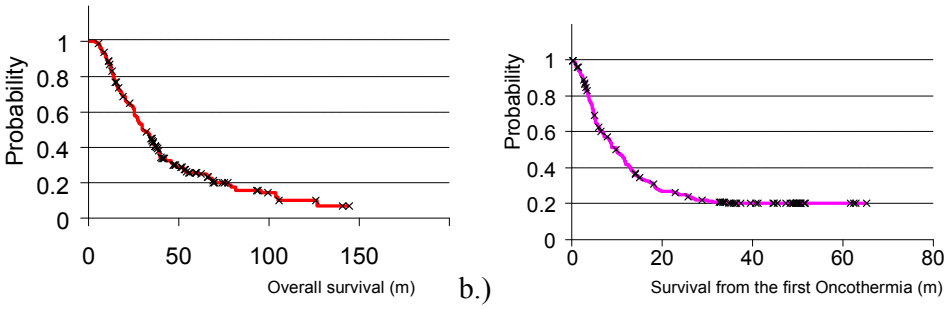


Figure 44. Survival plots of all the colorectal patients. Overall survival (a) and oncothermia survival (b) are shown

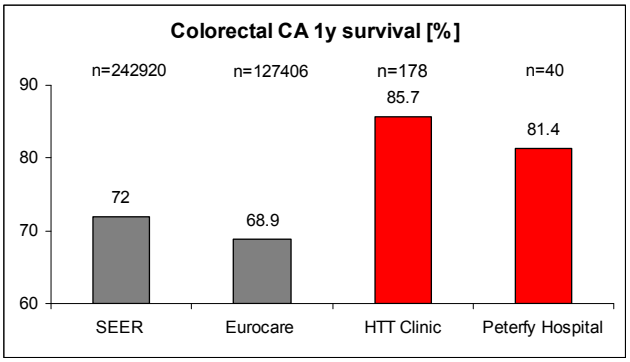


Figure 45. Comparison of the first year survival of colorectal tumor patients Oncothermia was applied for advanced cases only

The median of colon, rectum and sigma cohorts are 25.6m, 27.4m and 28.0m, respectively Figure 46.

The parametric decomposition shows medians 59.5m and 21.4m for responders and for non-responders in case of colon, and 54.3m and 22.6m for responders and for non-responders in case of rectum, respectively, Ratio of responders by the parametric decomposition were 44.2% and 57.1% for colon and rectum, respectively (see Figure 47.). Their comparison shows (see Figure 48.) almost identical non-responders survival curve and a slightly different responders survival. This indicates the very similar effects of oncothermia for both sites.

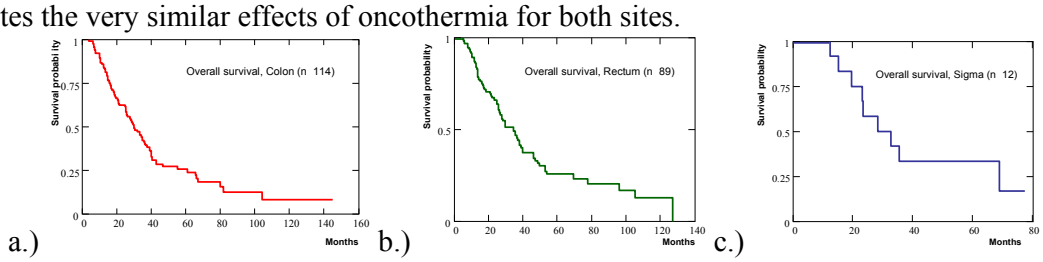


Figure 46. Overall survival plots of colon (a), rectum (b) and rectosigmoid junction (c) oncothermia treatments

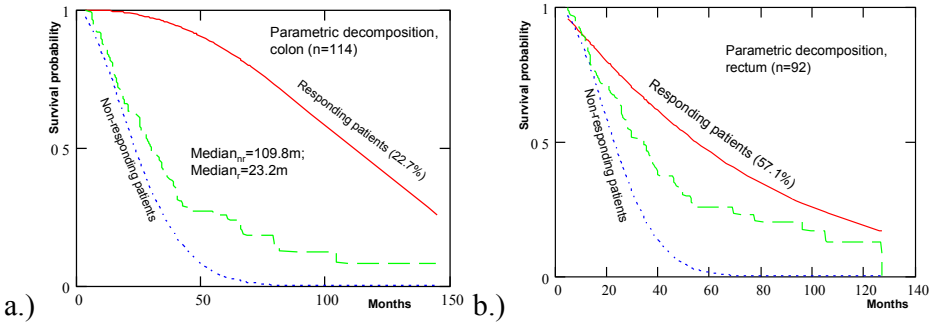


Figure 47. Parametric decomposition of colon (a) and rectal (b) sites of oncothermia treatment

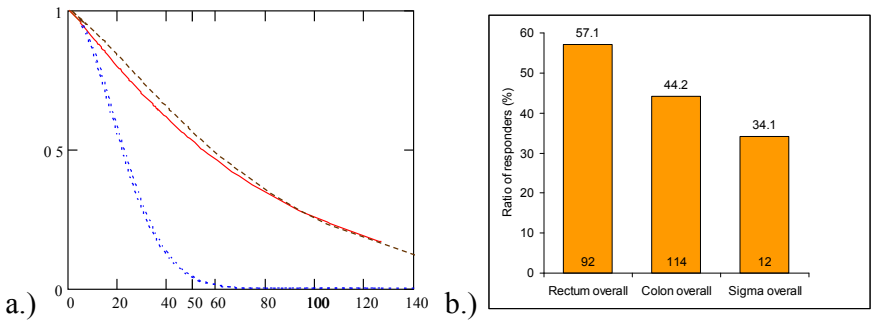


Figure 48. Comparison of the decomposed colon and rectum survival plots (a). [The solid and dashed lines are the responders of colon and rectum sites, respectively. The dots are the non-responders from both groups.] The main difference between them is the responders ratio (b)

Esophagus study

Esophagus study I.

Advanced breast cancer was studied (n=12), **[31]**. (HTT-Med Clinic & Peterfy Hospital, Budapest. Investigators: Dr. T. Magyar, Dr. A. Varkonyi & Dr. A. Dani.) The medians are 28.5m and 8.6m (mean 34.4m and 14.8m) for overall and oncothermia survivals, Figure 49. Oncothermia was applied weekly 2-3 times 10-12 treatments with 10cm and 20 cm diameter electrodes.
The parametric decomposition shows medians 29.4m and 8.5m for responders and for non-responders, respectively, Figure 50. The responders by the parametric decomposition were less than the half, 35% (n_r=4) of the total treated patients (n=12).
First year survival rate for oncothermia was 41.7%, (In comparison the SEER and Eurocare data are 31.9% and 30.3%, respectively.) In the second year survival the difference between the data base registered data and the measured by oncothermia became larger (see Figure 51.).

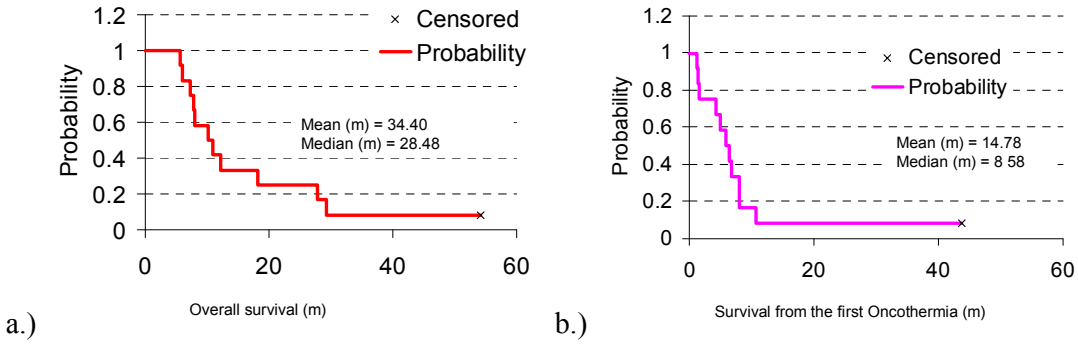


Figure 49. Plots of overall (a) and oncothermia(b) survivals

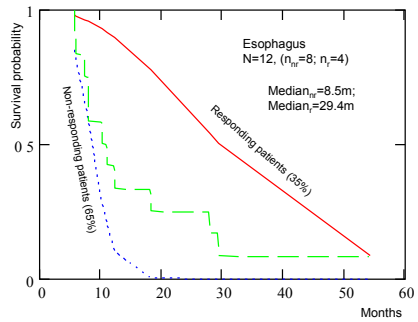


Figure 50. Parametric decomposition of the overall survival of esophagus study. The original measured curve is dashed

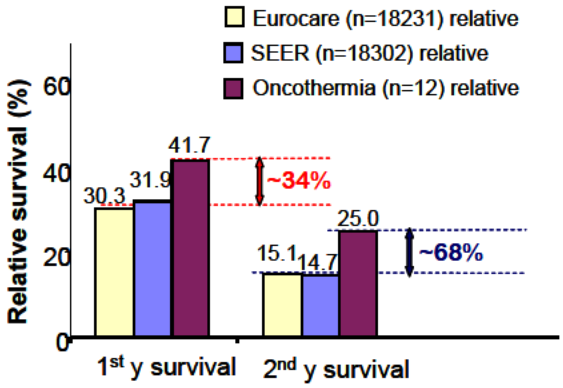


Figure 51. The relative survival (%) in first and second years, in comparison with the large databases

Esophagus study II.

This small controlled study (n=7) was done on definitely inoperable (R2) patients **[49]** (Klinikum Nord, Nürnberg, Germany. Investigator: Prof. H. Renner.) Trimodal therapy was administered: radiotherapy: 45+5 Gy, (fractional); Chemotherapy: 5-FU+Mitomicine-C (2x); Oncothermia: 60 min, diam.30 cm (8-10x). The local clinical response rate of the treatment was excellent (100%), no progress of the disease was observed Figure 52. The CR case was defined as good PR by imaging (CT) but the histology showed complete necrotic tissue only.

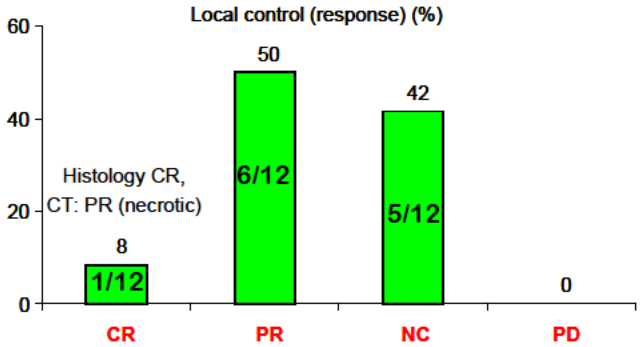


Figure 52. Local clinical response in the esophagus study by oncothermia

Median time of overall survival was 6.8m (mean was 7.5m), see Figure 53. The separation of the survival to no-change (NC) and active response (CR+PR) shows certain (but not significant (p=0.14) difference between the subgroups, see Figure 54.

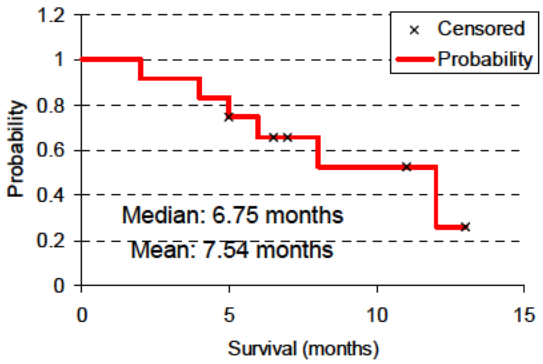


Figure 53. Kaplan-Meier plot of overall survival

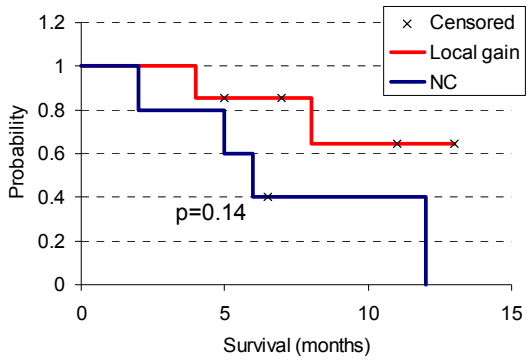


Figure 54. The NC local clinical response has shorter survival

Gynecological (pelvic) cancer study

Ovary study

This ovary study (n=27), was done in Peterfy Hospital, Budapest. (Investigator: Dr. T.Magyar.) The inclusion criteria are as usual: the high-line treatment for refractory ovarian cancer. The medians are 37.8m and 20.4m (mean 55m and 23m) for overall and oncothermia survivals, see Figure 55. Oncothermia was applied weekly 2-3 times 6-10 treatments with large (30cm diameter) electrode, to cover the disseminated malignancy.
The parametric decomposition shows medians 132.7m and 19.4m for responders (67%) and for non-responders (33%), respectively, see Figure 56.
The first year survival rate was 100%, (In comparison the SEER and Eurocare data are 66.9% and 65.4%, respectively.) The second year survival rate (70.4%) also transcends the large databases (SEER 49.3%, Eurocare 50.8%).

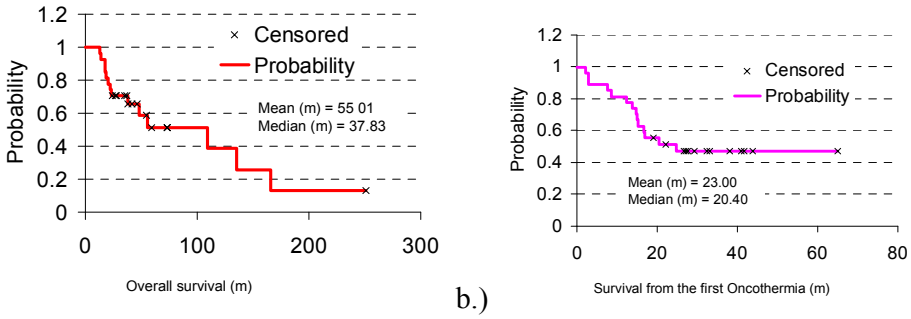


Figure 55. The Kaplan-Meier plot of overall (a) and oncothermia (b) survivals of ovarian cancer

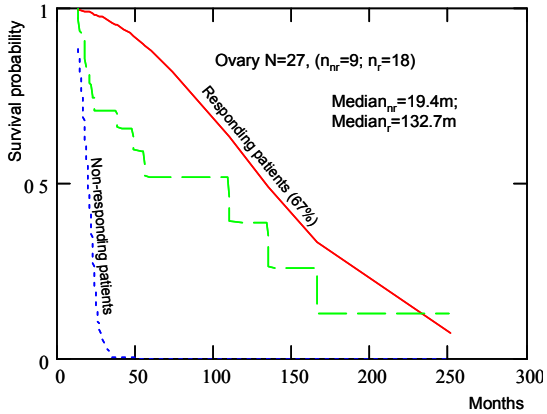


Figure 56. The parametric decomposition of the overall survival of ovarian cancer (the measured plot is the dash-line)

Uterine corpus cancer

Only a low number of patients was collected in the study of uterine cancer (n=9). (Peterfy Hospital, Budapest. Investigator: Dr. T. Magyar.) The inclusion criteria are the high-line treatment for refractory uterus (corpus) cancer. The medians are 61.5m and 6.13m (mean 52.3m and 9.2m) for overall and oncothermia survivals, Figure 57. Oncothermia was applied weekly 2-3 times 4-8 treatments with standard (20cm diameter) electrode.
The parametric decomposition shows medians 68.5m and 32.0m for responders (62%) and for non-responders (38%), respectively, see Figure 58.
The first year survival rate was 100%, (In comparison the SEER and Eurocare data are 86.3% and 87.6%, respectively.) The second year survival rate (77.8%) also transcends the large databases (SEER 77.0%, Eurocare 80.0%).

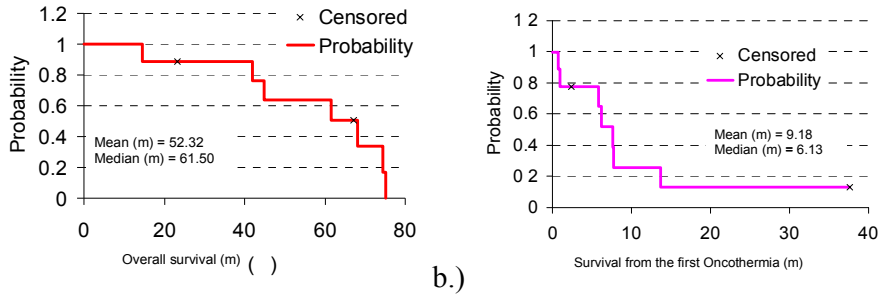


Figure 57. Kaplan-Meier plot of overall (a) and oncothermia (b) survivals of cancer of corpus uterus

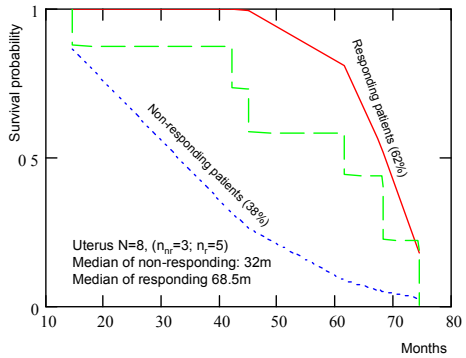


Figure 58. The parametric decomposition of the overall survival of uterine cancer (corpus) (the measured plot is the dash-line)

Uterine cervix

Advanced cervical cancer (stage FIGO IIb – Iva) was studied (n=38). (Peterfy Hospital, Budapest. Investigator: Dr. T. Magyar.) The medians are 27.6m and 3.8m (mean 31.2m and 8.56m) for overall and oncothermia survivals, see Figure 59. Oncothermia was applied weekly 2-3 times 4-8 treatments with standard (20 cm diameter) electrode.
The parametric decomposition shows medians 63.5m and 20.9m for responders and for non-responders, respectively, see Figure 60. The responders by the parametric decomposition were only 25% (n_r=10) of the total treated patients (n=38).
First year survival rate was 86.8%, (In comparison the SEER and Eurocare data are 82.0% and 83.0%, respectively.)

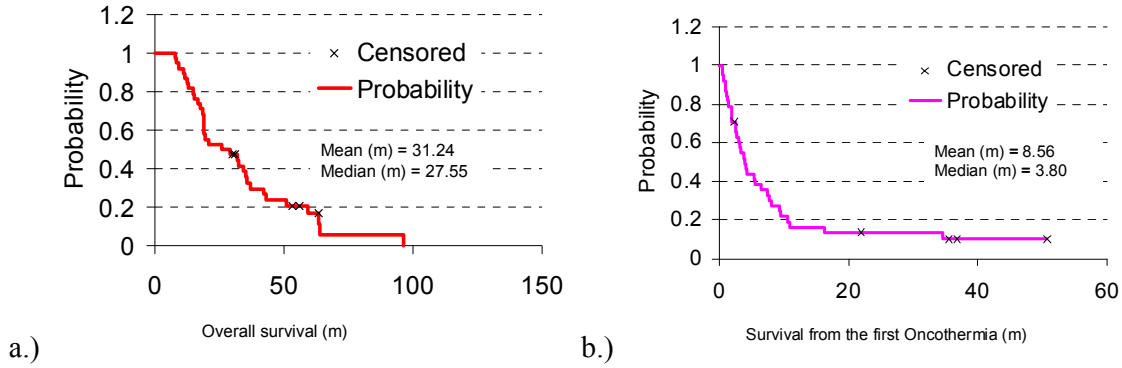


Figure 59. Kaplan-Meier plot of overall (a) and oncothermia (b) survivals of cancer of corpus uterus

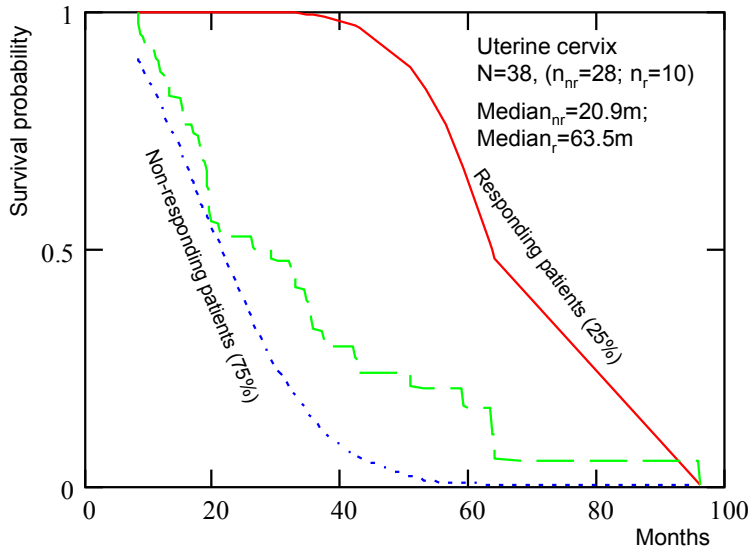


Figure 60. The parametric decomposition of the overall survival of uterine cancer (corpus) (the measured plot is the dash-line)

Comparison of oncothermia in pelvic gynecology

Compare the gynecology data, the first year survival is better at all the treated sites than the SEER data, (see Figure 61.). The median survival shows high success for ovarian and uterus oncothermia treatments, but the cervix is less successful, Figure 62. This discrepancy is perhaps the well known fact of the human papilloma viruses, which could be well treated in most of the cases, but the oncothermia patients are out form the conventionally controllable regime. The hard situation for cervix is indicated by the parametric evaluation also, when the responding patients are in minority (25%), see Figure 63. The high response rate for ovarian cases indicated by the parametric decomposition (see Figure 63.), probable is due to the high selectivity of oncothermia on cellular level, which has central importance in the case of the ovarian malignancies, which are promptly disseminated in the pelvic volume.

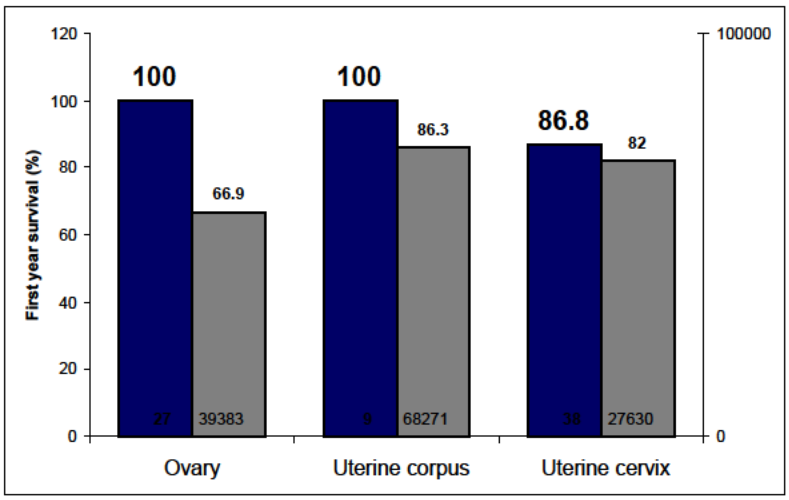


Figure 61. First year survival (%) of various pelvic gynecological malignancies treated by oncothermia. SEER data are shown for comparison, (right hand side columns). (Number of patients involved in the study is shown at the bottom of the columns.)

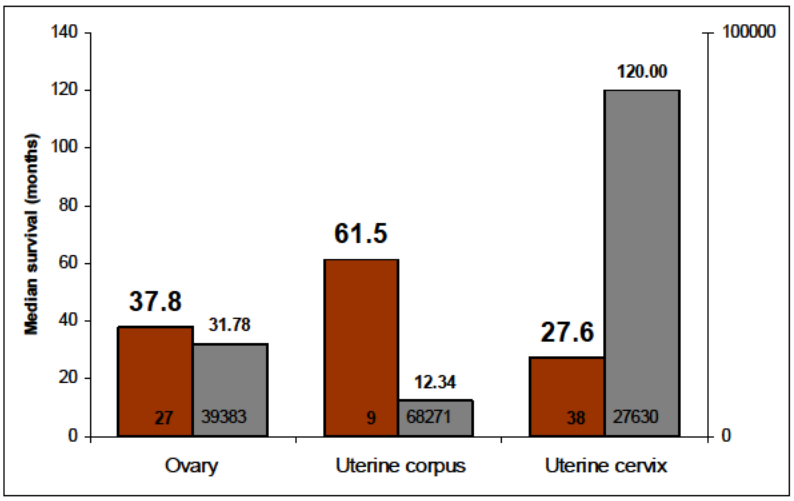


Figure 62. Median survival times (months) for various pelvic gynecological sites. SEER data are shown for comparison, (right hand side columns). (Number of patients involved in the study is shown at the bottom of the columns.)

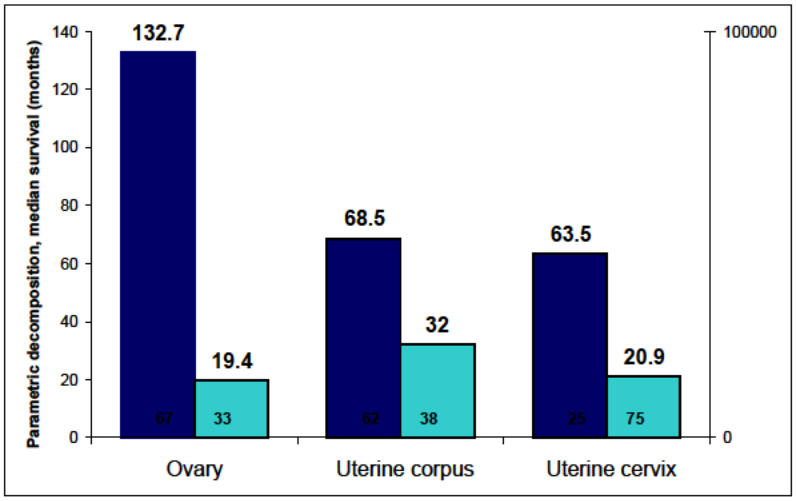


Figure 63. Results of the parametric fit of the pelvic gynecological malignancies. (Percentages of responders/non-responders are shown at the bottom of the columns.)

Head and neck study

Various advanced head and neck cases (n=64, see Tab. 17.) were collected **[45]**. (HTT-Med Clinic & Peterfy Hospital, Budapest. Investigators: Dr. T. Magyar, Dr. A. Varkonyi & Dr. A. Dani.) The medians are 26.1m and 7.4m (mean 41.9m and 15.7m) for overall and oncothermia survivals, see Figure 64. Oncothermia was applied weekly 2-3 times 8-12 treatments with 10 cm diameter electrodes.

Localization	ICD code	Number of patients
Lip	C00	1
Tongue	C01-C02	17
Oral cavity	C03, C05-C06,9	7
Floor of mouth	C04	3
Salviary glands	C08	1
Tonsil	C09	6
Oropharynx	C10	8
Nsopharynx	C11	4
Hypopharynx	C12-C13,9	8
Pharynx/Other buccal	C14	9

Table 17. Identification of head&neck localizations, included into the study

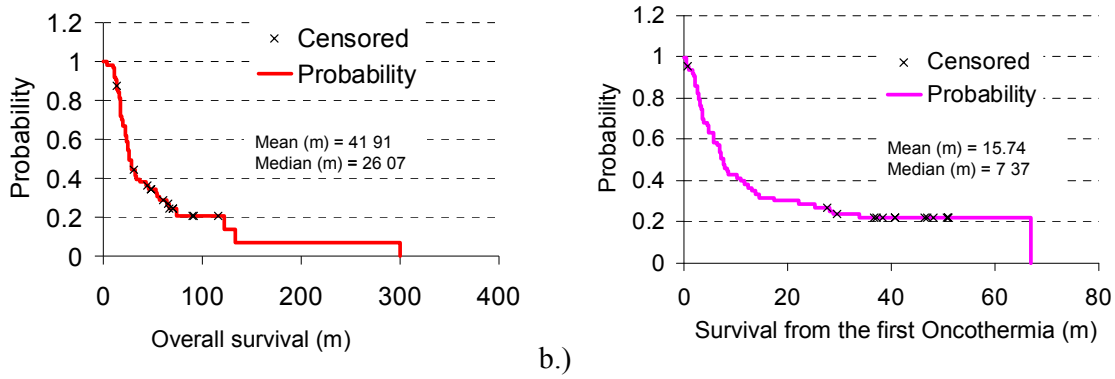


Figure 64. Overall (a) and oncothermia (b) survival plots

First year survival rate for oncothermia was 92.2%, (In comparison the SEER and Eurocare data are 74.9% and 67.4%, respectively.)

Kidney study

Advanced kidney cancer was studied (n=39) **[45]**. (HTT-Med Clinic & Peterfy Hospital, Budapest. Investigators: Dr. T. Magyar, Dr. A. Varkonyi & Dr. A. Dani.) The medians are 35.9m and 10.1m (mean 49.2m and 14.7m) for overall and oncothermia survivals, Figure 65. Oncothermia was applied weekly 2-3 times 10-12 treatments with 20 cm diameter electrodes.
The parametric decomposition shows medians 78.4m and 33.7m for responders and for non-responders, respectively, see Figure 66. The responders by the parametric decomposition were less than the half, 48% (n_r=19) of the total treated patients (n=39).
First year survival rate for oncothermia was 84.6%, (In comparison the SEER and Eurocare data are 67.5% and 70.9%, respectively.)

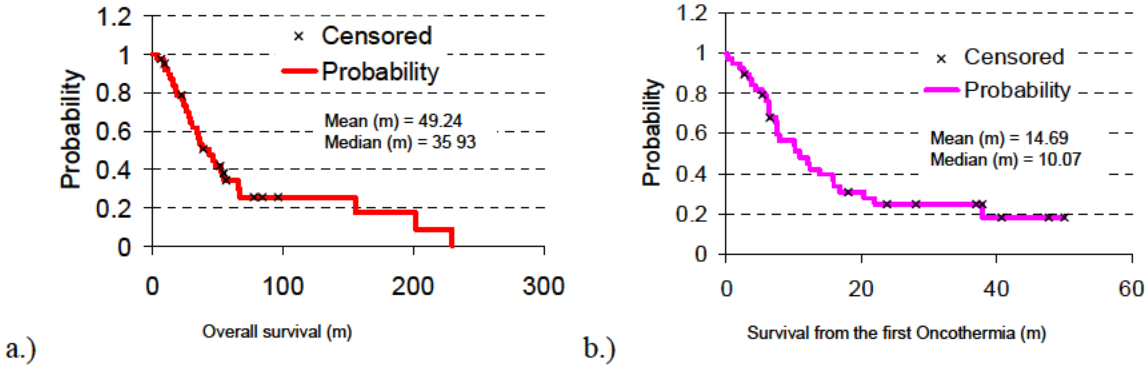


Figure 65. Kaplan-Meier plots for overall (a) and oncothermia (b) survivals

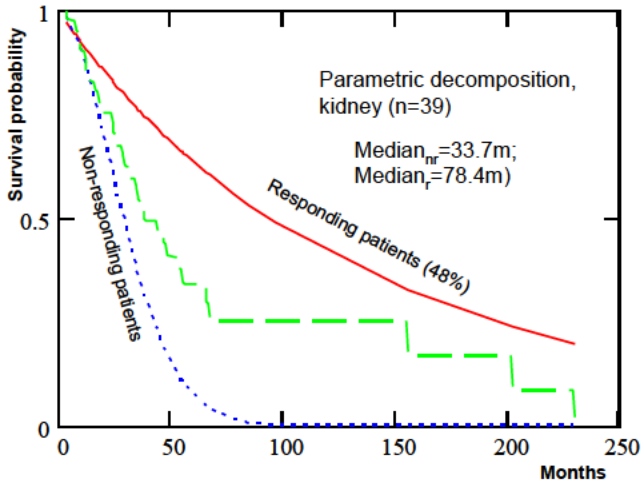


Figure 66. The parametric decomposition of the survival plot. The ratio of the responding patients is 48%

Liver studies

Study of liver metastases colorectal origine

One of the earliest study of oncothermia on colorectal metastases to liver (n=80) was published in 1999, [97]. (Biomed Clinic, Bad Bergzabern, Germany Investigator: Dr. D. Hager.) Histology of the tumor is adeno-carcinoma. Prior liver resection was made for 16% of patients Prior chemotherapies were unsuccessful. 37.5% of patients had palliative chemotherapy concomitantly with oncothermia (dominantly [65%] 5-FU+Leukovorine), others had oncothermia as monotherapy. Many patients had also other than liver metastases, with bed prognosis factors (see Figure 67.). The CA 19-9 and CEA tumor-markers at the first diagnosis were over 24 [U/I] and 2.5 [ng/l], at 80% and 70% of the patients, respectively.

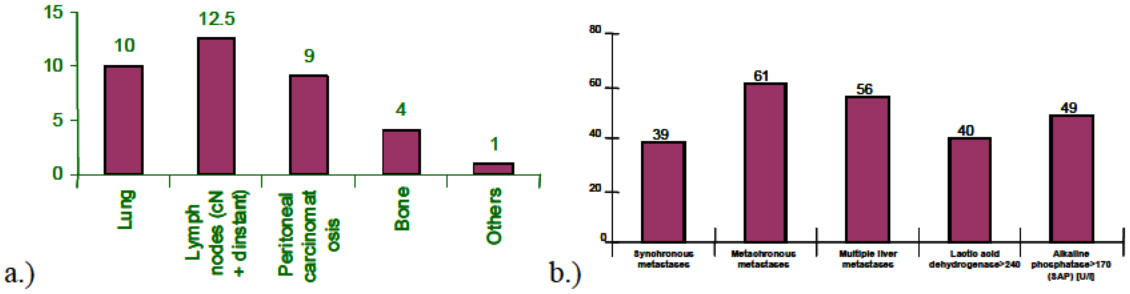


Figure 67. Additional metastases (%) (a) and the prognosis factors (%) (b) of patients involved in the study

The median survival was significantly higher with oncothermia than expected without this treatment (see Figure 68.). It is interesting the monotherapy results were higher, but far not significantly (p=0.31), than their complementary counterpart. The yearly survivals are also better than expected, see Figure 69.

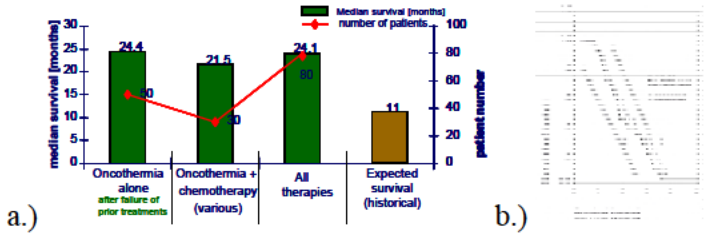


Figure 68. The median survival (a) and the Kaplan-Meier survival plot (b) for patients having complementary of monotherapy with oncothermia

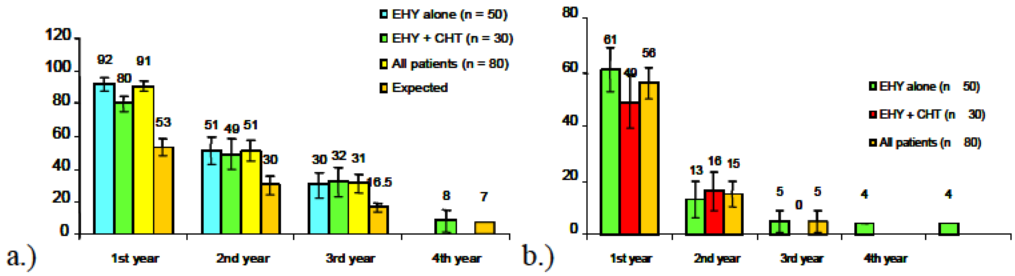


Figure 69. The yearly survivals from the first diagnosis (a) and from the first oncothermia treatment (b). [EHY=oncothermia, made by EHY2000 device]

Study of advanced liver metastases colorectal origine II.

Study was made for advanced liver metastases for colorectal carcinoma (n=22) at Department of Oncology, Spedali Civili, Brescia, Italy, **[53]**. (Investigator: Prof. VD. Ferrari.) The stage of patients was C (of BCLC classification). Patient's characteristics: non-operable: 15/22, (68%), portal vein-thrombosis: 16/22, (72%), distant metastasis (other than liver) was observed at 9% of the patients. The concomitant chemotherapy was Oxalyplatine (50 mg/m2) for 64% of the patients. Oncothermia treatment protocol was: 60 min/session, 2 sessions/week, 10 sessions/cycle, (median 1.5 cycle [1-4]), 80-140 W, (41-47°C). The local clinical response of liver metastases was 28%, see Figure 70; the quality of live reported better for 50% of the patients. The local toxicity of oncothermia was relative high (32%), (see Figure 71.).

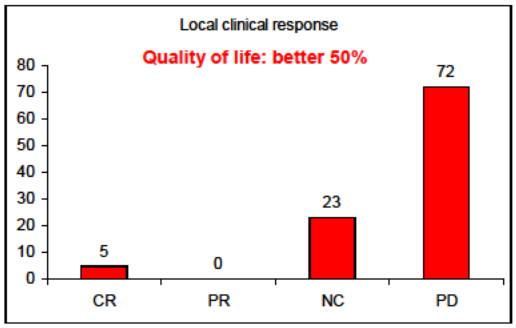


Figure 70. The local clinical response of liver metastases for the patients involved in the study

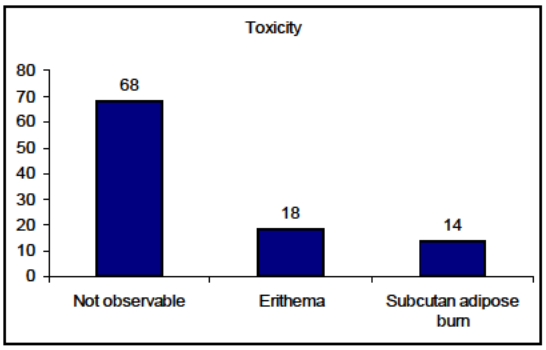


Figure 71. Local toxicity of oncothermia, measured at the trial (n=22)

Comparison study of treatment lines of colorectal liver metastases

This study is devoted to compare of first-line (without oncothermia) and second-line (with oncothermia) therapies for colorectal cancer liver metastasis (n=15) **[52]**. (Investigator: Prof. H. Kirchner & Dr. P.P anagiotou. Department of Hematology & Oncology, Hospital Siloah, Hannover, Germany.) Oncothermia is applied after the first line treatment was fallen, in second line only. The treatment protocol is shown in Table 18. The local response after the second line was better than after the first one, see Figure 72., without extra toxicity for the patients, see Figure 73.

Drug	Day1							Day8							Day15							22
Irinotecan 80 mg/m^2	X							X														Repetition
Capecitabine 2 g/m^2	O	O	O	O	O	O	O	O	O	O	O	O	O	O								
Oncothermia	↓		↓		↓			↓		↓		↓			↓		↓					

Table 18. Protocol of the second-line treatment in the study

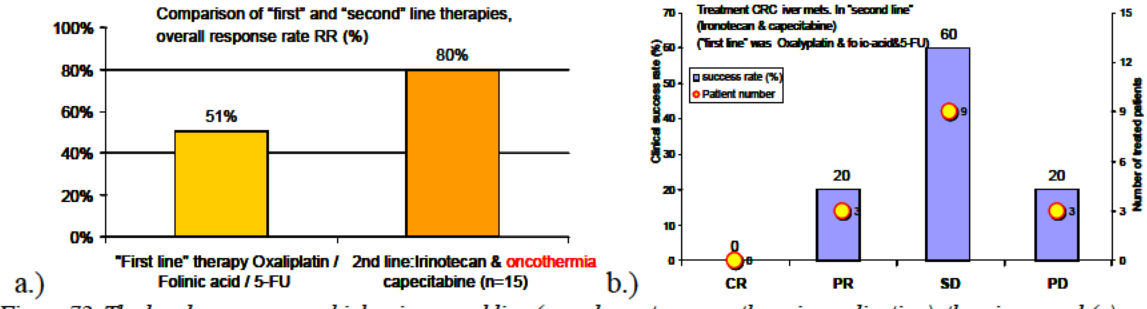


Figure 72. The local response was higher in second line (complementary oncothermia application), than in second (a), and only 20% of the patients had progressive disease (PD), (b)

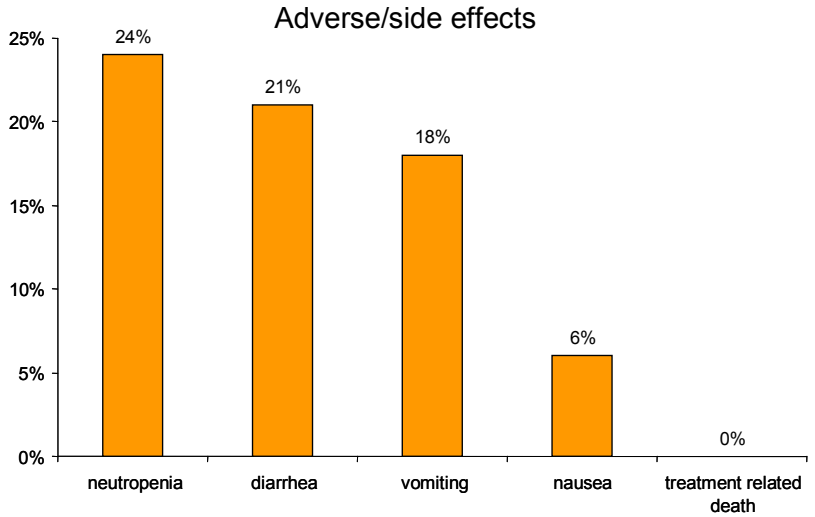
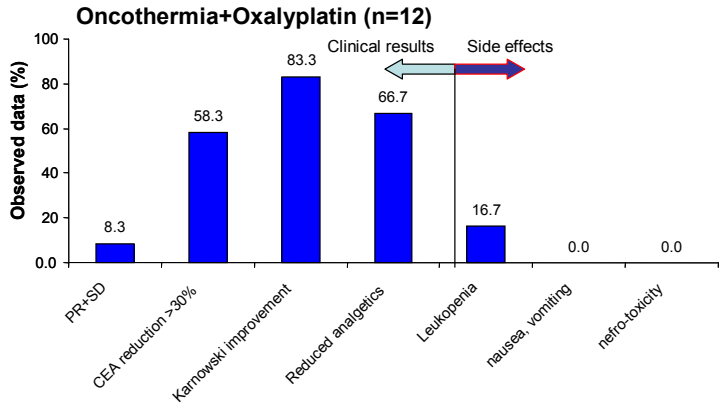


Figure 73. Adverse/side effects were still the expected, while chemotherapy (XELIRI) is administered without oncothermia

The median survival was 23 months, while the historical expectation: 10-20 months. An important observation was registered in the study: if a progression occurred initially or after a stable phase it was observed in nearly 80% outside the electromagnetic field.

Study of platinum derivatives with oncothermia for liver metastases from colorectal origine

This first-line, phase II. study (n=30) was devoted to compare the effect of platinum derivatives of liver metastases from colorectal cancer origin, **[54]**. (Investigator: Prof. G. Fiorentini, Department of Oncology, St. Giuseppe Hospital, Empoli (Florence) Italy.) The median survival time was 22m, (10-34), while the median relapse-time was 9m (6-18). All the platinum-derivatives show 20% response rate and 50% improving the quality of life (KPS). The main side effect was the anxiety reduction (83% of the patients), the nausea, vomiting was 13.3% while the other side effects were under 10%. Definite oncothermia side effect (erythematic + mild adipose burn) was observed in 6.7%. Independent study of Oxalyplatine +oncothermia (n=12) and of Cisplatin + oncothermia (n=18) shows definite differences, see Figure 74. The local response rate was definitely higher for Cisplatin, while the other benefits shows significantly lower results, the side effects differs also significantly.



a.)

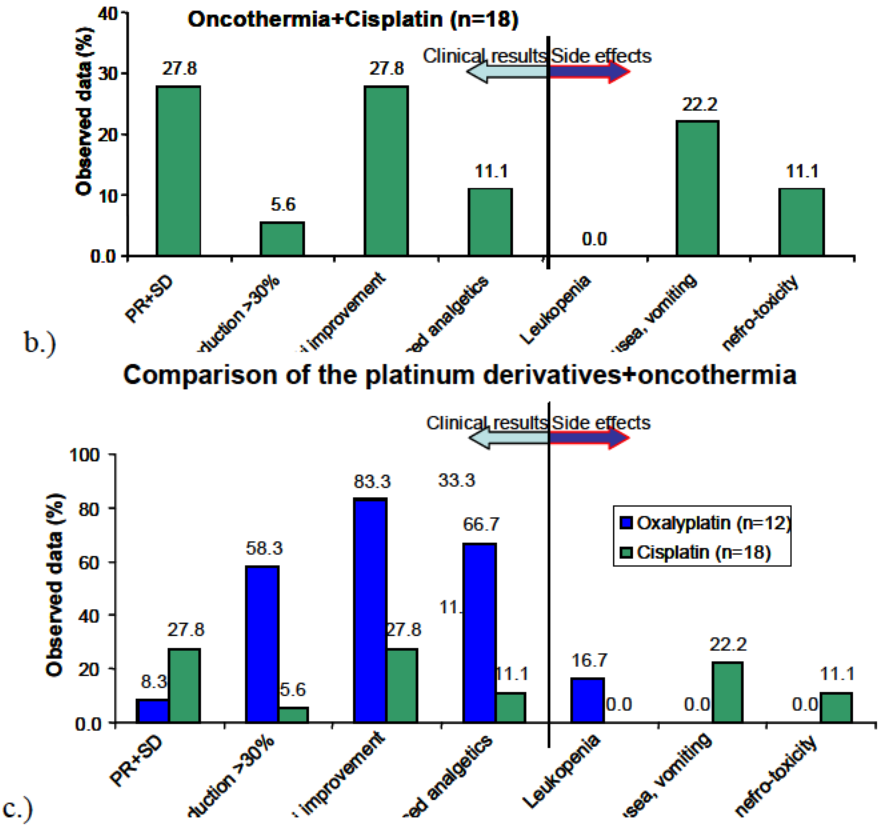


Figure 74. The oncothermia results concomitantly applied with Oxalyplatine (a) and Cisplatin (b)

Study of liver metastases rectal origine

This study was made for advanced, non-operable rectal carcinoma (n=65) and its liver metastases (n=29), **[62]**. (Investigators: Prof. E. Mako & Prof. Z. Vigvary, Department of Radiology, Semmelweis University, Budapest.) Oncothermia was applied by 2-3x / week with concomitant chemotherapy. Adriamycin and/or Mitomycin C + Gelaspon (selective artery chemo-embolisation was applied for liver metastases). Concomitant radiotherapy was LDR Cs-137. Additionally intraluminal cryotherapy was made for rectal treatment. Regular control was made by abdominal ultrasound and CT-scan. Local clinical responses for the primary and the metastatic lesions are shown in Figure 75.

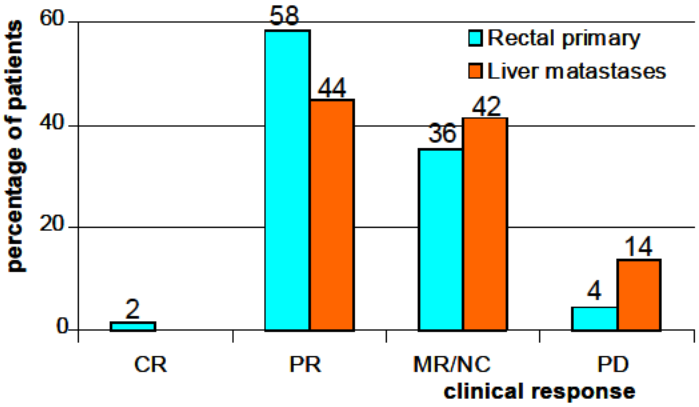


Figure 75. Local clinical response for advanced, inoperable rectum tumors (n=65) and its liver metastases (n=29)

Study of liver metastases various origine

Advanced, refractory liver metastases (n=25) with various origin was made by HTT-Med Clinic Budapest, **[50]**. (Investigators: Dr. A. Varkonyi & Dr. A. Dani.) The treatments were applied as

monotherapy. Medians of Kaplan-Meier survivals (see Figure 76.) are 20.5m and 7.0m for overall and oncothermia survivals, respectively.

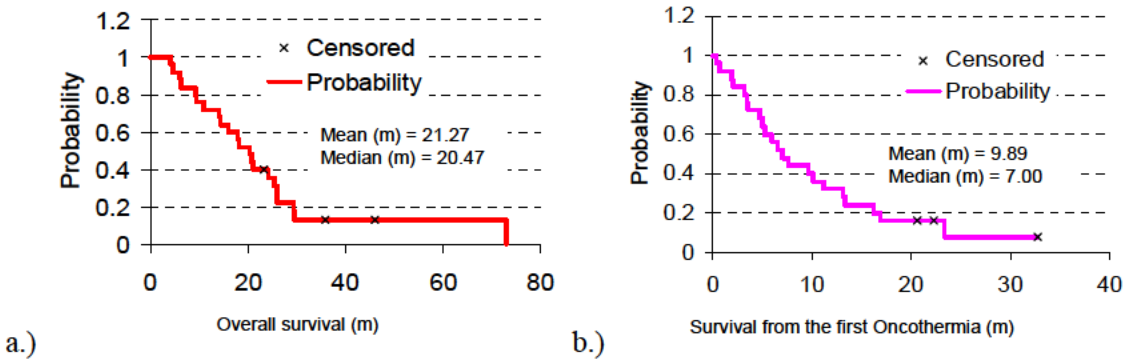


Figure 76. Kaplan-Meier plots for overall (a) and for oncothermia (b) survivals

Study of far advanced liver metastases various origines. Comparison of complementary therapies

This study (n=28) is devoted for comparison of complementary oncothermia to radiotherapy and chemotherapy, as well as to monotherapy applications for liver metastases of various kind of primer tumors **[46]**. (Investigator: Prof. H. Aydin; Clinic & Institute of Radio-Oncology, Zentralkrankenhaus Reinkenheide, Bremerhaven, Germany.) Table 19. shows the treatment protocol. Oncothermia was applied two time in a week. Concomitant radiotherapy: 10MV, 1.5-1.8 Gy fractional radiation 5x /week, overall dose: 21-24 Gy; concomitant chemotherapy: Vinorelbine (20 mg/m^2/week). Local control (overall response) was 81%, 38% and 25% for oncothermia + radiotherapy, for oncothermia + chemotherapy and for oncothermia as monotherapy, respectively (see Figure 77.).

Therapy / week-days	Mon.	Tue.	Wed.	Thu.	Fri.	Number of patients
Radiotherapy +	RT	RT	RT	RT	RT	16
Oncothermia		OT		OT		
Chemotherapy +			CHT			8
Oncothermia		OT		OT		
Oncothermia monotherapy		OT		OT		4

Table 19. The applied protocol

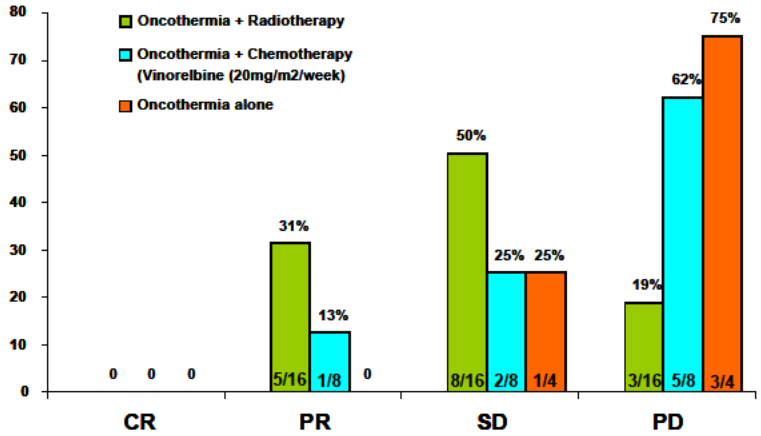


Figure 77. Local clinical response at different treatment protocols. (Number of patients involved in the study is shown at the bottom of the columns.)

Comparison of studies of liver metastases

Compare the above studies (see Figure 78.), similarities and differences appear which probable due to the problems of the patient's cohorts and different pre- and concomitant treatments. The oncothermia protocol was unified (2-3 times a week, 60 min/session).

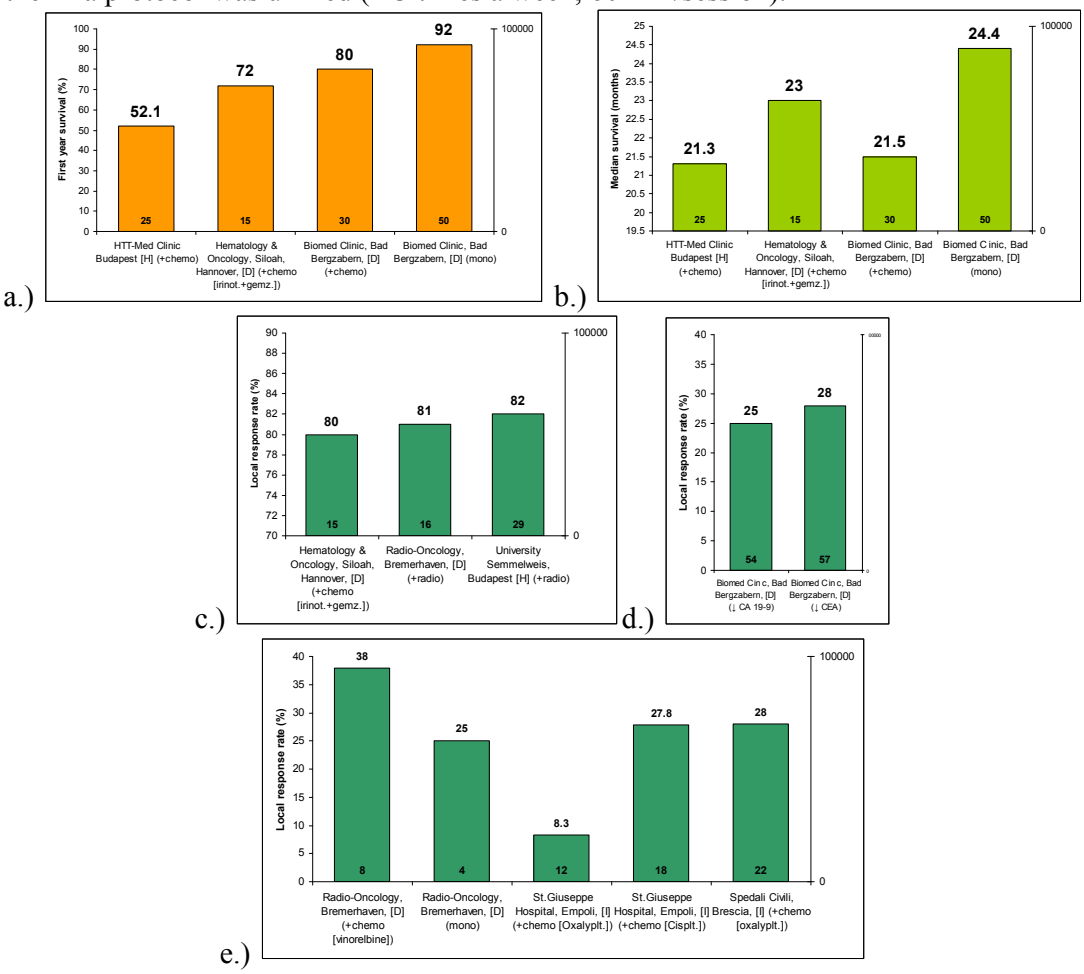


Figure 78. Comparison of the parameters of various oncothermia studies of metastatic liver. The first year survival (a) has large variations but the median of overall survival (b) shows homogeny for obtained results. The local response rate (panels (c), (d) & (e)) shows non-unified data-set. (The response rate is measured by the tumor-size ((c) & (e)), while the data on panel (d) is measured by the decrease of the relevant tumor-markers.) (Number of patients involved in the study is shown at the bottom of the columns.)

Lung studies

Oncothermia lung study I.

Study is obtained from an open-label, single-arm, monocentric study, (n=61) made in Peterfy Hospital, Budapest, Hungary, [referred as PFY]. Investigator: Dr. T. Magyar. The involved patients are analyzed according to an intention-to-treat (ITT) schedule. Recruiting time was from April 1997 to August 2002, altogether 64 months. The primary endpoints of the study were the overall survival time (OS) and the survival time from the first oncothermia treatment. The dates of exitus were checked by the National Death Register, so the actual and accurate data were collected. The final check of the deaths was December, 2003. Inclusion criteria were: (1) Inoperable or sub-totally resected, or recurrent primary pancreas tumor, (2) progression after radio- and/or chemo-therapy, (3) KPS ≥ 30% and the inclusion was irrespective of the localization of the

lesion in the lung. Patients started the oncothermia process in their late/advanced stages, where most of them had failed to respond to any of the applied conventional therapies.
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 age-distribution of n=61 patients was near to normal (p=0.82); no outlier was present. The median age was 58 y (38 - 77), the mean-age was 58.97 y (Std. err= 1.17). The gender distribution was 21/40 female/male (34.4/65.6 %). The ratio of the elderly (>68 y) patients were 21.3%. Oncothermia was performed in two/three sessions per week. Treatment time per session was 60 minutes. The power was gradually and linearly raised depending on the patient's tolerance from 40-80W to 100-150W. The applied average energy was 300 kJ/treatment (250-450). The applied applicators were 3.1 dm^2 and 7.1 dm^2, depending on the tumor volume.
Most of the patients (49, 80.3%) had distant metastases. They were heavily pre-treated; everybody received at least one chemotherapy and underwent other treatments (surgery, radio- or second chemo-therapy, see Figures 79., 80.).

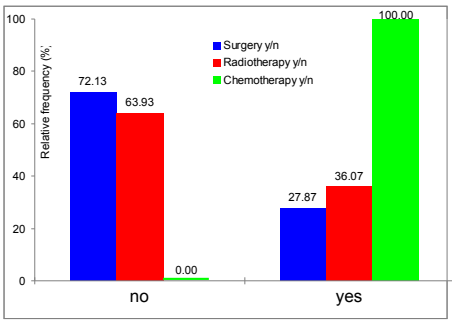


Figure 79. Pre-treatments of the patients

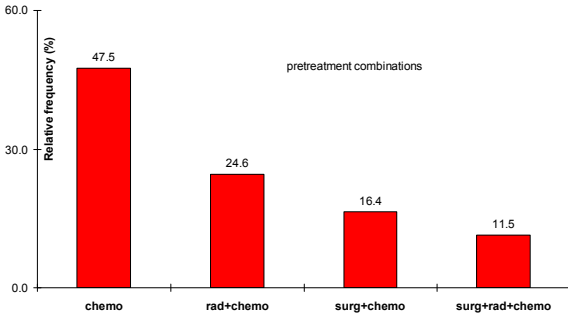


Figure 80. Pretreatment combinations

The actual staging was made at the first diagnosis (44% was in advanced [WHO IIIb or IV] stages) and at the first oncothermia treatment (75% was in advanced stage).
The median of the elapsed time from the 1st diagnosis to the 1st oncothermia was 8m (0.4-172), while its mean was 16.3m (st.err.3.1). The elapsed time ratio to the overall survival was more than 50% (median 59.9%, [6.5-99.1], mean 59.4 [st.err.3.5]); the patients received their first oncothermia in the second half or their survival time.
The oncothermia treatment was provided twice a week, the treatment number was in average 8.1 (st.err.0.55) and its median 8 (2-23).
The Kaplan-Meier plots of the overall survival (median 16.4m, [1.7-181.9]; mean 25.6m, [st.err.3.8]) and the survival from the first oncothermia treatment (median 5.7m, [0.1-44.9]; mean 9.2m, [st.err.1.3]) are shown in Figure 81. For elderly patients neither the overall survival nor the oncothermia survival was different (p~0.68).

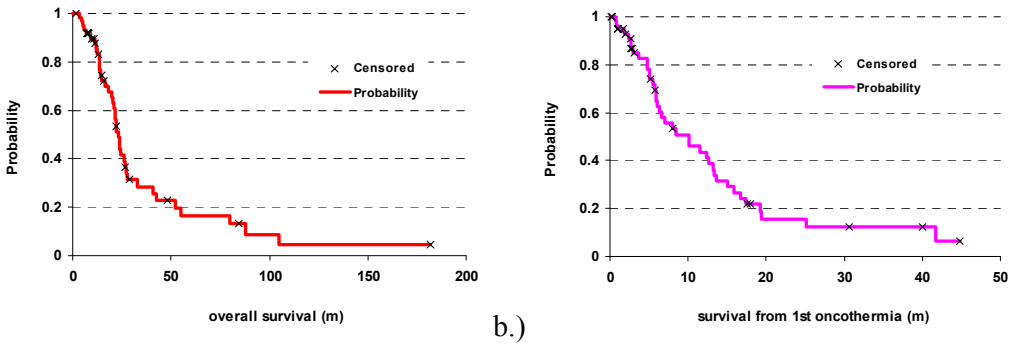


Figure 81. Overall (a) and oncothermia treatment time (b) survivals by Kaplan-Meier plot of the patients in PFY study

Naturally, the survival was significantly different for patients without or with metastases, (p=0.0003 p=0.031 for overall survival and oncothermia survival, respectively), see Figure 82.

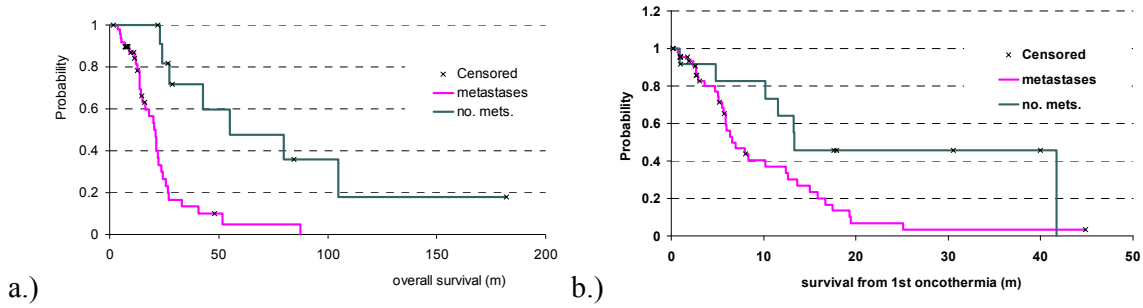


Figure 82. Overall survival(a) and oncothermia survival(b) survivals of the patients with metastases

The elapsed time to the first oncothermia shows an important parameter. Namely, this is of course is smaller (p=0.0019) for the patients with advanced disease in their first diagnosis (n=34, median, 13.0m [1.5-142]; mean 24.0m, [st.err.5.2]; and n=27, median, 6.5m [0.4-19.9]; mean 6.67m, [st.err.0.83] for non-advanced and advanced, respectively). Although, the opposite was registered (p=0.14) when the staging at the first oncothermia was studied (n=15, median, 4.10m [1.5-29.3]; mean 8.9m [st.err.2.3]; and n=46, median, 8.3m [0.4-142]; mean 18.78m, [st.err.4.0]; for non-advanced and advanced, respectively).

This tendency is more obvious to register the overall survival and oncothermia survival depending on the ratio of the elapsed time till first oncothermia to the overall survival, dividing the patients to the "early oncothermia" and "late oncothermia" categories. The overall survival shows the expected result: the low survivals are starting quicker (p=0.0065) the oncothermia (n=31, median, 16.4m [4.7-79.7]; mean 19.62m, [st.err.2.61]); than the long survivals, (n=30, median, 17.4m [1.7-182]; mean 31.7m, [st.err.7.07]). While the oncothermia survival was opposite (p=0.073): the early start (n=31, median, 8.4m [2.4-44.9]; mean 12.7m, [st.err.1.9]) was longer survival, than the late, (n=30, median, 2.7m [0.1-40.0]; mean 5.6m, [st.err.1.6]).

The number of treatments does not influence the overall survival significantly (p=0.61), but the oncothermia survival(p=0.0023) and the follow-up time after the last oncothermia (p=0.01) well depends on the number of oncothermia treatments, see Figure 83.

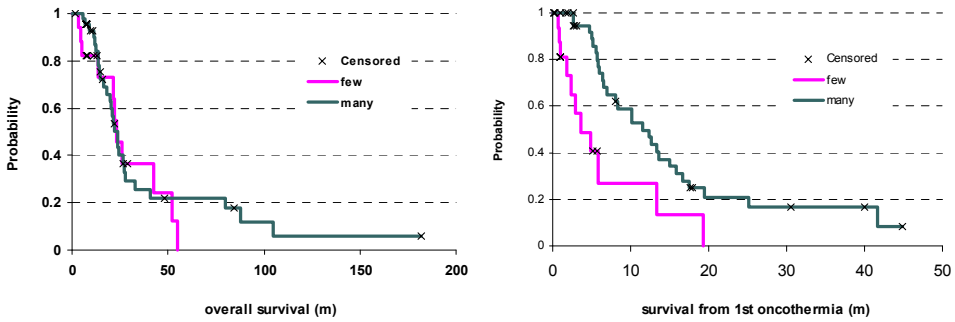


Figure 83. The various survival times for patients depending on the treatment session time. ("few" lower than the median number, "many" higher than the median number of the treatments)

Interestingly, the surgical pretreatment was especially (p=0.0005) important for the longer survival (see Figure 84.), but the other pre-treatments did not affect significantly neither the overall survival nor the oncothermia survival rates.

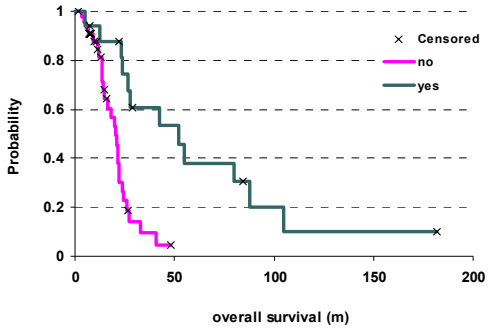


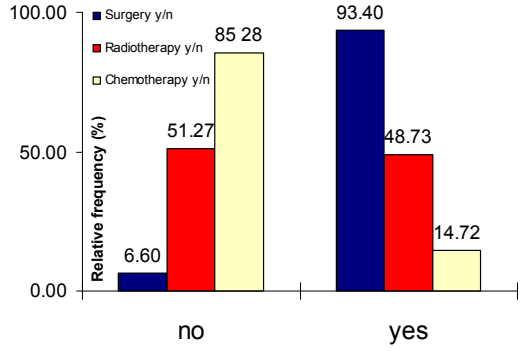
Figure 84. Effect of the pretreatment operation is significant considering the overall survival

The effect of the experience of the treating medical personnel by the data before and after the median time of the study is measured also. In the early experience (n_{ee}=33) the overall survival median 22.3m, (1.7-181) mean 33.7 (st.err.6.4); the oncothermia survival median 8.0m, (0.1-45) mean 11.6 (st.err.2.07); and the elapsed time to first oncothermia median 10.3m, (1.5-142) mean 22.1 (st.err.5.3) were measured. In the late experience (n_{le}=28) the data were: overall survival median 12.3m, (3.6-51.9) mean 15.9 (st.err.2.2); oncothermia survival median 5.0m, (0.1-25.1) mean 6.37 (st.err.1.24); elapsed time to first oncothermia median 5.9m, (43-77) mean 61.1 (st.err.1.8). The differences between the early and late experiences are significant in the case of overall survival (p=0.028) and elapsed time to first oncothermia (p=0.012), but not significant in oncothermia survival (p=0.19). The significantly better survivals in the first half of the study-time compared to the second one probably originated from the fact, that the patient spectrum had been shifted to the more advanced side. In the early experience the ratio of the advanced cases was 33%, while in the late experience advanced 57%, but both of them increased (76% and 75%, respectively) when measured at the first oncothermia treatment. (The nearly equal percentage of the advanced cases in both the categories (growing up from very different starts) indicates the assumption, that the patients start the oncothermia treatment at nearly the same stage irrespective of their elapsed time from the 1st diagnosis to the 1st oncothermia.

Oncothermia lung study II.

The age-distribution of n=197 patients was acceptably normal (p=0.59); no outlier was present. The median age was 57 y (16 - 84), the mean-age was 56.71 y (Std. err= 0.77). The gender distribution was 62/135 female/male (31.5/68.5 %). The ratio of the elderly (>68 y) patients were 20.3%.

Most of the patients (157, 79.7%) had distant metastases, (one two and three metastases were observed for 101, 43 and 13 patients, respectively). They were heavily pre-treated; most of them (93.4%) underwent surgery and subsequent radiation-therapy (see Figures 85., 86.).



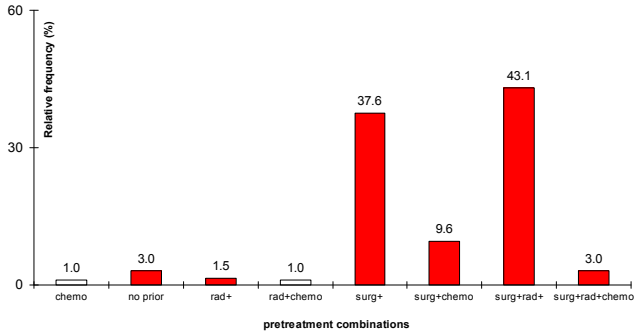


Figure 85. Pretreatment distribution of HTT patients *Figure 86. Pretreatment combinations*

The actual staging was made at the first diagnosis (46.2% was in advanced [WHO IIIb or IV] stages) and at the first oncothermia treatment they were at a more advanced status.
The median of the elapsed time from the 1st diagnosis to the 1st oncothermia was 5.5m (0.2-111.3), while its mean was 10.6m (st.err.1.0). The elapsed time ratio to the overall survival was near 50% (median 45.4%, [1.6-96.7], mean 45.7 [st.err.3.9]).
The oncothermia treatment was provided twice a week, the treatment number was in average 7.9 (st.err.0.4) and its median 6 (3-40). The median treatment time was 60 min, (45-135) and the mean was 69.6 min (st.err.1.3), while the median equivalent temperature was 52 (43-59) and its mean was 51.4 (st.err.0.3). Note that the equivalent temperature is not the real temperature. It is the calculated value from the actual energy-absorption and the impedance, meaning of the actual destruction rate, which is as high, as would have been at the purely temperature oriented case.
The Kaplan-Meier plots of the overall survival (median 15.6m, [1.1-122.1]; mean 22.4m, [st.err.1.31]) and the survival from the first oncothermia treatment (median 7.57m, [0.1-68.6]; mean 11.8m, [st.err.0.91]) are shown in Figure 87. For elderly patients neither the overall survival nor the oncothermia survival was different (p~0.37 and p~0.49, respectively).

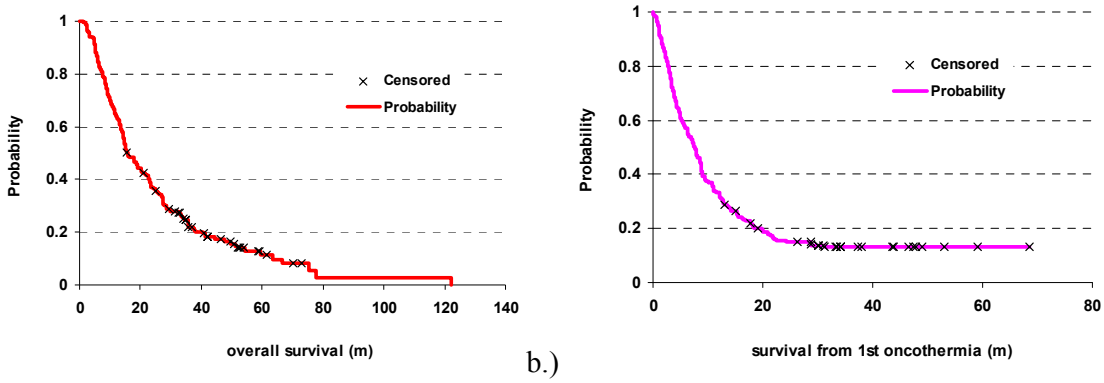


Figure 87. Overall survival (a), and survival from the first oncothermia (b) for the patients entered in the HTT study

The differences between patients without or with metastases in their overall survival and oncothermia survival were not significant (p=0.33 and p=0.07 for overall survival and oncothermia survival, respectively) Figure 88.

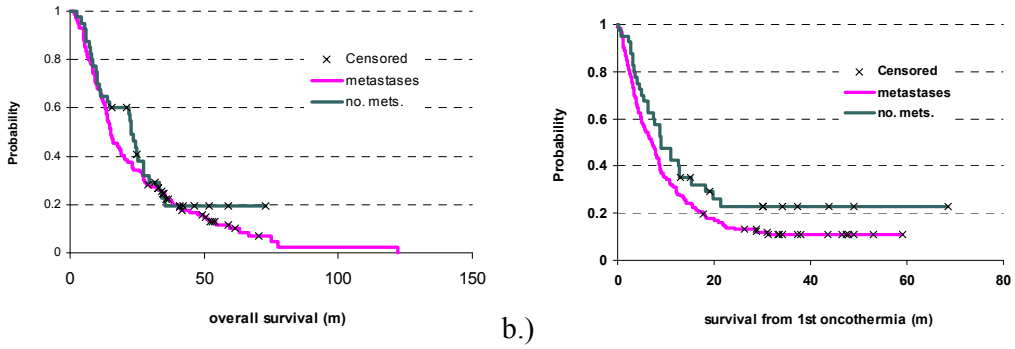


Figure 88. The effect of metastases on the overall survival(a) and oncothermia survival(b) survivals for HTT patients

The number of treatments significantly influences the overall survival(p=0.048) and the oncothermia survival(p=0.00046) and the follow-up time after the last oncothermia (p=0.0017) very much depends on the number of oncothermia treatments.
Interestingly, the surgical pretreatment was especially (p=0.0005) important for the longer survival either for overall survival(p=0.005) and oncothermia survival(p=0.016) (see Figure 89.), but the other pre-treatments did not affect significantly neither the overall survival nor the oncothermia survival rates.

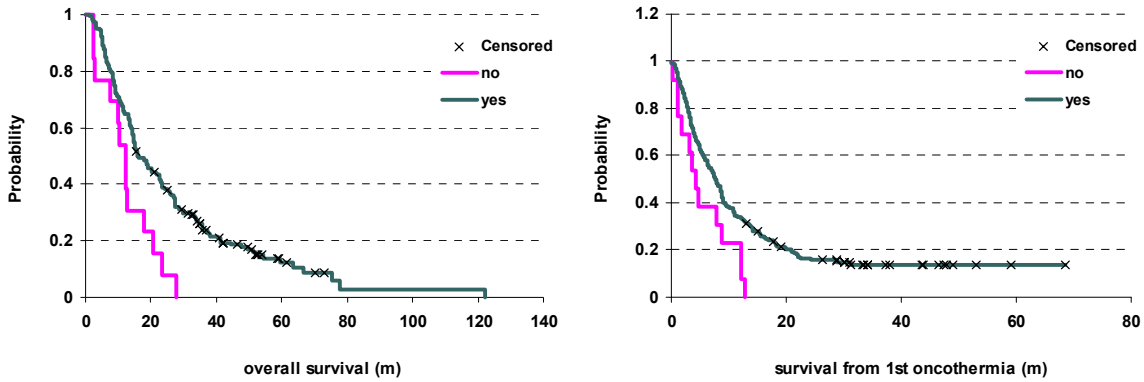


Figure 89. Effect of surgical pre-treatments on the overall survival(a) and oncothermia survival(b) survivals

We studied the effect of the experience of the treating medical personnel by the data before and after the median time of the study. In the early experience (n_{ee}=94) the overall survival median 15.3m, (2.4-122.1) mean 24.0 (st.err.2.17); the oncothermia survival median 7.2m, (0.3-68.6) mean 11.8 (st.err.1.5); and the median of elapsed time to first oncothermia is 5.37m, (0.4-111.3) mean 12.2 (st.err.1.8) were measured. In the late experience (n_{le}=103) the data were: overall survival median 15.83m, (1.1-77.7) mean 21.0 (st.err.1.5); oncothermia survival median 8.13m, (0.1-43.9) mean 11.8 (st.err.1.1); elapsed time to first oncothermia median 5.6m, (0.2-64.8) mean 9.1 (st.err.1.1). The differences between the early and late experiences are not significant in the case of overall survival (p=0.85), oncothermia survival(p=0.17) and elapsed time to first oncothermia (p=0.21).

Meta-analysis of oncothermia lung studies

The age-distribution of the altogether n=258 patients was near to normal (p=0.71); and no outlier was present. The median age was 57 y (16 - 84), the mean-age was 57.2 y (Std. err= 0.7). In the spectrum of the PTF a shift to the elderly patients was present (see Figure 90.). The overall gender distribution was 83/175 female/male (32/68 %), and no significant difference could be measured between the places. The ratio of the elderly (>68 y) patients were 20.5%, (20.3 and 21.3% in PFY and HTT, respectively). The PFY/HTT patient ratio was 61/197 (24/76 %).

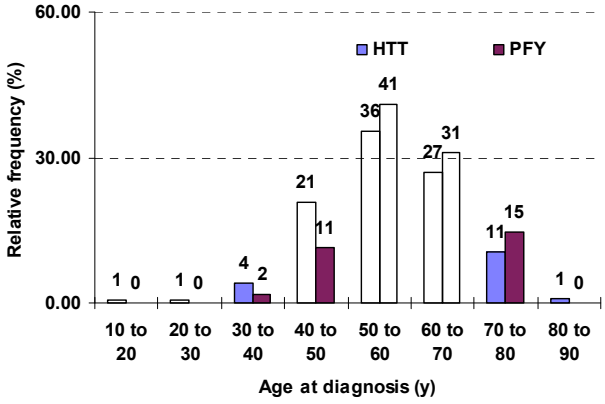


Figure 90. Comparison of the age distribution in the given studies

80% of the patients had distant metastases in both study-places (see Figure 91.) and half of them were in advanced stages at the first diagnosis of the disease (see Figure 92.). Patients were heavily pre-treated (see Figure 93.), in PFY the chemo-therapy, in HTT the surgery was the most frequent modality.

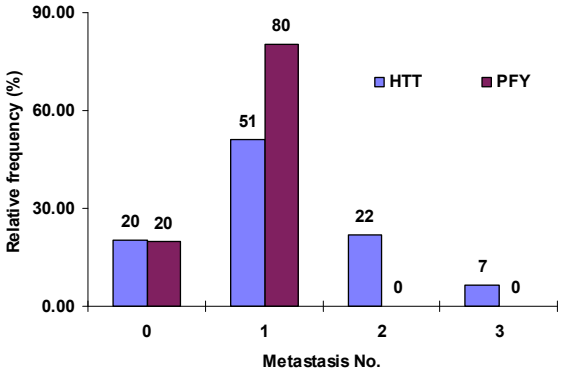


Figure 91. Comparison of metastatic cases

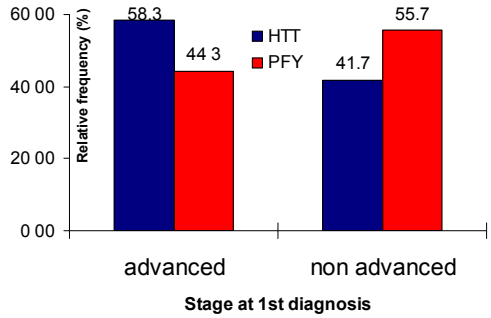


Figure 92. Staging differences

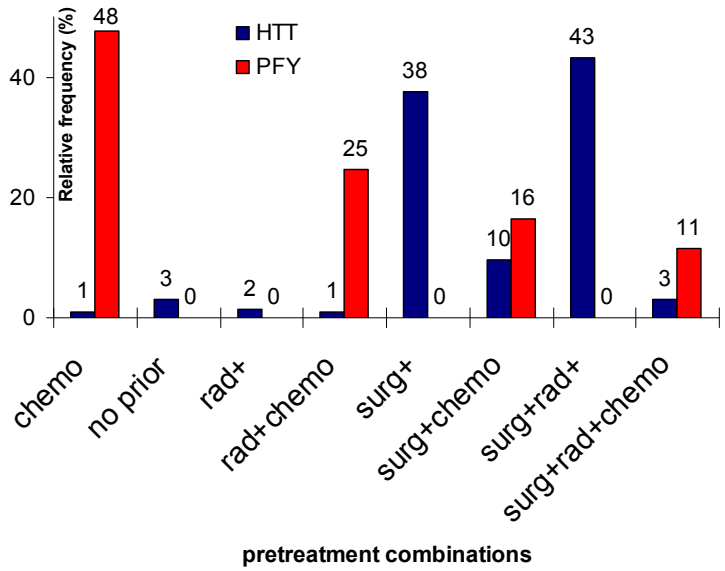


Figure 93. Pretreatment combinations show the different emphases in the treatment strategies

The median elapsed time to 1st oncothermia from the first diagnosis (ETO) was significantly (p=0.028) shorter in HTT than in PFY, Figure 94.

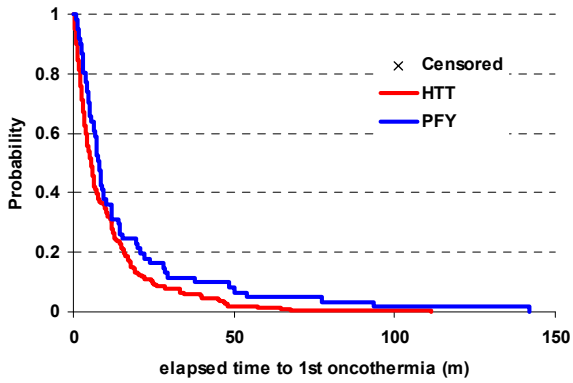


Figure 94. Elapsed time to first oncothermia is significantly shorter for HTT patients

The oncothermia treatment was provided twice a week, the number of treatments in average was more in PFY than in HTT procedures, (see Figure 95.).

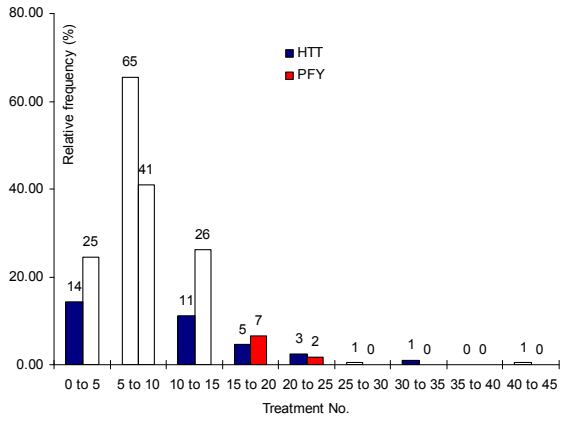


Figure 95. The treatment numbers in the two institutions

The overall survival (OS) and the survival from the first oncothermia treatment (OSO) are shown in Figure 96/a,b. The overall survivals significantly lower in HTT case (p=0.044) but in the oncothermia survival there are no significant differences (p=0.53). Survival after the treatment was not different in the two places (p=0.55). However, for elderly patients neither the overall survival nor the oncothermia survival was different (p~0.38 and p~0.86, respectively), see Figure 96/c.

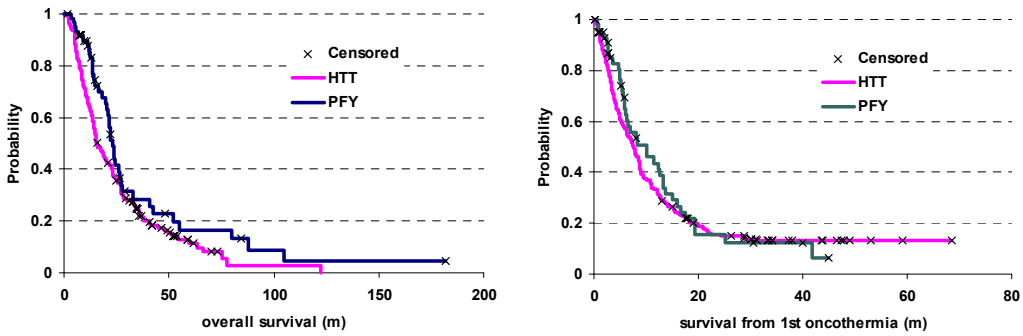


Figure 96. The difference between the overall (a), oncothermia survival (b), for patients involved in the studies

In both of the places most of the patients reported subjective improvement of their quality of life. No extra toxicity or safety problem was observed during the treatments.

The above two studies were performed by the same guidelines but in entirely independent hospitals, with no overlap in medical personnel. The two retrospective data sets can be regarded as independent. The study of the expertise of the personnel in the two places was the same, their training was enough to make the optimal performance from the very start of the treatment.

The patients' pre-treatments were mostly dominated by surgery and chemo-therapy in HTT and PFY, respectively. As well as the elapsed time to first oncothermia was significantly different having earlier start of oncothermia in HTT, and surprisingly the overall survival was also significantly lower. Looks the patients treated by HTT were more advanced at their first diagnosis, (more metastases were detected) than the PFY counterparts, which explains the difference. Despite the difference in overall survival, the oncothermia survival does not differ significantly between the two places. The yearly survival rates could be regarded identical (p>0.99) within the measurement error, (see Figure 97.). This could be indication of the oncothermia leveling action as well.

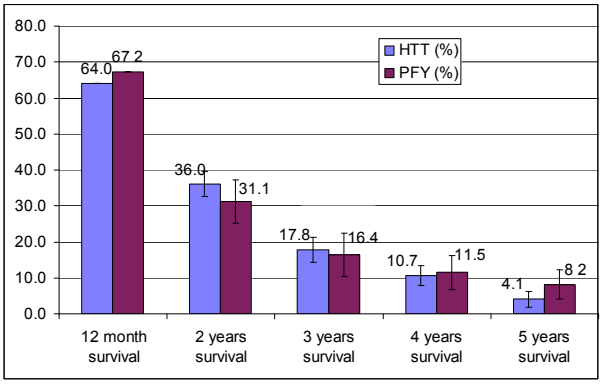


Figure 97.Yearly survivals of the patients in the two institutions. (no significant difference exists.)

Compare to historical control

A historical (retrospective) control (n=53) was collected from the St. Borbala Hospital (Tatabanya, Hungary), for comparison. The data-set is the patients of one of the present authors (AD) who had worked at St. Borbala Hospital, so the comparison of his own data is feasible. The overall survival Kaplan-Meier plot shows significant benefit of the oncothermia (p=0.033) Figure 98. (Median 15.8m (1-182) and mean 23.1m (St.err.1.3); for oncothermia and 14.0m (1-84), 18.5m (St.err.2.3) for the historical control.

The common pool of the PFY and HTT data (n=258) is decomposed (see Appendix 35.) for responders and non-responders, see Figure 99.

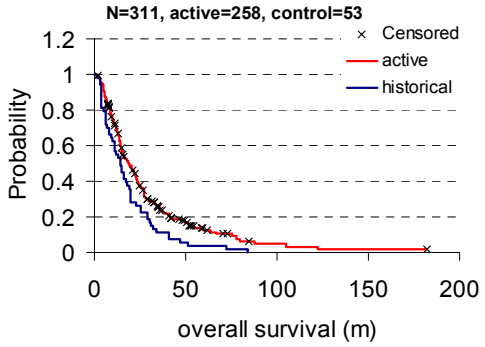


Figure 98. Kaplan-Meier plot for the historical and active arms in the study. The difference is significant (p=0.033)

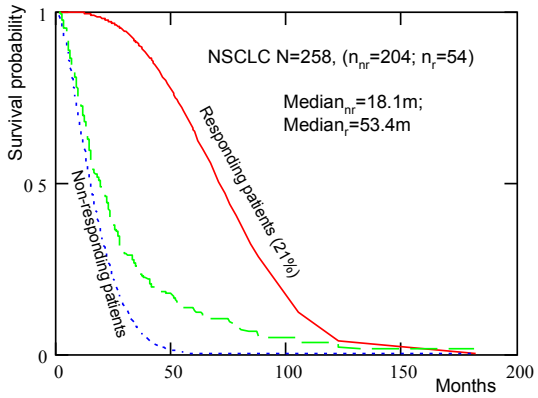


Figure 99. Decomposition of the common database

Patients were divided to subgroups of advanced (III, IIIa, IIIb, IV.) (n=140) and not-advanced (I, Ia, Ib, II, IIa, IIb.) (n=77) stages. (Data were not available for a smaller group (n=41), their data

were not used in this evaluation.) It is not surprising the two subgroups are significantly different (p=0.038) by their survival, see Figure 100.

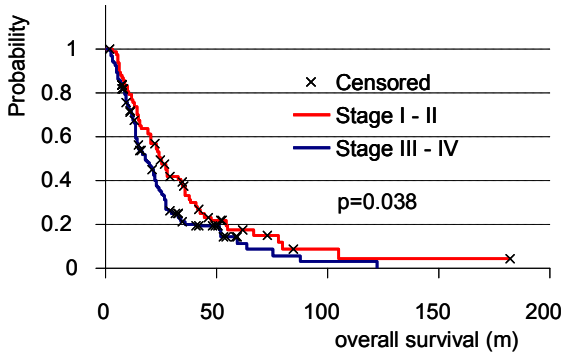


Figure 100. Survival difference between (p=0.038) advanced and non-advanced NSCLC subgroups

The non-advanced subgroup (Stages I, Ia, Ib, II, IIa, IIb.) has all together 87 patients (77 active, 10 control) and the advanced subgroup (Stages III, IIIa, IIIb, IV.) 183 patients (a40 active, 43 control). Make comparison for both the subgroups with the relevant subgroup of the historical control, the effect of oncothermia becomes more pronounced, in advanced cases (III+IV) (active arm: median 14.7 months, [n=132], control arm: median 11.0 months [n=43]) Result is significant, p=0.023, than in the non-advanced case subgroup, where the differences were not large, and were not significant (see Figure 101.).

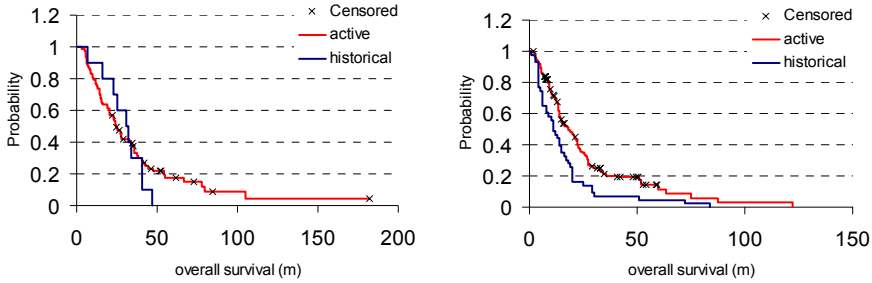


Figure 101. Comparison of subgroups with the relevant part of the historical data. (Non-advanced subgroup: N=87, (77, 10), p=0.63; advanced subgroup N=183, (140,43), p=0.0017.)

Analyzing both the subgroups parametrically, the ratio of responders in non-advanced group is only 17%, while in advanced group 88%.

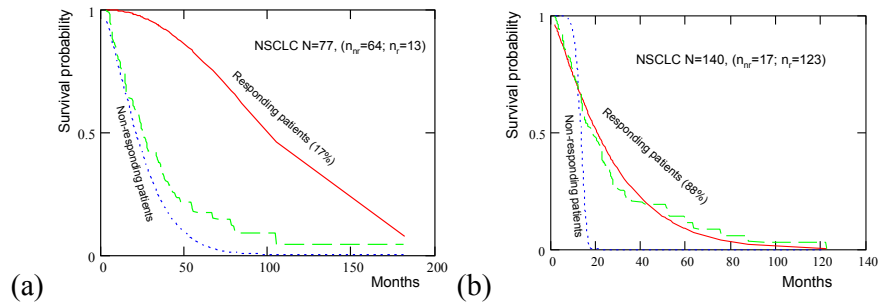


Figure 102. The non advanced cases a) n=77 are less responding than the advanced ones b) n=140

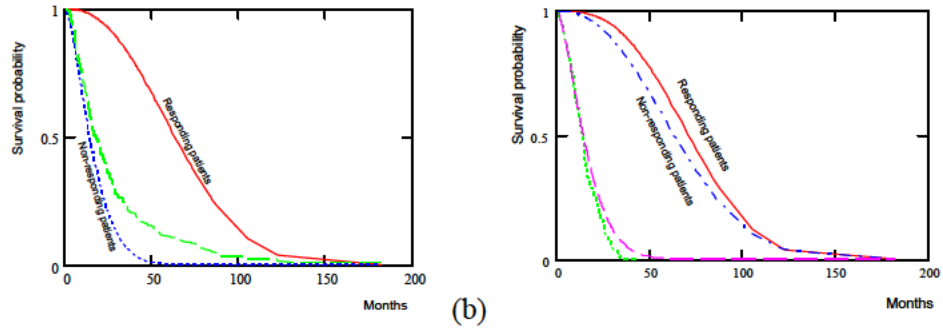


Figure 103. The distribution together with the historical control (n=311) only slightly differs from the distribution without the control group (n=258)

The results could be well compared to the available SEER [**6**] and Eurocare [98] data, see Figure 104. The yearly survival rate is definitely much higher (significant) in the first three years than the database average. This result is remarkable taking into consideration the advanced patient-spectrum of oncothermia treated patients. The decrease of the difference by years is probably due to the very small influence on the longer survivals of the late-stage applied oncothermia for a short time. The most rapid cases are earlier in their stage to start oncothermia, so their overall survival is strongly influenced by the oncothermia treatment. This is supported by the fact that despite the significantly lower elapsed time to first oncothermia the survivals are not notably different in the two institutions.

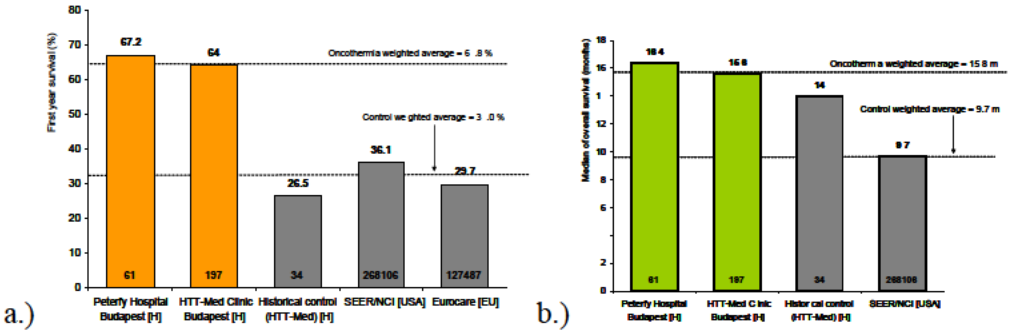


Figure 104. The comparison of the first year (a) and the median (b) survival results with SEER and Eurocare data

Pancreas studies

Pancreas efficacy study I.

The place of the study was the Hospital Peterfy in Budapest. Investigator Dr. Magyar T. This Phase II. study is designed as observable, open-label, single-arm. The involved patients are being analyzed according to an intention-to-treat (ITT) schedule. Recruiting time was from Apr. 1997 to Aug. 2002, all together 64 months. Patients (n=26) were dominantly in late/advanced stages, where the traditional oncotherapies were unsuccessful. The primary check of the efficacy of a curative method in such a lethal kind of disease is the survival time. The primary endpoints of the present study therefore were the overall survival oncothermia treatment time and the survival time from the first oncothermia treatment (oncothermia treatment survival time. The date of death (or alive) were checked by the Hungarian National Death Register, so the actual and accurate data were collected. The latest check of the deaths was 31. December of 2003.

Inclusion criteria were: (1) Inoperable or sub-totally resected or recurrent primary pancreas tumor, (2) progression after surgery and/or chemo-therapy, (3) KPS $\geq$ 30%. and the inclusion was irrespective of the localization of the lesion in the pancreas. Most of the patients failed to respond to any of the applied conventional therapies. 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 calculated average equivalent temperature in the tumors was above 43 ^{o}C in more than 90% of the treatment time. The targeted area was treated by the properly covering applicator system. Oncothermia was performed in two/three sessions per week. Treatment time and power range per session were 60 minutes, and 150 W. The power was gradually and linearly raised up depending on the patient tolerance. The applied average energy was 300 kJ/treatment (250-450). The applied applicators were 3.1 dm^2 and 7.1 dm^2, depending on the tumor volume.
The age-distribution of n=26 patients was near to normal (see Figure 105.); no outlier was present. The median age was 64.5 y (37 - 77), the mean-age was 62.5 y (Std.err= 1.99). The gender distribution was 14/12 female/male (53.8/46.2 %). The ratio of the elderly (>68 y) patients were 42.3%.

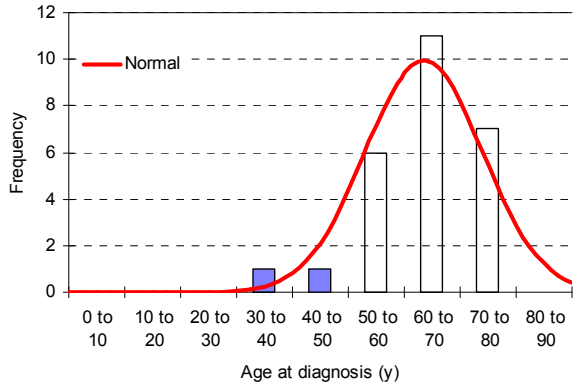


Figure 105. Age-distribution at diagnosis

Most of the patients (23, 88.5%) had distant metastases. They were heavily pre-treated, everybody received at least one chemotherapy and most of them underwent surgery (see Figure 106.).

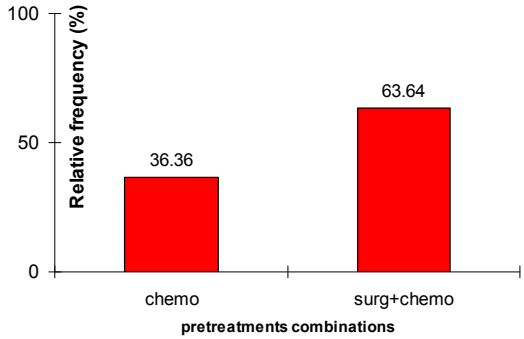


Figure 106. The pretreatment distribution in patient population

The actual staging was made at the first diagnosis: 23, [88.5%] was in advanced [WHO III or IV] stages, and at the first oncothermia treatment 100% was in advanced stages, 19 (73.1%) were in the worst stage.
The median of the elapsed time from the 1st diagnosis to the 1st oncothermia was 4.1m (0.8-75), while its mean was 8.6m (st.err.3.0). The elapsed time ratio to the overall survival was more than 35% (median 37.3%, [5.9-86], mean 44.3 [st.err.4.2]).
The oncothermia treatment was provided 2-3 times a week, the treatment number was in average 9.0 (st.err.0.86) and its median 6 (3-16), (see Figure 107.).

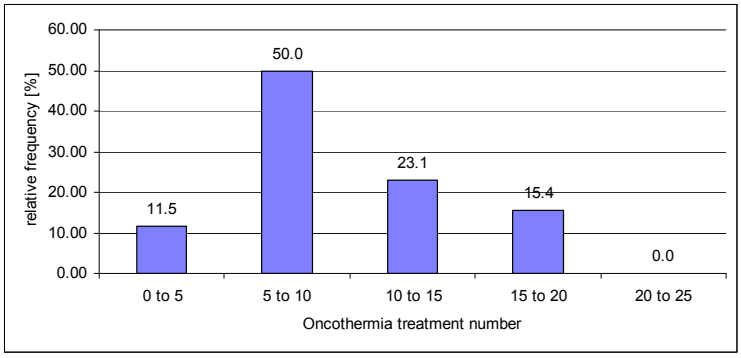


Figure 107. Treatment number of oncothermia is dominantly in the 5-10 interval

The Kaplan-Meier plots of the overall survival (median 12.0m, [2.3-115.5]; mean 17.5m, [st.err.4.4]) and the survival from the first oncothermia treatment (median 6.3m, [0.7-40.4]; mean 8.9m, [st.err.1.9]) are shown in Figure 108. For elderly patients the survival plots were not different (p=0.41 and p=0.61, for overall survival and oncothermia survival, respectively).

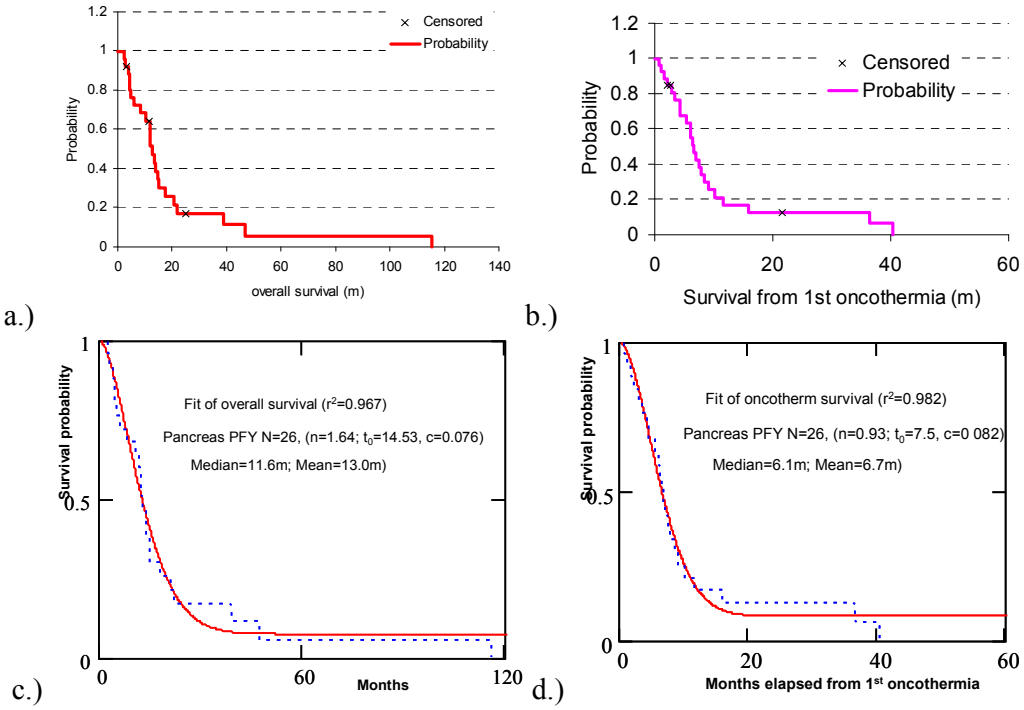
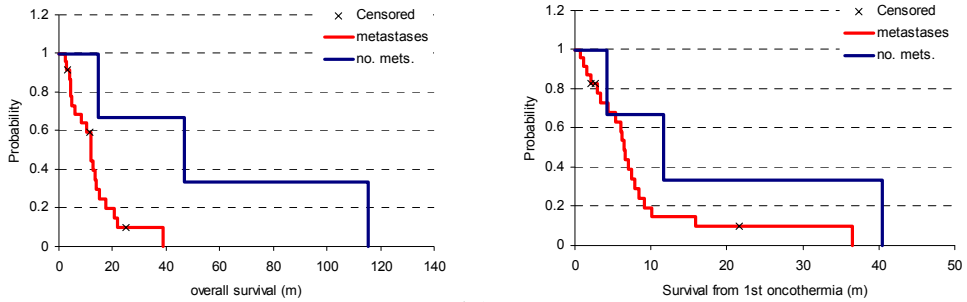


Figure 108. The overall survival (a) and oncothermia survival (b) Kaplan-Meier plots. The Weibull parametric fit and its results are shown on panel (c) & (d)

The parametric decomposition of the survival plots gives for responding patients 58%, the decomposed distributions are not significantly different.

The survival was significantly different and for patient without or with metastases in their overall survival, (p=0.039), but was not significant in their oncothermia survival (p=0.20) see Figure 109.



a.) b.)

Figure 109. Overall survival (a) and oncothermia survival (b) survivals depend on the preliminary surgery

We studied the effect of the experience of the treating medical personnel by the data before and after the median time of the study. No observable effect could be registered: overall survival (p=0.86) and oncothermia survival (p=0.69). The elapsed time to the first oncothermia from the first diagnosis is lower in the late experience, (medians are 5.17 m [0.8-75.1], and 3.27 m [0.9-35.3], in early and late experience period, respectively) but the difference is not significant either (p=0.29).

Pancreas efficacy study II. (HTT)

The trial (Phase II.) was identically designed by the previously described one. It was performed at day-clinic HTT-MED (HTT), [Investigator: Dr. A. Dani]. The age-distribution of n=73 patients was near to normal (see Figure 110.); no outlier was present. The median age was 58 y (24 - 79), the mean-age was 59.1 y (Std. err= 1.3). The gender distribution was 33/40 female/male (45.2/54.8%). The ratio of the elderly (>68 y) patients were 26.0%.

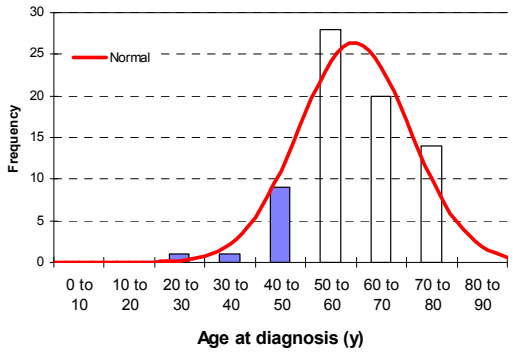


Figure 110. Age distribution of patients in HTT trial

Most of the patients (54, 74.0%) had distant metastases, (one, two and three metastases were observed for 43 (58.9%), 10 (13.7%) and 1 (1.4%) patients, respectively). They were heavily pre-treated, mostly (93.4%) underwent surgery and subsequent radiation and/or chemo-therapies, see Figs. 111., 112.).

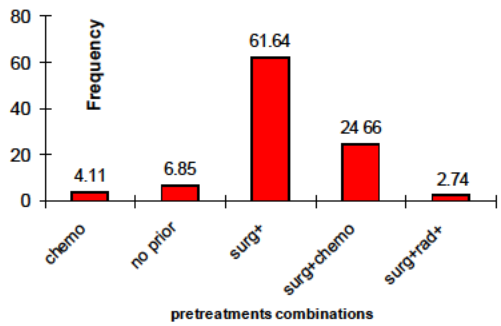


Figure 111. Pretreatment combinations

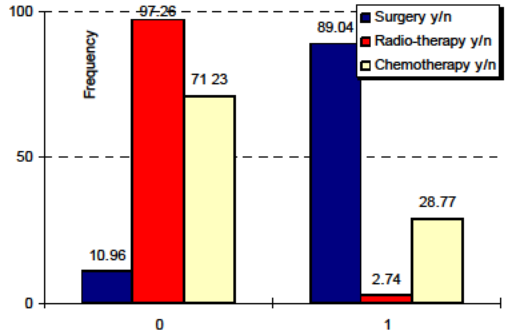


Figure 112. Pretreatment distribution

The actual staging was made at the first diagnosis (45, 61..6% was in advanced [WHO III or IV] stages) and at the first oncothermia treatment they were in more advanced status.
The median of the elapsed time from the 1st diagnosis to the 1st oncothermia was 3.3 m (0.3-85.7), while its mean was 6.6 m (st.err.1.3). The median of the elapsed time ratio to the overall survival was 37.1% (5.1-96.0], mean 41.2 [st.err.3.4]).
The oncothermia treatment was provided twice a week, the treatment number was in average 8.0 (st.err.0.6) and its median 6 (3-26), (see Figure 113.). The equivalent temperature in average was 50.7 (sd.err.0.6), median 51 (43-59). (Note, that the equivalent temperature is not the real temperature. It is the calculated value from the actual energy-absorption and the impedance, meaning the actual destruction rate, which is as high, as it would be in a purely temperature oriented case.) The applied treatment time in average was 67.2 min, (st.err.1.8) and its median was 60 (45-120).

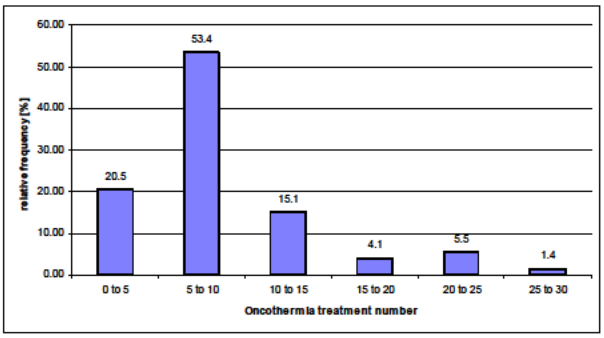
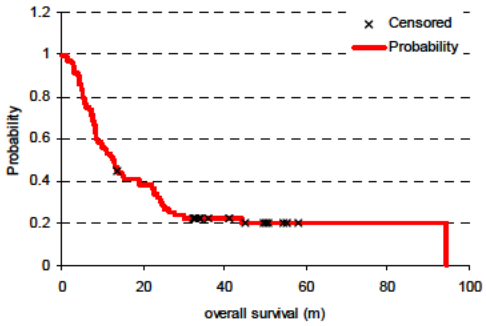
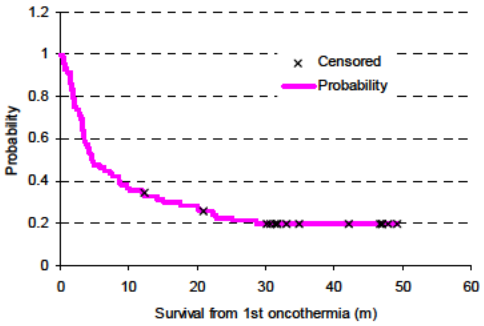


Figure 113. Number of oncothermia treatments

The Kaplan-Meier plots of the overall survival (overall survival) (median 12.7 m, [1.2-94..5]; mean 19.2 m, [st.err.2.1]) and the survival from the first oncothermia treatment (oncothermia survival) (median 4.7 m, [0.3-49.2]; mean 12.6 m, [st.err.1.7]) are shown in Figure 114. For elderly patients neither the overall survival nor the oncothermia survival were different (p~0.23 and p~0.42, respectively).



a.)



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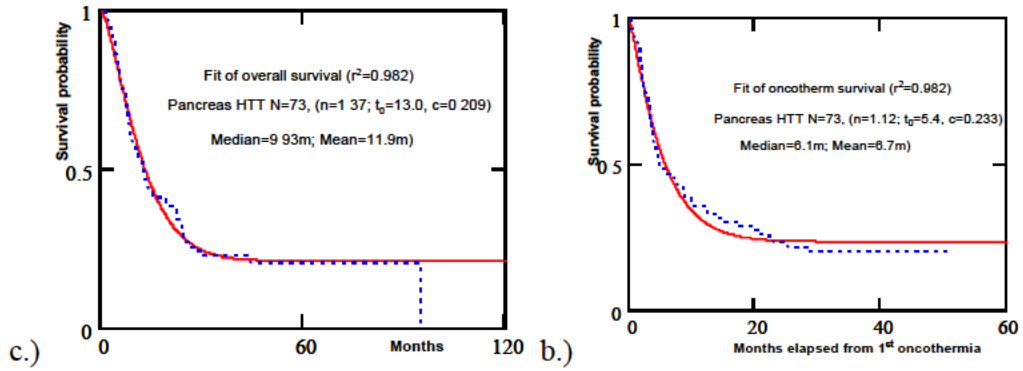

Figure 114. Overall survival (a) and oncothermia survival (b) of HTT-study, and their parametric fits, (c) & (d)

The parametric decomposition significantly divides the cohort on two subgroups (responders and non-responders), but the responders was obtained, only slightly more than non-responders (58%), (see Figure 115.); well corresponding with the results in the PFY study.

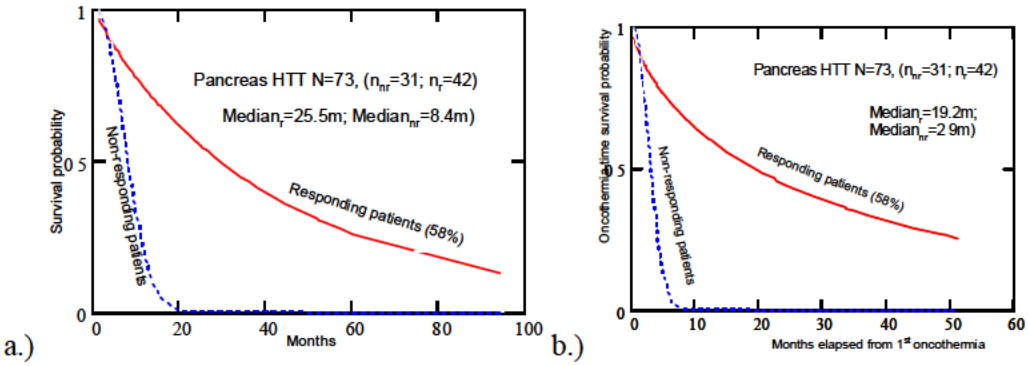

Figure 115. Decomposition curves from parametric fits: overall survival (a) and oncothermia survival (b)

The differences between patients without or with metastases in their overall survival and oncothermia survival were significantly different (p=0.016 and p=0.004 for overall survival and oncothermia survival, respectively), see Figure 116.

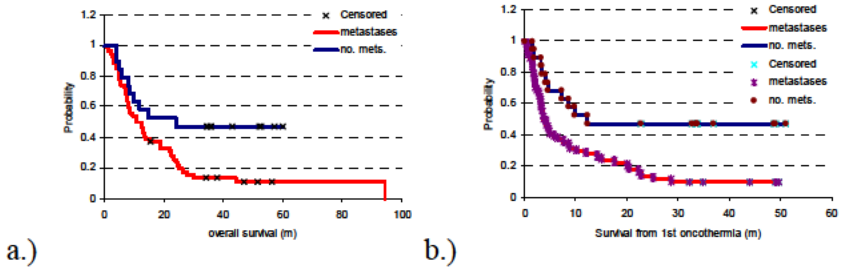

Figure 116. Dependence of the survival from the number of metastases [a) overall and b) oncothermia survival respectively.]

Number of treatments do not significantly influence the overall survival(p=0.24) and the oncothermia survival (p=0.16) and the follow-up time after the last oncothermia (p=0.23, see Figure 117.

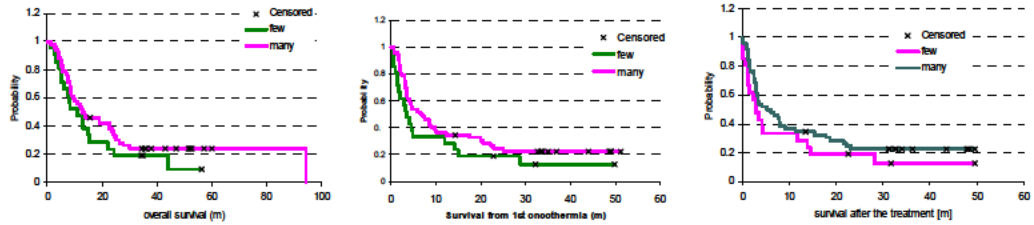

Figure 117. The typical survival times do no depend significantly on the number of treatments (few = below median, many = above median number of treatments)

Interestingly, the anyway necessary surgical pretreatment wasn't significantly important for the longer survival for these patients, either for overall survival (p=0.84) and oncothermia survival (p=0.87) (see Figure 118.). This was probable because the surgery in these patients was not complete, the tumor was only partially resected, or the surgery was only for palliation.

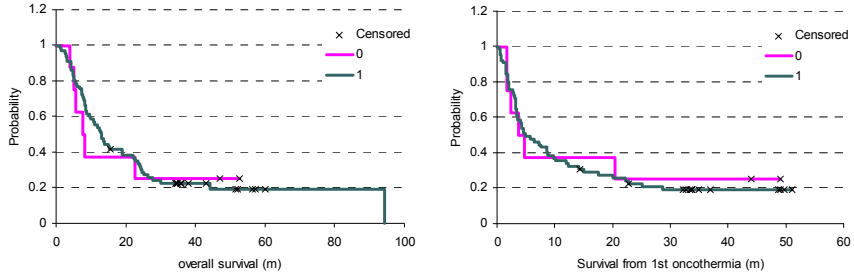

Figure 118. The survivals' dependence on the surgery ((0) – no; (1) – yes

We studied the effect of the experience of the treating medical personnel by the data before and after the median time of the study. There is some difference (not significant) in the overall survival, oncothermia survival and elapsed time to the 1st oncothermia (p=0.15; p=0.077 and p=0.52, respectively), (see Figure 119.).

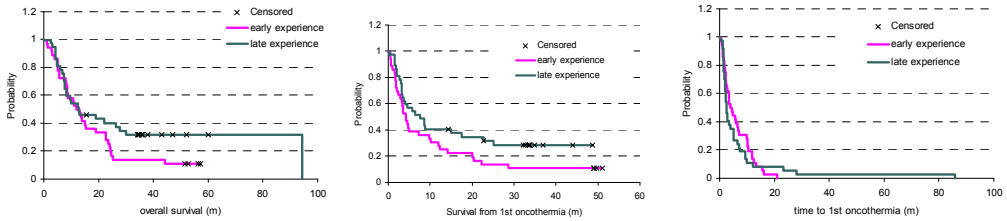

Figure 119. The experience of the treating personnel did not modify the results significantly ("early experience" = the treatment was started earlier than the median time of the study; "late experience" = the treatment was started later than the median time of the study)

Additional historical control to HTT pancreas study

For additional check a historical control (n=34) from the St. Borbala Hospital (Tatabanya, Hungary) was given as comparison to the HTT data. The reality of this comparison is the fact that one of the physicians (AD) had worked at HTT and at St. Borbala Hospital parallel, and so the comparison of his own data is feasible. The median overall survival of the control was 6.5 m (1-31), and the mean survival was 8.7 m (St.err.1.29), while the compared HTT (n=73), median 12.7 m (1.2-94.5), mean 19.6 (std,err.2.1). This control arm is equivalent with the published data form the Hungarian pancreas center [99], which published mean is 8.3m (Chemotherapy: Gemzar+5-FU+Leukovorin). The parametric fit of control shows unified cohort (see Figure 120.).
The comparison of the Kaplan-Meier survival curves of the control and the active arms demonstrates the cogently significant difference ($p<10^{-4}$), (see Figure 121.).

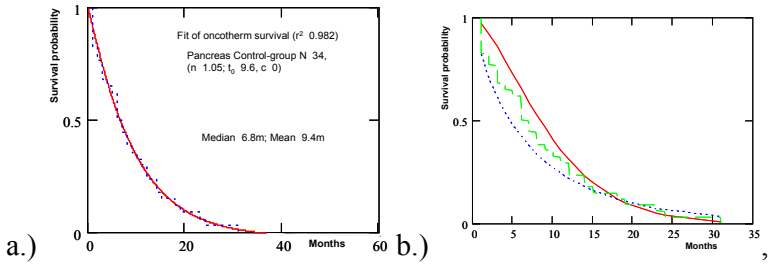

Figure 120. The fit is simple Weibull (a), its decomposition [equal additions of the sub-curves], (b) is inside the confidence interval of the Kaplan-Meier-fit

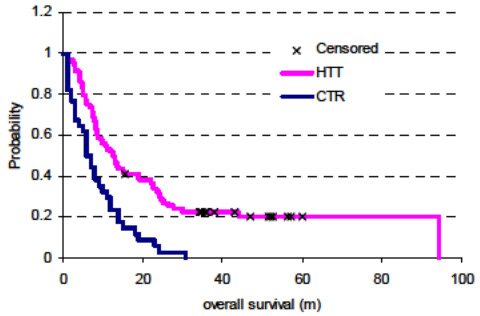

Figure 121. *The comparison of the Kaplan-Meier survival curves of the results by HTT and the historical control, collected for HTT by the same treating physician who works at HTT and in St. Borbala Hospital*

Comparison of pancreas efficacy studies I. & II.

By the comparison of the two Hungarian studies [100], the parallels enforce the validity of the data.

The age-distribution of the altogether n=99 patients was near to normal (see Figure 122.); and no outlier were present. The median age was 60 y (24 - 79), the mean-age was 60 y (Std. err= 1.1). In the spectrum of the PFY a shift to the elderly patients was present (see Figure 123.). The gender distribution was 47/52 female/male (47/53 %), and no significant difference could be measured between the places (see Figure 124.). The PFY/HTT patients' ratio is 61/197 (24/76 %).

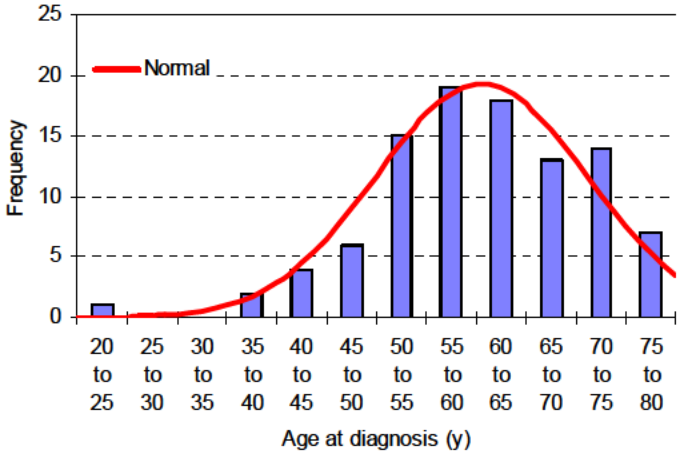

Figure 122. *Age-distribution of lung tumor patients (n=99)*

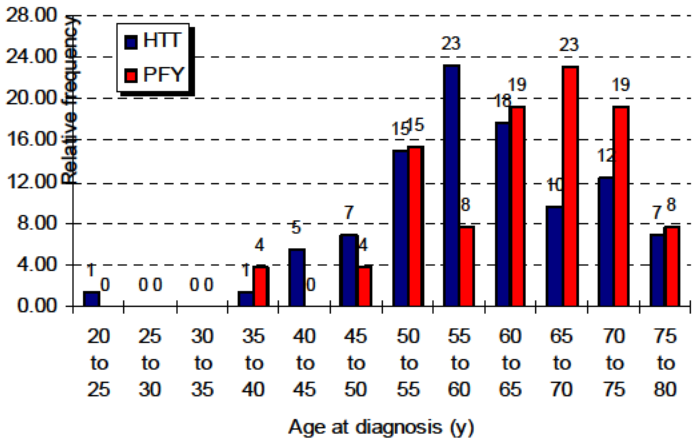

Figure 123. *The age-distribution differences in the given clinics*

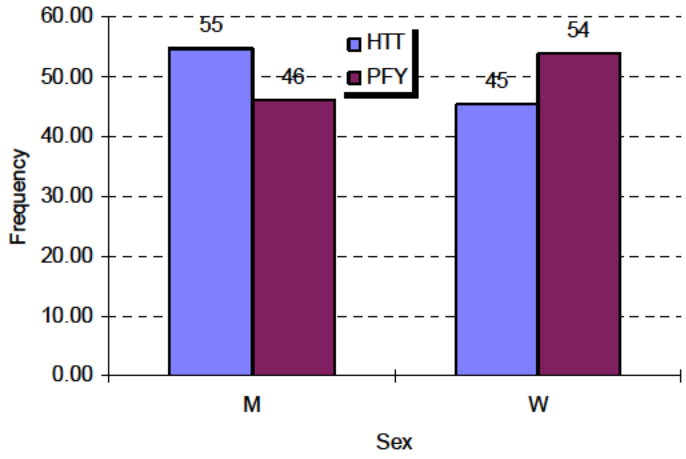

Figure 124. The gender distribution in the given clinics

74% and 88% of the patients had distant metastases in HTT and PFY groups, respectively (see Figure 125). Patients were heavily pre-treated (see Figure 126.), in PFY the chemo-therapy, in HTT the surgery was the most frequent modality.

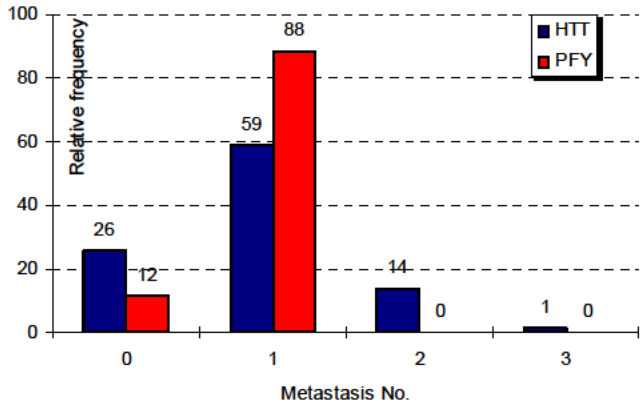

Figure 125. Number of metastases of the patients involved in the study

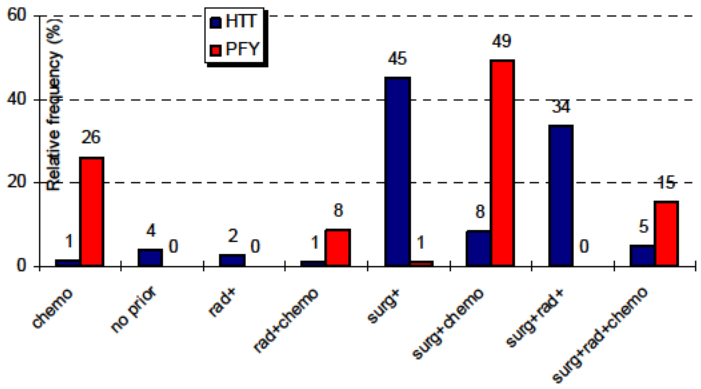

Figure 126. Pretreatment distribution

The elapsed time to 1st oncothermia from the first diagnosis was identical (p=0.69) in the two places, see Figure 127.

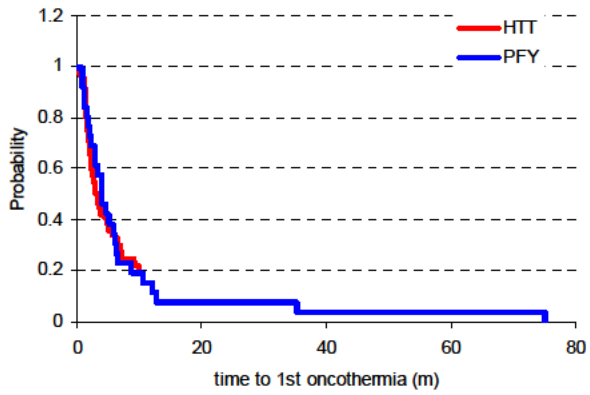

Figure 127. The distribution of the elapsed time to the first oncothermia treatment

The oncothermia treatment was provided twice a week, the treatment number was in average was more in PFY than in HTT procedures, (see Figure 128.).

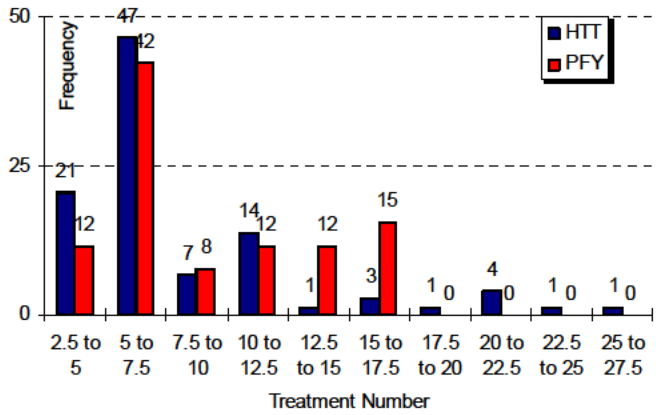

Figure 128. The number of treatments for the patients in the study

The overall survival (OS) and the survival from the first oncothermia treatment (OSO) are shown in Figures 129 and 130. Neither of the measured parameters differed from each other (p=0.38 and p=0.39, respectively).

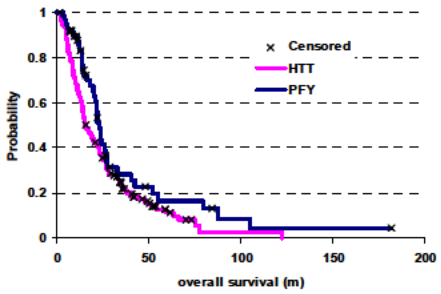

Figure 129. The overall survival comparison of the studies

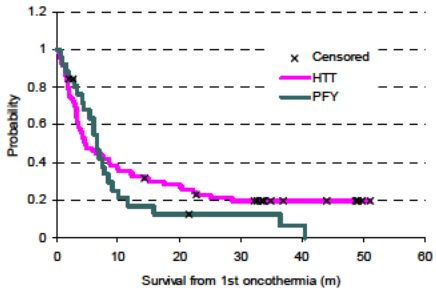

Figure 130. The oncothermia survival comparison of the studies. No significant difference could be observed

Survival after the treatment was not different in the two places (p=0.34, see Figure 131.).

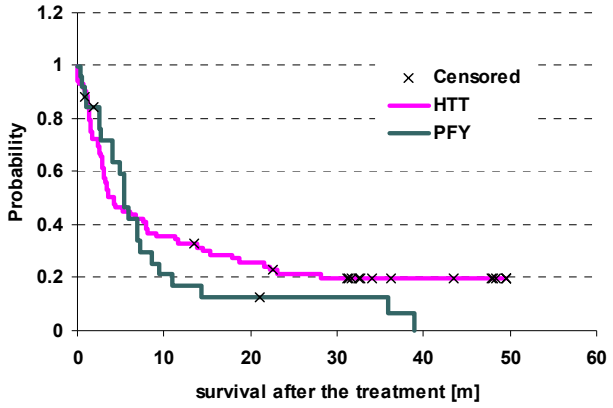

Figure 131. The follow-up-time does not differ in the two studies either

Results show the identical survival parameters in the two independent places. The yearly survival rate is also not significantly different (see Figure 132.)

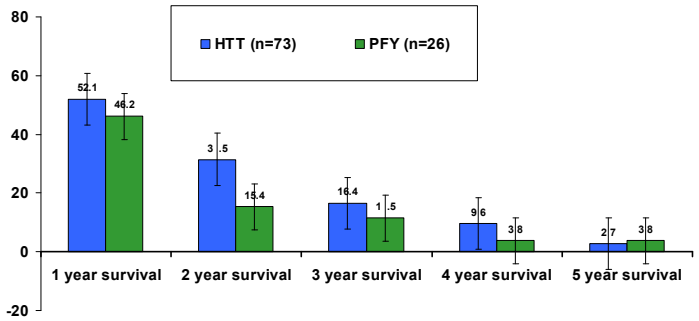

Figure 132. The yearly survivals are well corresponding in the two studies

The results could be well compared to the available SEER [**6**] and Eurocare-3 **[7]**. data. The comparison of the yearly survival rate is shown in Figure 133. The gain of the first few years is obvious, while the difference gradually vanishes approaching the 5th year. The reason is the difference of the treated patients. When the patient has a long survival, His/Her oncothermia treatment starts only at the end of the available conventional treatments; the patient receives oncothermia only in a small fraction of His/Her survival time, therefore the survival time does mostly not depend on the end-application of oncothermia. While in case of the short survivals a considerable lifetime depends on the oncothermia application.

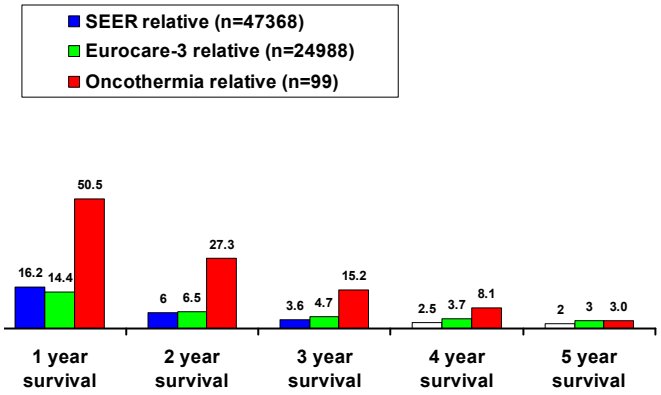

Figure 133. The comparison of the results with SEER and Eurocare-3 data in first five years survival-rate (%)

The parametric evaluation of the united studies (metaanalysis) shows accurate fit of the Weibull function for the elapsed time from the first diagnosis to the first oncothermia, (see Figure 134.); which indicates the homogeneity of the inclusion of patients in the study.

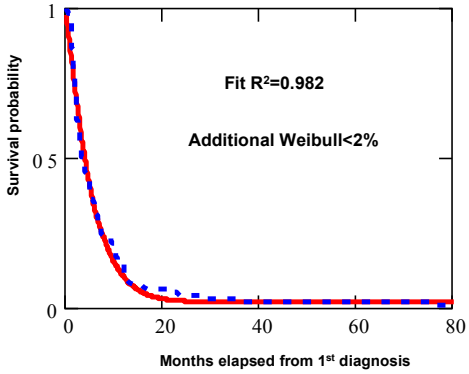

Figure 134. The proper cohort construction is supported by the proper fit of a single Weibull on the elapsed time from first diagnosis to first oncothermia. (The additional Weibull correction is only 2%.)

The parametric division to find the group of responders shows only 40%, and significantly differs from the non-responders, (see Figure 135.).

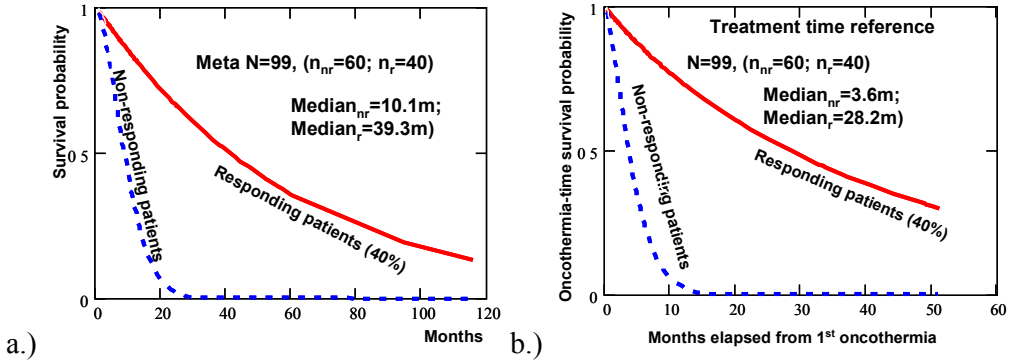

Figure 135. The parametric division of the survival curves for overall survival (a) and for oncothermia survival (b)

Pancreas efficacy study III.

A strong evidence of oncothermia application is shown by Clinic St. Georg (Bad Aibling, Germany) and published in two subsequent papers [101], [102]. Distribution of the n=30 patients by their age is shown on Figure 136. The aggressive, mostly even palliative inoperable patients were treated in second line. The first line treatment was chemotherapy (see Figure 137.). The oncothermia was concomitantly applied with Mitomycin-C (8mg/m^2; 1-5 days) + 5-fluorouracil (5-FU, 500 mg/m^2) + Leukovorine (calcium folinate, 200 mg/m^2). Oncothermia was applied on treatment days 1, 3, 5, and 10 for 60min each. The equivalent temperature of the targeted tumor tissue was 42-44 °C over 90% of the treatment time. Oncothermia treatment was repeated every 4 weeks until next progression.

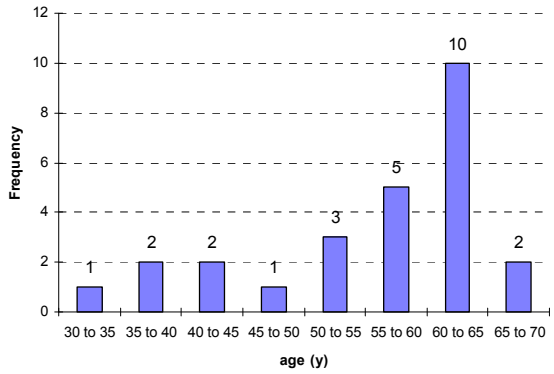

Figure 136. The age distribution of the patients involved in the study

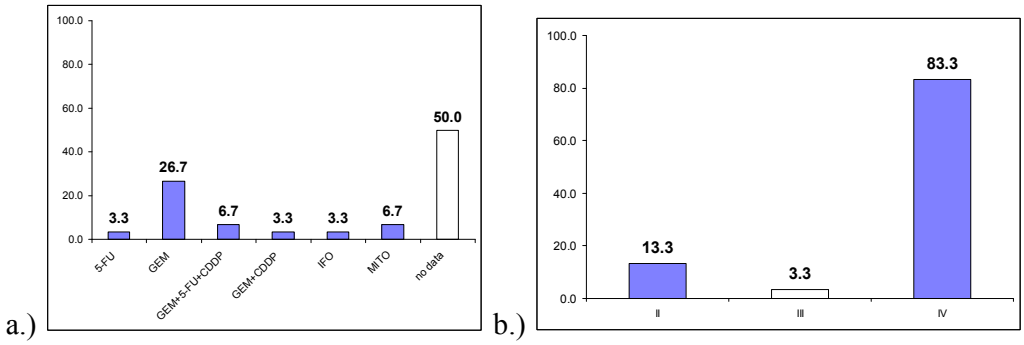

Figure 137. The pretreatment chemotherapies (a) and the stages at the first oncothermia treatment (b) of patients involved in the study

The local clinical response was high in the cases of stage IV patients (see Figure 138.).

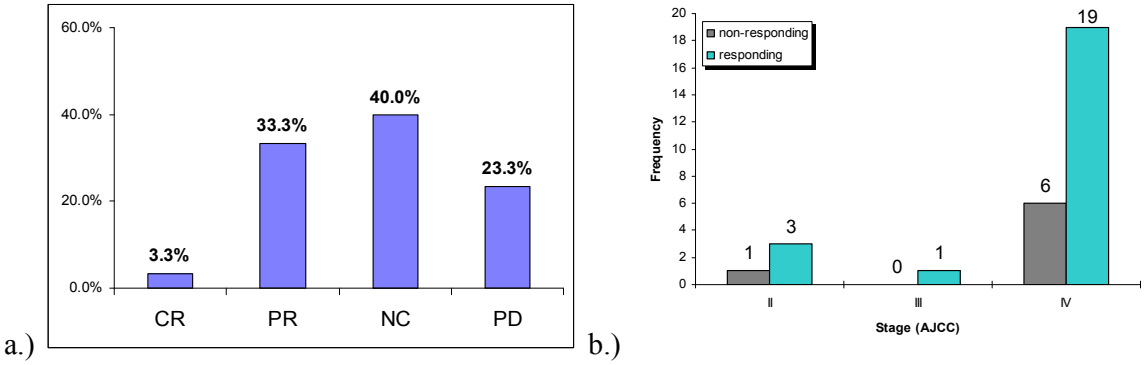

Figure 138. Local clinical responses (a) and their distribution by stages ("responding"=CR+PR+NC; "non-responding"=PD) of the patients involved in the study (b)

The progressive disease (PD) local response was observed at the cases, when only 1-2 oncothermia treatment was made, (see Figure 139.).

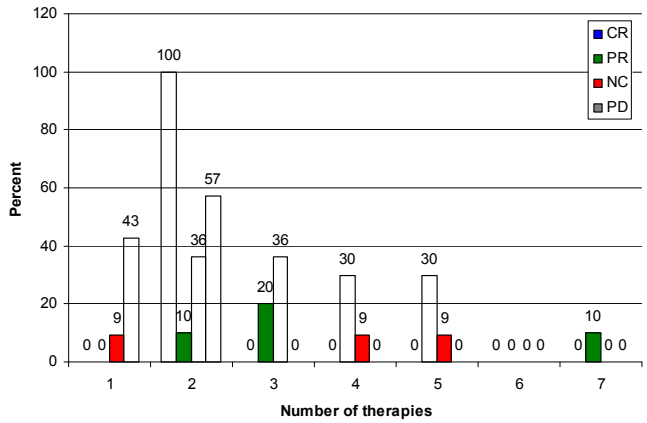

Figure 139. Local response by the number of oncothermia treatments. (Percentages of categories. PD occurred only at low treatment numbers.)

The survival time form the first oncothermia treatment (median 7.5m, mean 13.05m) and its parametric separation for responders and non-responders is shown on Figure 140. (The overall survival time has no complete data-set for its exact evaluation.)

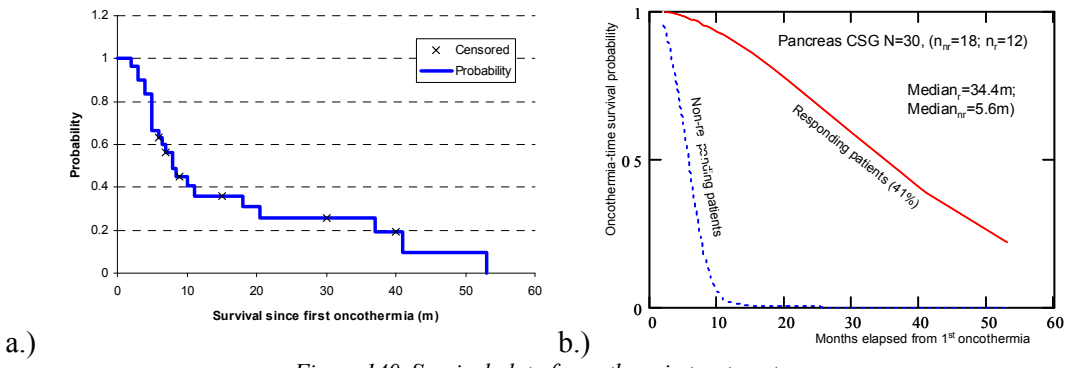

Figure 140. Survival plot of oncothermia treatment

Calculating the direct response (CR+PR) shows good correspondence with the parametric separation (see Figure 141.).

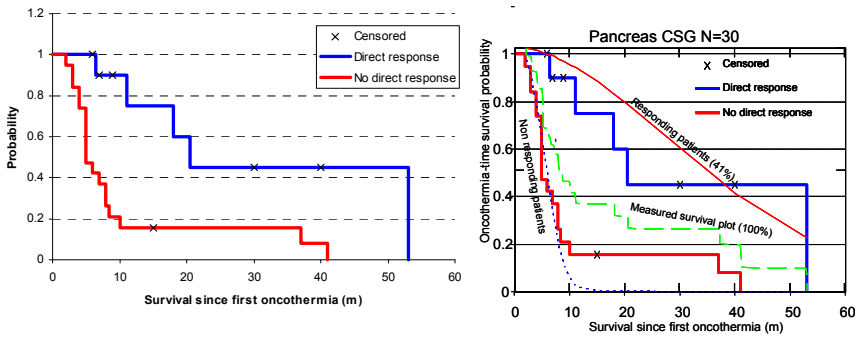

Figure 141. Significant correspondence of the measured and calculated separation of the patient's survivals by their local response

It is interesting to see the prognostic value of the CA-19-9 tumor marker. It is division of the patients for responders and non-responders makes a little more positive information than the real clinical response, but its difference is far not significant (see Figure 142.). The median of the two curves only slightly different, but the longer survivals (counted to the mean values) have definite differences.

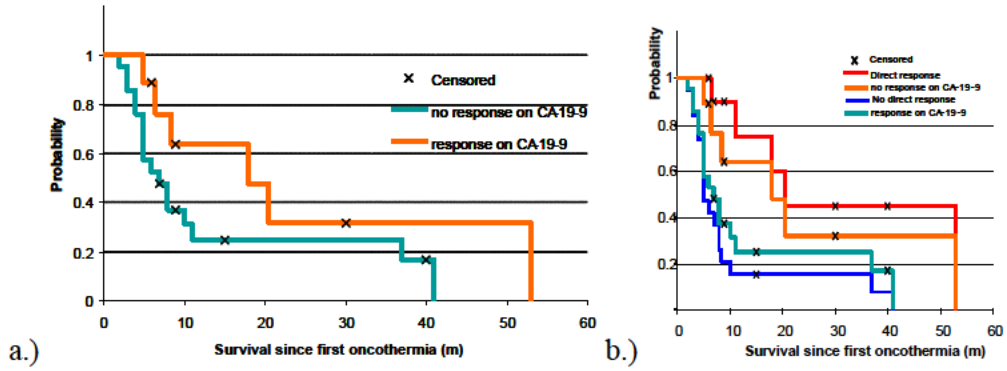

Figure 142. The prognostic value of CA-19-9 tumor-marker in the present pancreas study. The survival is significantly separated to responders and non-responders on CA-19-9 (a). In comparison with the local clinical response separation, (b), the tumor-market is a little more optimistic, but not significantly

The usual toxicity counted by labor-values is shown for Hemoglobin (anemia) and for leukocytes by the response reactions, see Figure 143. Interesting the high-grade toxicity has good response rate. Even more emphasized this tendency on the thrombocytes, where the only normal values had no-response on the oncothermia therapy, see Figure 144.

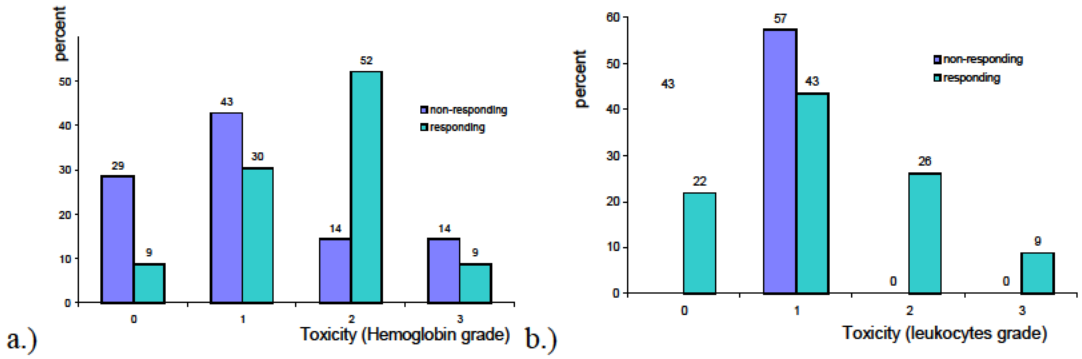

Figure 143. The haemo-toxicity of the patients by their responses, Hemoglobin (a) and Leukocytes (b)

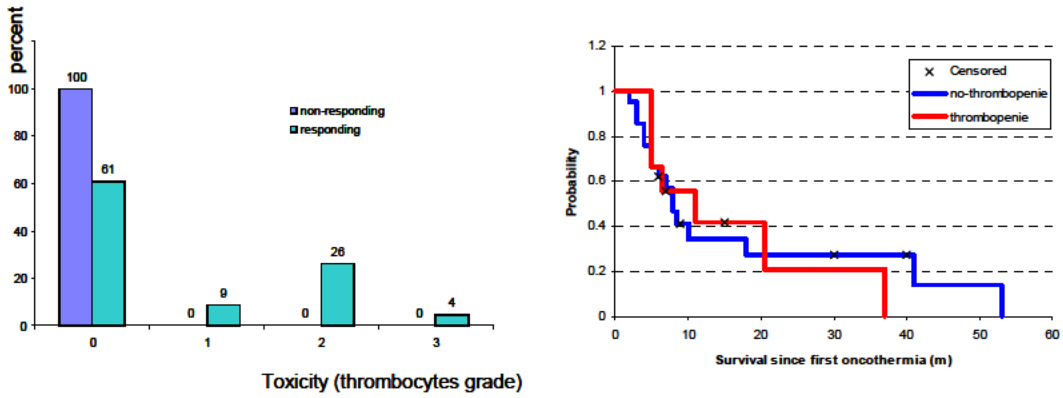

Figure 144. The thrombocytes correlating well with responses. Interestingly the no-thrombocyte-toxicity has only patients with no-response (a) but the survival has no significant difference (b)

Pancreas efficacy study IV.

An other additional retrospective oncothermia trial (n=42) was performed by VeraMed Clinic, (Investigator: Dr. M. Kalden) **[58]**. The trial included heavily pre-treated, advanced stage pancreas carcinoma cases, see Figure 145.

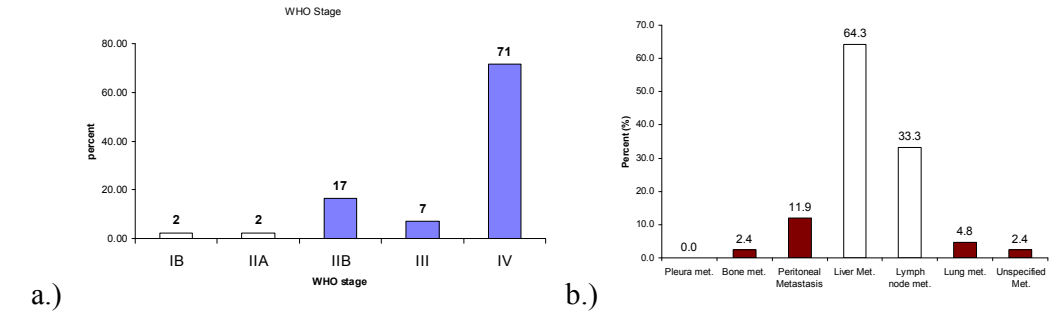

Figure 145. The stage distribution of patients at the first oncothermia treatment (a) and the status of metastases (b)

The local clinical response had no complete remission, but all together it was over the half of the patients (54.8%), see Figure 146. The importance of the multiple oncothermia treatments in these cases is proven by the remission-distribution.

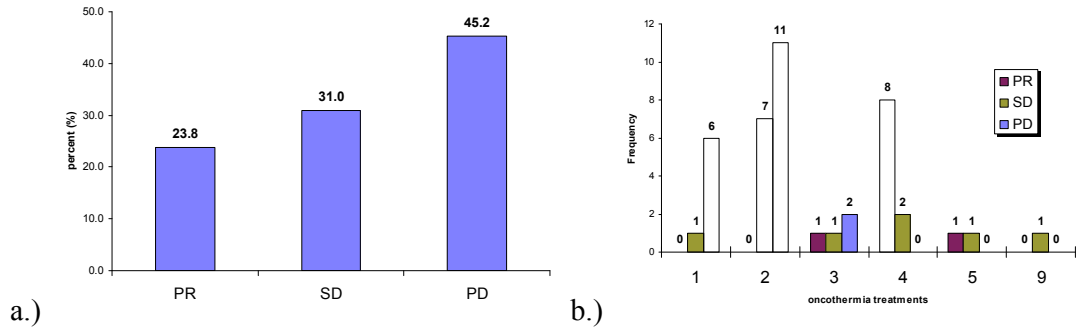

Figure 146. The local clinical response of the patients (a), and their response by the number of oncothermia treatments (b)

Both the overall and oncothermia survivals support the previous studies (see Figure 147.). The overall survival is well distinguishable by the local remissions, but not significant (p>0.3), see Figure 148. The parametric evaluation has again good and significant correspondence with the measured data, see Figure 149.

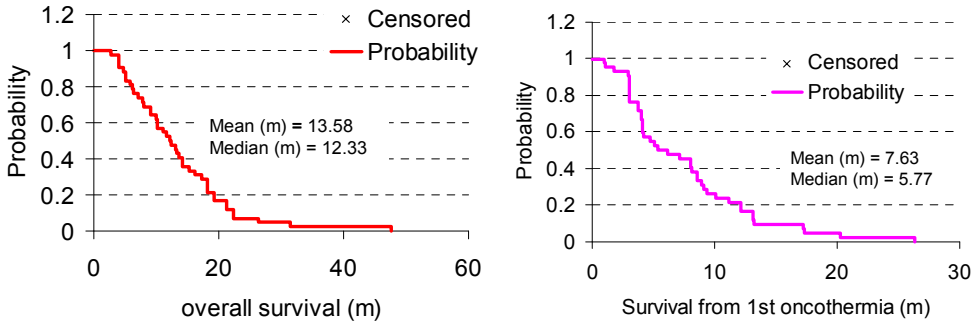

Figure 147. Overall (a) and oncothermia (b) survivals of the additional retrospective study (n=42)

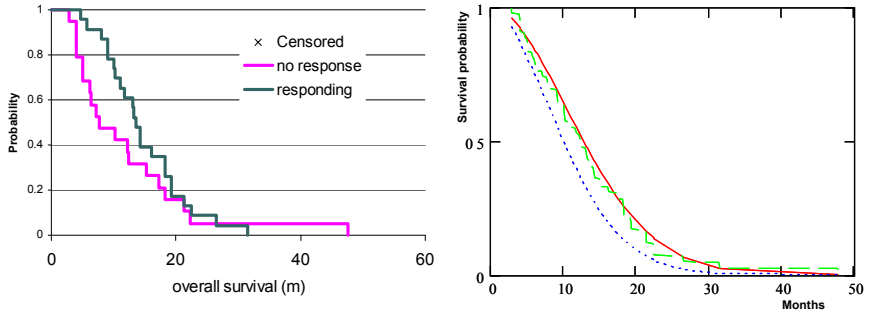

Figure 148. The overall survival by local clinical response (a) and its parametric evaluation form the original survival curve (see Figure 147.) [the dashed line is the original, the thin solid and dot lines are the decomposed plots], (b)

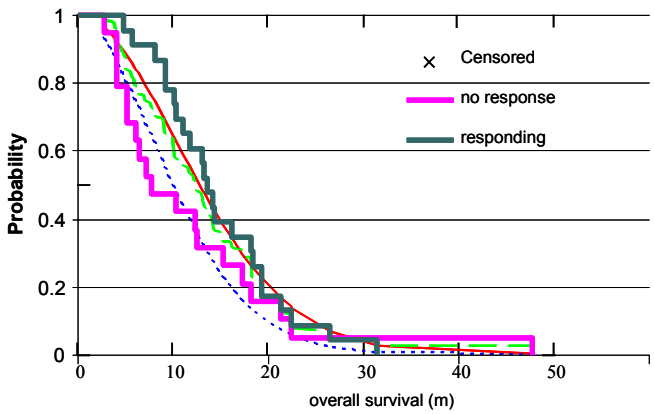

Figure 149. Comparison of the plots of Figure 147. The acceptable fit of the real and theoretical decomposition is demonstrated

Other oncothermia pancreas studies and their comparison

Additional clinical results for oncothermia therapy for pancreas carcinoma could be cited. One of these is made in Praxis Klinikum Nord, Nürnberg, Germany [referred as PKN], (n=13) **[59]**. (Investigator: Prof. Dr. H. Renner & I Albrecht). They used trimodal therapy {RT+CHT+OTH}, [CHT=Gemzar]. The trial showed median survival 11.9 m (4.4-211.4), mean survival 29.2 m (std.Err.15.35). Its overall survival plot is shown in Figure 150.

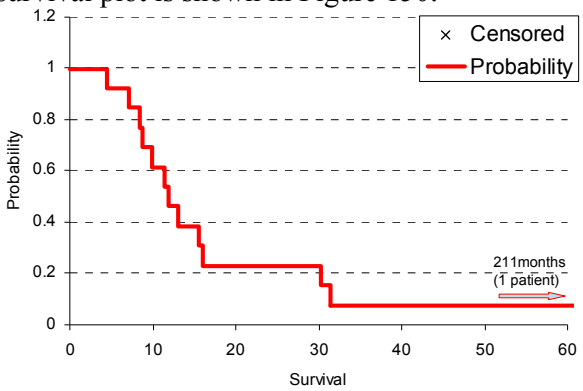

Figure 150. Kaplan-Meier survival plot of trimodal therapy of pancreatic cancer

For clear evidence of the results let us compare the first year survivals and the median survivals obtained in various clinics in comparison to the historical control and the large databases. The result is shown on Figures 151. and 152. The result convincingly demonstrates the significant difference between the oncothermia and the general retrospective data.

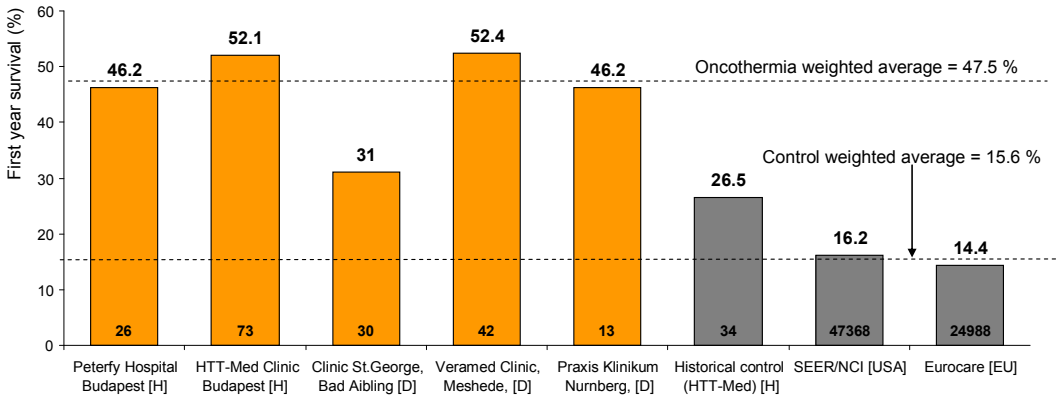

Figure 151. Comparison of the first year survival-rates (%) in various clinics. (The number of the patients involved in the study is shown at the bottom of columns.)

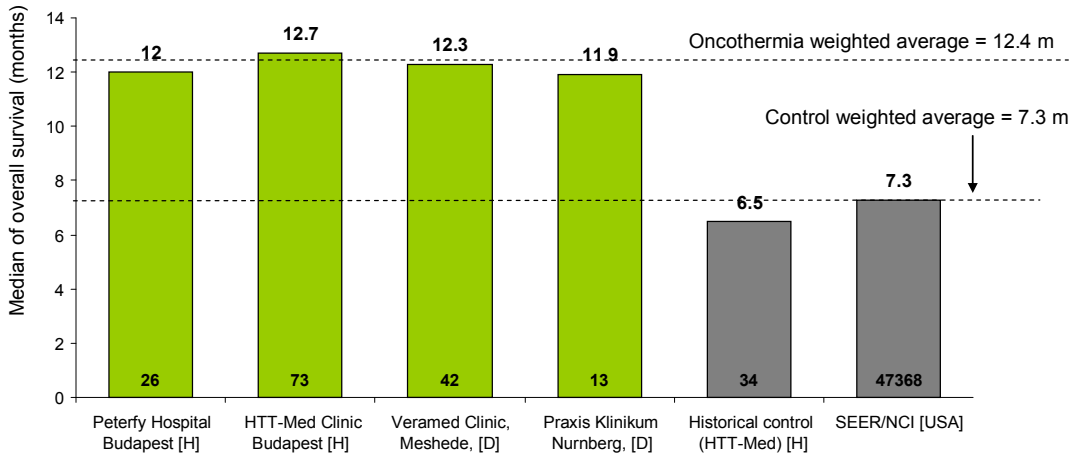

Figure 152. Comparison of the median of overall survival (months) in various clinics. (The number of the patients involved in the study is shown at the bottom of columns.)

Prostate study

Advanced prostate cancer was studied (n=18), **[31]**. (HTT-Med Clinic, Budapest, Hungary. Investigators: Dr. I. Philip.) The medians are 38.8m and 10.9m (mean 46.5m and 14.4m) for overall and oncothermia survivals, see Figure 153. Oncothermia was applied weekly 2-3 times 10-12 treatments with 20 cm diameter electrodes.
First year survival rate for oncothermia was 88.9%, (In comparison the SEER and Eurocare data are 85.9% and 82.7%, respectively.)

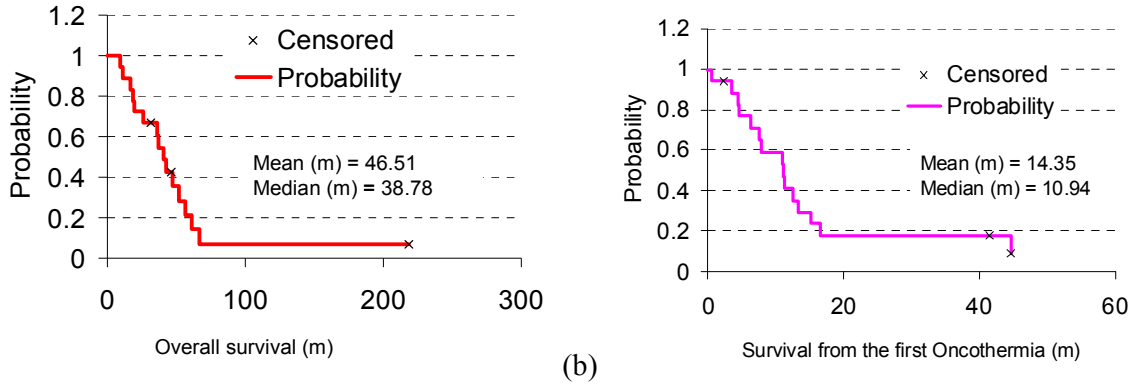

Figure 153. Overall (a) and oncothermia (b) survivals

The parametric decomposition shows medians 42.0m and 22.6m for responders and for non-responders, respectively, see Figure 154. The responders by the parametric decomposition had high percentages, 72% (n_r=13) of the total treated patients (n=18).

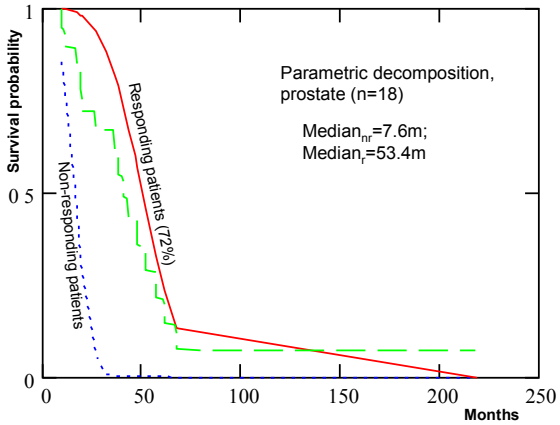

Figure 154. Parametric decomposition of the prostate survivals for responders and non-responders for oncothermia treatment

Soft-tissue malignancies

Advanced soft-tissue cancer was studied (n=16), **[31]**. (HTT-Med Clinic, Budapest, Hungary. Investigators: Dr. A. Varkonyi & Dr. A. Dani.) The medians are 35.9m and 13.3m (mean 46.8m and 16.3m) for overall and oncothermia survivals, Figure 155. Oncothermia was applied weekly 2-3 times 10-12 treatments with 20 cm diameter electrodes.

The parametric decomposition shows medians 115.3m and 31.3m for responders and for non-responders, respectively, see Figure 156. The responders by the parametric decomposition is 31% (n_r=5) of the total treated patients (n=16).

First year survival rate for oncothermia was 100%, (In comparison the SEER and Eurocare data are 76.7% and 77.7%, respectively.)

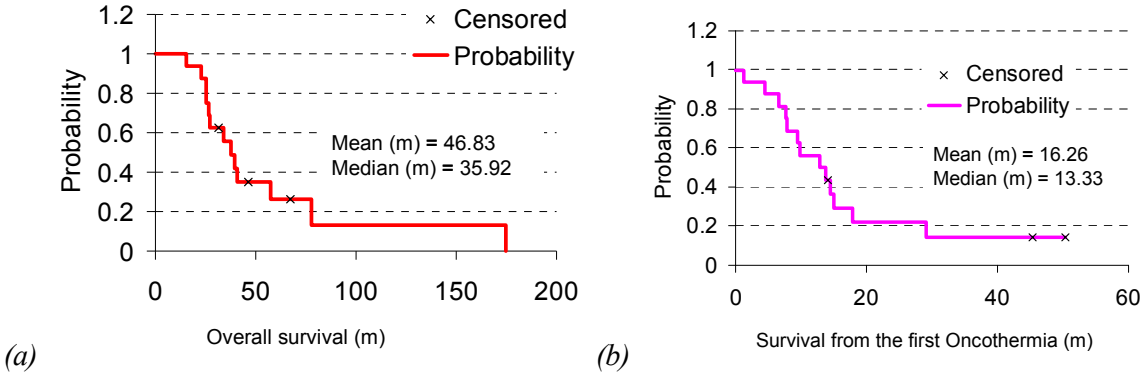

Figure 155. Overall (a) and oncothermia (b) survival plots

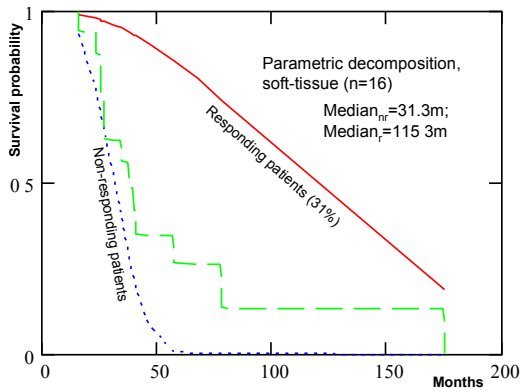

Figure 156. Parametric decomposition of overall survival for responding and non-responding patients

Stomach study

Advanced stomach cancer (n=68) was studied in bicentral study (HTT-Med Clinic & Peterfy Hospital, Budapest. Investigators: Dr. T. Magyar, Dr. A. Varkonyi & Dr. A. Dani.) **[31]**. The median survival time is 14.4m (mean 20.5m), while the median time from the start of oncothermia therapy was 4.8m (mean: 9.6m), see Figure 157. Oncothermia was applied weekly 2-3 times 8-10 treatments with 20 cm diameter electrodes.
First year survival rate for oncothermia was 58.8%, (In comparison the SEER and Eurocare data are 39.7% and 40.2%, respectively.) In the second year survival the difference between the data base registered data and the measured by oncothermia became shallow (oncothermia: 29.4%, SEER 23.8%, Eurocare: 27.8%). In the comparison of the two places the difference is significant, but these are also significantly differ from the large databases, see Figure 158.

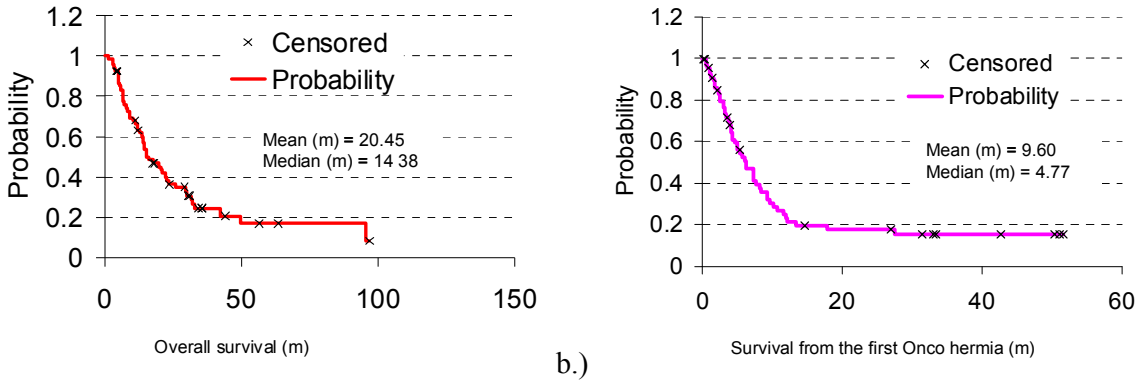

Figure 157. Survival plots for overall (a) and for oncothermia (b) results for stomach

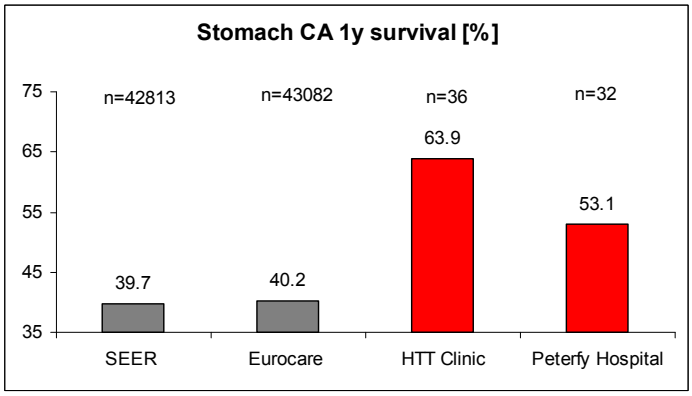

Figure 158. Comparison of the first year survivals from the two places and the large databases

Urinary bladder malignancies

Advanced urinary bladder cancer was studied (n=18), **[31]**. (HTT-Med Clinic, Budapest, Hungary. Investigators: Dr. A. Varkonyi & Dr. A. Dani.) The medians are 36.5m and 9.9m (mean 47.2m and 20.2m) for overall and oncothermia survivals, see Figure 159. Oncothermia was applied weekly 2-3 times 10-12 treatments with 20 cm diameter electrodes.
The parametric decomposition shows medians 42.0m and 22.6m for responders and for non-responders, respectively, see Figure 160. The responders by the parametric decomposition had high percentages, 73% (n_r=13) of the total treated patients (n=18).
First year survival rate for oncothermia was 85%, (In comparison the SEER data is 81.5%.)

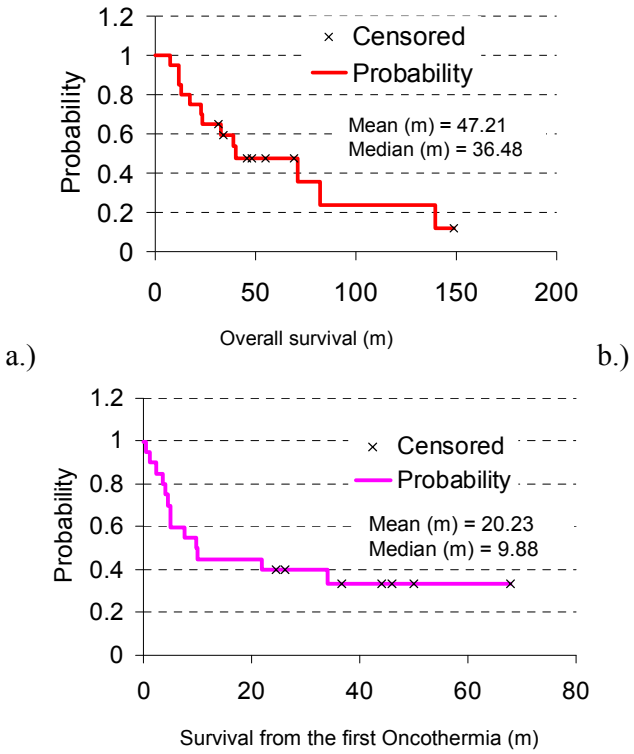

Figure 159. Kaplan-Meier plots for overall (a) and oncothermia (b) survivals

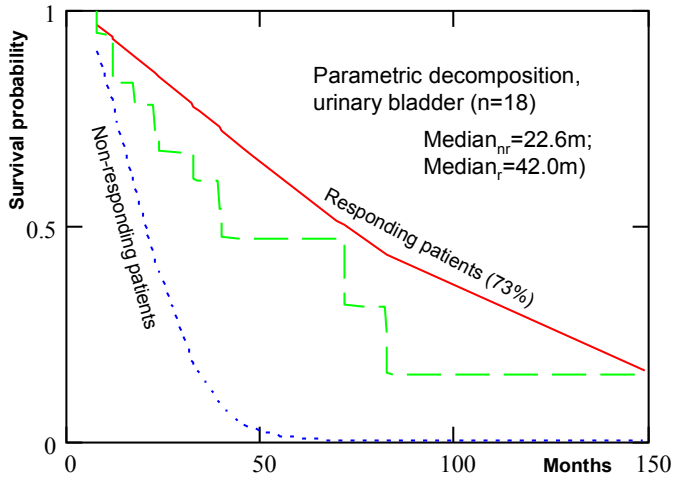

Figure 160. Parametric decomposition of urinary bladder overall survival curve

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