

Clinical study for advanced pancreas cancer treated by oncothermia

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Abstract

Pancreas cancer (PCA) is an aggressive, common malignant tumor. We present two retrospective clinical studies of PCA done in 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 centers and make a metaanalysis of the data as well. Results show a remarkable survival benefit for the patients compared to the historical data. The comparison of the studies shows a good correspondence in the data, which strengthens the reliability of the studies, and points out the feasibility of the oncothermia application on PCA.

Key words:

pancreas cancer, clinical-study, hyperthermia, oncothermia, survival-time, comparison.

Introduction, objectives

Pancreas cancer [PCA, (topographic ICD: C25)] is a very aggressive tumor, one of the major unsolved health problems of the present, [1]. The PCA is one of the most aggressive malignant disease with rapid progression-rate and short survival-time. Despite the massive efforts to find the adequate therapy, relatively low progress could be achieved in survival-rate of the disease.

The prognosis of the disease is extremely poor; only less than a quarter of the pati-

ents are operable, and less than a quarter of those survive to 5 years, and its incidence does not decrease in the past five years, [2]. Its gold-standard management is the resection, but most of the patients are unresectable, [3]. The radiation therapy is more palliative than curative, [4], [5]. This is the reason, why the chemotherapy in this disease has an especially important role. The subsequent reviews point out the importance of the adjuvant and neoadjuvant therapies, [6], [7], [8], and the Gemcitabine (Gemzar) + 5-fluorouracil + leucovorin combination had shown a remarkable efficacy [9], [10], [11], [12], table I.

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 properly understood yet. Although some widely accepted effects had been recognized: It has been shown that an increase in temperature can cause vasoconstriction in certain tumors leading to decreased blood perfusion and heat conduction, and also inhibit angiogenesis [60], [61], [62]. At the same time, the elevated temperature causes vasodilation in the healthy tissues, leading to its increased blood perfusion and heat conduction [63]. These effects functioning like an effective heat trap [64], selectively increase the temperature in the tumor [65]. Furthermore it has long been known that hyperthermia can cause softening or melting of the lipid bilayer [66], [67], [68], it can change lipid-protein interactions [69], and it can denature proteins [70]. All of these events

can significantly disrupt a tumor cell's capacity to divide. It is shown, that the increased temperatures cause a drastic change in transmembrane currents [71] and structurally alters the transmembrane proteins causing a change in active membrane transport and membrane capacity [72], leading to substantial changes in potassium, calcium, and sodium ion gradients [73], membrane potential [74], cellular function [75], [76], and induce thermal blocks of electrically excitable cells [74], [77]. Hyperthermia changes the pH values by increasing the biochemical reaction rates [78] and therefore also the metabolic rate. The lack of the oxygen for this forced metabolism results hypoxia [79] and the anaerobe metabolism produces lactate [80] and cell destruction by acidosis. Furthermore, the increased metabolism can significantly decrease the cellular ATP stores leading to increased cell destruction [80]. The DNA replication process is also altered by heat. The increased temperatures can slow down or even block DNA replication [81], [82], as well as stimulate the immune system [81], with observed increases in natural killer cell activity [83]. Moreover, the elevated temperature distributes tumor-specific antigens on the surface of various tumor cells [84] and assists in their secretion into the extracellular fluid [85]. It is important to mention for the clinical outcome the improvement in the quality of life due to the significant pain reduction [86], which can be prolonged and enhanced by the electric field using TENS effects [87]. This pain-reduction has special importance at such painful disease like PCA. Additionally, hyperthermia is an ideal combination therapy. It has low toxicity, mild side

Pts.#	RR (%)	1 y surv. (%)	Median surv. (m)	Ref.
16	25			[13]
16	25		5.25	[14]
36	14		4.4	[15]
163			5.4	[16]
164			6.7	[16]
12	25			[17]
16	31		9.6	[18]
54	3.7		7	[19]
34	17		5.7	[20]
26	19.3		8.5	[21]
24	8			[22]
52	31			[23]
44	13		6	[24]
48	9		6	[24]
28	29		8	[25]
24				[26]
24	38	2.5	6	[27]
12	8.3		8.5	[28]
41	11		8.2	[29]
26	19.2		10.3	[30]
27	7.4	22	7	[31]
42	5.7	28	6.5	[32]
29	10		4	[33]
25	8		9.6	[34]
62	25.9		9	[35]
64	29			[36], [37]
13	23			[38], [39]
11	9.1			[40]
19	0			[41]
24	35		9	[42]
23	34.7		9	[43]
38	5		9.3	[44], [45], [46]
24	13		7.5	[47]
14	7		6.1	[48]
42	26		7.1	[49], [50]
40	20			[51]
25	20		6.75	[52]
49	58		11	[53]
43	19		9	[54]
14	14			[55]
21	19		5.5	[56]
16	19		4.7	[57]
15	13		8	[58]
12	25			[59]

Table 1.: Clinical studies on efficacy of Gemzar combination

effects, and has been shown to provide synergies with many of the traditional treatment modalities. It enhances the effect of chemotherapy [88], [89]; and also has pronounced advantages for surgical interventions.

One of the most advanced treatment HT-modalities devoted to oncology is oncothermia (OT), [90], [91]. Due to the limited effectiveness of established therapies, OT could be one of the important future methods to improve the treatment facilities of PCA, [92], [93].

Our objective in this article is to present a retrospective clinical study for PCA. The study concentrates on the effects of the survival time as one of the most important factors to measure the success of a treatment in oncology.

The retrospective data are indications only, the prospective, randomized, controlled study should clarify the situation as according to evidence based medicine. However, we present data from two study-places, showing their similar results, and also present a comparison of the first year survival by oncothermia with two more independent clinics.

Method

The present results are obtained from an open-label, single-arm, retrospective study. 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. 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 (OS) and the survival time from the first oncothermia treatment (oncothermia treatment survival time, OSO). 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.

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. In order to support the reliability of the retrospective data-set, two independent hospitals were involved in the present study. One is the Peterfy Hospital, Budapest (PFY). It is a governmental hospital involved in the regular health-service network. The other one is a private day-clinic (HTT-Med Polyclinics, (HTT)), serving the patients only on private basis. The two trial-places were in tight information-contact, making the treatments with the same practical conditions and guidelines.

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

Inclusion criteria were: (1) Inoperable or sub-totally resected or recurrent primary pancreas tumor, (2) progression after surgery and/or chemo-therapy, (3) Karnofsky Performance Score (KPS) > 40%. 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 study had a couple of possible negative biases: (1) the treatment is paid or co-paid by the patients, who do it on a voluntary basis (ITT) in strict control of the oncologist who was responsible for the patient treatment till that time; (2) no randomized control arm exists, the trial is compared to the historical control or to the available literature.

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

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

The used device was EHY2000 (Onco-

Therm), capacitive coupled, working on 13.56 MHz, time-domain (fractal) modulated, with 30-150 W power absorbed by the tumor, keeping the skin surface on 20 °C. (For further details of the method we would like to refer to some of our other papers, [71], [90], [91].) The treatment control was made by the absorbed energy [kJ], which was converted to the equivalent temperature [T]. The equivalent temperature is higher than the actual temperature value, calculated by the assumption that the energy makes only a temperature increase. The reality, that the energy together with the increase of the temperature is basically used for the distortion of the structures, change of the chemical bonds and compensate of the physiological regulations, [94], [95], [96]. The equivalent temperature is in average higher, about 10 °C, than the measurable one in the actual conditions, however it is always the function of the given conditions and mechanisms.

The calculated average equivalent temperature in the tumors was above 43 °C in more than 90% of the treatment time. The targeted area was treated by the properly covering applicator system. OT 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 dm² and 7.1 dm², depending on the tumor volume.

Results

Hospital Peterfy (PFY) (n=26)

The age-distribution of n=26 patients was near to normal; no outlier were 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%. Most of the patients (23, 88.5%) had distant metastases. They were heavily

pretreated, everybody received at least one chemotherapy and most of them underwent surgery.

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), (Fig. 1.)

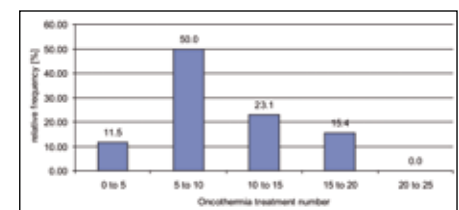
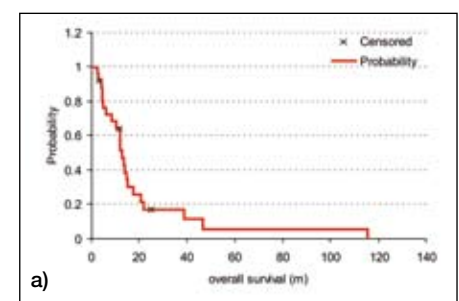


Fig. 1: Treatment number of oncothermia is dominantly in the 5-10 interval.

The Kaplan-Meier plots of the overall survival (OS) (median 12.0m, [2.3-115.5]; mean 17.5m, [st.err.4.4]) and the survival from the first oncothermia treatment (OSO) (median 6.32m, [0.7-40.4]; mean 8.9m, [st.err.1.9]) are shown in Fig. 2. For elderly patients neither the OS nor the OSO were different ($p=0.41$ and $p=0.61$, respectively).



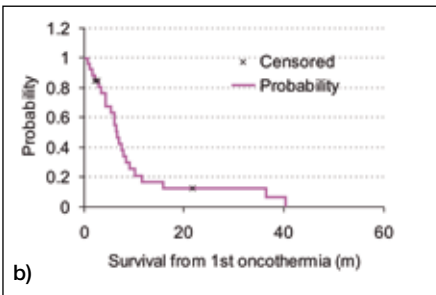


Fig. 2: The OS (a) and OSO (b) Kaplan-Meier plots

The survival was significantly different and for patient without or with metastases in their OS, ($p=0.039$), but was not significant in their OSO ($p=0.20$).

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: OS ($p=0.86$) and OSO ($p=0.69$). 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 ($p=0.29$).

HTT-MED Polyclinic (HTT) (n=73)

The age-distribution of $n=73$ patients was near to normal; no outlier were 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%. Most of the patients (54, 74.0%) had distant metastases, (one, two and three metastases were observed for 43 (58.9%),

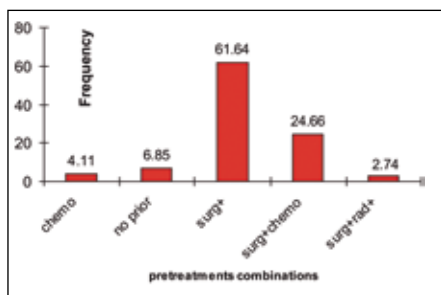


Fig. 3: Pretreatment combinations

10 (13.7%) and 1 (1.4%) patients, respectively). They were heavily pretreated, mostly (93.4%) underwent surgery and subsequent radiation and/or chemotherapy, Figs. 3, 4).

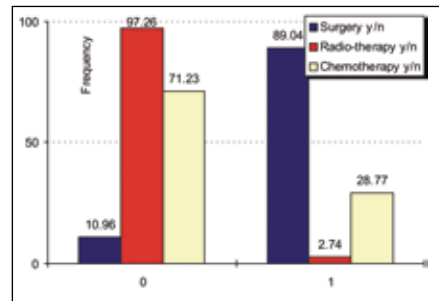


Fig. 4: Pretreatment distribution

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), (Fig. 5). 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

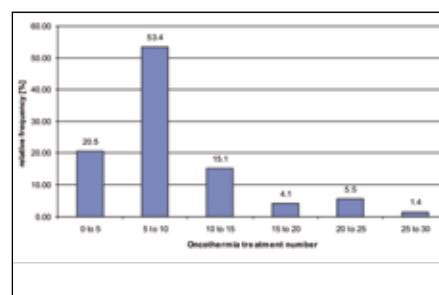


Fig. 5: Number of oncothermia treatments

applied treatment time in average was 67.2 min, (st.err.1.8) and its median was 60 (45-120).

The Kaplan-Meier plots of the overall survival (OS) (median 12.7 m, [1.2-94..5]; mean 19.2 m, [st.err.2.1]) and the survival from the first oncothermia treatment (OSO) (median 4.7 m, [0.3-49.2]; mean 12.6 m, [st.err.1.7]) are shown in Fig. 6. For elderly patients neither the OS nor the OSO were different ($p\sim 0.23$ and $p\sim 0.42$, respectively).

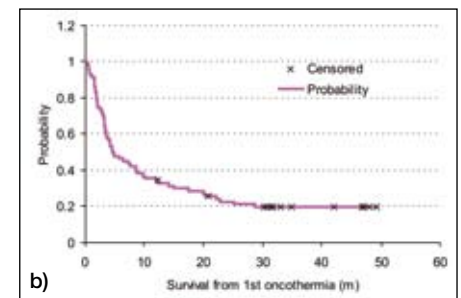
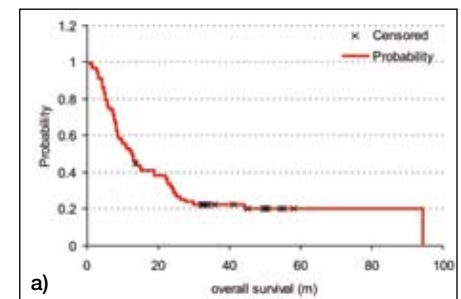


Fig. 6: OS (a) and OSO (b) of HTT-study

The differences between patients without or with metastases in their OS and OSO were significantly different ($p=0.016$ and $p=0.004$ for OS and OSO, respectively). The number of treatments does not significantly influence the OS ($p=0.24$) and the OSO ($p=0.16$) and the follow-up time after the last oncothermia ($p=0.23$, Fig. 7).

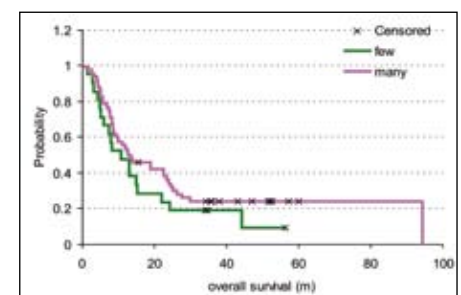


Fig. 7

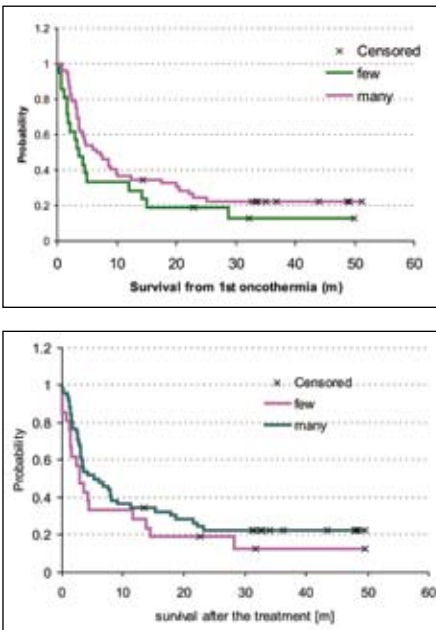


Fig. 7: The typical survival times do not depend significantly on the number of treatments (few = below median, many = above median number of treatments)

Interestingly, the gold-standard, the surgical pretreatment wasn't significantly important for the longer survival either for OS ($p=0.84$) and OSO ($p=0.87$).

This was probable because the tumor was only partially resected, or the surgery was only for palliation.

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 OS, OSO and ETO ($p=0.15$; $p=0.077$ and $p=0.52$, respectively), (Fig. 8.).

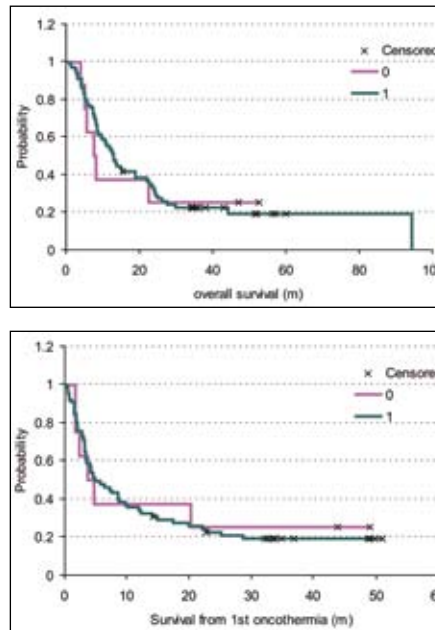
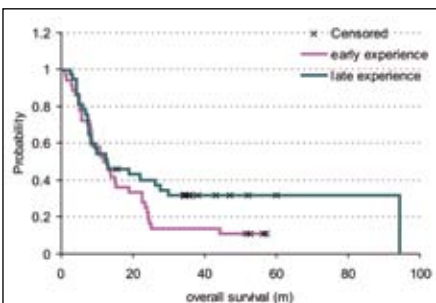


Fig. 8: The experience of the treating personnel did not modify the results significantly ("early experience" = the treatment was started earlier than the median time of the study; "late experience" = the treatment was started later than the median time of the study)

Comparative-analysis

The age-distribution of the altogether $n=99$ patients was near to normal; 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 PTF a shift to the elderly patients was present. The gender distribution was 47/52 female/male (47/53 %), and no significant difference could be measured between the places. The PFY/HTT patients' ratio is 61/197 (24/76 %).

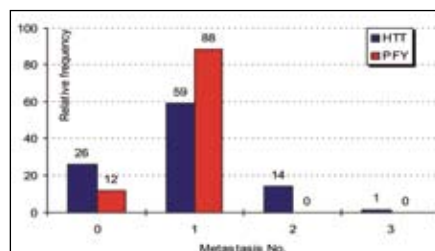


Fig. 9: Number of metastases of the patients involved in the study

74% and 88% of the patients had distant metastases in HTT and PFY groups, re-

spectively (Fig. 9). Patients were heavily pretreated (Fig. 10), in PFY the chemotherapy, in HTT the surgery was the most frequent modality.

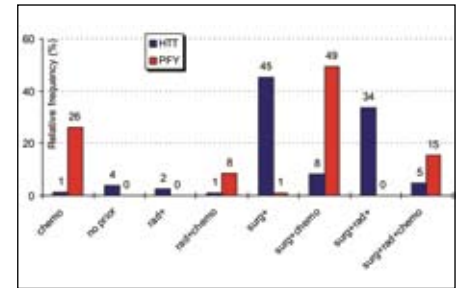


Fig. 10: Pretreatment distribution

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

The oncothermia treatment was provided twice a week, the treatment number was in average was more in PFY than in HTT procedures, (Fig. 11).

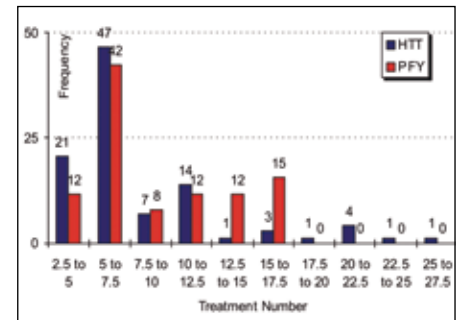


Fig. 11: The number of treatments for the patients in the study

Neither of the measured parameters, the overall survival (OS) and the survival from the first oncothermia treatment differed from each other ($p=0.38$ and $p=0.39$, respectively).

After the treatment was not different in the two places ($p=0.34$).

Discussion

Results show the identical survival parameters in the two independent places. The yearly survival rate is also not significantly different (Fig. 12).

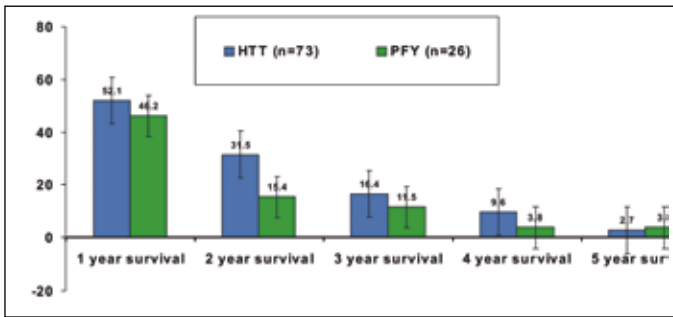


Fig. 12: The yearly survivals are well corresponding in the two studies

The results could be well compared to the available SEER [97] and Eurocare-3 [98] data. The comparison of the yearly survival rate is shown in Fig. 13. The gain of the first few years is obvious, while the difference gradually vanishes approaching the 5th year.

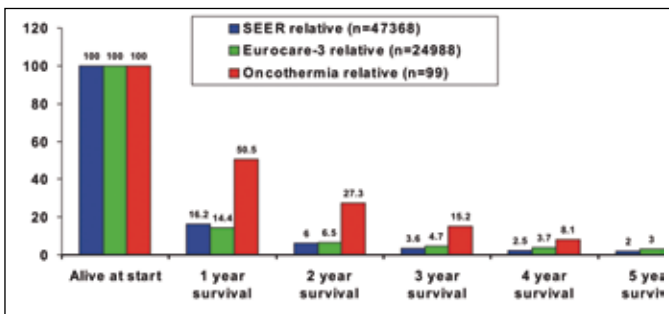


Fig. 13: The comparison of the results with SEER and Eurocare-3 data in first five years survival-rate (%).

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.

To prove the results we had compared the most surprising first-year survival with other independent clinical results from two German clinics. The two additional retrospective oncothermia trials were performed by VeraMed Clinic, [99] and Nurnberg Town Hospital [100]. The result is shown on Fig. 14 The result convincingly demonstrates the significant difference between the oncothermia and the general retrospective data.

For additional check a historical control (n=34) from the St.Borbala Hospital (Tatabanya, Hungary) was given as comparison to the data. The reality of this comparison is the fact that one of the author (AD) had worked at HTT and at St.Borbala Hospital at the same time and so the comparison of his own data is feasible. The median OS of the control was 6.5 m (1-

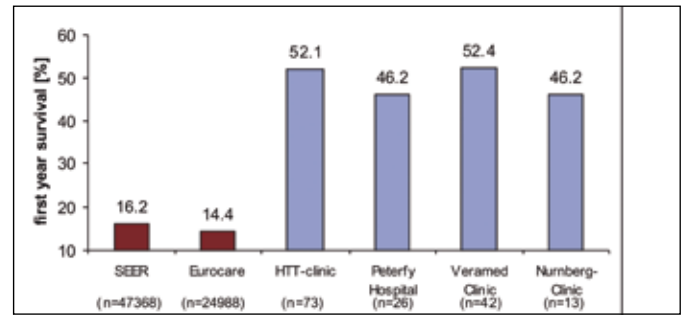


Fig. 14: Comparison of the first year survival-rates (%) in various clinics.

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).

The comparison of the Kaplan-Meier survival curves demonstrates the cogently significant difference ($p < 10^{-4}$), (Fig. 15).

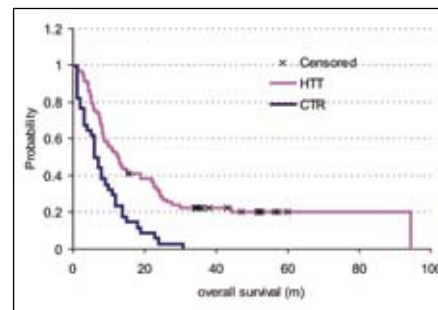


Fig. 15: The comparison of the Kaplan-Meier survival curves of the results by HTT and the historical control, collected by the same treating physician in St.Borbala Hospital.

Conclusion

Our present paper indicates the feasibility of the oncothermia treatment of PCA. The results are well indicating the benefit of treating PCA by oncothermia:

1. Oncothermia was applied for pancreas tumors, showing a valid treatment potential and safe application.
2. No safety or notable toxicity problem has occurred. The development of an edema or burn, which was a complication of hyperthermia applications in the past, is not the case with oncothermia. The treatment is safe and convenient to use.
3. The survival time, as one of the most important parameters, was increased for the patients making progress by other treatments.
4. The quality of life of the patient was improved by oncothermia according to their subjective reports.

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.

