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Clinical study for advanced non-small-cell lung cancer treated by oncothermia

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Abstract
The non-small-cell-lung-cancer (NSCLC) is a common malignant tumor. We present two retrospective clinical studies for NSCLC done by two medical centers (HTT-MED Day-clinic and Peterfy Hospital). Both of the centers made the treatments by oncothermia in combination with the conventional tumor-therapies. We present the data from both of the centers and make a metaanalysis as well. Results show a remarkable survival benefit for the patients compared to the historical data. The comparison of the studies demonstrates a good correspondence in the data, which strengthens the reliability of the studies, and greatly points out the feasibility of the oncothermia application on the NSCLC.

Key words: non-small-cell lung-cancer, clinical-study, hyperthermia, oncothermia, survival-time, comparison.

Introduction, objectives

Modern lung-cancer treatment is based on platinum-containing doublets (Carboplatin and Cisplatin) and more recently Gemcitabine, Taxol (Paclitaxel and Doxitaxel), Vinorelbine and Navelbine. Analysis of 52 clinical studies show the advantages of the cisplatinum based therapies (10% 1y survival increase), which reduce the risk of exitus by 27%, [1] compared to the applied supportive therapies.
The Gemcitabine-based triplets and doublets (Paclitaxel/Carboplatine/Gemcitabine; Paclitaxel/Carboplatine/Vinorelbine; Paclitaxel/Gemcitabine; Gemcitabine/Vinorelbine); had 37%, 29% 40% and 49% for one year survival and 9.6, 9.9, 8.7, 10.7 month median survival, respectively, [2]. The Gemcitabine-based doublets had better lower response rate, but longer survivals and less adverse effects.
In general, the median survival ranges between 6 and 12 months, with 7 in average. The one year survival is 24-51 %, 25-30 % in average.
Despite the well developing results, ration of the lung cancer incidence to mortality rate (0.8) is more than double of the average incidence/mortality ratio (0.3) among the <65 y population. [3]. The incidence rate of the lung cancer between the ≥65 yrs and <65 yrs old patients exceeds 14. Furthermore, lung cancer is one of the leading mortality causes for humans.
Our present paper indicates the feasibility of the oncothermia treatment of NSCLC. The study concentrates on the significance of the survival time as one of the most important factor to measure the success of a treatment in oncology.
Hyperthermia (HT), combined with radiotherapy (RT) and chemotherapy (CT), seems to be a promising method for cancer treatment, although many of the underlying molecular mechanisms of this combination treatment are not clearly understood even today. A great number of studies show that HT inhibits angiogenesis, enhances chemo- and radio-sensitivity and induces a high concentration of drugs within a tumor [4], [5].
However, there are some restrictions for HT in general, that hamper its use in lung cancer treatment. Namely, it could aggravate preexisting pleural liquids.
Some successful clinical trials had shown the feasibility of the hyperthermia method for lung cancer. Most of these are combined with radiotherapy, having 14÷70 Gy dose in the given session. The measured response rate (RR) was surprisingly high RR=75%, (n=12, [6]), and RR=100% (n=13, [7]). Others had a comparison to a control-arm (not randomized), growing the RR from RR=70% (n=30), and RR=53.8% (n=13), to RR=94.7% (n=19, [8]), and RR=76.9% (n=13, [9]), respectively.

The second year survival also increased remarkably: from 15% and 15.4% to 35% and 44.4%, respectively. (The first year survival was measured as well, increasing from 30% to 55%.
The chemo-thermotherapy combination was also investigated for NSCLC with success. In preclinical trials the cisplatine was shown to be effective, [10], so the clinical studies were concentrating on this drug combination. Special case report has shown the feasibility [11], and the median survival gain (from 15 (n=20) to 25 (n=32) months), [12]. The median survival was measured in another study [13], as 19.2 months, the RR=73% and the 1 year-survival is 75%. The 5y median survival was measured in another study [14], showing rather high numbers (24.5%, n=30).
One of the most advanced HT-modalities devoted to oncology is oncothermia (OT). In the preliminary reports [15], [16], [17] the feasibility of the OT application was demonstrated.
Our objective in this article is to present a retrospective clinical study for NSCLC patients, treated/followed from October 9, 1997 to December 10, 2003.
With this present paper, we would like to study the feasibility of OT for NSCLC, and its effect on the survival times. Although the retrospective data are only indications, the prospective, randomized, controlled study should clarify the situation. We present data from two study-places, showing their similar results, and we compare our data to the large databases (SEER and Eurocare).

Method

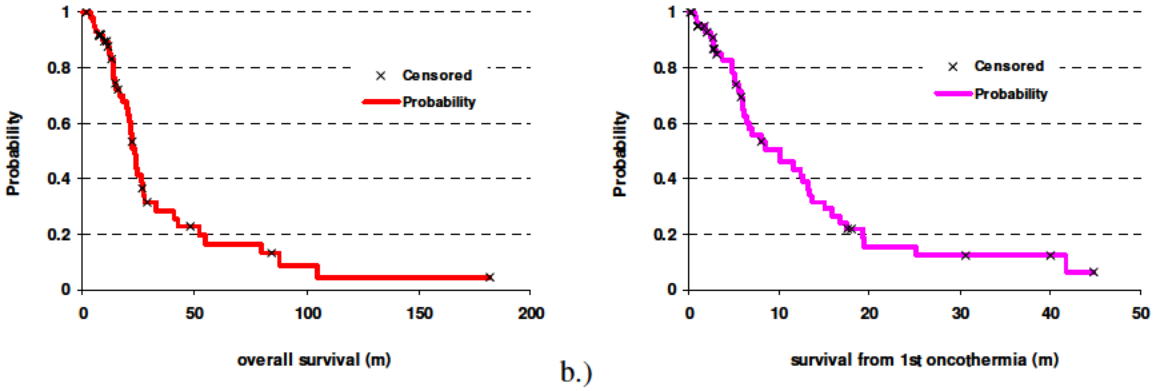
The provided results are obtained from an open-label, single-arm, monocentric, retrospective study. The involved patients are analyzed according to an intention-to-treat (ITT) schedule. Recruiting time was from April 1997 to August 2002, altogether 64 months. The primary endpoints of the study were the overall survival time (OS) and the survival time from the first oncothermia treatment (overall survival oncothermia treatment time, OSO). 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) Karnofsky Performance Score (KPS) > 40% and the inclusion was irrespective of the localization of the lesion in the pancreas. 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 evaluation-methods were: descriptive biostatistics, log-rank survival tests (Kaplan-Meier plot), and comparison with large studies and databases and/or local historical data. Data were collected independently from two hospitals. One of them is the Peterfy Hospital, Budapest (PFY). It is a governmental hospital involved in the regular health-service network. The other is a private day-clinic (Htt-Med Polyclinics, Budapest, (HTT)), serving the patient only on a private, out-patient basis. The two trial-places were in information-contact, providing the treatments with the same practical conditions and guidelines.
The study had a couple of possible negative biases: (1) the treatment is paid or co-paid by the patients, who undergo it on a voluntary basis (intention-to-treat, ITT). All the process was under strict control by the oncologist who was responsible for the patient treatment till that time; (2) no randomized control arm exists; the trial is compared to available literature, large databases and to historical data. The reliability of the trial is checked by comparison of the independent hospital retrospective collections.
Nevertheless, the present study has a few possible positive biases as well: (1) patients are treated in their advanced stages, when other treatments had failed and/or are not possible; (2) the involved hospitals are engaged in the regular health-care system, they are not as well-equipped as the special institutes/universities; (3) the involved patients had no extra “trial-attention”.
The used device was EHY2000 (OncoTherm), capacitive coupled (oncothermia, OT). It works on 13.56 MHz, which is time-domain (fractal) modulated, with 40-150 W power absorbed by the tumor.

The treatment control was made by the absorbed energy [kJ], which was converted to the equivalent temperature [T]. The calculated average equivalent temperature in the tumors was above 40 °C in more than 90% of the treatment time. For further details of the method we would like to refer to ([18], [19], [20]) where it is explained in detail. The reality, the energy together with the increase of the temperature is basically used for the distortion of the structures, change of the chemical bonds and compensation of the physiological regulations [21], [22]. OT 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.

Results

Hospital Peterfy (PFY) (n=61)

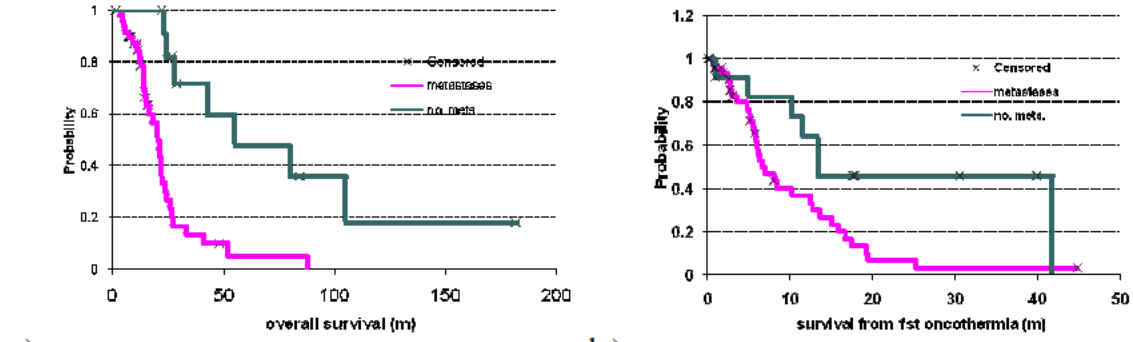
The age-distribution of n=61 patients was near to normal (p=0.82); no outlier was present. The median age was 58 y (38 - 77), the mean-age was 58.97 y (Std.err= 1.17). The gender distribution was 21/40 female/male (34.4/65.6 %). The ratio of the elderly (>68 y) patients were 21.3%.
Most of the patients (49, 80.3%) had distant metastases. They were heavily pretreated; everybody received at least one chemotherapy and 28% had surgery, 36% received radiotherapy.
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 (OS) (median 16.4m, [1.7-181.9]; mean 25.6m, [st.err.3.8]) and the survival from the first oncothermia treatment (OSO) (median 5.7m, [0.1-44.9]; mean 9.2m, [st.err.1.3]) are shown in Figure. 1. For elderly patients neither the OS nor the OSO was different (p~0.68).



a.) b.)

Figure. 1. 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 OS and OSO, respectively), see Figure. 2.



a.) b.)

Figure 2. OS (a) and OSO (b) survivals of the patients with metastases

The elapsed time to the first oncothermia (ETO) shows an important parameter. Namely, the ETO 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 OS and OSO depending on the ratio of the ETO to the OS, dividing the patients to the "early OT" and "late OT" categories, depending on whether their ETO/OS ratio is below or above the median of the data-set. The OS 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 OSO 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 OS significantly (p=0.61), but the OSO (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 3.

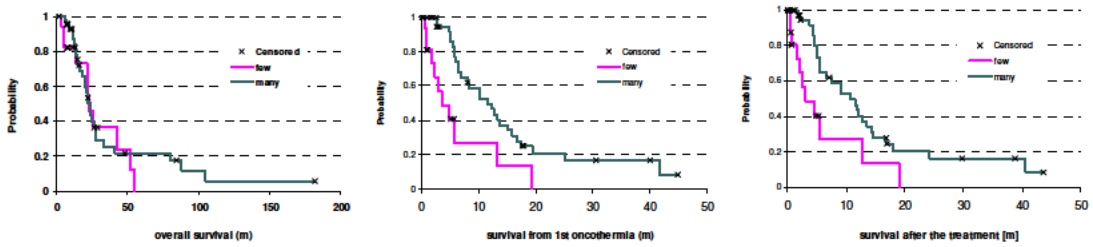


Figure 3. The various survival times for patients depending on the treatment session time. ("few" lower than the median number, "many" higher than the median number of the treatments).

Interestingly, the surgical pretreatment was especially (p=0.0005) important for the longer survival (see Figure 4.), but the other pretreatments did not affect significantly neither the OS nor the OSO survival rates.

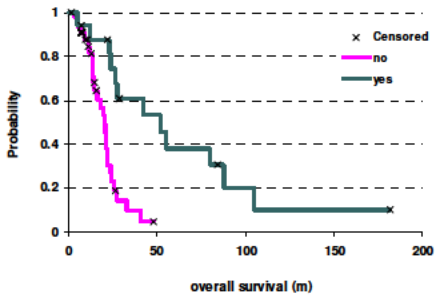
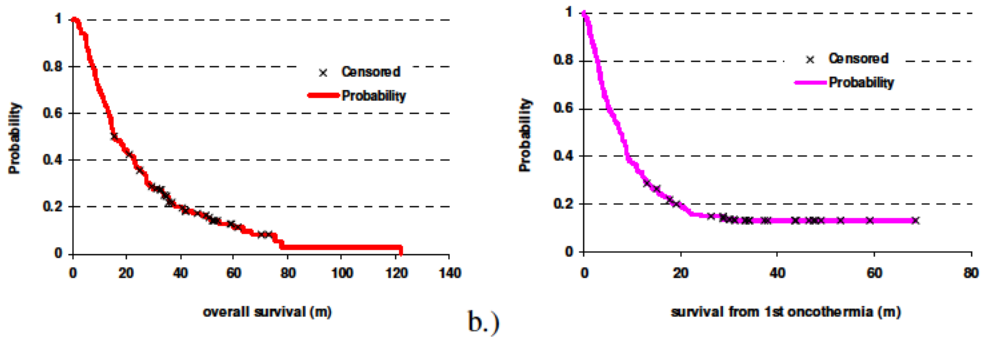


Figure 4. Effect of the pretreatment operation is significant considering the overall survival.

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}=33) the OS median 22.3m, (1.7-181) mean 33.7 (st.err.6.4); the OSO median 8.0m, (0.1-45) mean 11.6 (st.err.2.07); and the ETO 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: OS median 12.3m, (3.6-51.9) mean 15.9 (st.err.2.2); OSO median 5.0m, (0.1-25.1) mean 6.37 (st.err.1.24); ETO 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 OS (p=0.028) and ETO (p=0.012), but not significant in OSO (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.

Htt-Med Polyclinic (HTT) (n=197)

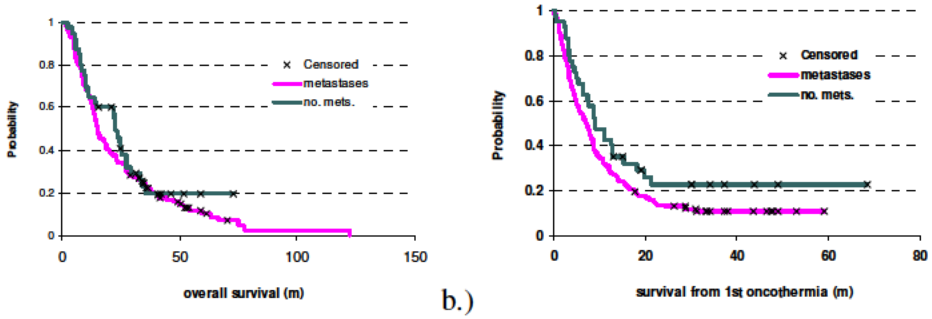
The age-distribution of n=197 patients was acceptably normal (p=0.59); no outlier was present. The median age was 57 y (16 - 84), the mean-age was 56.71 y (Std.err= 0.77). The gender distribution was 62/135 female/male (31.5/68.5 %). The ratio of the elderly (>68 y) patients were 20.3%.
Most of the patients (157, 79.7%) had distant metastases, (one two and three metastases were observed for 101, 43 and 13 patients, respectively). They were heavily pretreated; most of them (93.4%) underwent surgery and subsequent radiation-therapy (49%).
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 (OS) (median 15.6m, [1.1-122.1]; mean 22.4m, [st.err.1.31]) and the survival from the first oncothermia treatment (OSO) (median 7.57m, [0.1-68.6]; mean 11.8m, [st.err.0.91]) are shown in Figure 5. For elderly patients neither the OS nor the OSO was different (p~0.37 and p~0.49, respectively).



a.) b.)

Figure 5. 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 OS and OSO were not significant (p=0.33 and p=0.07 for OS and OSO, respectively) Figure 6.



a.) b.)

Figure 6. The effect of metastases on the OS (a) and OSO (b) survivals for HTT patients

The number of treatments significantly influences the OS (p=0.048) and the OSO (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 OS (p=0.005) and OSO (p=0.016) (see Figure 7.), but the other pretreatments did not affect significantly neither the OS nor the OSO survival rates.

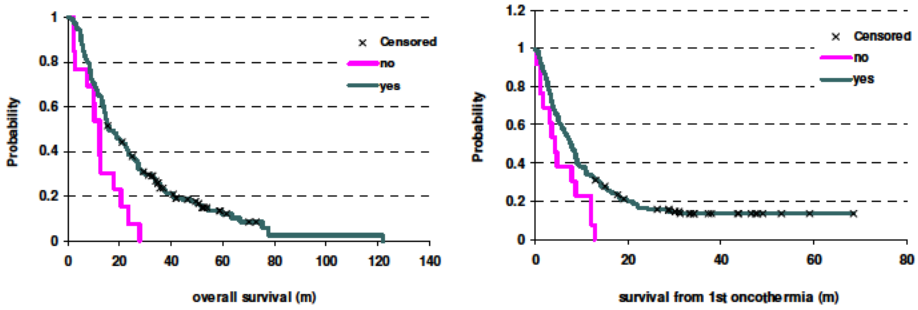


Figure 7. Effect of surgical pretreatments on the OS (a) and OSO (b) survivals

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 OS median 15.3m, (2.4-122.1) mean 24.0 (st.err.2.17); the OSO median 7.2m, (0.3-68.6) mean 11.8 (st.err.1.5); and the ETO median 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: OS median 15.83m, (1.1-77.7) mean 21.0 (st.err.1.5); OSO median 8.13m, (0.1-43.9) mean 11.8 (st.err.1.1); ETO 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 OS (p=0.85), OSO (p=0.17) and ETO (p=0.21).

Comparative-analysis

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 little shift to the elderly patients was present. 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 %).
80% of the patients had distant metastases in both study-places (see Figure 8.) and half of them was in advanced stages at the first diagnosis of the disease (see Figure 9.). Patients were heavily pretreated (see Figure 10.), in PFY the chemo-therapy, in HTT the surgery was the most frequent modality.

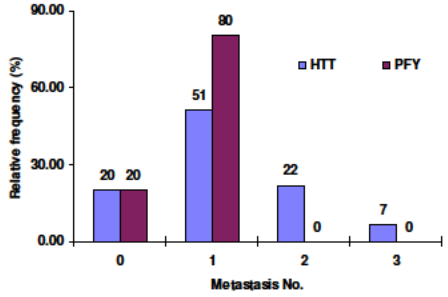


Figure 8. Comparison of metastatic cases

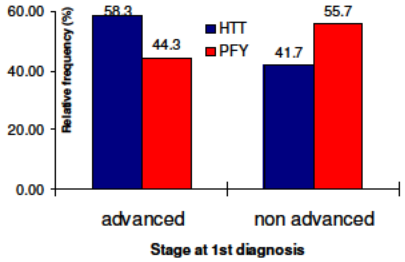


Figure 9. Staging differences

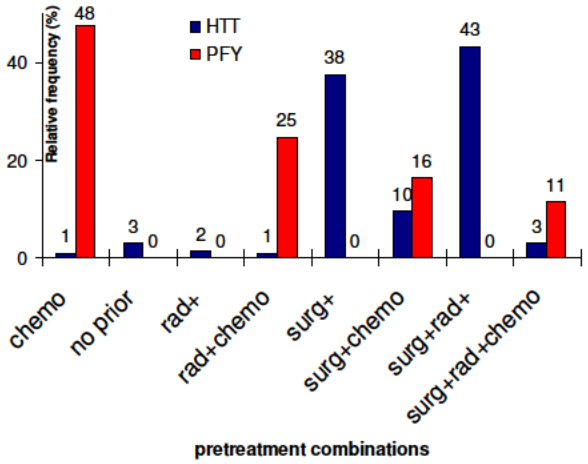


*Figure **Error! Bookmark not defined.**. Pretreatment combinations show the different emphases in the treatment strategies*

The median elapsed time to 1st oncothermia from the first diagnosis (ETO) was significantly (p=0.028) shorter in HTT than in PFY, see Figure 11.

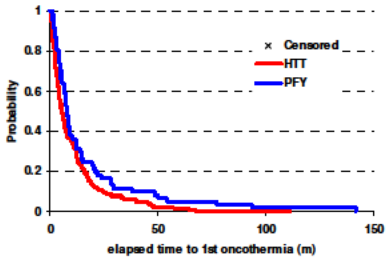


Figure 11. Elapsed time to first oncothermia is significantly shorter for HTT patients

The oncothermia treatment was provided twice a week, the number of treatments in average was 8.1 at PFY and 7.9 in HTT procedures.

The OS is significantly lower in HTT case (p=0.044) but in the OSO 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 OS nor the OSO was different (p~0.38 and p~0.86, respectively).
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.

Discussion

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' pretreatments were mostly dominated by surgery and chemo-therapy in HTT and PFY, respectively. As well as the ETO was significantly different having earlier start of oncothermia in HTT, and surprisingly the OS 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 OS, the OSO does not differ significantly between the two places. The yearly survival rates could be regarded as identical (p>0.99) within the measurement error, (see Figure 12.). This could be indication of the oncothermia leveling action as well.

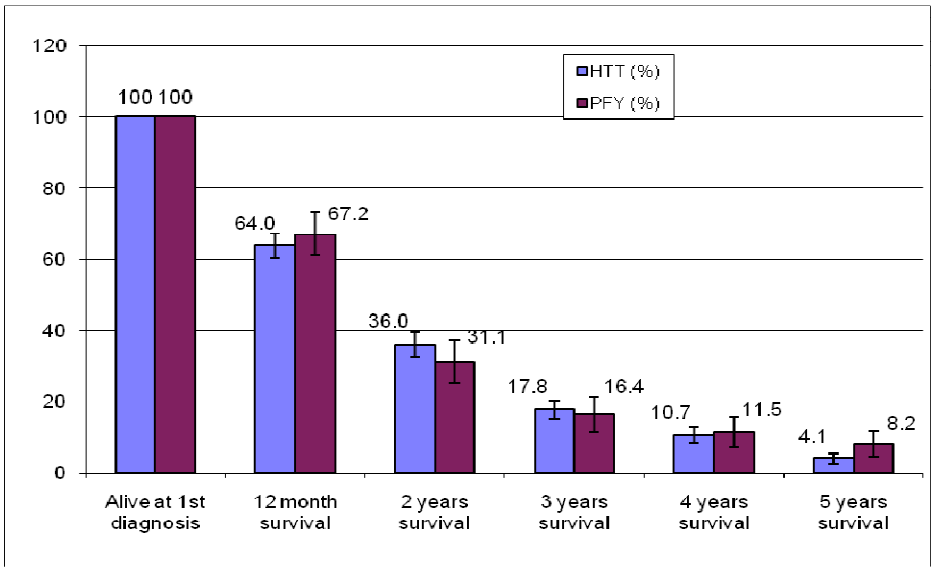


Figure 12. The yearly survivals of the patients in the two institutions. (no significant difference exists)

The results could be well compared to the available SEER [23] and Eurocare [24] data, see Figure 13.
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 ETO the survivals are not notably different in the two institutions.

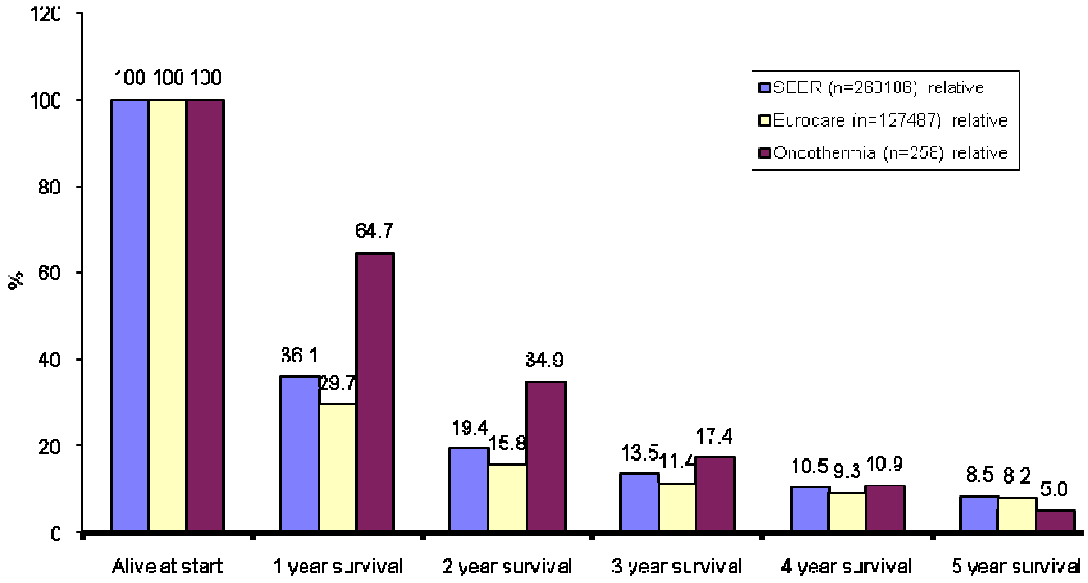


Figure 13. The comparison of the overall results with SEER and Eurocare data

We had collected a historical control (n=53) 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=0.0046) Figure 14. (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.

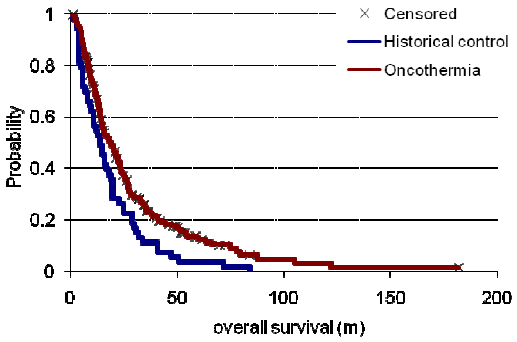


Figure 14. Kaplan-Meier plot for the historical and active arms in the study. The difference is significant

Conclusion

Our present paper showed strong indication of the oncothermia benefit by comparison of two independent retrospective studies with the method. According to the relatively large number of data (n=197 and n=61) of NSCLC patients, the oncothermia is feasible to treat advanced diseases. A comparison of the presently indicated data to the expected historical ones (n=53) and the data taken from the large databases (SEER and Eurocare3) shows a remarkable increase in overall and yearly survivals.

The results clearly indicate the feasibility and the benefit of the oncothermia treatment for NSCLC for a number of reasons:

1. Oncothermia was applied for NSCLC tumors, showing a valid treatment potential and safe application.

2. The survival time was increased by oncothermia for the patients making no benefit from other treatments.

Due to the limited effectiveness of established therapies, OT could be one of the important future methods to improve our treatment facilities. However, our present data are only retrospective indications of the efficacy of the oncothermia method. A prospective, randomized, controlled double-arm clinical study is needed for an evidence-based evaluation.

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