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Extended papers of the NOS 2011
Androtherm: Application for Peyronie disease (Study)
Case reports
A case of Apscopal Effect

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Editorial

Dear Reader,

I am happy to present you the first issue of the Oncothermia Journal of this year. As in the last issues we are presenting you a range of scientific articles, reports, extended abstracts from the last Oncothermia-Symposium and clinic portraits. We hope that the contents can help you in your deep understanding of the method and its scientific background as well as support you in your practical work. Our aim is common with yours: we would like to help the suffering patients, we commonly devote our best forces to support the world-wide war against cancer. Use our mutual interest and please let us know if you would like to place an article or if you have any special topic wishes.

2012 is a very special year for Oncotherm. From October 12th-14th we will host the annual conference of the International Clinical Hyperthermia Society (ICHS); combined with the 2nd International Oncothermia-Symposium. Apart from a two-day conference with international speakers we offer an educational day before the Conference devoted to the up to date knowledge and connected practical trainings (you can find all information regarding the event on www.ichs-conference.org). Joan Baez sang in her famous song “deep in my heart, I do believe: We shall overcome, some day.” This very much mirrors my feeling as well. Hyperthermia has gone through some rough times. A lot of experts have been sceptic and against us and we had to prove our results on the markets in times where many doubted that the method can help the patients. I am very happy that this thinking is changing. More and more doctors are using hyperthermia. Great results are presented in large events like the Oncothermia-Symposium. Also many patients experience the possibilities of our method. For me and for Oncotherm Group the most important point is that we can help your responsible work with the patients to live longer and to have a higher quality of life. The more patients you can help with oncothermia, the greater is our common success. The recognition of hyperthermia by authorities and experts of the school medicine is increasing. The base of this is the high quality scientific supports from the laboratories to the clinical bed. Oncotherm goes forward not only in the practical developments of the machineries, but goes ahead in the basic understanding of the long-life hyperthermia, giving new paradigm of the heat-therapies in oncology. It is a slow process, but still it brings us forward. I hope and wish that one day we will overcome scepticism and prejudices in full. I am proud to know that you kind reader are interested for the breakthrough movements of oncothermia, and it is devoutly to be hoped that “we shall overcome some day”, together with you of course.

I hope you enjoy reading this issue of the Oncothermia Journal and that I will meet you in Budapest in October! If you have any questions regarding the journal, the method or anything else related to oncothermia, please do not hesitate to contact us.

Sincerely

Prof. Dr. András Szász

Liebe Leser,

Ich freue mich, Ihnen die erste Ausgabe des Oncothermia Journals in diesem Jahr vorstellen zu dürfen. Wie auch in den Magazinen 2011 präsentieren wir Ihnen wissenschaftliche Artikel, Berichte, erweiterte Abstracts vom letzten Oncothermie-Symposium sowie Klinikportraits. Wir hoffen, dass diese Beiträge Sie in Ihrem tiefen Verständnis der Methode und ihres wissenschaftlichen Hintergrunds sowie in Ihrer praktischen Arbeit unterstützen. Unser Ziel deckt sich mit Ihrem: Wir wollen den Patienten helfen. Gemeinsam können wir unsere Kräfte im weltweiten Kampf gegen den Krebs einsetzen! Nutzen Sie unser gemeinsames Interesse und lassen Sie uns bitten wissen, falls Sie einen Artikel veröffentlichen möchten oder falls Sie spezielle Themenwünsche haben.

2012 ist ein ganz besonderes Jahr für Oncotherm. Vom 12.-14. Oktober werden wir die Jahreskonferenz der International Clinical Hyperthermia Society (ICHS) gemeinsam mit dem 2. Internationalen Oncothermie-Symposium ausrichten. Neben der zweitägigen Konferenz mit internationalen Vortragenden bieten wir am Tag vor der Konferenz einen Educational Day an mit neuestem Wissen und praktischen Trainings (alle Informationen zur Veranstaltung auf www.ichs-conference.org). Joan Baez sang in ihrem bekannten Lied „deep in my heart, I do believe: We shall overcome, some day.“ Dieses Zitat spiegelt auch meine Gefühle wider. Die Hyperthermie hat schwere Zeiten durchgemacht. Viele Experten waren skeptisch und gegen uns und wir mussten unsere Ergebnisse erst belegen und uns auf dem Markt beweisen in einer Zeit, in der viele daran zweifelten, dass die Methode Patienten helfen kann. Ich bin sehr glücklich darüber, dass sich diese Denkweise verändert hat. Immer mehr Ärzte nutzen Hyperthermie. Großartige Erfolge werden auf großen Veranstaltungen wie dem Oncothermie-Symposium präsentiert. Auch viele Patienten erleben die Möglichkeiten unserer Methode. Für mich und für die Oncotherm Gruppe ist der wichtigste Punkt der, dass wir mir unserer verantwortungsvollen Arbeit den Patienten helfen können, länger zu leben und eine höhere Lebensqualität zu genießen. Je mehr Patienten mit Oncothermie geholfen werden kann, desto größer ist unser gemeinsamer Erfolg. Die Anerkennung der Hyperthermie von den Autoritäten und Experten der Schulmedizin nimmt zu. Die Grundlage hierfür ist die hochqualifizierte wissenschaftliche Unterstützung vom Labor bis zur Klinik. Oncotherm entwickelt sich nicht nur im Hinblick auf die Technik der Maschinen weiter. Wir gehen voran mit dem Wissen um langlebige Hyperthermie und stoßen neue Paradigmen der Wärmetherapien in der Onkologie an. Es ist ein langsamer Prozess, aber er bringt uns weiter. Ich hoffe und wünsche mir, dass wir eines Tages alle Skepsis und Vorurteile besiegen. Es macht mich stolz zu wissen, dass Sie als Leser ein Interesse an den Bemühungen um Anerkennung der Oncothermie haben und es ist zu hoffen, „we shall overcome some day“. Natürlich gemeinsam mit Ihnen.

Ich hoffe, Sie erfreuen sich an dieser Ausgabe des Oncothermia Journals und dass wir uns im Oktober in Budapest sehen! Falls Sie Fragen zum Journal, der Methode oder einem anderen Thema im Zusammenhang mit der Oncothermie haben, zögern Sie bitte nicht, uns zu kontaktieren.

Mit den besten Grüßen

Prof. Dr. András Szász

As the editorial team we are committed to a firm and coherent editorial line and the highest possible printing standards. But it is mainly you, the author, who makes sure that the Oncothermia Journal is an interesting and diversified magazine. We want to thank every one of you who supports us in exchanging professional views and experiences. To help you and to make it easier for both of us, we prepared the following rules and guidelines for abstract submission.

Als redaktionelles Team vertreten wir eine stringente Linie und versuchen, unserer Publikation den höchst möglichen Standard zu verleihen. Es sind aber hauptsächlich Sie als Autor, der dafür Sorge trägt, dass das Oncothermia Journal zu einem interessanten und abwechslungsreichen Magazin wird. Wir möchten allen danken, die uns im Austausch professioneller Betrachtungen und Erfahrungen unterstützen. Um beiden Seiten die Arbeit zu erleichten, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope
The Oncothermia Journal is an official journal of the Oncotherm Group, devoted to support them, making a collective for using the results and making it common for general use. The Oncothermia Journal has an open-minded character, expecting the complete study-papers, case-reports, reviews, hypotheses, opinions, and all the informative materials which could be helpful for the international Oncotherm community. Advertisement connected to the topic is also welcome.

- *Clinical Studies:* Regional or local or multilocal oncothermia or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, Oncothermia in combination with other modalities, and treatment optimization.
- *Biological Studies:* Mechanisms of oncothermia, thermal-or non-temperature dependent effects, response on electric fields, bioelectromagnetic applications for tumors, Oncothermia treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- *Techniques of oncothermia*: Technical development, new technical solutions, proposals.
- Hypotheses, suggestions, opinions to improve the oncothermia and electro-cancer-therapy methods, intending the development of the treatments.

Further information about the Journal, including links to the online sample copies and content pages can be found on the website of the journal: www.Oncothermia-Journal.com.

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Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncotherm-Gemeinschaft hilfreich sein könnten, enthalten. Werbung mit Bezug zum Thema ist ebenfalls willkommen.

- *Klinische Studien*, regionale, lokale oder multilokale Oncothermie oder Electro Cancer Therapy (ECT) Behandlungen, Fallstudien, praktische Erfahrungen in komplexen Behandlungen, klinische Versuche, physiologische Effekte, Oncothermie in Kombination mit anderen Modalitäten und Behandlungsoptimierungen.
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- *Oncothermie*-Techniken. Technische Entwicklungen, neue technische Lösungen.
- Hypothesen, Meinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen.

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- *Title Page.* Title of the paper, authors and their affiliations, 1-5 keywords. At least one corresponding author should be identified, whose email address has to be provided with full contact details.
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Contents

CONTENTS

Articles

Oncothermia Journal 5:11-22 (2012)

AndroTherm application for Peyronie disease (Phase I/II study)

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AndroTherm application for Peyronie disease (Phase I/II study)

Abstract

A pilot study is performed for Peyronie's disease by oncothermia principle with a specially developed so called androthermia device. The case-studies and the preliminary efficacy results are promising, and show the feasibility of the new method to treat Peyronie's disease in various stages.

Keywords: Peyronie's disease, electric field, plaque, heat, androthermia

Introduction

Peyronie's Disease, (*Induratio Penis Plastica*) is a plaque forming disease on the penis, deforming it mostly during erection [1], [2]. It is painful, and frequently blocks the normal intercourse. One of the first authoritative descriptions of the disease was made as early as 1561 by Fallopius, and almost 200 years later was rediscovered Peyronie, in 1743, [3]. The Peyronie's disease is mostly observable at men of their middle ages (50-60 y) in Caucasian race, [4]. Earlier its morbidity was measured less than one percentage, [5]; but nowadays it is apparently more common. [6]: 1.5% in man at ages 30 and 6 % for those who older than 70. Men in their 40-60 are affected by Peyronie disease in 2-3% [7]. It is shown in general, Other study showed 9% morbidity among American men, [8], and by autopsy statistics may be that the Peyronie disease is present over 20% of men, [9]. There are large variety of penile deformations and presence of the disease in young men patients [10].

The abrupt penis deformation during sex may disrupt small blood vessels within the tunica albuginea, which process could trap blood between layers of the tunica. The actual trauma could lead to inflammation Bleeding and trauma are accompanied by the release of a number of chemicals that lead to inflammation, [11]. The closed, layered structure of the tunica may limit the ability to drain the produced inflammatory mediators away from the site of injury, leading to prolonged inflammation there. Inflammation is usually a good process helping of healing, however when it became chronic it could block the healing process, [12], [13]. This could change the elastin and collagen fibers, reducing the adaptability of stretch of the penis [14] and deforming it.

In fact there is no effective therapy exists for this disease. There are many non-surgical treatments for Peyronie's disease like Vitamin E, Carnitine, Colchicine, Pentoxifylline, and various herbal and complementary remedies like Acetyl L-Carnitine (ALC) and dimethyl Sulfoxide (DMSO), or the "Thacker formula"; enzymes like Wobenzym, Fibrozym, Vitalzym, and Neprinol; as well as the minimally invasive (local in-situ injection) treatments of Verapamil, Interferon, Collagenase, and various steroids (e.g. Glucocorticoids) could be applied. All of the treatments applied have no or poor efficacy. There are various surgical options to solve this problem, [15]. There are huge interet to treat this disease worldwide [16] and also comprehensive books published in the topic [17], [18].

The transdermal electrophoresis [19] could be effective for the treatment combined with definite drug-therapy called "transdermal electromotive drug therapy" (EMDA) [20]. This placebo controlled, double-blind study used Orgotein (8mg), Dexamethasone (8 mg), Lydocain (120 mg) for 20 min three times a weak in three weeks duration. The plaque reduction was 79%, the curvature improvement 62% and the pain reduction 100%. Others had also used EMDA with Dexamethasone + Verapamil combination [21], also compared to Lidocain effect alone [22]. EMDA application with Verapramil alone [23] also was effective.

Contrary the new review of non-surgical solutions to treat Peyronie's disease [24], hyperthermia also was applied with success for Peyronie disease [25]. They studied 60 patients with Peyronie's disease,

having a comparison between application of Verapamil and hyperthermia. The chosen cohort groups were identical in their main relevant parameters (see Figure 1.)

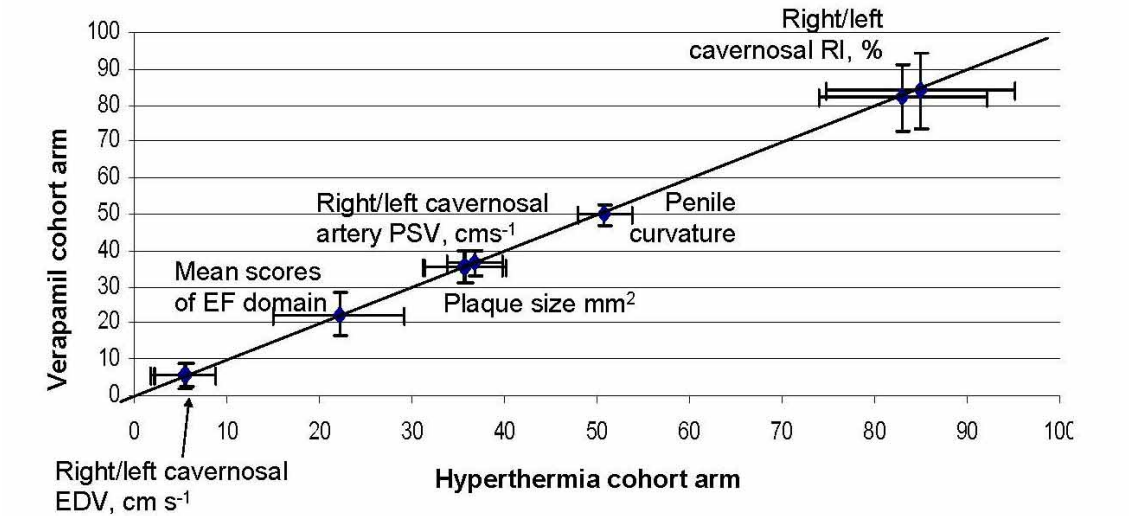

Figure 1. Comparison of the groups involved in the study [25]

Hyperthermia was applied for 20 minutes, twice a week for 5 weeks. A 2nd cycle was made after a 1 month having 10 treatments. The control group received 10mg injection of Verapamil once a week for 3 months. The Verapamil group had no real benefit of the treatment, (see Figure 2.). It was significant relief of both subjective and objective symptoms in hyperthermia treated group, without any adverse side effects (see Figure 3.). The penile curvature decreased by 55.9% with hyperthermia, while only 3.8 % with Verapamil, and the plaque-size decreased 42.1% and 2.2% with hyperthermia and Verapamil, respectively. Similar controlled clinical study is in progress to repeat the results, [26]. The clinical trial compare the only heat treatment and the treatment group is receiving a combination of Vitamin D and testosterone injections additional to heat by infrared heating.

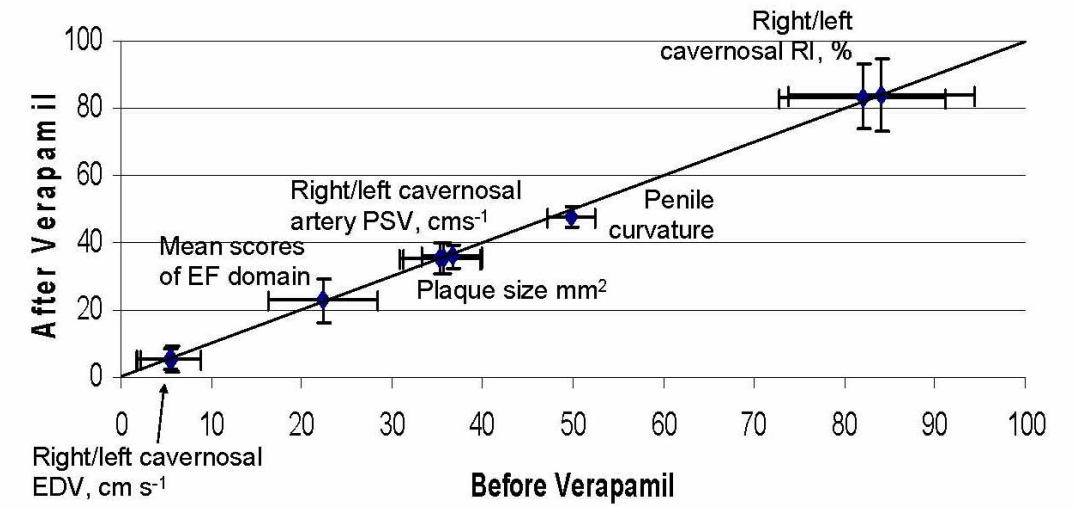

Figure 2. The group treated by Verapamil had no benefit from the therapy

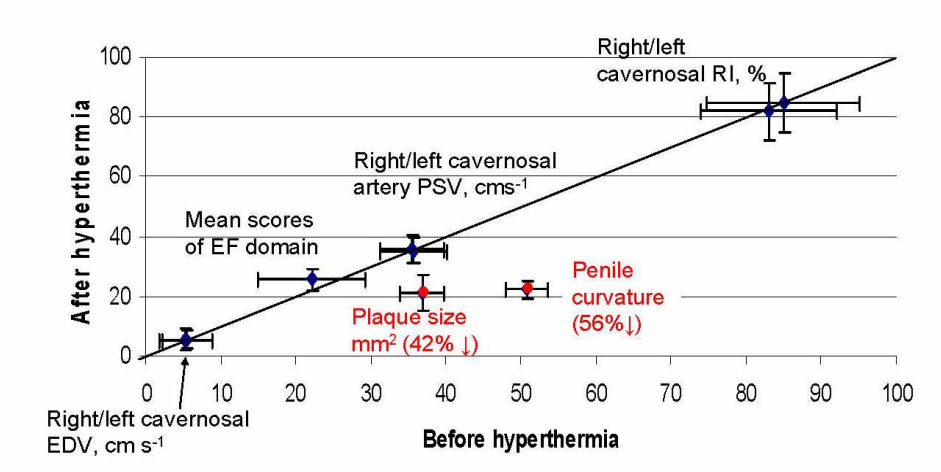

Figure 3. Hyperthermia had shown definite benefit for the patients

Learning the failures of many applied conventional treatments and seeing the possible applicability of the heat and the electric field, we had developed a new device for treatment of the penile disorders, including Peyronie's disease. The collected evidence based research data indicate inflammation processes. On this basis the Peyronie disease more similar to keloids than to scars. It is a benign tumor [27], which is

1. plaque fibroblasts are immortalized cells;
2. plaques and normal tunica albuginea have chromosomal differences;
3. induces immune response by the plaque fibroblasts and their products;
4. mitochondrial dysfunction is observed in plaque fibroblasts.

In coherence of the above conditions it is not a surprise that the apoptotic processes can play definite role in plaque formation and its elimination. There is a finding that apoptosis activation [28] in tunica albuginea plaques occurs. This, at least in part, is realized via the extrinsic pathway [29]. Probable the stem-cell activity has also role in the plaque formation in Peyronie diseases [30].

Peyronie's disease is known to be associated with Dupuytren's disease [31]. Main characteristic of the Dupuytren's disease is palmar aponeurosis hyperplasy and contract which lead to finger flexion contracture [32]. Peyronie's and Dupuytren's diseases have common pathophysiology, [33]. The imbalance between proliferation and apoptosis, producing malignant growth was thus confirmed for fibrosarcoma, but not the same form for Dupuytren's disease, [34], becase that is benign as well, similarly to Peyronie's. However both can be regarded as system's disease, [35], because the immune system is involved. It was hypothesize that periostin, secreted by Dupuytren's disease cord myofibroblasts into the extra-cellular matrix, promotes the transition of resident fibroblasts in the palmar fascia toward a myofibroblast phenotype, thereby promoting disease progression, [36]. The periostin can interact with other ECM proteins such as fibronectin and collagen I and may affect fibroblastic migration, [37].

The induced extrinsic pathway of apoptotic is involved in the novel hyperthermia method in oncology (oncothermia [38]). This is the reason, why the new development based on the oncothermia technology inducing apoptosis, is applied in the AndroTherm studies.

Method

The traditional hyperthermia had good benefit in the treatments of Peyronie disease, however it is controlled the only single thermodynamic intensive parameter, with the temperature.

Oncothermia is a special hyperthermia [38], working on the action of the modulated electric field in the locally treated lesion. It has long experience in the oncology [39]. Its idea to use the benefit of electric field makes feasible applying it for Peyronie disease, unifying the effect of EMDA and heat in a specialized treatment. Our objective is to perform a pilot study with application of special (adaptively modified) kind of oncothermia for Peyronie disease, called androthermia.

The method is based on the paradigm of the energy-dose control, replacing the single temperature concept [40], [41], [42]. With this approach oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which can not regarded as dose (the temperature does not depend on the volume or mass), oncothermia uses the energy (kJ/kg [=Gy]), like the radiation oncology uses the same (Gy) to characterize the dosing of the treatment.

The requested job is to change the structure of the target, for what a definite energy dose is necessary [43]. The historical energy-dose-like control (temperature multiplied by its application time), is physically incorrect, and operates with an overall energy average in the area, instead of a directed and well measurable energy-dose (measured in kJ).

So these points are realized, and called this procedure modulated electro-hyperthermia or oncothermia [44], and specialized now for andrology. Of course many theoretical considerations were done to make this idea working. The membrane effects by the outside electromagnetic field are shown against the old theories [45]. Also the modern fluctuation analysis (fractal-physiology) supports the method [46], [47]; as well as the resonance phenomenon is studied and used in the light of a new theory [48]. The hypoxia study [49] and special vector-potential theory [50] helps to complete the method. We also study the possible side-effects of the scattered radiation, [51], reduce the risk, and make the method as safe as possible. The acceptance of the new paradigm is a clear demand of the theory and the practice as well [52].

The presently applied radiative hyperthermia devices, operating one order of magnitudes higher frequency than oncothermia, are in fact also capacitive-coupled, because the applicators are definitely in the near-filed arrangements. However, these are far not optimally coupled and their frequency is also too high to be able to provide the desired effects. No artificial focusing needed for selectivity in the applied androthermia method, and no isotherms in space and time has to be controlled. Both effects are solved in oncothermia with a directed electric field. It is a well designed capacitive coupling on 13.56 MHz free-frequency, [53]. The process is controlled by the changes of the impedance, and by the absorbed energy, which both are accurately measured. In this meaning oncothermia is very similar to the RF-ablation hyperthermia, where the temperature is not measured, the effects is controlled by the measured impedance of the tissue. The power is ranging form 30 W to 150 W, which is far enough for heating up the tumor over 42 ºC in a well controlled focusing. (You may touch a working 12 W halogen lamp to be sure on its burning efficacy. Less than 20 W is enough to heat up a 5 cm diameter tumor from 36 ºC to 44 ºC at 3 minutes! The only clue is the focusing.)

The advantage of this method was clearly shown: the electric field has significantly higher effect as the temperature. Furthermore the temperature and electric field act synergistically, [54]. We expect that androthermia with modulated electric field effect works in synergy with the classical temperature- based hyperthermia concept. In preclinical conditions (in vivo and in vitro) many measurements were done in animals for oncology applications. The actual temperature development by the method would be too problematic to control in depth by the necessary invasive measurement approach. We worked out the energy-controlled dose. When necessary the temperature also could be measured, as we had shown in a sophisticated, well-controlled clinical temperature measurement [55]. The CT-guided fluoroptic sensor was positioned by interventional radiologist, and the patient (suffering with advanced sarcoma) was treated with the medium applicator. The maximal temperature in the tumor was 44 ºC, while the surface temperature

remained around 32 ºC.

Androtherm© device (Treat-therm® trade-mark), is the product of Oncotherm GmbH, Troisdorf, Germany) (see Figure 4.). It was developed for Peyronie disease, concentrating the plaque dissolution, using all the experiences and achievements from the past 20 years.

Figure 4. The front look of Androtherm device (Treat-therm ® trade-mark)

A set of special electrodes were developed for best performance (see Figure 5.)

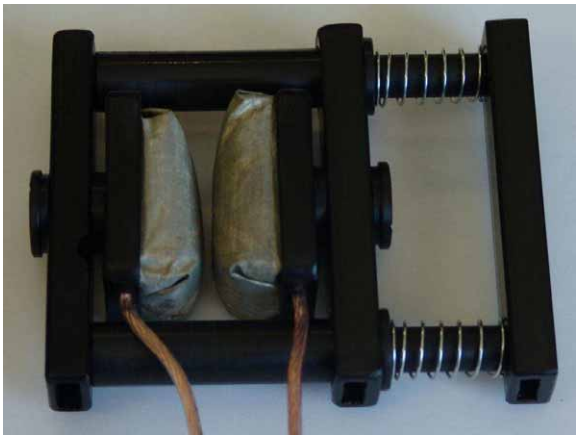

Figure 5. The electrode setup for penile treatment of plaques

The proposed and tested protocol of treatment was made 30 min two times a week, overall treatment number was 30 treatments/case in 3 cycles (10 sessions in each). One of the actual treatment setups is shown in (see Figure 6.).

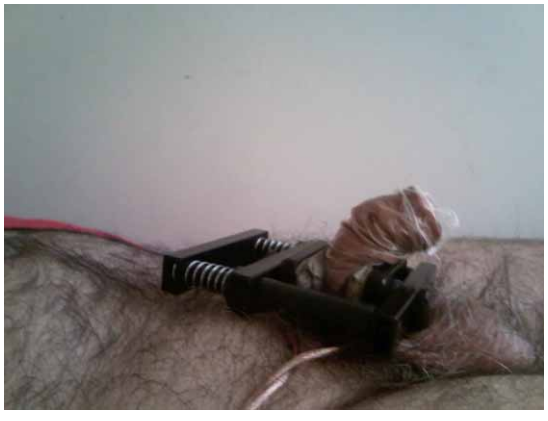

Figure 6. Actual treatment setup, shows the fit of the electrode on the penis

The treatments was used only as monotherapy, studying first the effect of the new method alone. All the patients were advanced stages, and their symptoms were measured in standard methods. The practical parameters to observe the expected changes were:

Size of the plaque
Curvature of the penis
Pain-reduction at erection
Erection function

Results

16 patients were studied till now. One of them was withdrawn (the patient subjectively evaluated no change). The age distribution was far from the normal (see Figure 7.) shifted to the elderly categories, which agrees with the epidemiological data **[4]**

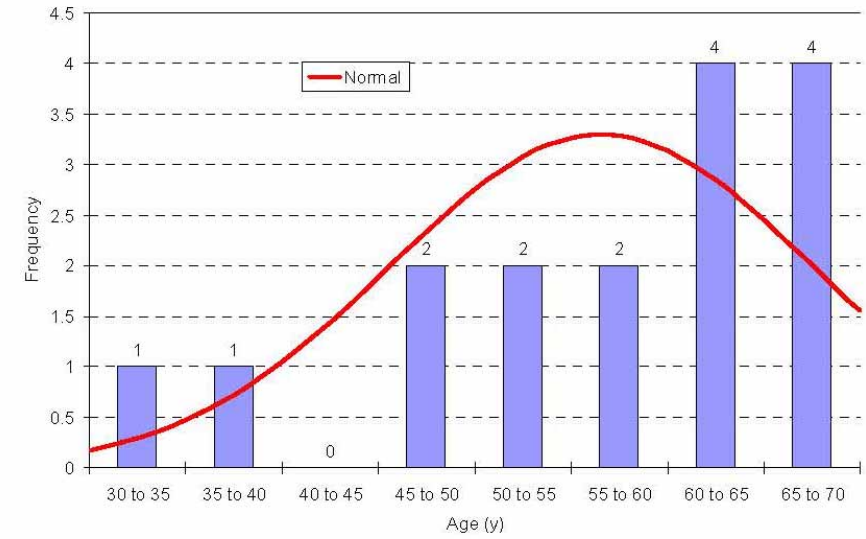

Figure 7. Age distribution of the patients involved in the study

The body-mass index (BMI) data follows the normal (Gaussian), distribution (see Figure 8.), which indicates the unbiased patient collection. Patients are dominantly overweighed.

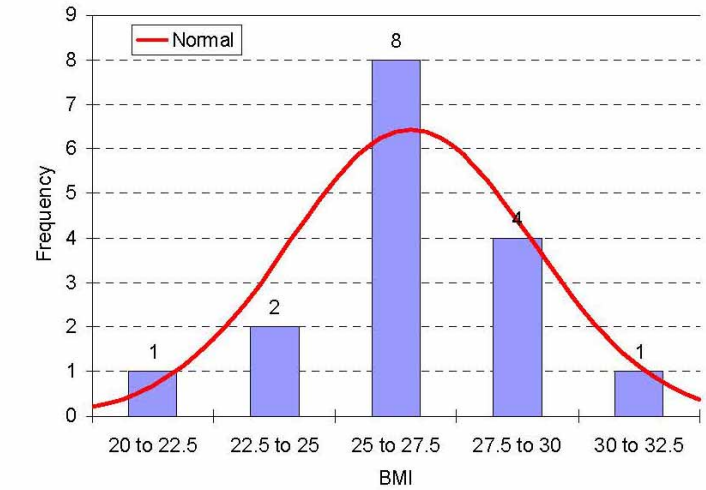

Figure 8. Distribution on the body-mass index

The age (y), weight (kg) height (cm) and the BMI (kg/m^2) is shown in Figure 9.

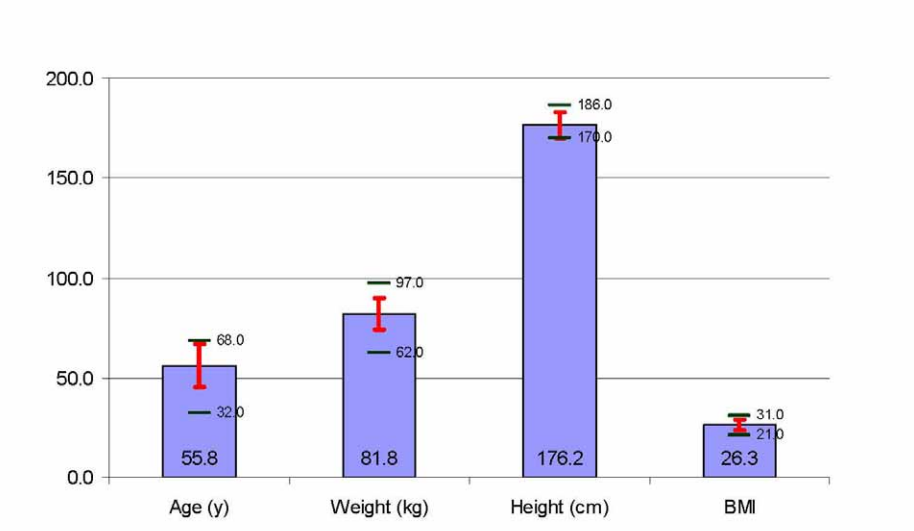

Figure 9. Descriptive values of the patients showing the averages (at bottom of the columns) the standard deviations (red intervals), and the minimal and maximal values in the given set of patients are shown by green lines

Typical cases are shown demonstrating the effect on curvature of the penis. The photos of the result before and after the treatment shows spectacular improvement (see Figures 10. and 11.)

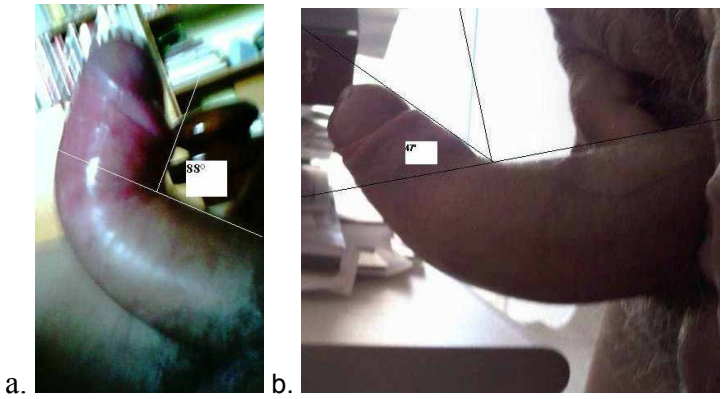

Figure 10. Patient #4 before (a) and after (b) the androthermia treatment sessions (Extreme penile curvature)

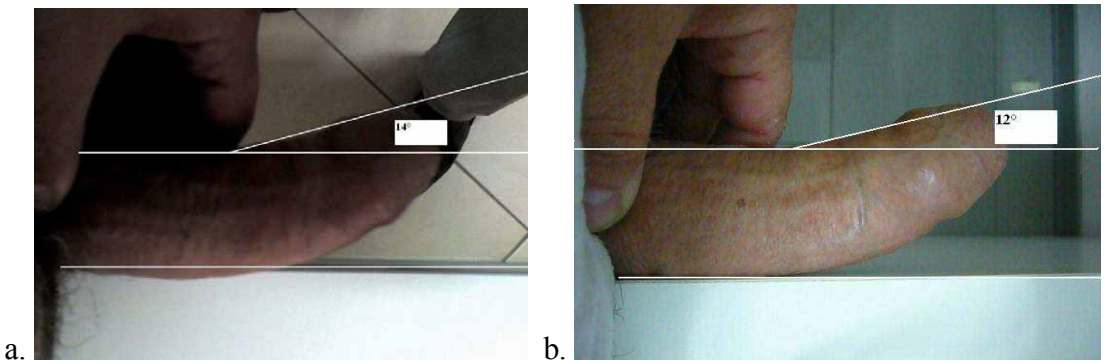

Figure 11.The penile curvature of the patient #16 before (a) and after (b) the androthermia treatment sessions (minor penile curvature)

The treatments were dominantly successful. All patient had benefit, improvement at least one of the investigated four (curvature, plaque, erection, pain) parameters. The plaque size before and after the Androtherm treatment decreased (see Figure 12.) except one case (#7), but the consistence of the plaque here also was softer after the therapy.

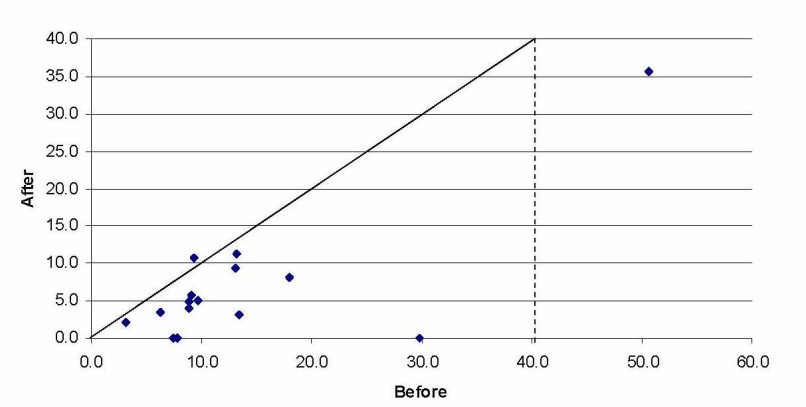

Figure 12. The plaque size before and after androthermia treapy. Except one case, all points are below the equal line, which means that after was the plaque size less than before (The equal-line is given to guide of the eye)

The change in percentages is shown in Figure 13.

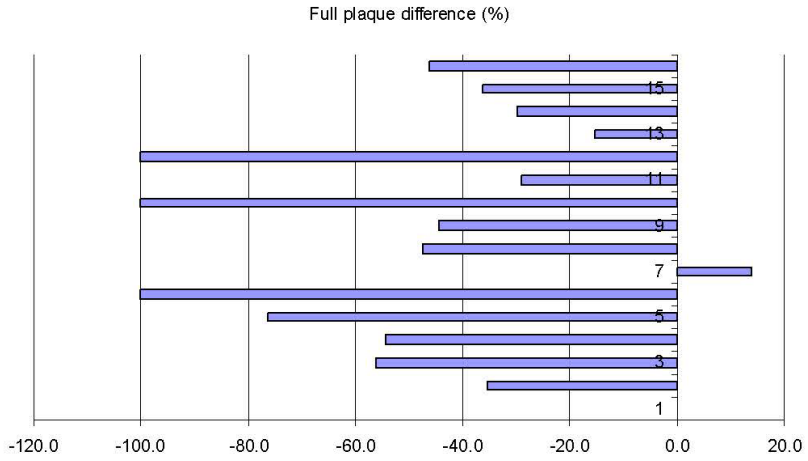

Figure 13. The plaques are reduced by considerable percentages

The average of the plaque size decreased by more than 50% (see Figure 14.).

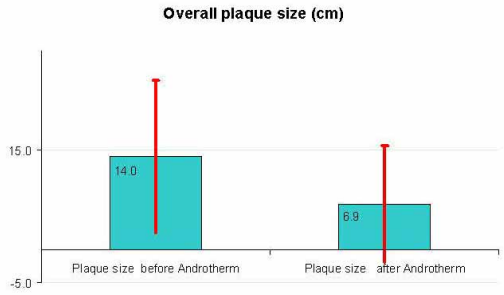

Figure 14. The average of the plaque size before and after androthermia. The red lines are the standard deviations

The curvature is also definitely improved, (see Figure 15. and Figure 16.), only in one case was unchanged (#11), but the curvature was originally small. One patient (#3) had no curvature and it was not changed.

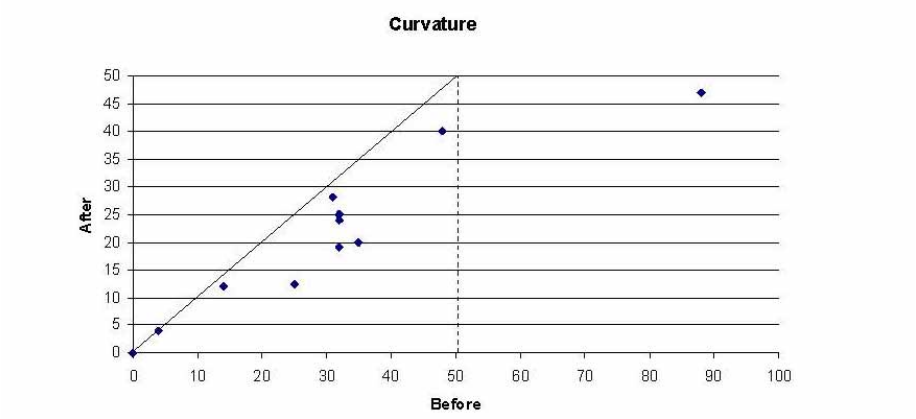

Figure 15. The penile curvature (degrees) before and after androthermia therapy (The equal-line is given to guide of the eye)

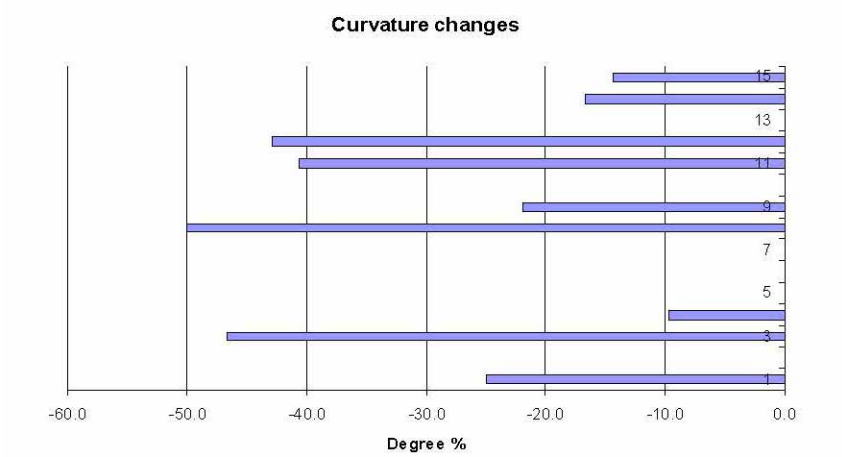

Figure 16. Change of curvature in percentages by androtherm therapy

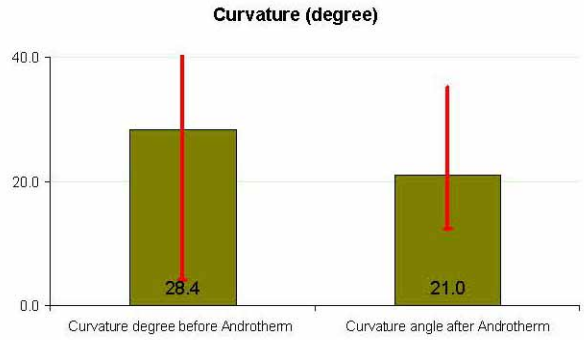

Figure 17. The average of curvatures (degrees in columns) and their standard deviations (red lines)

The IIF scores are also improved in general. In case of IIF5 [56] the results were not so significant (see Figure 18.) (only four patients reported better scores after the treatment) but the IIF15 [57] (see Figure 19.) was more successful, only slight worsening was in fourth cases but all the others had definite benefit for their IIF15 scores.

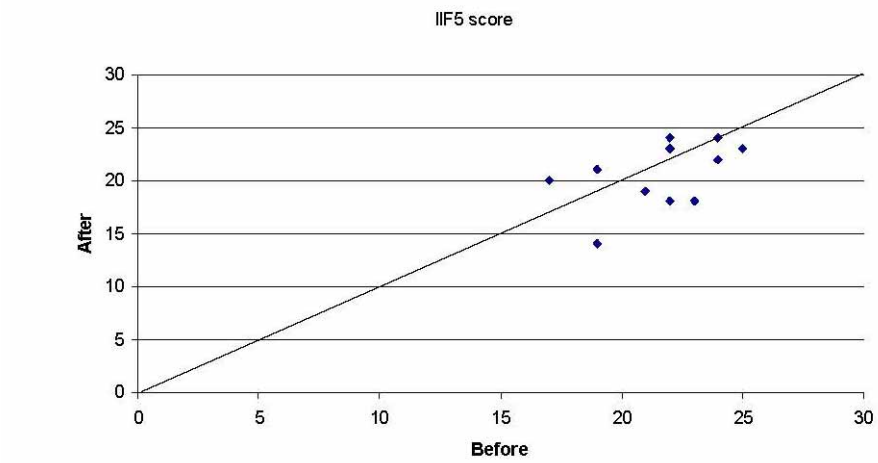

Figure 18. The IIF5 score before and after androthermia therapy. (The equal-line is given to guide of the eye.)

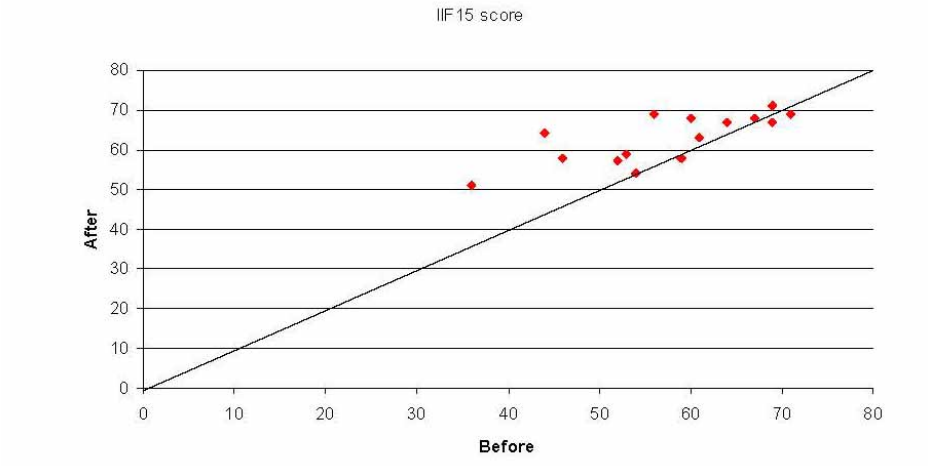

Figure 19. The IIF5 score before and after androthermia therapy. (The equal-line is given to guide of the eye.)

The averages of the IIF5 (see Figure 20.) and IIF15 (see Figure 21.) scores have no dramatic change, even the IIF5 slightly decreased, while IIF15 increased more than 9%.

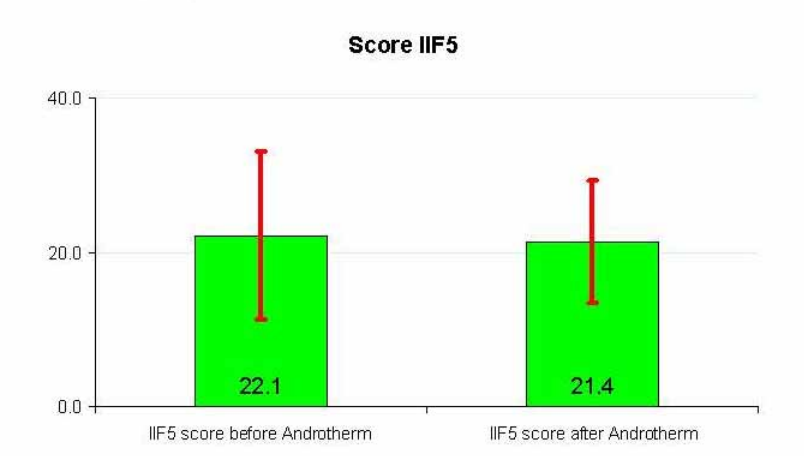

Figure 20. The IIF5 scores before and after androthermia therapy

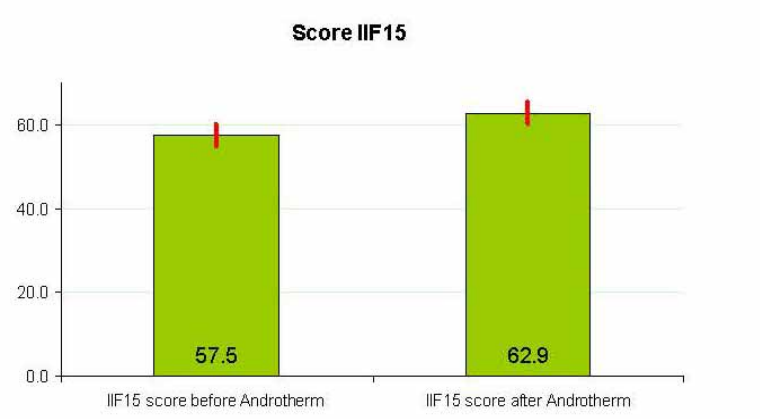

Figure 21. The IIF15 scores before and after androthermia therapy

In cases of the patients who had pain at erection, the pain was vastly reduced. The pain in most of the cases had disappeared at the end of therapy. The cases of erectile dysfunctions had functioning erection after the treatment.

Patients (except one) were subjectively satisfied, no adverse side effects were observed.

Conclusion

Androthermia is feasible and promising treatment modality for Peyronie disease. It is able to reduce most of the symptoms (see Figure 22) in most of the cases, and except one, no case was reported as non- effective.

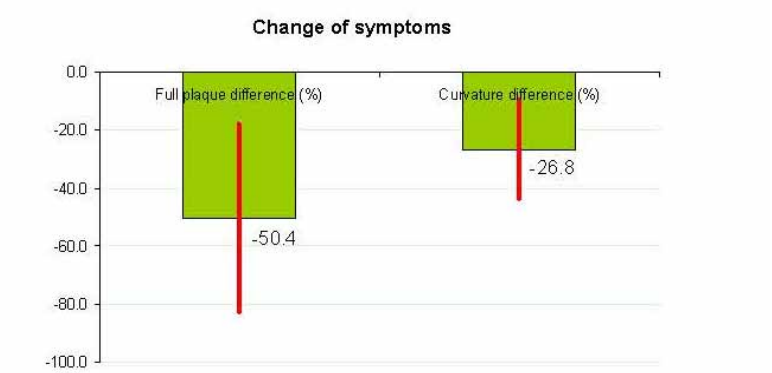

Figure 22. Change (percentages) of the main symptoms by androthermia therapy

Larger number of patients and more experience is necessary to make any conclusion. The further study is in progress.

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Clinical Research on Integrative Treatment of Colon Carcinoma with Oncothermia and Clifford TCM Immune Booster

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Clinical Research on Integrative Treatment of Colon Carcinoma with Oncothermia and Clifford TCM Immune Booster

Abstract

Nowadays oncology faces the challenge of non-toxic integrative therapies for cancer treatment. Clifford Hospital is devoted to this research and offers a full range of therapies, representing a synergy between the Traditional Chinese Medicine (TCM) and the state-of-art facilities of the Modern Western Medicine (MWM). Our present article reports research of the therapeutic efficacy and adverse reactions of integrative treatment of colon carcinoma with Oncothermia (OT) and Clifford TCM Immune Booster (CIB). The clinical study involved 157 patients in three-arms of treatments: CIB alone, OT alone and OT+ CIB combined. Results definitely prefer the combination therapy, which shows synergy of OT with CIB.

Keywords: Clifford TCM Immune Booster, Oncothermia, Traditional Chinese Medicine, randomized controlled clinical trial, colon carcinoma.

Introduction, background of the concept

The second-leading cause of cancer-related deaths in Europe and the USA is the colorectal cancer, [1]. Death from colorectal cancer is around half million in a year worldwide. The statistics has no mentionable gender differences but it is prevalent in ages over fifty. Genetic and environmental factors have definite role in development of colon-cancer, estimating 80% of the cases originated from environmental related sources, like alcoholic, low vegetable and folic acid intake, increased fat and red-meat diet and smoking habits [2].

Surgical resection remains the basic curative treatment for colon cancer, but often the patient is only partially resectable or inoperable. The prominent post-surgery prognostic factor is the stage of the disease. Patients with having no distant metastases survive more than five years by approx. 75%, while the metastatic cases show much less –five-year survival rate [3]. Metastases are dominantly start in liver from colorectal primary. Numerous kinds of adjuvant treatments are applied to prevent the potential relapse or actually invisible but developing metastatic lesions.

Chemotherapy applications

One of the oldest standard protocols for colon cancer is the adjuvant fluorouracil (5-FU) combined with leucovorin, [4], [5], [6], [7]. Irinotecan was developed for cases when the protocol of fluoracil+leucovorin was a failure [8], [9]. For comparison three different chemo-mechanisms were applied in advanced colorectal cancer cases: fluorouracil, irinotecan, and oxaliplatin; with successes, [10], [11]. Mechanism of the irinotecan and oxaliplatin are different than the elder fluorouracil, and so synergy expected, but at lest having no resistance against the treatment, [12], [13]. Until the middle of the last decade, colorectal cancer drug treatment was standardized by three active agents: 5- fluorouracil (+leucovorin), oxaliplatin, and irinotecan [14], [15], [16]. A large clinical trial was performed for 2135 unpretreated patients with advanced, poor-prognosis colorectal cancer, starting treatment with non-curative intent [17].The Kaplan-Meier survival test showed significant advantage of the combined therapies.

The disadvantages of the chemotherapies are their side effects and that the patients frequently develop multidrug resistance (MDR), which blocks the further chemo-applications. Immunotherapy is one of the non-chemical methods for colon cancer treatment. Instead of

the chemo-therapy many approaches are using antibodies and vaccines which could be highly effective in treating micro- metastatic disease [18], [19], [20].

Other strategy is the anti-angiogenic therapy which is less toxic than the conventional chemotherapies and has a lower risk of drug resistance [21], as well as could make the tumor vasculature more efficient for drug delivery increaseing the efficacy of conventional therapies [22].

Complementary therapies, TCM

Parallel with the active treatments of the disease, the prevention of the colorectal cancer was investigated also very intensively [23]. The positive role of the fiber-rich diets with increased intake of Omega-3 fatty acid and high volume of fresh vegetables and fruits was suggested for individuals to prevent the colon cancer. Folic acid, Vitamin E, Selenium and Calcium intake was emphasized also.

The diets and the quality of nutrients became important, and the relation between metabolic syndrome (MetS) and its components with colorectal cancer was studied, [24]. The study supported a direct association between MetS and both colon and rectal cancers in men, but not in women.

The connection of diet and of the gastrointestinal diseases (including cancer in this track) is recognized by long time [25], [26], [27]. Some natural extracts are used in China for a long time for colorectal cancer cases, like the Scutellaria Barbata D.Don. The effect of this plant was shown in laboratory conditions too [28]. There are numerous publications with TCM applications for rectal and colon neoplasms; colon cancer treated by TCM was published in 124 articles in 2001, [29]. It is very interesting that the effective active agent (name Camptothecin) of chemotherapy drugs Irinotecan, Topotecan, which widely used in MWM for colorectal carcinomas, had bee discovered in the old Chinese therapy by "Happy tree" (喜树), [30]. Other recipe offers for colon cancer the herbs of oldenlandia (60 %), scutellaria (15 %), solanum (60%), sanguisorba (30%), viola (15%), [31].

Oncologists are facing challenges to treat the patients with low toxicity, high quality of life and long survival time. They are looking for solutions in anticancer drugs in Chinese herbal medicine. Clinical data showed anticancer properties of some herbs [32], [33], [34]. Even the palliative and post- treatment care has herbal medicine with success [35].

The ancient philosophy of TCM has definite similarities of the novel hypotheses of integrative medicine, where the whole body in its integrity and the general overall complex system is studied, rather than the body-parts or individual processes in the system. The basis of theories of TCM leading to syndrome differentiation and examples of the corresponding treatment strategies are comparable in general with the evidence based medicine preferred by MWM, as shown in the Table 1. **[30]**.

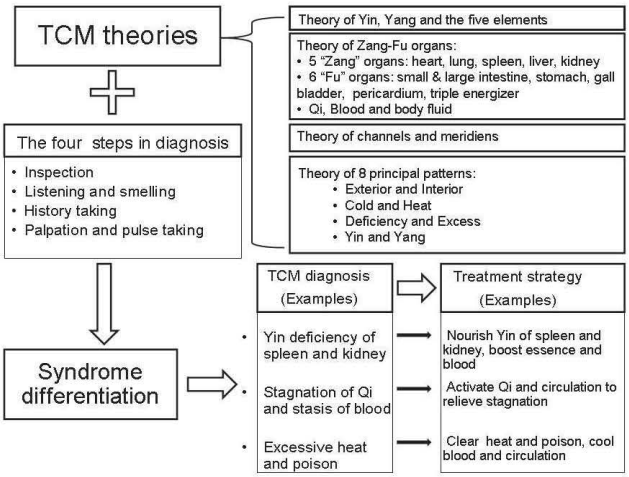


Table 1. The structure of TCM theories ***[30]***

The body is in homeostasis in normal healthy state. TCM is directly based on the general and overall homeostatic control of the human body. The homeostasis created by multiple negative feedback processes, keeping the actual state apparently constant. Each negative feedback can be described by a balance of the apparently controversial effects, a "dynamic overplay of opposing forces" [36], which is the basic of the dialectic philosophy. This was formulated by the ancient Chinese philosophy (Lao Tzu "The Old Master" [37], [38]), and approximately in the same time in Western (Greek) philosophy (Heraclitus of Ephesus, [39]) as well. Later Hegel had synergized the dialectics, [40], formulating the thesis-antithesis-synthesis unity behind of the dynamic movements. The dialectical points are considered also in the roots of medical thinking, [41]. The numerous well controlled negative feedback loops, keep the actual state definitely "constant" despite of its energetically open status. The disease breaks up the relative equilibrium, and the body tries to reestablish the homeostasis by forced natural feedback mechanisms.

When recognizing the disease, we can act to help the natural feedback loops (this is the aim of the TCM) or we can influence independently, operating outside constrains intending to modify the actually recognized local disturbances. This action is typical in MWM, when the wide range medical knowledge concentrates on the details of the body-parts, ignoring in some cases the interconnections and integrity of the body as a complex system. (Typical behavior of the complex system, that it is more than the simple addition of their parts.) MWM works against the natural homeostasis on this way in many cases. The constrained action induces new negative feedbacks from the natural physiologic control, to reestablish the homeostatic. The body integrity starts to fight against our constraints too, forcing the natural processes exposing it to cross-fire by the disease and the independent medical action. This controversial situation happens with classical hyperthermia, when the constrained massive temperature change is physiologically down-regulated (or at least the physiology works against it by the systemic [like blood-flow] and local [like HSP] reactions). The natural therapy must help the body's internal corrective actions to reestablish the healthy state.

The present study applied 'Clifford TCM Immune Booster, which is a well defined and carefully prepared mixture of TCM herbs. Main constituents are: Rhizoma Smilacis Blabrae, Radix Angelicae Sinansis, Rhizoma Atractylodis Macrocephalae, together with multiple minor additions mixed in the tincture.

Classical hyperthermia applications

Of course the independent constrains are necessary want the natural processes are too weak to make corrections or somehow entirely blocked in the actual disease, but the effect always has to consider the effects of disturbances in the entire system. This is the problem of the

unlimited force of hyperthermia, when the body tries to correct the increasing temperature, increasing multiple physiological answers trying to correct the shifted temperature. In this applications of hyperthermia starts a competition between the processes, and became difficult keeping the entire action under control. Anyway the forced local temperature increase offers many advantages for gastrointestinal track, [42]. The response rates of early treatments were remarkable, they were over 50% [43], [44], [45], [46], [47]. Certain palliative effect for pain was also observed in these applications, the pain was certainly reduced by 78%; 56%, **[46]**; 86%, **[45]**; 79%, **[42]**; for 32, 34, 48 and 69 patients involved in the study, respectively.

Recurrent, locally advanced colorectal cancer was studied by hyperthermia adjuvant added to standard radiotherapy protocol [48], [49]. The objective response rate was 54% with combined therapy while the radiotherapy alone reached only 36%. In recent studies, results on unresectable or locally recurrent, advanced colorectal tumors were studied with extreme surface cooling facilities, avoiding the surface burn, [50]. The median survival times were 24.3 and 17.1 months in combined and sole radiotherapy groups, respectively. Other study with the radiotherapy combined with capacitive hyperthermia for recurrent or nonresectable colorectal tumors had only two cases progressive disease from n=44 patients. [51]. Similar results were obtained with other studies [52], [53], [54] as well. Comparison **[53]** the active group (n=35) to a control one (n=36) had shown clear advantage of hyperthermia. Success could be obtained by hyperthermia applied together with chemotherapy in case of preradiated treatments [55]. In recent studies in combination with chemotherapy, the response rate of the treatment of refractory colorectal cancer as 2nd line treatment by 5FU/LV with the addition of Irinotecan is 22% and leads to a progression free survival of 6.3 months [56]. In combination with hyperthermia [57] the objective response rate was 33%, while the median time to progression was 8 months (1-28 months) and the median overall survival was 12 months (2-28 months). This hyperthermia study ([57]) concluded that hyperthermia does not increase the toxicity of the 5FU/LV/Irinotecan therapy, and indicates benefits form the combined treatment.

Application of hyperthermia was introduced preoperatively as well, [58]. Comparing the postoperative results [59], in case of tumors invading beyond the muscularis propria the overall survival was 86.5 and 50.9 months for with and without hyperthermia treatments, respectively. In cases of the lymph- node metastases the results were 92.5 vs. 51.7 months for with vs. without, respectively. Other, phaseII investigation of locally advanced rectal cancer [60] supported the feasibility of preoperative hyperthermia. The preoperative hyperthermia applications were also successful in trimodal (chemotherapy, radiotherapy and hyperthermia combination) approach, [61], [62] even when it was applied intraoperatively [63].

Oncothermia applications

The problem of the malignant diseases is clear: these diseases are systemic, their appearance is local, but it is illusory to treat it only locally. This systemic effect manifests itself in the dissemination of the cells from the original (primary) tumor, and in a second step the malignant cells travel in this way far away from their original place, and could clog in sensitive organs, like brain, lung, liver; forming lethal metastases. The disseminated cells attacking the organs which are crucial for life, form new tumors (metastases) in these organs, and this is the main danger of malignant tumors. (the benign tumors are really local, they are growing in the local volume, but no dissemination and no metastasis forming happen in these cases.) The heavy life-threatening effect of metastases has been observed on statistical basis on colorectal adenocarcinoma collecting data for 15 years [64]. When no metastases were present, the long-term (10 years) survival was around 90%; while was 60% in case of regional metastases and only 15% when distant metastases were developed by the patient.

The dissemination of the malignant cells is the consequence of the certain autonomy of the cells, which lost their cooperative control, escaped from the homeostatic harmony of the tissue organization. The tumor is a set of the autonomic cells, which are not connected to others for information exchange, and supporting each other, even oppositely, they are "individual fighters" to keep themselves alive in a hostile environment of the other malignant cells and the possible attacks of the overall controller the immune system. Physiologically the crucial point is the loosing communication between the cells, which is responsible not only for the lost "harmony" with the system but also blocs the availability to give natural outer signals for apoptosis and in the dissemination point of view, the lost connections made the cells freely movable. The autonomic, aggressively metabolizing and dividing cells are seeking for large amount of nutrients and oxygen, which are delivered by the blood-stream, so the dissemination of the independent cells into the blood-vessels is a natural consequences of their freedom.

Oncothermia had formulated a new paradigm [65]; it answers positively on the doubts above. It radically reforms the hyperthermic oncology, introducing new technology for selection of the target- tumor, for principles of its elimination, and for the dose concept controlling the therapy.

The targeting in oncothermia based on the microscopic energy-delivery, heating up the extracellular electrolyte in the immediate vicinity of the malignant cells instead of the artificially focusing on the full volume of the tumor. This controlled effect makes possible to concentrate the absorbed energy on the task, and not increase the temperature where it is not necessary. The biological basis of the selection is the high glucose flux consumption of the malignant cells compared to their healthy counterpart. (This difference is the basic of the positron emission tomography [PET] as well.) The higher ionic concentration of the extracellular electrolyte as well as the disordered structure forming by the autonomic malignant cells makes possible to distinguish these cells directly by their electromagnetic (impedance) properties to attack and kill them [66]. This controlled micro heating makes possible to introduce the dose as the absorbed power [67], [68]; like it is used in the standard radio-therapy as well. The physiological feedback loops to correct the higher local temperature and the constrained effects of local heating are hindered by oncothermia, and the energy of the electric field became a synergetic partner of the microscopic temperature increase [69]. This makes possible the oncothermia applications in wide range of malignant diseases [70], and introduces it [71] as the fourth column of the gold-standard oncological methods, additional to the surgery, radio- and chemo-therapies.

Oncothermia activates the natural processes to block the dissemination; it reestablishes the cellular connections between the malignant cells. Two kinds of such bonding connections are important between the cells among normal conditions: the adherent connections exchanging signals from neighboring cells, and the junctions (gap-junction, tight junction) allowing molecular exchanges between the cells. These connections represent mechanical/chemical bonds, which are limiting the cellular freedom to disseminate, avoiding their motility due to the lazy connections to the tumor mass. Oncothermia is able to reestablish both kind of connections (adherent- and junction-types) and with this blocks the number one life-threatening danger: the dissemination, [72]. The built up connections could force not only the sticking together, but make bridges between the cells for information exchange to limit the individuality, the competitive behavior of the malignant cells. The cells are able to make some-kind of harmonic cooperation again, and one of its consequences is the apoptotic cellular death. This kind of cellular life-regulation has additional benefit too: elimination of the cells does not liberates toxic materials and does not induce consequent inflammation in the tumor region. The inflammatory tumors have generally worst prognosis than the non-inflammatory ones, so oncothermia improves the life prognosis, helping the complex process of the longer survival

with better quality of life.

On the technical point of view, the reestablished connections between the cells rearrange the current distribution inside the tumor, developing a positive feedback mechanism to destroy the malignant cells on natural way.

One of the definite possibility to fight against the cancer diseases is to recognize the tumor as early as possible, to avoid the dissemination and metastases, and start the treatments as early as possible. Unfortunately, most of the patients are starting their oncothermia sessions, when the malignant cells already invaded into the blood-system. The blood-transported cells can be blocked easily by the brain, lung, kidney, liver, etc., as consequence of this process, and most of the patients starting to be included to oncothermia treatments, have distant metastases, which more likely causes fatality, shortens the overall survival time and badly affects the quality of life of the patients. This situation is a major challenge of the oncothermia treatments.

Oncothermia picks-up the gloves, and makes research to eliminate the distant metastases too. One of the main challenge to treat metastatic lesions in general is the diagnosis, recognizing where the metastases are present. Oncothermia is basically a local treatment. Of course, when the metatstatic tumor is recognized its treatment is simple, make it on the same way, as we do in case of primary tumors. However this is not enough in most of the cases. The disseminated cells forming various metastases, which are actually too small to detect, but their presence makes definite suppress of the life-span and the quality of life. In consequence, the task is to act systemically with the local treatment. It looks impossible, but studying the systemic behavior of the malignant effects (which acts systemically form a local source), the action is not impossible. According to our common knowledge the local therapy of radiation is not available in cancer patients with multiple metastatic lesions. However, one of the interesting, and so far not completely understood processes, is the systemic effect of the local treatments in radiotherapies, the so called abscopal (out of the target) or bystander effect. The first published observation on systemic effect of local radiotherapy was made by R.H. Mole, who proposed the term “abscopal effect” in 1953 [73]. This phenomenon shows a systemic effect only by local treating. Effect was observed [74] outside the treated field of ionizing radiation [75], but it is generally under-recognized in the clinical practice **[74]**. It is originally defined as the systemic effect of radiation therapy observed in distant tumors from the site of irradiation field. It is suggested that the abscopal effect relates to immune response mediated by cytokines, but the mechanism remains unclear because this phenomenon is so rare and poorly understood in clinical practice, showing many controversies also [76]. Sometimes it is used complementary to other type of local therapies including surgery, hyperthermia and immunotherapy [77]. These complementary applications have recently received attention as new therapeutic facility [78]. The possible effect of pulsed electric field and radiotherapy on abscopal process was studied, [79], so our studies targeting this process, replacing the radiotherapy with oncothermia. The effect was shown in mice experiments [80]. Oncothermia was able to produce the same effect, controlled by the local tumor-treatment on the untreated distant other tumor in mice model, (HT29 human colorectal adenocarcinoma xenograft). A strong abscopal effect was observed, when sterile inflammation (E. coli LPS) as immune-stimulator was applied [81].

The effect makes promising facility for the future oncothermia applications. There was a human case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. Patient was treated with fractional radiotherapy accompanied with oncothermia and granulocyte-colony stimulating factor (GM-CSF). The result [82] is amazing and clearly shows the future dictions of the oncothermia research.

Oncothermia has new facilities to treat advanced, heavily pre-treated (failed pre-treatments), colorectal cancer. A study was performed, [83], including n=218 patients. 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). 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 median of colon, rectum and sigma cohorts are 25.6m, 27.4m and 28.0m, respectively. 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.

Studies were performed for the most common distant metastases of colorectal primary neoplasm: the secondary malignancy in the liver. A study was devoted to see the preoperative application of oncothermia for liver metastases from rectum carcinoma [84]. The primer-tumors were inoperable (R2). 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 was: 71% of patients were in condition for complete resection (R0) while one was partially resected (R1) and one was not successfully operated, (remained R2).

One of the earliest study of oncothermia on colorectal metastases to liver (n=80) was published in 1999, [85]. The median survival was significantly higher with oncothermia than expected without this treatment. The overall median survival was expected as 11 months, while for the multidrug resistant, refractory patients where oncothermia was applied alone, the median survival time was 24.4 month, while for the patients eligible for resensitizing a chemotherapy and oncothermia applied as complementary, the median survival time was 21.5 month. Other study of advanced metastaic liver form colon was shown at ASCO [86]. The local clinical response of liver metastases was 28%; the quality of live reported better for 50% of the patients.

Other study is devoted to compare of first-line (without oncothermia) and second-line (with oncothermia) therapies for colorectal cancer liver metastasis (n=15) [87]. The local response after the second line was significantly better than after the first one, without extra toxicity for the patients. The median survival was 23 months, while the historical expectation: 10-20 months. Tumor-progression was observed mainly outside the applied electromagnetic field.

A first-line, phase II. study (n=30) was devoted to compare the effect of platinum derivatives of liver metastases from colorectal cancer origin, [88]. 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. The local response rate was definitely higher for Cisplatin, while the other benefits shows significantly lower results, the side effects differs also significantly.

This study was made for advanced, non-operable rectal carcinoma (n=65) and its liver metastases (n=29), [89]. Oncothermia was applied by 2-3x / week with concomitant chemo- and radio-therapy. Overall local clinical response (CR+PR+SD) was 96% for rectal primary and 86% for liver metastases.

Methods

TCM and MWM were combined to treat patients with advanced colon cancer. The principles used to treat cancer include eliminating toxins and pathogens, boosting immune system and enhancing their nutrition by CIB method, [90]. These therapies are non-invasive, non-toxic, safe, and effective; utilized in ways to support and enhance the effects of each other, while minimizing their deficiencies. The therapeutic protocol was the combination of oncothermia with Clifford TCM Immune Boosting (CIB) method.

Oncothermia was applied 3 times a week, 60 min/session, 20 cm electrode. The applied forwarded power was 100-150 W, depending on the personal tolerance of the patient. 15 sessions in a cycle, 7-10 days break between cycles. Oncothermia was not applied in female menstruation period.

The protocol of the Clifford TCM Immune Boosting (CIB) [91] was applied per os. It was administered one dose per day (divided into two equal portions), in 200ml portions. One portion, bid. (morning and night, after meal).

Standard oncothermia was applied in primary and secondary lesions (see Figure 1.)

Figure 1. A typical arrangement of oncothermia treatment for liver metastases from colon primary

The study was phase II, randomized, single-blind, controlled, having three comparable arms to measure the efficacy. For objective single-blind method individuals did not know which group they were in. In order to avoid bias, trial operators and therapeutic effect evaluation personnel were not the same members of the staff.

The three groups of patients were:

Croup A (treatment): 51 cases Oncothermia in combination with Clifford TCM Immune Booster
Croup B (control): 50 cases mono Oncothermia
Croup C (control): 53 cases mono Clifford TCM Immune Booster

Their inclusion criteria were:

1. Confirmed colon carcinoma diagnosis
2. Not suitable for surgery (inoperable cases) or patient refused surgery (personal not-eligibility)
3. Recurrence after surgery or carcinoma was not completely resected
4. Predicted survival time > 6 months
5. Score of Karnofsky Performance Status (KPS) > 50

The exclusion criteria:

1. Surgical intervention < 3 weeks
2. Incomplete healing of wound in Oncothermia treatment area
3. With active bleeding, or local blood circulation occlusion in treatment area
4. With emotional disturbance, personal refuse
5. Oncothermia arrangement cannot fit to the treatment area due to individual physical variation
6. Patient had metallic implants or replacements, or any electronic device in the treatment area

The logistics of the treatment protocol (see Figure 2.) was applied for N=154 patients, satisfied the criteria of the study. The final evaluation of the study was after two-years follow-up period, when statistically were evaluated

1. the efficacy of the therapy,
2. the quality of life
3. the survival data

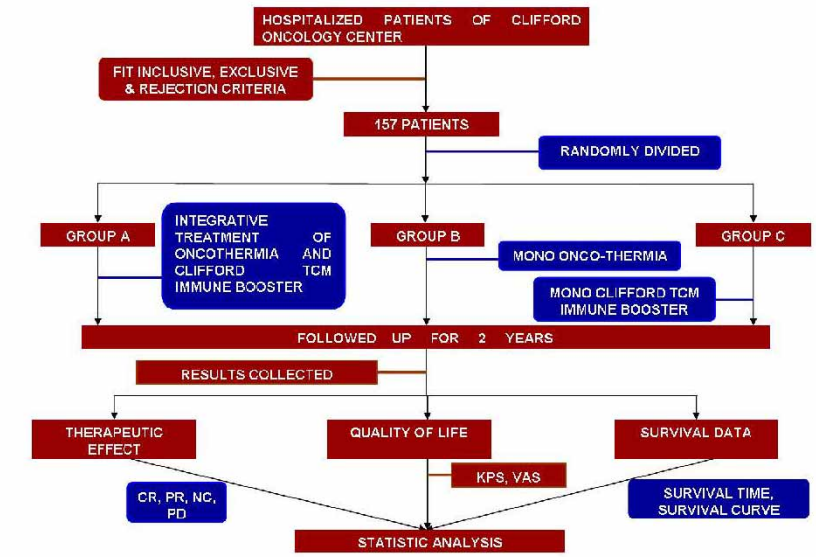


Figure 2. The randomization and logistics of the treatment protocol

The statistical evaluation was based on α=0.05 (CI=95%). Non-parametric survival analysis (Kaplan- Meier Plot) was applied together with:

- Ranks sum test
- *t* test and multiple factor variance analysis
- χ^2 test

Results

Case report

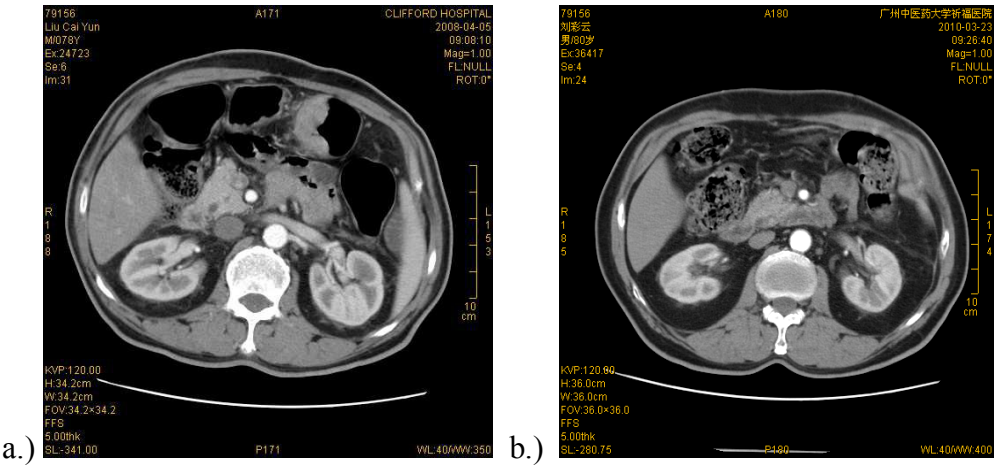
A typical successful case-report shows the process.

- Male patient, 80 year old, diagnosed with ulcerative transverse colon with moderately differentiated tubular adenocarcinoma of stage IV (T3N1M1, with lung metastasis) in April, 2008 (see Figure 3/a.)
- Radical resection of colon cancer was performed in May, 2008
- Came to Clifford Hospital for non-toxic integrative treatments for cancer after surgery

- Treated with Oncothermia in combination with Clifford TCM Immune Booster
- Along with the integrative treatments of chelation, medical ozone, acupuncture, nutritional therapy, Qigong, Taiji, etc

Patient was rechecked on March 23rd, 2010 (see Figure 3/b.):

- No relapse, no metastasis, good nutritional state, KPS 90, VAS 0~1, increase in body weight: 12 kg since surgery
- Normal blood routine and tumor markers results



a.) b.)

Figure 3. (a) before treatment, April, 2008; (b) after treatment, March, 2010

Therapeutic effects – local responses

The local clinical control and response was carefully measured according to the international standards, [92]. The distribution of the local clinical response by its efficacy is shown on Figure 4. The majority of the success in CR and PR categories were detected in the group A, where the complex treatment was applied.

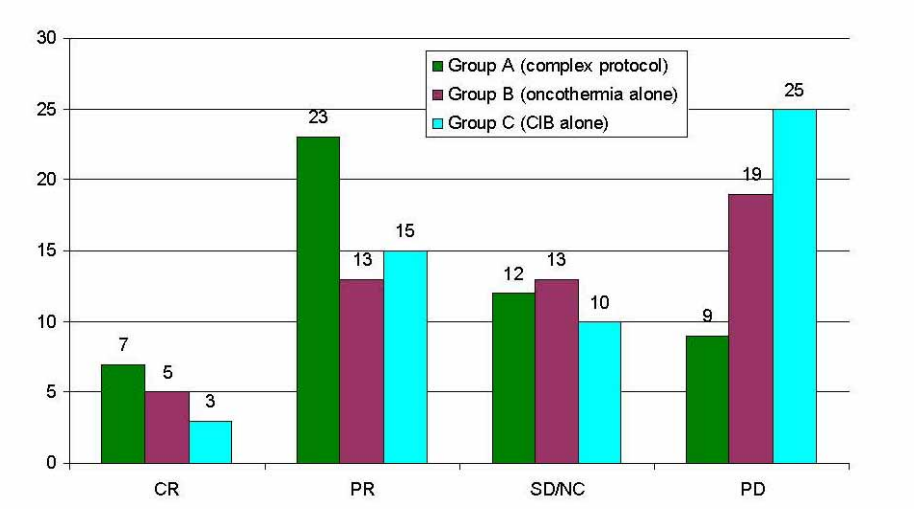


Figure 4. Local response of the patients involved in the study in all the groups. The number of patients are displayed

The grouping by the study-arms (see Figure 5.) shows a growth of the in-efficient categories in groups B & C, while in group A the vast majority of the results is partial remission, and less than 20% remained in progressive tumor-growth.

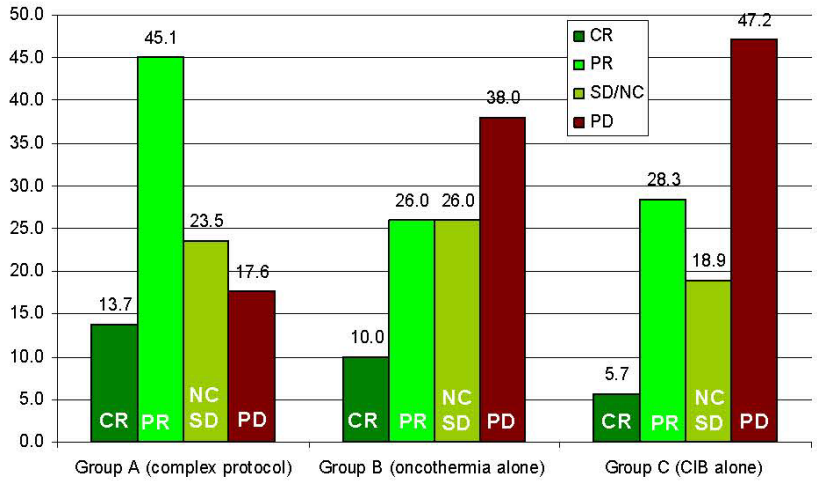


Figure 5. Efficacy of the local response by study-arms. There the percentages are shown by groups

The improvement (shrinking of tumors) produced by the treatment (CR+PR) is shown by arms and by improvement categories, (see Figure 6.). The no-change (NC) in the advanced stages like in the cases of the patients involved in the study is the result of stabile disease (SD), also a kind of response, the further growth of tumor had been stopped. The overall response in this meaning (CR+PR+NC/SD) is shown in Figure 7.

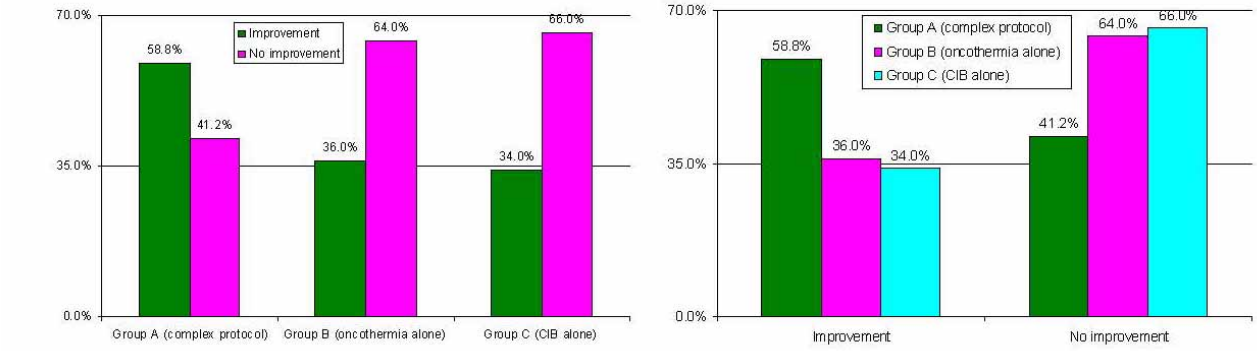


Figure 6. The improvement by the various treatments (Values are in percentages)

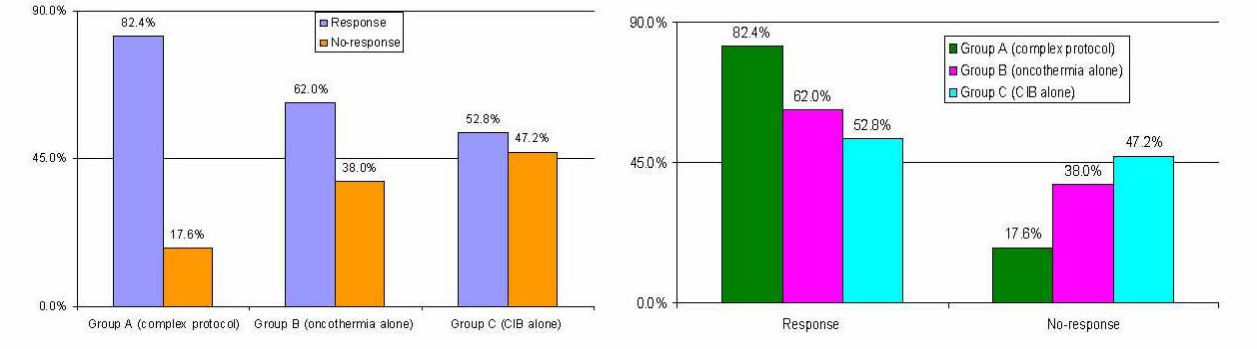


Figure 7. The overall response by the various treatments (Values are in percentages)

Therapeutic effects – survival time

The survival time was measured by non-parametric distribution evaluation (Kaplan-Meier plot, [93], see Figure 8.).

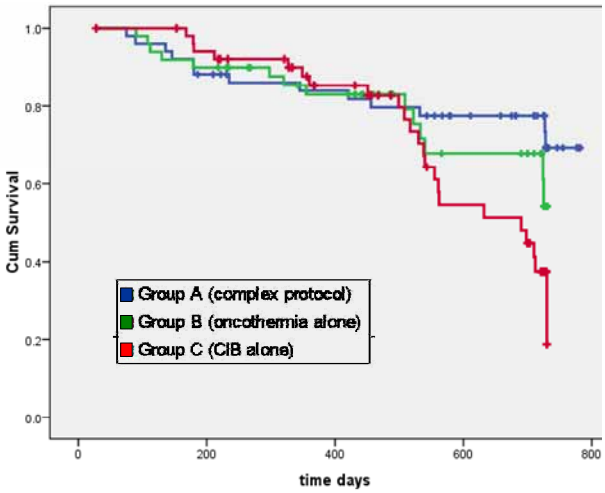


Figure 8. Kaplan-Meier plot of the survivals

Therapeutic effects – quality of life

The quality of life was measured partly with Karnofsky Performance Score status, (KPS, [94], [95]; partly with Visual Analogue Scale VAS [96]).

KPS is an assessment tool intended to assist clinicians and caretakers in gauging a patient's functional status and ability to carry out activities of daily living. The three arms of the study shows that the Group A (complex treatment) has definitely different distribution than its counterparts B & C, (see Figure 9.)

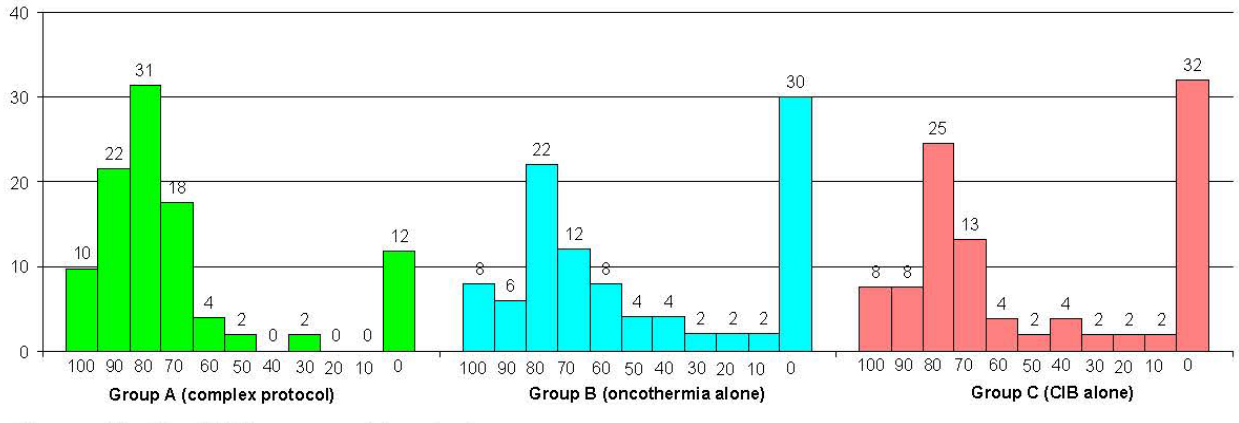


Figure 9. The KPS grouped by study-arms

Describing the major categories, three groups of KPS can be formed, as shown Table 2. According to this categorization the patients' quality of life is shown by study-arms (see Figure 10.) and by KPS grouping (see Figure 11.).

Able to carry on normal activity and to work; no special care needed (KPS=80-100)
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed (KPS=50-70)
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly (KPS=0-40)

Table 2. Major groups of KPS

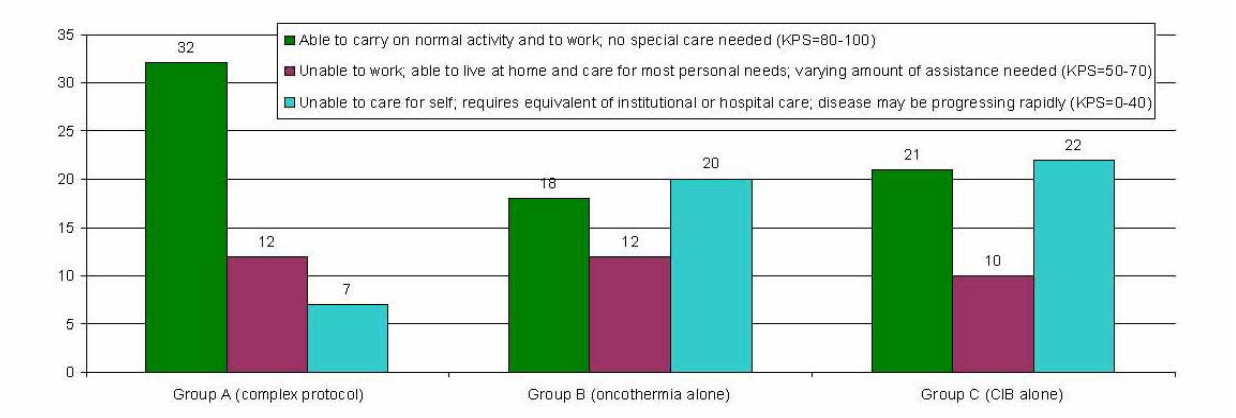


Figure 10. KPS grouped by study-arms

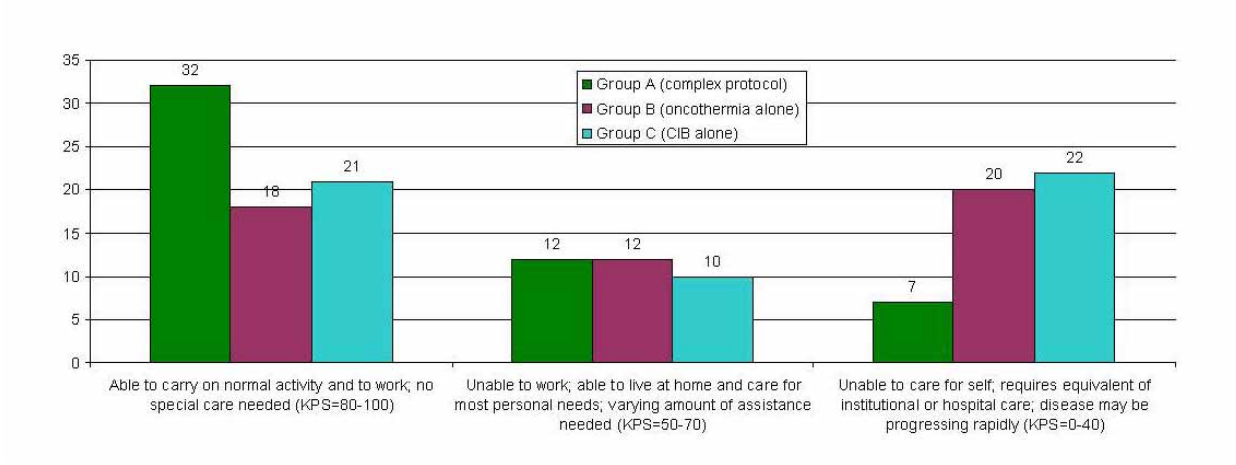


Figure 11. KPS grouped by major categories of quality of life

VAS score measures mainly the pain-effect as a decisional factor of the quality of life for cancer patients. This important quality factor is shown for all the patients in Figure 12. The VAS score grouped by main VAS categories (see Figure 13.) and by study-arms (see Figure 14.) shows definite differences favouring the group A again.

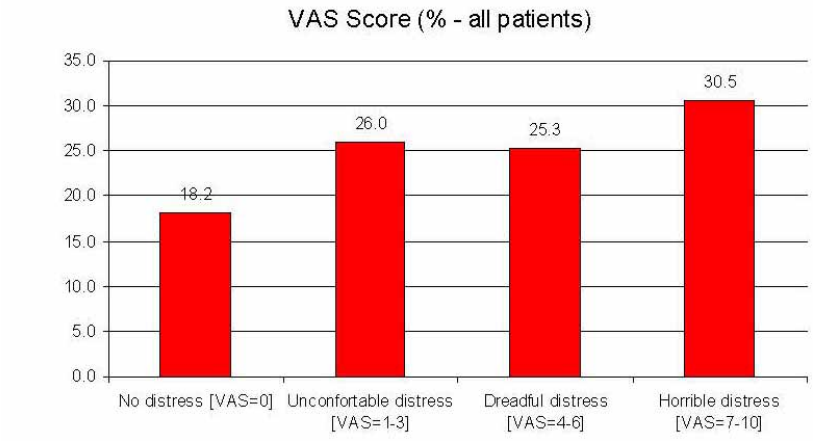


Figure 12. Overall VAS score after the full therapy regime of all the patients involved in the study (values are in percentages)

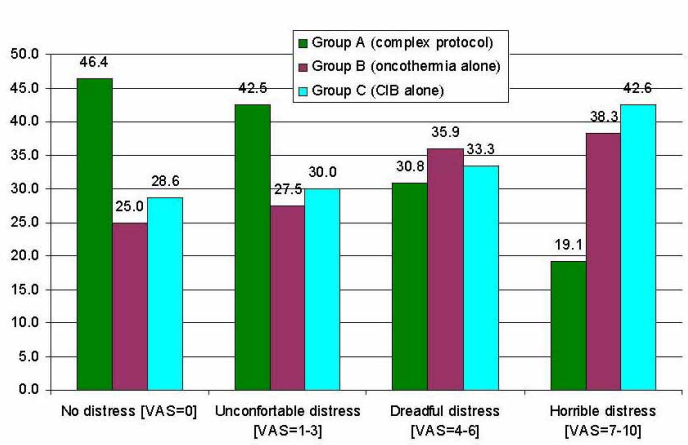


Figure 13. VAS score grouped by main VAS categories (values are in percentages)

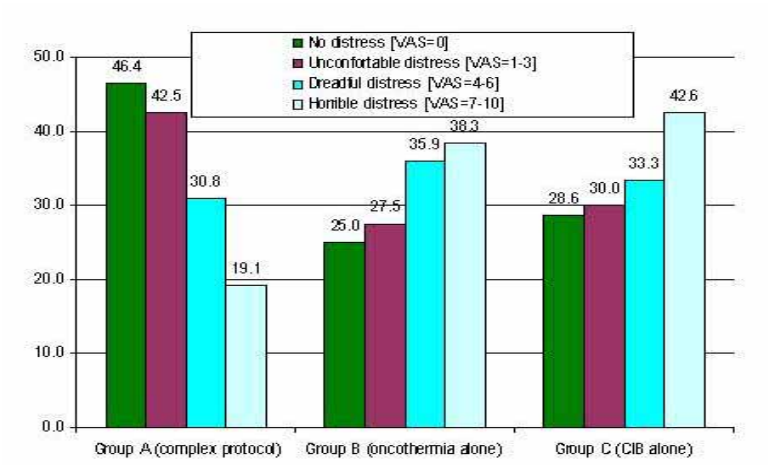


Figure 14. VAS score grouped by the study-arms (values are in percentages)

The data of the statistical evaluation are shown in Table 3. and Table 4.

Rank Sum Test on KPS of 3 Groups

	u	*P*	
Group A and Group B	-3.0906	0.002	<0.05
Group A and Group C	-2.9906	0.0028	<0.05
Group B and Group C	-0.0133	0.9894	>0.05

Table 3. Rank-sum test for group-pairs

Rank Sum Test Results on Every Two Groups

Groups	*P*	
Group A and Group B	0.0204	<0.0500
Group A and Group C	0.0362	<0.0500
Group B and Group C	0.9392	>0.0500

Table 4. Rank-sum test results for group-pairs

Adverse reactions of oncothermia in treatment are was some solitary fat-burn in adipose regions in the treatment area. Temporarily slight erythematic spot and slight pain could happen. No other toxicity was observed.

Discussion

Results are showing significant synergy of oncothermia and Clifford TCM Immune Boosting (CIB) method. The clinical local response (tumor control) is significantly better in the complex treatment than its counterpart options. However the malignant disease is not local, so we were intensively looking for the systemic (integrative) evaluation, which are the survivals and the quality of life. Both of these parameters are definitely enhanced by the synergy of oncothermia with CIB. It is important to also, how the groups B and C are equivalent ($p>0.9$!), which convinces the researchers that both of the methods are natural and acting in the dynamism of the homeostatic control. Oncothermia disclaims the old approach, introducing a new paradigm: with application of micro-heating it makes considerable less physiological feedback to work against the action, and with application of the electric field it uses such an effect, for what the body has no physiological answer. With this new paradigm oncothermia helps the natural feedback mechanisms to reestablish the healthy state. The philosophy of oncothermia follows simply the line of Hypocrates: "Nil Nocere" ("Do not harm") Of course this has to be understood on the way as "be natural as more as possible". This is the basic of the great harmony with the TCM methods, which philosophy based on the same principles. Both the treatment modalities support the natural processes of living organisms, applying the normal physiological, biophysical and biochemical reactions of the body, using these to fight against the malignancy on standard way. This is the solid basis of its application in combination of the TCM methods, and especially with CIB therapy, which concentrates on the immune effects, to keep the effectors of the homeostatic balance forceful.

Both the treatments are very safe, no similar side effects appear as we had seen in most of the MWM methods, like the chemo- and radio-therapies.

Conclusion

Integrative treatment of colon carcinoma with Oncothermia and Clifford TCM Immune Booster is safe and therapeutically effective.

- It can prolong survival time and improve the quality of life of patients.
- Only a few minor adverse reactions appeared which were rapidly resolved in a short time without treatment and had no effect on the quality of life of patients.
- This integrative treatment of Oncothermia and Clifford TCM Immune Booster is an important contribution to the non-toxic approach to treatment of cancer.

The research is in progress for other cancer lesions too.

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Complete Remission of SCLC with Chemotherapy and Oncothermia (Case Report)

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Abstract

Nowadays, most oncologists have treated their patients with solid tumors by using hyperthermia with good results even though they have a large amount of different thoughts on the mechanism of oncological hyperthermia. We have treated our patients with solid tumor confirmed lung carcinoma with chemotherapy or radiotherapy with oncothermia [1] at the Department of Thoracic and Cardio-vascular Surgery at Gangnam Severance hospital since Jan, 2008. Our objective in this paper showing a case of a patient with Small Cell Lung Cancer (SCLC). The patient was and treated by chemotherapy andand oncothermia in 2008, at the Thoracic and Cardio-vascular Surgery Department, Gangnam Severance Hospital, Seoul, Korea. We report a complete remission of this patient after chemotherapy with oncothermia (2 cycles) in follow-up for 3 years.

Introduction

Hyperthermia for cancer therapy has been documented for thousands of years. [1] Conventional hyperthermia heated the surface of the body, and was supposed to achieve curative influence in the malignant tumors. Various procedures have been applied to deliver heat into the malignant tumor, e.g. hot-bath, surface heaters including heat-blanket, heat radiators etc. The aim was to change the pH- environment of the malignant tissues by the elevated temperature developed by higher rate of metabolism causing acidosis. And Hyperthermia was revived around the end of 19th Century, when the deep penetrating energy transfer was solved by electromagnetic way.

There are intensive scientific discussions about the treatment of the cancer by chemotherapy (CT) or by radiotherapy (RT) complementary with hyperthermia. [2], [3].

Although hyperthermia can have significant benefits, there are several problems to be solved.

1. Hyperthermia dosing andtreatment control is not standardized, which is a a basic challenge. While hyperthermia is the overheating of the targeted tumor tissue, the heat-dose and the method of heating tumors is not accurately defined. The blood- flow inequalities influence the developed temperature in the target, even in cases when the specific absorption rate (SAR) is homogeneous.

2. Inadequate focusing of heat and the natural temperature smearing may certainly heat up the healthy tissues around, causing definite nutrient-supply to the tumor together with increasing risk of dissemination. The misfocusing also could cause unwanted burn.

3. Heat-shock proteins (HSPs) are induced by heat-stress and the developed HSP- assisted adaptation mechanism decrease the efficacy of hyperthermia. The target can develop resistance to heat, and could become refractory for chemo- and radiation-therapies.

The description of the role of the temperature in clinical oncological hyperthermia has not concensus yet and the explanation of the heat-dose (energy absorption) dependence of the curative effects in tumor tissues is also debated, and, [4] many details have not been clarified yet. The proliferation and the metabolism of tumor tissues are more active than in their healthy counterpart, and this requests a large amount of energy consumption. Consequently, their heat production is higher than usual. Hence, the tumor tissue is usually warmer than its healthy environment. Furthermore, the additional increase of temperature by hyperthermia enforces the

tumor tissues to increase their metabolism, [5].

The temperature of the healthy tissues is regulated by the blood flow with physiological thermo-regulation. The blood flow in the healthy tissues around tumor tissues is not increased due to not increased temperature in the healthy tissues during the ideally conducted hyperthermia, till the temperature is well focused and not smeared by time, [5].The temperature increase in tumor has a supporting fact, that the thermo-regulation of the blood flow in tumor has no same physiological control, than its healthy neighborhood, [6], [7]. Consequently, there insufficient oxygen supply is available due to unchanged blood flow, the increased metabolism due to increased temperature in tumor tissues has a lack of nutrients and oxygen by constrained metabolic activity during hyperthermia. The resulting hypoxia though increased aerobic metabolism produces severe the occurred progressively acidosis and the results could be the destruction of tumor cells, [7], [8]. Furthermore, the increased metabolism decreases the ATP content of cells and therefore increased metabolism forces the cell destruction in tumor tissues, [6]. The DNA replication can be blocked also by the heat effect; the reproduction processes of DNA is slowed down in tumor tissues, [9], [10], [11].

Moreover, hyperthermia supplies the hypoxic tissues by oxygen, which increases the efficacy of radiotherapy, [12], [13].

The thermally increased metabolism enhances the reaction rate of drugs, while the increased blood perfusion supports the absorption of cytotoxins. Together with the high chemo-metabolism the drug-delivery is also high, making effective the complementary application of hyperthermia with chemotherapy. Significant pain-reduction and the few side-effects are the specific advantage of hyperthermia. These effects may contribute to considerable improvement of life quality, [14]. Hyperthermia enhances the efficiency of the immune-reactions as well, **[10]**, **[11]**; and it has primary effect to destruct the tumor cells above 42.5□, **[12]**, **[13]**.

Despite of the geart advantages of hyperthermia, it suffers a lack of acceptance, because of the controversial clinical results in practice. When the thermal effect is not adequately supplied and focused, this may increase the oxygen supply of tumor cells and activate the growth of tumors. The inappropriate focusing of heat may increase the risk of necrosis of surrounding healthy tissues and activate metastasis (cellular dissemination) of tumor cells. Also the concentration of heat shock proteins (HSP) in tumor cells is increased by the inappropriate applied heat, [15], [16]; which works against the heat-promoted processes described above.

Furthermore the developed extra HSP concentration degrades the efficacy of thermo-treatment generating a risk of heat- multi-drugs and radiation-resistances.

Unfortunately it is technically difficult to control the heat transfer reproduction and stability; furthermore there is no adequate parameter exists to detect the success and degree of hyperthermia.

Recent modulated electro-hyperthermia (oncothermia, **[1]**) is devoted to enhance the efficiency of classical hyperthermia by thermal and thermally induced but not temperature effects with the suppressing the existing disadvantages of the classical thermal treatments.

The electric field has smaller penetration depth than the magnetic one, however, its energy delivery and absoption are relatively high. The energy absorption determined by the electric parameters (dielectric constant and electric conductivity) of the targeted tissues, and also it is frequency-dependent (material dispersion). The conductivity in malignant tissues is about three times higher than that of normal tissues, [17], [18]. The higher electric conductivity is accompanied by higher dielectric constant in malignant tissues; and the extra-cellular matrix in there absorbs more energy than in the healthy areas, [19], [20]. The absorbed energy from the electric field effectively heats up the extracellular electrolyte and the temperature increases there rapidly. The cytoplasm of cell will be heated by heat diffusion through the membrane and heat diffusion acts considerably slower in the cell than the direct heat does in the extra-cellular liquid, [21]. Moreover, the suppressed warming of intracellular field reduces the non-

thermal HSP synthesis.

Tremendous heat-flow, 1500nW/μm^2, transmits through the membrane by the above mechanisms, while the natural heat-flow by metabolism, is only 20nW/μm^2. The heat-gradient in the cell allows distinct membrane currents because of its definite thermodynamic driving force. The forced current is also remarkable high: 150pA/μm^2, which is dominantly Na^+ influx into the cell. (the natural ion currents are 12pA/μm^2, sodium efflux) and the presence of these currents decreases the dynamic stability of cell membrane. In addition to the thermal flux electro-osmotic effects induce higher pressure in the cell, reaching 1.32MPa. Since malignant cells have relatively rigid membranes by their increased phospholipids concentration, the increase of the intracellular pressure distorts the cellular membranes of the malignant cells before the heat affects healthy ones, [22]. Consequently this actual pressure has a selective action to destroy the membrane of the malignant cells.

These processes allow a very important effect: the cell membrane of malignant cells is damaged before the heat reaches the cell-nuclei to synthesize HSP resisting the stress of invasion. However, membrane HSP is induced by penetratable membrane, which are supporting the apoptotic signals, to eliminate the malignant cells on the natural way.

The energy is primarily absorbed in the extra-cellular matrix by oncothermia, and penetrates into the cell by thermal diffusion through the cell membrane resulting in the damage of the cellular integrity.

Oncothermia is based on the differences between the dielectric constants, dielectric losses and on the selective absorption features of surrounding electrolyte of the cells. Malignant tumor cells are autonomic, they are not collective like their healthy counterpart. The applied frequency and its modulation is able to select the heating site on cellular basis, targeting the malignant cells individually. EHY2000 oncothermia was developed by capacitive coupling for modulated electro- hyperthermia uses a well-tuned RF (13.56MHz) electric field. Relatively little total power can be applied because of the good selectivity and well-focused heat absorption concetrates the energy on the effective way. On this way the EHY2000 regional oncothermia is for the treatment of deep-seated, organic tumors (brain, liver, kidney, lung, pancreas). This is a non-invasive, universal, easy controllable device and does has little risk of complications. Practically, there is not any complication except a few mild skin burn or burning sensation. This is one of the effective treatments in oncologic treatment field and a new modality of cancer treatment. This oncothermia is more gentle and safer than the conventional classical hyperthermia and can extend the thermal treatment efficiency to thermal and non-temperature dependent effects too. The heat dose (absorbed energy) and the applied field (electromagnetic influence) are the primary determinants of efficacy of oncothermia, [23]. It is based on a capacitively-coupled energy transfer applied at a frequency that is primarily absorbed in the extracellular matrix due to it's inability to penetrate the cell membrane, [24].

The case

The 67 years old male patient had cough and mild fever and registered in our outpatient clinic at the Department of Thoracic and Cardio-vascular Surgery at Gangnam Severance Hospital, Seoul, Korea at Aug. 10th. 2008. The chest PA and chest Computed Tomogram (CT) should about 3.6cm mass on Left Upper Lobe (LUL) with abutting to descending aorta with another small nodule in left lower lobe. Multiple enlarged lymph-nodes were seen in left hilum and left paratracheal area. We established a lung cancer, stage T3/4N2Mx. Bronchial washing cytology showed negative finding with broncho-fiberscopy, but transbronchial lung aspiration biopsy cytology revealed small cell lung carcinoma. The needle aspiration cytology showed also positive for malignancy favoring small cell lung carcinoma.

Somatometry	level
Body weight, kg	58
Height, cm	174
BMI, kg/㎡	19.16

The patient somatometry and the laboratory findings are listed in tables below:

Serum	level
WBC count, 10^3/㎕	6.27
Hb,g/㎗ - Hct,%	11.8 - 35.0
PLT count, 10^3/㎕	134
BUN, ㎎/㎗ - Cr., ㎎/㎗	17.3 - 1.1
AST, IU/L - ALT, IU/L	26 - 21
Albumin, g/㎗	3.9

The tumor markers were at Aug. 2008.

Tumor markers	level
CEA, ng/㎗	0.8
CYFRA 21-1, ng/㎗	2.3
NSE(Neuron Specific Enolase), ng/㎗	24.2

He was treated with chemotherapy Irinotecan(60 ㎎/㎡) and Cisplatin(60 ㎎/㎡) 12 cycles since Aug. 2008 to Nov. 2009 complementary with oncothermia for 1hr per session, 2 times in a week for 12 weeks (2 cycles) from Aug. 2008 to Nov. 2008. The following checks by chest PA and chest CT showed marked regression of the size of lung cancer in left upper lobe and also regression in multiple lymph-nodes in left hilum. Tumor markers at Oct. 25th. 2010 was decreased as blow.

Tumor markers	level
CYFRA 21-1, ng/㎗	2.9
NSE(Neuron Specific Enolase), ng/㎗	12.4(decreased)

He has been followed for 3 years without chemotherapy and oncothermia, having the last check-up in April 2011 at outpatient clinic. Chest PA and Chest CT showed marked regression of tumor in LUL, but residual small sized LNs in the mediastinum and left hilum were observed at Feb. 9th. 2011. However in the same time the chest PA and Chest CT showed complete regression of tumor in LUL suggesting of complete remission of SCLC.

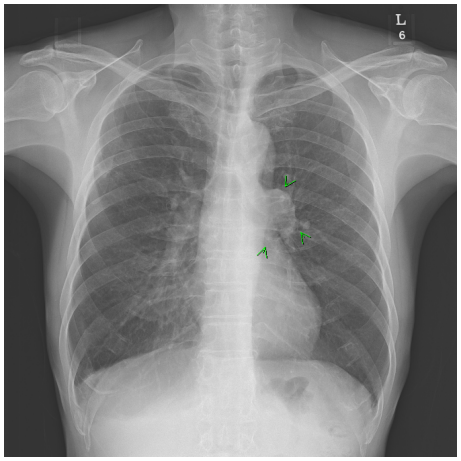


Figure 1. Chest PA showed prominent tumor at left hilum at Aug. 2009.

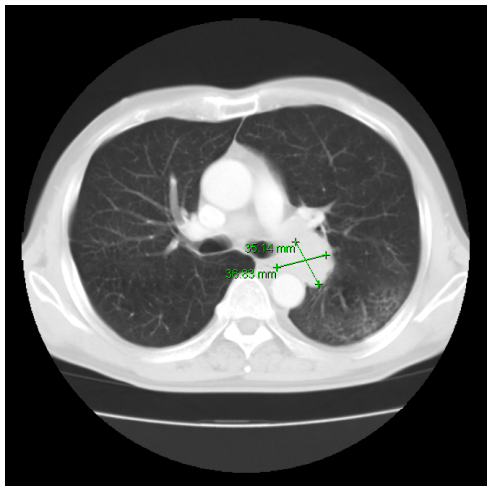


Figure 2. Chest CT showed tumor abutting to descending aorta in left hilum at Aug. 2009.

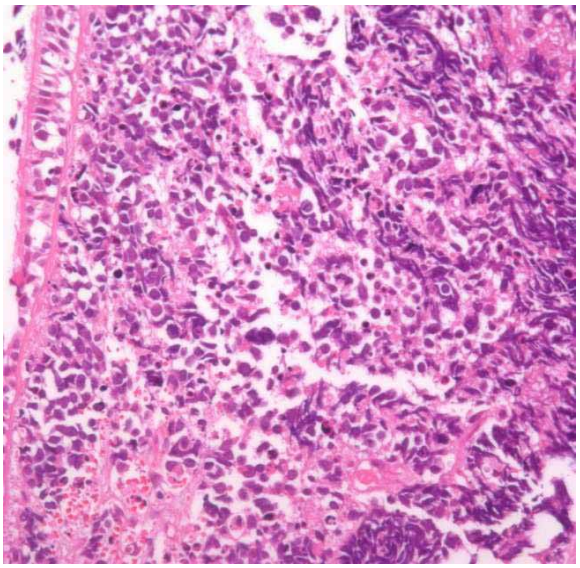
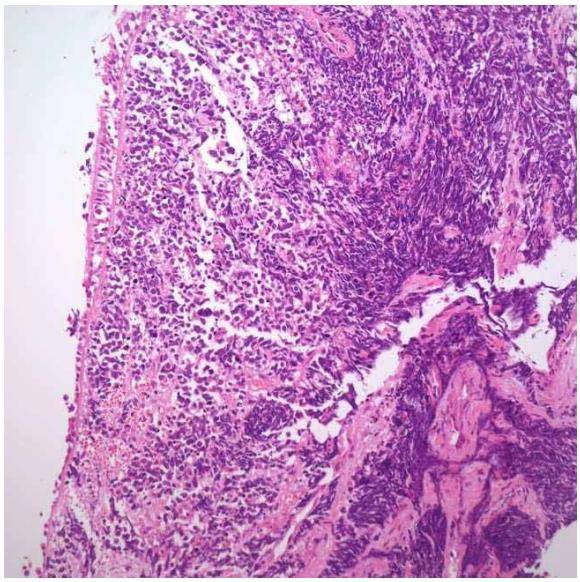
a.)  b) 

Figure 3. (a) HandE, x200; (b) HandE. x400

Subepithelial infiltration of tumor cells showing hyperchromatic nuclei, scanty amount of cytoplasm, and frequent squeezing artifact. These findings are compatible with small cell carcinoma. (HandE, x200 and x400).

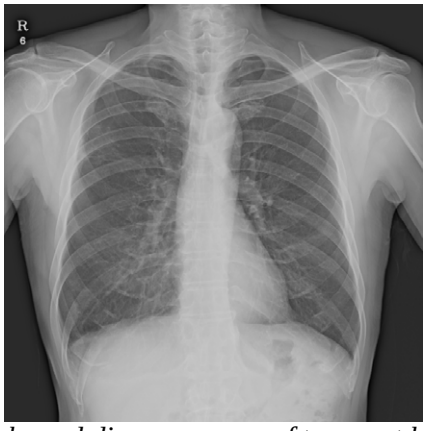


Figure 4. Chest PA showed disappearance of tumor at left hilum at Oc. 2010

Figure 5. Chest CT showed total remission of tumor at left hilum at Oc. 2010

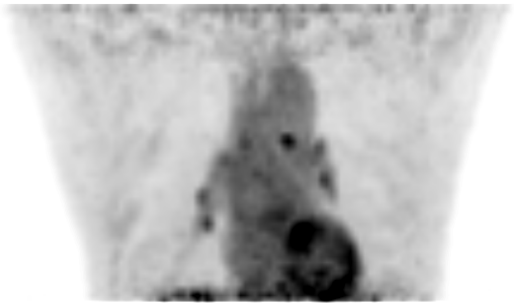


Figure 6. PET CT showed no hot uptake in the whole body at Oct. 2010

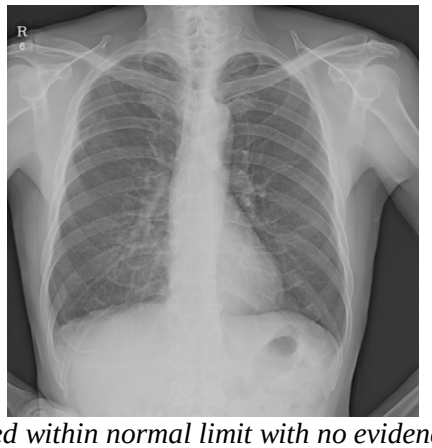


Figure 7. Chest PA showed within normal limit with no evidence of tumor at April 2011

Figure 8. Chest CT showed no evidence of tumor at left hilum at April 2011

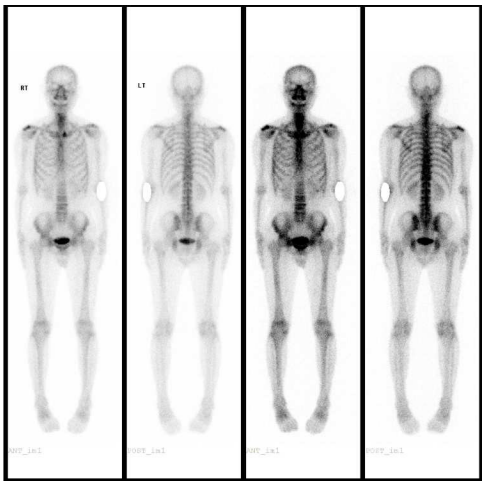


Figure 9. Whole Body Bone Scan showed no hot uptake suggesting metastatic evidences to skeletons at June 2011

Discussion

Modern lung-cancer treatment is based on platinum-containing doublets (Carboplatin and Cisplatin) and 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%, [27] 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, [28]. 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. [29]. 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.

Hyperthermia (HT), combined with radiotherapy (RT) and chemotherapy (CT), seems to be a promising method enhances chemo- and radio-sensitivity and induces a high concentration of drugs within a tumor [30], [31].

However, there are some restrictions for HT in general, that hamper its use in lung cancer treatment. Namely, it could aggravate preexisting pleural liquids, as well as the lung is a complicated tissue for hyperthermia because of the permanent cooling- ventilation due to the continuous breathing.
However, 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, [32]), and RR=100% (n=13, [33]). 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, [34]), and RR=76.9% (n=13, [35]), 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%, **[25]**).

The chemo-thermotherapy combination was also investigated for non-small-cell lung cancer (NSCLC) with success. In preclinical trials the cisplatine was shown to be effective, [36], so the clinical studies were concentrating on this drug combination. Special case report has shown the feasibility [37], and the median survival gain (from 15 (n=20) to 25 (n=32) months), [38]. The median survival was measured in another study [39], as 19.2 months, the RR=73% and the 1 year-survival is 75%. The 5y median survival was measured in another study [40], showing rather high numbers (24.5%, n=30).

One of the most advanced HT-modalities devoted to oncology is oncothermia. In the preliminary reports [41], [42], **[25]** the feasibility of the OT application was demonstrated. Oncothermia, due to the development of non-equilibrium state, is an ideal approach for the destruction of tumor cells in lung. **[25]**, **[26]**.

Oncothermia has given complete remission of malignant lsmall-cell lung cancer for more than 3 years after 2 cycles of oncothermia and chemotherapy in the Department of Thoracic and Cardio-vascular Surgery, at Gangnam Severance Hospital, YUMC, Seoul, Korea.

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Case of Abscopal effect with Metastatic Non-Small-Cell Lung Cancer

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Case of Abscopal effect with Metastatic Non-Small-Cell Lung Cancer

Abstract

The abscopal effect is originally defined as the observational effect of radiation therapy at site distant to the treated field. Recently systemic effects of local radiotherapy including hyperthermia and immunotherapy have received attention as a new therapeutic modality. We report a case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. Patient was treated with fractional radiotherapy, modulated electro-hyperthermia (oncothermia) and granulocyte-colony stimulating factor (GM-CSF).

Key words: Abscopal effect, Radiotherapy, Hyperthermia, GM-CSF, Non-small-cell lung cancer

Introduction

During the last decade, there has been an amazing progress in cancer research and treatment in the world and also in Korea. Nevertheless, the overall 5-year survival rate of lung cancer patients in 2001 - 2005 period was still 15.6% in South Korea. This type of cancer is usually diagnosed in advanced stage, consequently the overall survival did not show noticeable improvement, [1].

Poor performance status and/or multiple co-morbidities limit the treatment options for elderly patients [2]. Their poor prognosis is commonly accompanied with a common refusal of cytotoxic chemotherapies even adequate chemotherapy would be available with acceptable expected tolerance **[2]**. Options about the actual cancer treatments are deeply affected by subjective opinion of patients and their family members, who are avoiding the treatment-related several side effects [3]. In such cases radiotherapy could be considered as curative or palliative treatment option [4].

The newly available orally administered medicaments for non-small-cell lung cancer (NSCLC) are frequently refused also due to the requested co-payment and the lack of enough proper evidences [5].

According to our common knowledge the local therapy of radiation is not available in cancer patients with multiple metastatic lesions. However, systemic, so called abscopal effect, is observed [6] outside the treated field of ionizing radiation [7], but it is generally under-recognized in the clinical practice [**6**]. The first published observation on systemic effect of local radiotherapy was made by R.H. Mole, who proposed the term "abscopal effect" in 1953 [8]. It is originally defined as the systemic effect of radiation therapy observed in distant tumors from the site of irradiation field. It is suggested that the abscopal effect relates to immune response mediated by cytokines, but the mechanism remains unclear because this phenomenon is so rare and poorly understood in clinical practice, showing many controversies also [9]. Sometimes it is used complementary to other type of local therapies including surgery, hyperthermia and immunotherapy [10]. These complementary applications have recently received attention as new therapeutic facility [11].

Case reports on abscopal effect were published in various malignancies including lymphoma, malignant melanoma, chronic lymphocytic leukemia, adenocarcinoma of the esophagus, papillary adenocarcinoma, and hepatocellular carcinoma. However, according to our knowledge, there is

no report regarding NSCLC [12], [13] with abscopal effect, however some pulmonary applications were experienced [14], and clinically applied [15], [16].

In our present paper we assumed the possible boosting of abscopal effect of radiotherapy in combination of modulated electro-hyperthermia **[10]** and immunotherapy. Case of abscopal effect was observed in a patient with multiple metastatic NSCLC, treated with 3-D Conformal Radiation therapy (3DCRT), electro- hyperthermia (oncothermia) and granulocyte-colony stimulating factor (GM-CSF).

Case description and applied methods

A 72-year-old male patient was diagnosed with unclassifiable NSCLC by other hospital in July 2009. The classification of the tumor at first diagnosis was cT2N2M0, stage IIIB. Despite of the advanced case the patient refused any treatment. Five months later (December 2009), he visited outpatient department of complementary and alternative medicine with complaints of hemoptysis and dyspnea on exertion gradually worsened 4 weeks before. He was referred to medical oncology department and admitted for re- evaluation.

Staging work-up including chest CT and PET scans showed 9.5cm sized cavitary mass at right middle lobe with multiple regional and metastatic lymph nodes. He had no co- morbidities and no medical history (see Figure 1.). However, he still refused chemotherapy and together with his family members requested other possible treatment options.

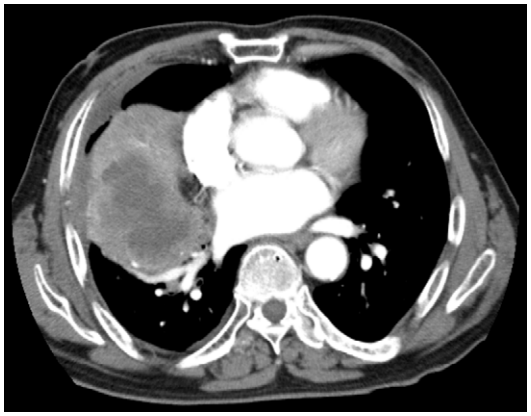
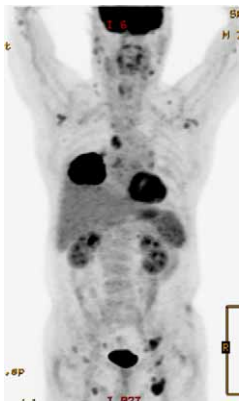
a.)  b) 

Figure 1. CT CT chest scan (a) and whole body FDG-PET scan (b) of the patient. About 9.5 cm sized huge lung mass with central necrosis was detected in right lower lobe and the mass had a hypermetabolic walled cavity. Multiple metastatic lesions were also showed in both of neck, axillas, inguinal regions and mediastinum including right hilum

In these circumstances we made radiotherapy in combination with oncothermia and GM-CSF expecting to induce abscopal effect. Local field radiation therapy to lung mass was delivered at a dose of 1.7 cGy in 28 daily fractions for 5-6 treatments in a week. It was followed by oncothermia after radiation 3 times a week (see Figure 2.). After 2 weeks of treatment, GM-CSF (250 microgram, Leukine®, USA) was administered subcutaneously once a day for 10days.

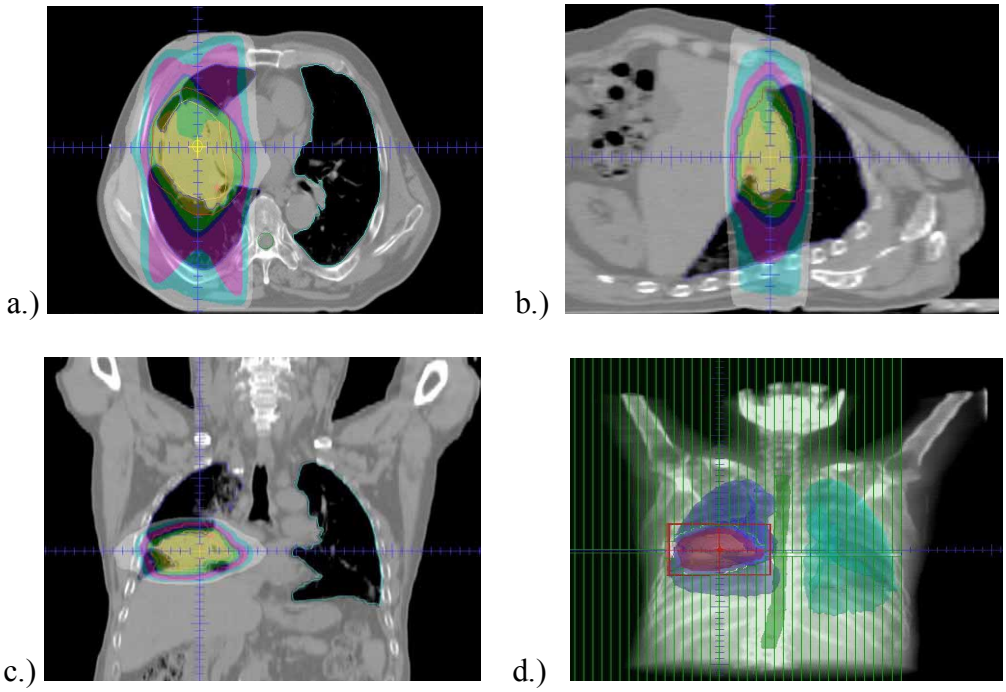


Figure 2. Multi-leaf collimator (MLC) shaping surrounding target and radiation dose distribution in 3 directions for a patient with metastatic non-small-cell lung cancer. Scheme of the axial (A), sagittal (B) and coronal (C) images show the radiation dose distribution for lung mass of primary site. The isodose distribution of individual colors showed as yellow (100%), Green (95%), blue (90%), magenta (70%), cyan (50%) and white (30%) associated to prescribed dose. (D) MLC shaping in anterior beam's eye view

Oncothermia is an emerging method [17], having positive studies [18], and its radiotherapy application is established, [19]. It is a loco-regional deep heating with RF- conductive current by modulated 13.56MHz radiofrequency current [20], having definite synergy of the heat and applied electric field, **[10]**. Hyperthermia can also enhance the immune reactions with increase of natural killer cell activity and distribute tumor- specific antigens on the surface of tumor cells [21].

According to preliminary data of clinical study designed **[11]**, GM-CSF in dose 125 IJg/m^2 was given subcutaneously for 14 days after one week of radiotherapy. The result supported that using GM-CSF was feasible and its effect enhanced the immune therapy.

GM-CSF was also evaluated to detect its immunostimulatory and antitumor effects in breast cancer and melanoma as neoadjuvant or adjuvant treatment complementary with chemotherapy or applied as monotherapy [22], [23]. In these studies, GM-CSF was administered for 10 to 14 days and the results were encouraging and promising.

Results and discussion

Treatments were provided without any complications. Patient presented no severe adverse effects except grade 1 fatigue at the end of treatment period. By follow-up process, just after finishing radiation treatment series PET scan showed nearly complete remission in multiple metastatic lymph nodes, which were distantly away from radiotherapy field (see Figure 3.).

Figure 3. FDG PET scan at the end of radiotherapy combining with hyperthermia and GM-CSF. The image shows excellent response in lung mass of primary site which was irradiated and complete remission in all metastatic lesions which were outside the radiation field

Evaluating the case we think that the activated immune response was the key factor of the present result. We think, oncothermia had parallel effects in our case, by local oxygenation had sensitized more the local radiotherapy effect, as well as the immune response was more activated by its electric field process [**10**]. Furthermore, probable the granulocyte-colony stimulating factor (GM-CSF) promoted the growth and differentiation of dendritic cells which is one of the most promising approaches in cancer immunotherapy. We suppose the radiotherapy combined with oncothermia and GM-CSF can be feasible and more effective than the radio-monotherapy is [**6**].

Patient was satisfied and discharged with successful response. The follow-up of the patient is continuing.

Conclusion

Our case describes a successful abscopal effect with local radiotherapy in combination with oncothermia and GM-CSF immune-stimulation. This attempt seemed to be more effective in immune response than radiotherapy alone. Our present report orients our attention to make further observations of the phenomenon in similar cases when its application is requested. Further studies on the abscopal effect are necessary to evaluate the significance of this cancer treatment option.

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Bluttests für onkologische und immunologische Fragestellungen

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Bluttests für onkologische und immunologische Fragestellungen

Der Erfolg einer Krebstherapie hängt ganz entscheidend vom Zeitpunkt der Diagnose und der Charakterisierung des Tumors z.B. hinsichtlich der Invasivität und Therapieresistenz ab, denn je früher die Erkrankung entdeckt und je genauer die Tumoren beurteilt werden können, desto höher sind die Heilungschancen. Aufgrund dessen ist es von großer Wichtigkeit, dass diagnostische Verfahren etabliert werden, die dies ermöglichen.

Mit Hilfe eines neuen immunologisch-diagnostischen Verfahrens **(EDIM-Technologie, Epitop-Detektion in Monozyten)** lassen sich Tumoren aufgrund der Aufnahme (Phagozytose) von Tumorzellen durch Makrophagen wesentlich früher als bisher erkennen und genauer charakterisieren. Bislang werden mit Hilfe des Verfahrens zwei Proteinmarker bestimmt: **Apo10** und **TKTL1**.

Der Marker **Apo10** wird unabhängig von der Tumorentität hochspezifisch in Tumorzellen exprimiert und bei einer gestörten Apoptose akkumuliert. Dies haben Untersuchungen an über 25 Tumorentitäten und mehr als 5000 Patientenproben ergeben. Durch den Nachweis des Apo10-Antigens in Makrophagen ist es nun möglich, Störungen der Apoptose zu messen und hierüber einen frühzeitigen Hinweis auf proliferative Störungen und Tumoren zu erhalten.

Tumore können zudem ihren Stoffwechsel verändern und trotz der Gegenwart von Sauerstoff von dem Verbrennungsstoffwechsel (oxidative Phosphorylierung) mittels Abschalten der Mitochondrien auf den Vergärungsstoffwechsel (aerobe Glykolyse) umschalten. Bei dem Vergärungsstoffwechsel entsteht als Endprodukt Milchsäure, die eine Matrixdegradation verursacht und dadurch Tumorzellen ermöglicht, **invasiv** zu wachsen und zu **metastasieren**. Gleichzeitig wird durch die Milchsäure die **Immunantwort blockiert** (u.a. durch die Hemmung der natürlichen Killerzellen). Aufgrund der Umschaltung von der Verbrennung auf die Vergärung werden diese Tumorzellen auch **resistent** gegenüber radikal- und apoptoseauslösenden Therapien. Außerdem weisen vergärende Tumorzellen eine **erhöhte Glukoseaufnahme** auf. Diese Eigenschaft wird mit dem bildgebenden FDG-PET/CT-Verfahren diagnostisch genutzt. Verantwortlich für diese Umschaltung des Stoffwechsels ist das **Transketolase-like-1-Protein (TKTL1).**

Diese Eigenschaften von TKTL1 wurden in über 30 wissenschaftlichen Publikationen weltweit gezeigt. Zuletzt sind zwei große Studien der Universitätsmedizin Mannheim und der Universitätsklinik Freiburg erschienen. Hierin könnte für Darm- und Lungenkrebs an mehreren hundert Patienten gezeigt werden, dass eine TKTL1 Überexpression mit einer Resistenz gegenüber Standardtherapien, einer höheren Rate an Metastasen und Rezidiven und einer schlechteren Prognose verbunden ist.

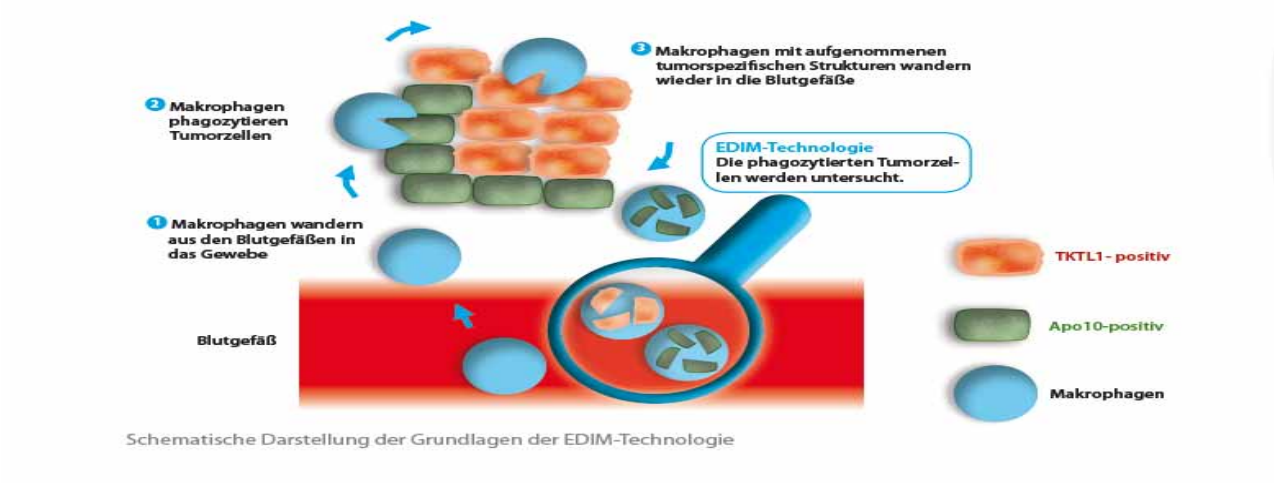
Ergänzt wird die Detektion und Charakterisierung von Tumoren mittels der Marker Apo10 und TKTL1 durch eine detaillierte Analyse des Immunsystems **(Lymphozytärer Tumorstatus)**, wodurch Defizite oder Überaktivitäten des Immunsystems feststellbar sind.

EDIM-Technologie

Basis der Immunphänotypisierung von Makrophagen

Durch molekulare und biochemische Änderungen werden in Tumor- und Krebszellen Proteine wie Apo10 und TKTL1 gebildet, die mittels der EDIM-Technologie für eine Diagnose und Charakterisierung von Tumoren genutzt werden können. Wenn das Immunsystem benigne oder maligne Tumorzellen (Krebszellen) erkennt, werden Abwehrmechanismen wie die Phagozytose ausgelöst. Dieses Erkennen und Eliminieren von unerwünschten Zellen wird hochspezifisch von

Monozyten/ Makrophagen durchgeführt, die anschließend wieder in das Blut zurückkehren und über eine einfache Blutentnahme isoliert werden können.
Diese Eigenschaft des Immunsystems nutzt das EDIM-Testverfahren (Epitop Detektion in Monozyten), das mit Hilfe der Durchfluss-Zytometrie durchgeführt wird. Hierbei werden durch spezifische Antikörper Immunzellen im Blut markiert und detektiert und gleichzeitig die Präsenz von aufgenommenen Proteinen wie Apo10 und TKTL1 in Makrophagen bestimmt.



Schematische Darstellung der Grundlagen der EDIM-Technologie

Vorteile der EDIM-Technologie

1. **Hochspezifisch:** Die natürlichen Mechanismen des menschlichen Immunsystems werden genutzt
2. **Hochsensitiv:** Antigene werden in Makrophagen angereichert und nicht im Serum verdünnt
3. **Große Auswahl** an geeigneten Biomarkern steht zur Verfügung
4. Die EDIM-Technologie fungiert wie eine **nichtinvasive Biopsie**. Selbst Tumore, bei denen keine Biopsie möglich ist und die operativ nicht entfernbar sind, werden über die Makrophagen erreicht.

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Locoregional hyperthermia in combination with chemotherapy for metastatic breast cancer patients: The Mammatherm- trial

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Locoregional hyperthermia in combination with chemotherapy for metastatic breast cancer patients: The Mammatherm-trial

Abstract

Treatment options for patients with metastatic breast cancer should be both as effective and preferably as little toxic as possible. However to date there is no standard therapy available but treatment regimens for metastatic breast cancer vary much. Locoregional hyperthermia might show additive effects to chemotherapy due to an increased perfusion and a simultaneous occurring of interstitial acidosis in tumor tissue. Primary objective of the multicenter prospectively randomized phase I/II German Mammatherm-trial is to evaluate if metastatic breast cancer patients regarding progression free survival benefit from locoregional hyperthermia given additionally to a chemotherapy regimen. Phase I of this study was a dose-finding-study for liposomal doxorubicin administered in combination with locoregional hyperthermia. Dose-escalation-levels were at 40/50mg/m^2 and in each level 3 patients had to be treated without showing severe toxicity. The first eligible patient (i.e. metastatic lesions accessible to locoregional hyperthermia) entered the study in August 2007, the last patient was recruited in May 2011. Phase II (recruitment of 300 patients planned) will compare 2 different treatment regimens in a randomized setting: Arm A comprises 6 cycles of liposomal doxorubicin 40mg/m^2 i.v. d1 q22d x 6 and cisplatin 20 mg/m2 i.v. d1, 8, 15 q22d x 6 in combination with locoregional hyperthermia administered at d1, 4, 8, 11, 15, 18 q22d x 6. In arm B patients are treated according to the same chemotherapy regimen but without adding the hyperthermic treatment. Intentions of the study are that patients in the experimental arm will benefit from locoregional hyperthermia administered additionally to chemotherapy, i.e. that progression free survival as well as overall survival (as secondary study objective) can be prolonged significantly without being accompanied by increased toxicity or reduced quality of life. Final results for phase I are expected by the end of 2012.

Keywords— hyperthermia, breast cancer, metastatic treatment, chemotherapy

I. Introduction

Breast Cancer is the most common malignancy of females, responsible for 18% of cancer deaths in women. [1].

Unfortunately, a large proportion of patients develop metastatic disease and require chemotherapy to palliate symptoms and improve quality of life [2]. The median survival in this stage has been reported to be 18 to 24 months for most patients. The treatment is palliative in intent and the goals of treatment include improving quality of life and if possible prolongation of life. Treatment in metastatic cancer will usually involve hormone therapy and/or chemotherapy.

Anthracyclines are among the most active agents used in the treatment of advanced breast cancer, and doxorubicin and epirubicin can achieve response rates of around 20% to 40% (when used as single agents) and up to 60% (as part of combination regimens in the first-line setting) [3].
Various analogues and derivatives of doxorubicin were investigated, with the aim of finding chemotherapeutics with less cardiotoxic characteristics while providing the same, or better, cytostatic efficacy. An alternative approach besides the chemical variation of the agent is the variation of formulation.

Until now, non-pegylated liposomal doxorubicin has been investigated in five phase III studies for the treatment of metastatic breast cancer all showing less cardiotoxicity compared to conventional doxorubicin and equal efficacy. [4], [5], [6], [7], [8], [9].

Concerning combination of liposomal encapsulated doxorubicin and hyperthermia Merlin showed already in 1993 that Thermosensitive liposome-encapsulated doxorubicin (TLED) yielded additive effects in the resistant cells while potentiation was observed in the sensitive cells, proclaiming that the possibility of obtaining additive cytotoxicity using TLED combined with hyperthermia may represent an alternative way of intensification of doxorubicin cytotoxicity **[9]**.

The origin of hyperthermia dates back to experiences in ancient days, when it was observed that endogenous fever had an antiproliferative effect on tumor growth. Since the second half of the 20th century, the methods of inducing hyperthermia are mainly based on the administration of exogenous energy. Since the 1930's, the hyperthermic water bath has been used as a source of energy (two-chamber hyperthermic tub).

Later, short wave radiation was applied with quartz lamps or various other sources of infra-red radiation. Since the 1980's adverse effects (mainly skin burns) have been decreased and tolerance rates have been improved by filtering the applied radiation either by water or gold-alloyed metal reflectors (wave length 0.75 - 1.40 μm). This type of filtered infra-red-A radiation is highly equivalent to natural sun-rays under the earth's atmosphere and is therefore better tolerated.
Various in-vitro and in-vivo experiments have shown that tumor circulation and oxygenation are increased by higher temperatures while an interstitial acidosis occurs [10], [11], [12].

Several conditions might contribute to a potentially improved antiproliferative efficacy of cytostatic drugs combined with hyperthermia:

- Higher concentrations of the cytostatic drugs can be found in the regions of tumor, even in case of decreased perfusion.
- Cytostatic potency of various cytostatic drugs such as cisplatinum, ifosfamide, doxorubicin and bleomycin is increased [13], [14], [15].
- The uptake of cisplatinum into the intracellular space can be improved under hyperthemic conditions [16].
- Sensibilisation of previously cisplatinum-resistent cells under hyperthermic conditions was shown [17].
- Under hyperthermia significantly higher concentrations of tumor necrosis factor and interleucins were observed [18].

In randomized clinical trials the addition of hyperthermia to radiation in advanced breast cancer was associated with improved outcome [19], [20]. To our knowledge so far there are no randomized clinical trials evaluating the effect of a combination of hyperthermia and chemotherapy in breast cancer.

II. Patients and methods

In this open-label, multicenter phase I / II study a total of 310 patients with metastatic breast cancer will be randomized into the experimental treatment group receiving chemotherapy in combination with locoregional hyperthermia or the control group receiving the same chemotherapeutic regimen but without hyperthermic treatment.

In order to assure adequate toxicity assessment, a phase-I-trial was preponed: At each dosage escalation level (Myocet 40 or 50 mg/m^2) 3 patients had to be treated and complete 4 treatment

cycles according to the protocol arm B without any severe side effect or dose limiting toxicity (DLT).

Primary objective of the study was to compare the time to progressive disease (TTPD) in a target volume amenable to locoregional hyperthermia in patients treated with liposomal-encapsulated Doxorubicin (Myocet®) and Cisplatin (MC) chemotherapy versus MC-chemotherapy combined with locoregional hyperthermia.

Secondary objectives of the study are to compare the following items in the two regimen arms:

- Response rate
- Survival time after randomisation
- Toxicity
- Changes in quality of life over time as defined by EORTC QLQ-C30 and QLQ-BR23 questionnaire

The first patient was recruited in August 2007, the last patient entered the study in May 2011. After final analysis of the phase I the study will proceed into phase II.
In phase II 300 patients will be randomized into two treatment groups: The experimental arm will comprise a regimen of 6 cycles of liposomal-encapsulated Doxorubicin 40mg/m² i.v. body surface area administered on day 1, repeated on day 22 and Cisplatin 20mg/ m² i.v. administered on day 1, 8 and 15, repeated on day 22 combined with locoregional hyperthermia d1, 4, 8, 11, 15, 18, repeated on day 22. In the control group patients will receive the same chemotherapy regimen without hyperthermia.
Application of locoregional hyperthermia will be performed either by capacitive hyperthermia (Oncotherm©) or by Radiofrequency hyperthermia (BSD 2000© by the BSD Medical Corp.)

III. Results

Intentions of the study were to show in phase I that metastatic breast cancer patients can be treated with a combination therapy of chemotherapy and locoregional hyperthermia without severe toxicities. Phase II will evaluate if patients in the experimental arm benefitted from locoregional hyperthermia administered additionally to chemotherapy, i.e. that progression free survival as well as overall survival (as secondary study objective) can be prolonged significantly without being accompanied by increased toxicity or reduced quality of life. Final results for phase I are expected by the end of 2012.

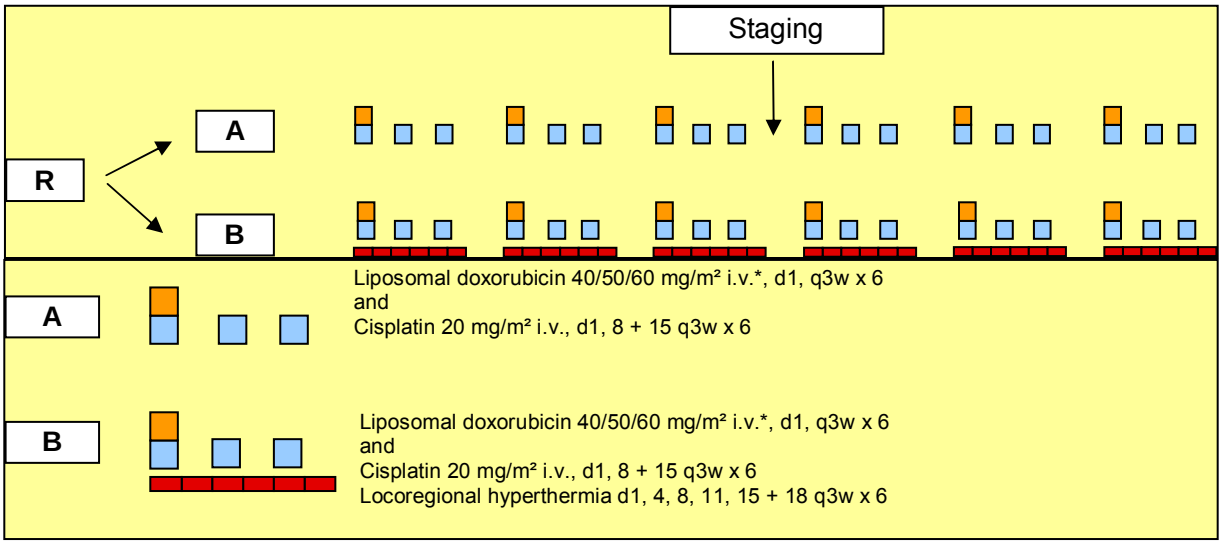

Figure 1. Design of the Mammatherm-trial

IV. Conclusions

Phase I of the Mammatherm-trial will show if a combination treatment of chemotherapy and locoregional hyperthermia is feasible and shows a tolerable toxicity profile in metastatic breast cancer patients. Phase II of the trial will evaluate is those patients have a prolonged progression free survival by adding locoregional hyperthermia to a chemotherapy regimen.

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Neue Herausforderungen im Praxis- und Klinikmanagement: Prozessoptimierung durch echtes Factoring

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Neue Herausforderungen im Praxis- und Klinkmanagement: Prozessoptimierung durch echtes Factoring

1.) Ausgangslage

Moderne Behandlungsmethoden, zunehmende Bürokratie im Berufsalltag sowie ein Wandel von Zahlungsmoral und Wertvorstellungen in weiten Teilen der Bevölkerung stellen das Praxis- und Klinikmanagement immer wieder vor neue Herausforderungen.

Für die **Privatabrechnung** – eine entscheidende Erlösquelle sowohl im ambulanten als auch im stationären Bereich – sind aufgrund dieser Veränderungen insbesondere zwei Konsequenzen auszumachen.

Zum einen müssen Patienten immer mehr Leistungen, die von Kassen und Versicherungen als medizinisch nicht notwendig erachtet werden, aus der eigenen Tasche bezahlen. Dies gilt für den schulmedizinischen Bereich ebenso wie für den Sektor der Komplementärmedizin. Neben den klassischen Privatversicherten oder Zusatzversicherten etabliert sich somit ein regelrechter Zweitmarkt der sogenannten „Selbstzahler".

Zum anderen lässt der erhöhte Abwicklungs- und Verwaltungsaufwand eine konsequente Verfolgung der zu Recht bestehenden Forderungen des Arztes kaum noch zu. Gepaart mit einer tendenziell sinkenden Zahlungsmoral, die von einschlägigen Instituten in den vergangenen Jahren gemessen werden konnte[1], sind Außenstände und Einnahmeverluste in zum Teil erheblichen Umfang eine nur logische Folge.

Wie aber kann dieser Situation entgegen gewirkt werden?

Klassische Abrechnungsdienstleister bieten schon seit jeher Möglichkeiten, den Forderungseinzug auszulagern und Praxis bzw. Klinik zumindest zu entlasten. Damit schafft sich der Arzt zwar Freiraum für die Konzentration auf seine Kernkompetenz. Eine Lösung für das Gesamtproblem ist diese isolierte Betrachtungsweise in der Regel aber nicht.

Ausgangslage für die Dienstleistung von BFS ist daher zunächst eine klassische betriebswirtschaftliche Frage: Wie stellt sich aus einer Gesamtbetrachtung der gesamte „Lebenszyklus" einer Forderung dar, angefangen von der Forderungsentstehung bis zum endgültigen Ausgleich der Forderung?

Unter der Prämisse, dass es unterschiedliche Anforderungen und Situationen der einzelnen Akteure im Gesundheitswesen gibt, entsteht so eine Matrix von Dienstleistungsbestandteilen, die flexibel auf die jeweilige Situation angewendet werden können. Kernstück des Angebots der BFS ist dabei ein Forderungskauf – „**echtes Factoring**" –, bei dem unter anderem klassische Abrechnungsdienstleistungen, konstante Liquiditätsversorgung sowie Absicherung von Erlösen kombiniert werden.

Ziel des folgenden Abstracts ist es, einen kurzen Einblick in das Thema zu geben, um anschließend die Besonderheiten und Implikationen speziell für das Gesundheitswesen herauszuarbeiten.

2.) Begriff und Funktionen des Factoring

Factoring nennt man den Verkauf einschließlich der Abtretung von Forderungen aus Warenlieferungen und Dienstleistungen an ein Factoring-Institut[2].

Beim Factoring-Geschäft sind drei Wirtschaftssubjekte beteiligt:
- das Factoring-Unternehmen („**Factor**“)
- der Leistungserbringer oder Anschlusskunde („Factoring-Kunde“, z. B. die **Praxis oder Klinik**)
- der Schuldner des Factoring-Kunden (Schuldner oder „Leistungsempfänger“, hier: der **Patient**)

Der Factoring-Kunde verkauft seine Forderung gegen den Leistungsempfänger an den Factor und tritt diese ab. Im Gegenzug überweist der Factor zum vereinbarten Termin – z. B. sofort zur Zeit der Rechnungslegung – seinem Kunden den Rechnungsbetrag.
Beim klassischen Factor wird die Forderung bei Fälligkeit vom Factor im eigenen Namen auf eigene Rechnung eingezogen. Dabei übernimmt der Factor auch das gesamte Debitorenmanagement für den Factoring-Kunden. Ferner haftet er für den bonitätsbedingten Ausfall der Forderung[3].

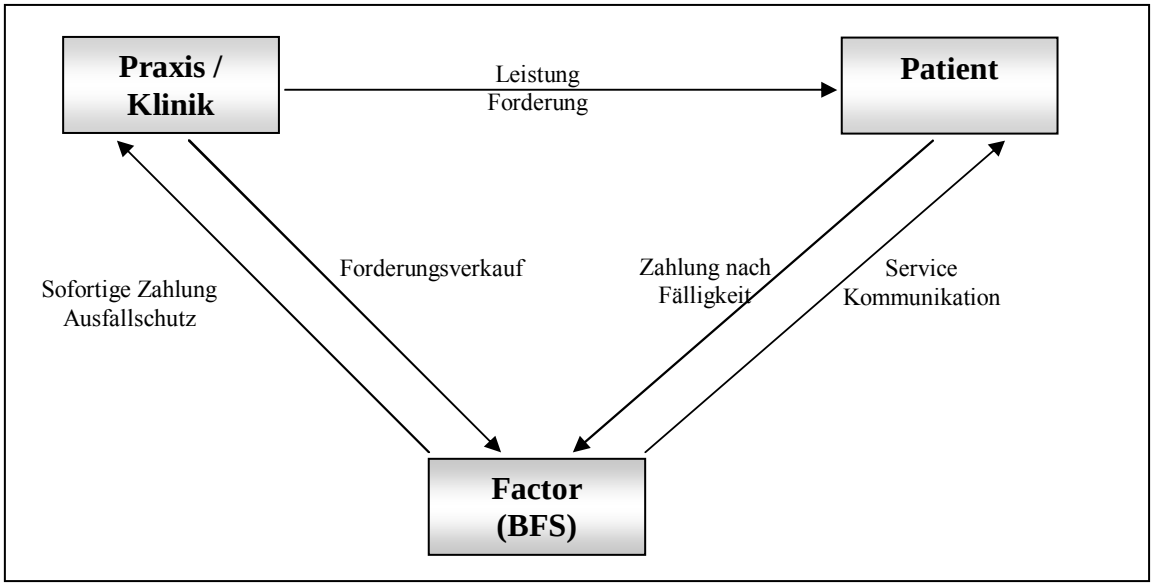

Abb. 1: Darstellung der Akteure und grundsätzlichen Prozesse beim Factoringgeschäft

Insofern erfüllt das Factoring-Geschäft drei wesentliche Funktionen[4]:

a) **Finanzierungsfunktion**: Der Factor zahlt dem Factoring-Kunden den Forderungsgegenwert sofort aus, ungeachtet der tatsächlichen Fälligkeit der Forderung oder gar Zahlung durch den Leistungsempfänger.
b) **Dienstleistungsfunktion**: Anders als beim reinen Darlehen übernimmt der Factor i. d. R. alle im Zusammenhang mit der Forderungsrealisierung stehenden Tätigkeiten, insbesondere das komplette Debitorenmanagement sowie die Kommunikation mit dem Leistungsempfänger.
c) **Delkrederefunktion (Ausfallschutz)**: Der Factor übernimmt das Ausfallrisiko der abgetretenen Forderung ähnlich wie eine Kreditversicherung und haftet somit für den wirtschaftlichen Ausfall.

3.) Juristische Grundlagen

Basis des Factoring ist ein schuldrechtlicher Forderungskauf nach § 433 BGB[5]. Je nach Ausgestaltung der Zusammenarbeit lassen sich dann verschiedene Factoringarten unterscheiden.

Anders als bei reinen Inkassodienstleistungen, Darlehensverträgen oder ähnlichen Rechtsgeschäften sind sich Factor und Factoring-Kunde beim echten Factoring z. B. einig, dass das Eigentum der Forderung gegen den Drittschuldner (Leistungsempfänger, Patient) auf den Factor übergeht mit allen Konsequenzen und Problemen, die sich bei der Forderungsrealisierung ergeben können. Die Forderungsübertragung erfolgt nach §§ 398 ff BGB, nach welcher der Factor neuer Gläubiger der Forderung wird.

Dies bedeutet insbesondere auch, dass das Risiko der Uneinbringlichkeit der Forderung auf den Factor übergeht. Dieser tritt somit nicht nur finanziell in Vorleistung, indem er den Forderungsgegenwert an den Factoring-Kunde ungeachtet der Fälligkeit der Forderung überweist, sondern er haftet auch im Falle eines Ausfalls der Forderung und somit für die Bonität des Schuldners.

Beim **unechten Factoring** bleibt dagegen die Regressmöglichkeit des Factors gegenüber seinem Factoring-Kunden erhalten, wenn die Forderung nach Ablauf einer definierten Frist ausfällt. Das Risiko der Bonität verbleibt also beim Factoring-Kunden.

4.) Wirtschaftliche Konsequenzen

Je nach spezieller Situation der Klinik oder der Praxis entstehen vielfältige wirtschaftliche Nutzen aus dem Factoring[6].

a) Finanzieller Spielraum und planbare Liquidität
Durch die sofortige Begleichung der Forderungsgegenwerte entsteht ein beschleunigter Liquiditätsfluss, der verschiedene positive Auswirkungen mit sich bringt:
- Erhöhung der Kreditlinie
- Nutzung von Boni oder Skonti bei anderweitigen Liefergeschäften
- Beschleunigung des Liquiditätsflusses für Investitionen
- Vermeidung von Sollzinsen im Kontokorrent-Bereich

b) Finanzielle Sicherheit
Sinn und Zweck der Delkrederefunktion ist insbesondere die finanzielle Entlastung und Sicherheit für den Factoring-Kunden:
- Erlössteigerung und Erlössicherung durch Vermeidung von Zahlungsausfällen
- Auslagerung juristisch intensiver und kostenrelevanter Tätigkeiten (gerichtliches Mahnwesen, Gerichtsverfahren)

c) Ressourcenschonung oder -freisetzung
Durch die Übertragung wesentlicher, z. T. spezialisierter Tätigkeiten können betriebsinterne Ressourcen anderweitig eingesetzt oder freigesetzt werden:
- Übertragung des gesamten Debitorenmanagements, kaufmännischen Mahnwesens und Inkassos an einen spezialisierten Dienstleister
- Verlagerung zeitintensiver Kommunikationstätigkeiten, z. B. bei Einreden durch Kostenträger oder bei Zahlungsschwierigkeiten

d) Bilanzielle Entlastung
Für bilanzierende Häuser ergeben sich positive Implikationen für die Bilanz und damit für die Wirtschaftlichkeit des Unternehmens:
- Bilanzverkürzung als Folge frühzeitiger Reduzierung von Forderungen und Verbindlichkeiten aufgrund beschleunigtem Liquiditätsfluss

- Die dadurch entstehende höhere Eigenkapitalquote führt wiederum zu einer besseren Rating-Einstufung bei Fremdkapitalgebern und somit ggf. auch zu günstigeren Kreditkonditionen

5.) Prozessoptimierung

Grundsätzlich ist – wie man aus der vorangehenden Aufstellung erkennen kann – der wirtschaftliche Nutzen je nach Situation der Praxis oder Klinik unterschiedlich
Wenn ein Wirtschaftssubjekt eine Factoringlösung in Erwägung zieht, sollte daher zunächst die Ausgangslage analysiert und geprüft werden. Es gibt je nach Situation eine Vielzahl an Dienstleistungsvarianten, so dass man an dieser Stelle nicht für ein allgemeines Patentrezept plädieren kann.

Wichtig ist, dass sich der Dienstleister – also der Factor – flexibel den Bedürfnissen des Factor-Kunden anpassen kann. Das gilt nicht nur für den Umfang der Dienstleistung, sondern auch für die technischen Möglichkeiten und organisatorischen Gegebenheiten der Praxis/Klinik, wie z. B. die Art und Weise der Forderungseinreichung.

Wir befinden uns somit in einem Bereich individueller Prozessoptimierung. Am Beispiel eines Referenzkunden, der onkologischen **Klinik St. Georg von Dr. Douwes** in Bad Aibling, kann ein solch optimierter Prozess beispielhaft wie folgt aufgezeigt werden:

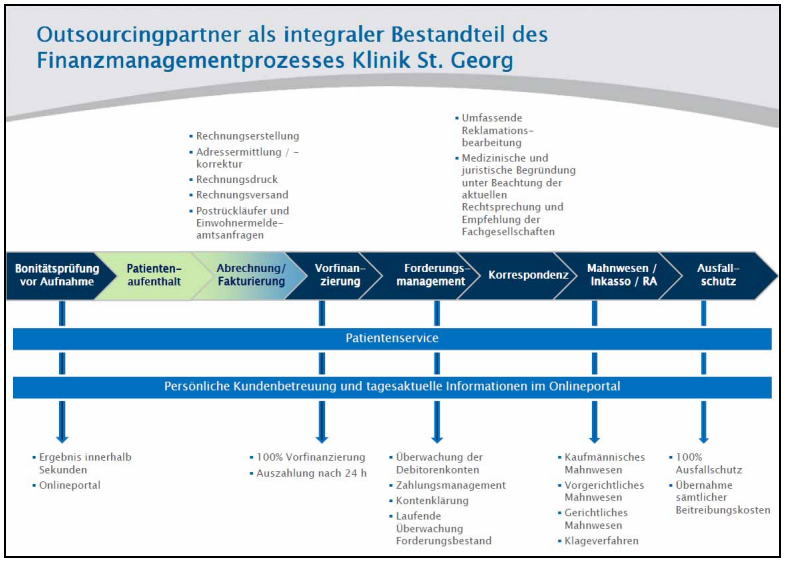

Abb. 2. Abrechnungs-Prozesskette der Klinik St. Georg von Dr. Douwes, Bad Aibling

Die einzelnen Prozessbestandteile sind größtenteils modular und flexibel anwendbar, so dass sich nahezu jede Praxissituation abbilden lässt. Abweichend von der Darstellung besteht auch die Möglichkeit, die medizinischen Dokumentationen (Krankenakten) durch den Factor (BFS) auswerten, prüfen und optimieren zu lassen.

6.) Besonderheiten im Gesundheitswesen

Obwohl das **echte Factoring** in vielen Ländern und Branchen eine gewichtige Rolle einnimmt und mittlerweile schon zu einem fast historischen Finanzierungsinstrument zählt, zeigt sich im Gesundheitswesen eine noch geringere Verbreitung.

Dieser Umstand lässt sich zum einen dadurch erklären, dass die Mittelherkunft öffentlicher Häuser und Praxen bis zu einem gewissen Umfang reguliert und garantiert gewesen ist, so dass sich anders als in anderen Bereichen der Bedarf an alternativen Finanzierungsinstrumenten auf ein Minimum beschränkte. Es bleibt abzuwarten, inwieweit der **Strukturwandel** im Gesundheitswesen die Öffnung zu flexibleren Lösungen in Gang setzen wird. Erste Tendenzen und zunehmende Anfragen sowie die Erfahrungen aus dem parallel verlaufenden Zahnarzt-Markt zeigen, dass echtes Factoring zunehmend zum Gesprächsthema und als Lösungsmöglichkeit für auftretende Problemfelder genutzt wird.

Zum anderen finden wir im Gesundheitswesen eine spezielle Situation vor, die wesentlich **höhere Anforderungen** an einen Dienstleister stellt als in anderen Branchen. Eine konsequente Ausrichtung auf die Belange einer Praxis/Klinik, umfassender Sachverstand für medizinische Sachverhalte und das notwendige Feingefühl in der Fortsetzung des Arzt-Patienten-Verhältnisses darf hier zu Recht von einem Dienstleister verlangt werden, dem man die Realisierung seiner Forderungen anvertraut.

7.) Fazit

Unter dem Stichwort „Prozessoptimierung durch echtes Factoring“ sollte ein Einblick in eine markt- und zeitgerechte Lösung für die Privatabrechnung gegeben werden, die den heutigen Umständen und Anforderungen Rechnung trägt.

Ressourcenschonung, Liquidität und Erlössicherung sind die drei wesentlichen Ziele, die durch eine Factoringlösung angestrebt werden. Durch echtes Factoring werden nicht nur entscheidende wirtschaftliche Nutzenvorteile geschaffen. Ein wesentlicher Punkt ist überdies die Flexibilität des Dienstleisters, sich an die verschiedenen Belange der unterschiedlichen Akteure im speziellen Gesundheitsmarkt anpassen zu können, so dass für die Praxis/Klinik ein möglichst reibungsloser Prozessablauf entsteht.

Die zunehmende Verbreitung dieser Abwicklungsmethode lässt den Schluss zu, dass echtes Factoring analog zu zahlreichen anderen Branchen sich zunehmend auch im Gesundheitsmarkt etablieren wird.

Quellennachweise:

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[3] Frhr. von Thannhausen, Markus, Das Inland-Factoring, Diss. jur., Würzburg 1984, S. 108
[4] Blaurock, Uwe, Grundstruktur und aktuelle Fragen des Factoring, in: JA, 21. Jg. 1989, Heft 6, S. 273 f.
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BFS finance

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Hyperthermie Chemotherapie beim Harnblasenkarzinom

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Hyperthermie Chemotherapie beim Harnblasenkarzinom

Abstract

Das Harnblasenkarzinom ist ein relativ häufiger maligner Tumor, der sich grundsätzlich in zwei Risikogruppen aufteilen lässt. Einerseits gibt es das so genannte oberflächliche oder nicht muskelinvasive Harnblasenkarzinom und andererseits gibt es das muskelinvasive Harnblasenkarzinom. Das Erstere wird endoskopisch operativ diagnostiziert und therapiert, während das zweite durch radikale chirurgische Maßnahmen mittels der Zystektomie oder einer systemischen Radiochemotherapie behandelt wird.

Aus sozioökonomischer Sicht ist das Harnblasenkarzinom die teuerste maligne Erkrankung, die es überhaupt in der medizinisch-onkologischen Versorgung gibt. Dies gilt sowohl für Europa als auch die Vereinigten Staaten. Der Hauptkostenfaktor liegt in der chronisch rezidivierender Erkrankungssituation beim nicht muskelinvasiven Harnblasenkarzinomen, welches dazu führt, dass die Tumorerkrankungen zur regelmäßigen und teilweise kurzfristigen stationären Behandlungen führt, die eine endoskopisch operative Behandlung jedes Mal aufs Neue notwendig macht. Die Neigung zur Rezidivierung in diesem Krankheitsbild hängt einerseits von der Aggressivität des Tumors und andererseits von der endoskopischen, operativen Qualität des behandelnden Arztes ab. Zur Verbesserung der Situation wurde schon vor geraumer Zeit (40 Jahre) eine adjuvante Therapie mittels Chemotherapie oder Immunmodulation eingeführt. Diese adjuvanten Therapieansätze haben aber nachvollziehbar nur einen Vermeidungseffekt von etwa 15 %, was bei einem Risiko bis zu 70 % relativ niedrig ist. Über die bisherigen Dekaden hat sich daher an der Verteilung der Operationsindikation zwei Drittel Rezidiv OP's ein Drittel Neudiagnosen im Grunde nichts wesentlich geändert.

Es ist also grundsätzlich an der Zeit zu überlegen, ob eine andere Behandlungsstrategie das Rezidiv Risiko effektiver senken kann. Die Hyperthermie Chemotherapie bietet hierzu einen strategischen Ansatz, der die Effektivität der Mitomycin Chemotherapie, als Blaseninstillation, aufgrund von physikalischen und biologischen Gegebenheiten deutlich verbessert. Im Vortrag werden einerseits die Hintergrundinformationen zur Epidemiologie des Harnblasenkarzinoms und die biologisch-physikalischen Grundlagen vorgestellt. Auf dieser Grundlage wird erläutert warum der Einsatz der Hyperthermie Chemotherapie sinnvoll ist. Die Indikation besteht grundsätzlich nur für das nicht muskelinvasive Harnblasenkarzinom. Eine Anwendung bei Muskel infiltrativem Tumor ist kontraindiziert. Die Indikationsstellung wird für zwei unterschiedliche Risikoklassen unterschiedlich gehandhabt.

Die niedrig- und mittelgradig riskanten Harnblasenkarzinome nach EORTC

in diesem Fall wird eine so genannte adjuvante Therapie durchgeführt. Sie zeichnet sich durch eine Gabe von zweimal 20 mg Mitomycin in die Harnblase mit einer Behandlungszeit von jeweils 30 min aus. Die Behandlung wird insgesamt sechs Mal wöchentlich durchgeführt. Nach weiteren sechs Wochen erfolgt die erste endoskopischer Kontrolluntersuchung. Diese wird mittels Video Cystoskopie durchgeführt. Danach folgen Hyperthermie Behandlungen alle sechs Wochen in der gleichen Dosierung mit einer einmaligen Gabe. Insgesamt ist der Patient damit über einen Zeitraum von knapp elf Monaten zwölfmal behandelt worden. Nach der ersten cystoskopischen Kontrolle erfolgen weitere cystoskopiesche Kontrollen mit Videodokumentation in Abstand von drei Monaten. Die Kontrollen werden auch auf das zweite Jahr außerhalb jeder Therapie ausgedehnt, um das Maß der Rezidive kontrollieren zu können. Die Qualität dieses Therapieverfahrens wird mit der Rezidivquote innerhalb von zwei Jahren bei allen in der

Indikation behandelten Patienten qualitativ beobachtet und als Kohortenanalyse im Hyperthermie Zentrum Gießen analysiert.
Die aktuelle Effektivität in Gießen liegt hierbei, bei 87,5 % Rezidiv Vermeidung.

Die zweite Indikation ist die Behandlung von High-Risk Tumoren nach EORTC

Hierunter fallen sowohl Personen, an die eine kurzfristige Rezidivierung unter andersartiger adjuvanter Therapie erlebt haben aber besonders Patienten die ein Carcinoma in situ oder einen pT1 G3 Tumor Befund haben. Hinzu kommt ferner eine Gruppe mit besonderem Risiko, hierbei handelt es sich um Personen die nach einer erfolgten BCG-Therapie ein Rezidiv unter BCG-Therapie erlebt haben. Nach Leitlinienvorgabe müssten diese Patienten eigentlich eine Zystektomie erfahren.
Kann aber durch ausgiebige und intensive Diagnostik sichergestellt werden, dass das Carcinoma in situ lediglich in der Harnblase begrenzt und ohne invasiven Anteil ist, dann kann ein Organ erhaltender Therapieversuch mit der so genannten ablativen Hyperthermie Chemotherapie gemacht werden. Bei diesem Therapieansatz erhält der Patient über acht Wochen in wöchentlicher Gabe zweimal 40 mg Mitomycin unter gleichzeitiger Überwärmung mit Medikamentenwechsel nach 30 min. In der Folge dieses Therapieschrittes wird in drei Wochen nach der letzten Hyperthermie eine endoskopische Resektion durchgeführt. Die gewonnene Histopathologie wird dazu benutzt den Patienten zu kategorisieren. Sollte kein Tumor mehr nachweisbar sein, so kann er in der Erhaltungsphase mit Hyperthermie Chemotherapie alle sechs Wochen weiter behandelt werden. Sollte er jedoch weiterhin Tumor in den histologischen Proben aufweisen, so ist er einer Zystektomie unweigerlich zuzuführen. Sollte der Patienten in die Erhaltungstherapie eintreten, so ist er ebenfalls vierteljährlich Video endoskopisch zu überprüfen. Auch hier wird in einer Kohortenanalyse die Effektivität der Therapie überprüft und die Datenlage einmal jährlich aktualisiert. Der Anteil der Patienten, die nach zweijähriger Therapie einen Organerhalt erreicht haben, liegt bei ca. 60 %.

Biologische Wirkung

Das Prinzip dieser Therapie wird in ihrem dreifachen Synergismus im Vortrag erläutert. Es kommt zu einer erhöhten Gewebeeindringfähigkeit, einer verbesserten Bindung des Mitomycin an den DNA Strang und damit zu mehr potentiellen Strangabbrüchen in der Replikation von Tumorzellen. Ergänzend wird durch die Wärme die Fähigkeit der DNA-Synthasen gehemmt die eingetretenen Strangabbrüche am DNA-Strang zu reparieren. In der Konsequenz haben wir also durch diesen Therapieansatz eine vermehrte Erreichbarkeit des Ziel Kompartiments, vermehrte Schädigung an der DNA und eine verschlechterte Reparaturfähigkeit. Dieser Synergismus ist multiplikativ und erhöht die therapeutische Effektivität um ein Vielfaches gegenüber der Kalt-Instillation von Mitomycin. Die Effektivität wird ferner dadurch bestätigt, dass durchaus ein gehöriger Anteil der maximal therapiert Patienten (BCG-Therapie) nach einem BCG Versagen durch die Hyperthermie Chemotherapie vor einem Organverlust der Harnblase und einer mittelfristigen Rezidivierung bewahrt werden.

Kritische Betrachtungen

Wie jede Methode unterliegt aber auch die Hyperthermie Chemotherapie einer kritischen Verlaufskontrolle und man muss sich darüber bewusst sein, dass die Onkogen induzierte Transformation von Urothelzellen durch eine solche Behandlung auf Dauer nicht unterbunden werden kann. Die Behandlung zielt auf verbliebene, residuale Tumorzellen innerhalb des Zellverbandes der Harnblase ab und kann zu einer erfolgreichen Eradikation von Tumorzellen

führen. Eine Onkogen induzierte Neubildung von Harnblasenkarzinomen in der weiteren Zukunft kann hierdurch jedoch nicht vermieden werden. Dies ist auch leicht verständlich, da die Hyperthermie Chemotherapie keinerlei therapeutischen Ansatz bietet die Onkogenbelastung im betroffenen Organismus zu reduzieren. Hierbei spielt es keine Rolle ob diese Expositionen historisch waren oder noch anhalten oder aber chronisch fortgeführt werden. Natürlich ist bei chronischer Fortführung das Risiko grundsätzlich höher.
Da es sich bei der Urothelkarzinom Entwicklung innerhalb des Harntraktes um einen generalisiertes Problem handeln kann (urotheliale Pan-Cytopenie), welches durch onkogene Noxen sowohl im oberen als auch im unteren Harntrakt erfolgen kann, ist es leicht nachvollziehbar, dass Tumoren auch im oberen Harntrakt (außerhalb des therapeutischen Anwendungsgebietes der Hyperthermie Chemotherapie) sowohl unter der laufenden Hyperthermie Chemotherapie als auch in einer chronologischen Folge entstehen können. Verlaufskontrollen unter Einschluss von Urincytologie Untersuchungen und Urin assoziierten Tumormarkern sind hierbei existenziell wichtig, um auch solche Ereignisse frühzeitig feststellen zu können.

Datenlage

Die therapeutische Effektivität, die sowohl durch internationale Publikationen in der kurzfristigen wie in der langfristigen Wirksamkeit belegt sind, als auch die positive Rückkopplung durch erfolgreich behandelte Patienten, die sich im Rahmen von Selbsthilfegruppen organisiert haben, trägt dazu bei, dass der Zustrom von Patienten aus überregionalen Gebieten nach Gießen erfolgt. Dies trägt auch zu einem wirtschaftlichen Profit für die anbietende Klinik bei. Außerdem wird die Urologie Gießen als Zweitmeinungszentrum mehr und mehr von Betroffenen aufgesucht, um eine Beratung zur Steuerung des bestmöglichen Therapieweges zu erhalten. Besonders hoch ist natürlich der Beratungsbedarfs bei Patienten denen schon eine Zystektomie als Therapieoption bzw. therapeutisches Muss angeboten wurde. Dies führt sicherlich auch zu einer deutlichen Steigerung der Negativselektion in unserem Patientengut und zur vermehrten Behandlung von Hochrisikopatienten. Umso mehr muss hier in der medizinischen Verantwortung die Indikationsstellung strengstens geprüft werden, da eine falsche Indikation (Muskel-invasives Karzinom) zu einer direkten Gefährdung des Patienten führt. Ein Urothelkarzinom welches unterschätzt wurde und zu einer Metastasierung führt hat ein Bedrohungspotenzial von 90 %tiger Todeswahrscheinlichkeit innerhalb von drei Jahren nach Diagnosestellung der Metastasierung.

Zusammenfassung

Sie können also hieraus leicht ersehen, dass die Hyperthermie Chemotherapie in der Behandlung des Harnblasenkarzinoms einerseits eine ausgesprochen positive Optionen zur Senkung des Risikos ist, aber auch gleichzeitig eine ausgesprochene Herausforderung für den durchführenden Therapeuten darstellt, da die Verantwortung besonders für die hoch bedrohten Patienten komplett auf der Kompetenz des behandelnden Arztes liegt.

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Oncothermia and traditional Chinese medicine

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Oncothermia and traditional Chinese medicine

Abstract

Aim of this article to show the possibility and great advantage of the synergy of oncothermia with traditional Chinese medicine, on the common basis of equilibrium demand. We use the recognition of the deviations from the complex harmony of the organism or its part for selection to act properly.

Introduction

Hyperthermia is an ancient oncology method. It is the very first treatment modality for this type of disease, having 5000 year history [1], based on the Sun as the overall curative force in ancient Egypt. Later Hippocratic paradigm described it using physiological process (acidosis) to eliminate the malignant tissue. This natural approach is in well correlation with the far-away developed medical concept in the same ancient time: the Traditional Chinese Medicine (TCM) [2]. This medical philosophy was also based on natural harmony inside and outside the human organism. In progress of historical time TCM had been more sophisticated and developed, but the hyperthermia could not keep abreast with the development of the medicine, and was hindered by other western medical methods (WMM). However in late 80th of last century a new paradigm of hyperthermia was developed. It is the oncothermia method (OTM) [3]. OTM applies the ancient hyperthermia on different way, replacing the static thermal driving force to dynamical equilibrium concept, promoting the natural processes in curative direction [4]. Asian governments hope that high-volume screening and rigorous clinical trials will unlock the secrets of ancient herbal remedies—and that the results will pass muster with Western scientists [5]. It is a matter-of-course to make synergy between the two approaches, uniting the best line of TCM and OTM. Our present article underlines the main connections with the TCM and oncothermia.

TCM Oncology traces it's roots as far back as the 16th – 11th centuries BCE, as recorded on bones & tortoise shells. Oncology was first recorded in text form in *Zhou Li* compiled between 221 & 207 BCE. Tumors were first discussed in the earliest recorded book on Chinese Medicine *Huang Di Nei Jing.* The Jin, Sui & Tang Dynasties, 220 – 907 CE. The etiology , pathology & treatment of tumors was explored & studied. The use of Herbs, Acupuncture & Moxibustion for the treatment of tumors was further recorded in Chinese Medical texts. Diet Therapy began to be discussed around 581 CE. The Song & Qing Dynasties, 960 – 1911 CE. Theories of tumors developed very rapidly during this period especially between 960 & 1368 CE. Herbal prescriptions were more widely used in the treatment of Cancer. Pattern identification & treatment as well as prognosis became more well developed. Integrative Medicine, 1949 – Present The development of Western Cancer treatments. Large scale clinical & laboratory research into integrated Chinese & Western medicine on the prevention, diagnosis & treatment of Cancer. Integrative medicine treatments of Cancer are the wave of the future.

The TCM is a complex thinking of the integrative frame about the balances of the body and its homeostasis. The basic principle of TCM is centering on the points of the same disease with many patterns and many patterns on same disease balance according to person, time and place. Its pathology based on the imbalance Yin-Yang (negative feedback control of the healthy state), states the disharmony of "Qi" and blood, detects the dysfunction of organs and the local manifestation of toxic pathogenic factors. The diagnosis of TCM is in its basic principles, based on holism, complex approach of the living system and its environment; with identification of patterns and conditions (trying to detect the root causes of disease).

The TCM etiology contains:

- External pathogenic factors,
- Internal damage of 7 emotions
- Improper diet
- Deficiency & depletion of the organs
- Stagnation of Phlegm Fluid
- Stagnation of Qi & Blood

The main features of TCM effects in Western perspective are

- Enhance immune function.
- Restore the balance of the endocrine system.
- Promote blood production.
- Protect the marrow & the function of the Heart, Liver & Kidneys.
- Improve absorption in the digestive tract.
- Boost the metabolic function.
- Stimulate the body's self-regulating ability.
- Reduce the side effects of surgery, radiotherapy & chemotherapy while improving their effectiveness.

These are in complete harmony with the principles and effects of oncothermia which centers on helping the natural feedback processes to reestablish the lost homeostatic equilibrium in the case of malignancies. Oncothermia acts directly in the primary tumor by its apoptotic cell-killing mechanisms. The apoptotic effect as a main selective killing mechanism of malignant cells by oncothermia was proven as well as the blocked dissemination and the abscopal effect on far distant metastases was also proven by measurements and in clinical use. These effects in summary are:

- Apoptosis shown by micro- and macro-morphologies of the cellular death with the end of the apoptotic bodies [6],
- Oncothermia induces the action of p53 tumor-suppressor gene [7],
- The intensive apoptosis in malignancy is shown by cleaved caspase 3 in early and TUNEL in last phase of apoptotic phases [8],
- The apoptosis was controlled by the DNA laddering [9],
- Oncothermia furthermore suppresses the proliferation in the primary tumor [10],
- Oncothermia forms leukocyte invasion around the primary lesion [11],
- Oncothermia activates the neutrophils [12], which also measured by mileoperoxidase presence [13],
- Oncothermia as new targeted therapy is completed by the blocking of dissemination by rebuilding the adherent connections [14] and the junctions [15] between the malignant cells
- Oncothermia acts on far distant metastases by bystander (abscopal) effect [16].

Homeostatic control as basis of synergy of Oncothermia and TCM

The life is based on energetically open systems, where the environmental conditions determine the life as equilibrium. The living equilibrium is the homeostasis. The actual homeostatic state is definitely “constant” despite its energetically open status, (see Figure 1.). Normal healthy state of any living systems is in homeostasis, which is not static, but dynamically changing in time, forming a relatively stable state. This relative stability makes possible to recognize the various individuals, despite millions of their cells are actually vanishing and millions of those reborn. The homeostasis is controlled by numerous negative feedback loops [17], [18], making the micro- and macro-structures in equilibrium.

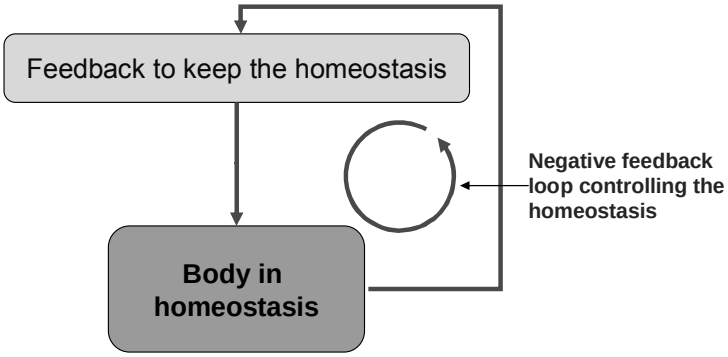


Figure 1. The natural healthy state is stabilized by the negative feedback loops of physiology

The disease breaks the relative equilibrium, risks the relative stability of the system. The system tries to reestablish the homeostasis. For this enhanced negative feedback control is enforced (see Figure 2.).

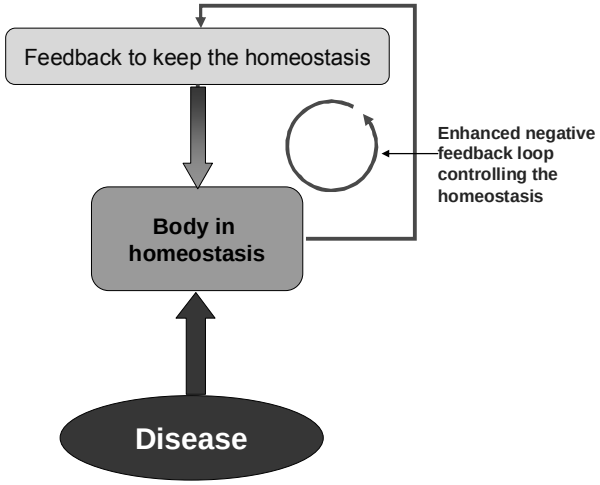


Figure 2. The disease breaks the homeostasis, so the physiology tries to compensate and correct the damage

The natural therapy must help the body's internal corrective actions to reestablish the healthy state. Recognizing the disease most of the medical approaches act with changes of the conditions (diets, medicaments, other supplies) trying constrain the body in the previously working equilibrium. However, in many cases, it works against the natural homeostasis, the constrained action induces new homeostatic negative feedbacks from the living object. The living organism starts to fight against our constraints together with the fight against the disease (see Figure 3.) [19].

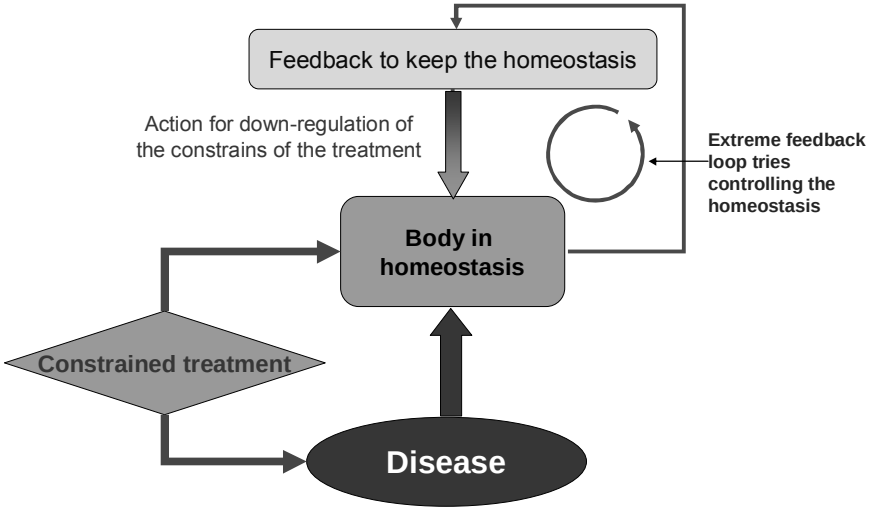


Figure 3. The classical hyperthermia introduces a new constrained effect which induces even more physiological feedback, forcing the body for the "double front" fighting

This controversial situation happens for example in case of the classical hyperthermia, when the constrained massive temperature change is physiologically down-regulated (or at least the physiology works against it by the systemic [like blood-flow] and local [like HSP] reactions) [20]. Oncothermia disclaims the old approach, introducing a new paradigm: with the application of micro-heating induces considerably less physiological feedback to work against the action, and with the application of the electric field it uses such effect, for which the body has no physiological answer. With this new paradigm, oncothermia helps the natural feedback mechanisms to reestablish the healthy state (see Figure 4.).

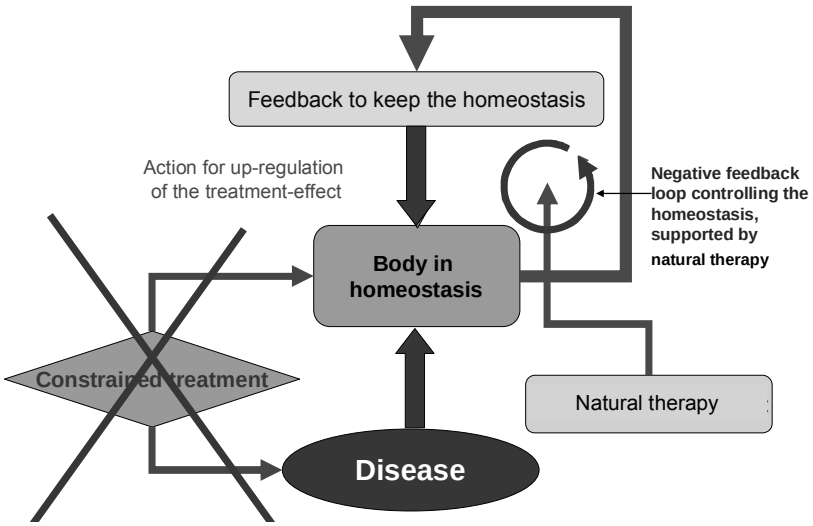
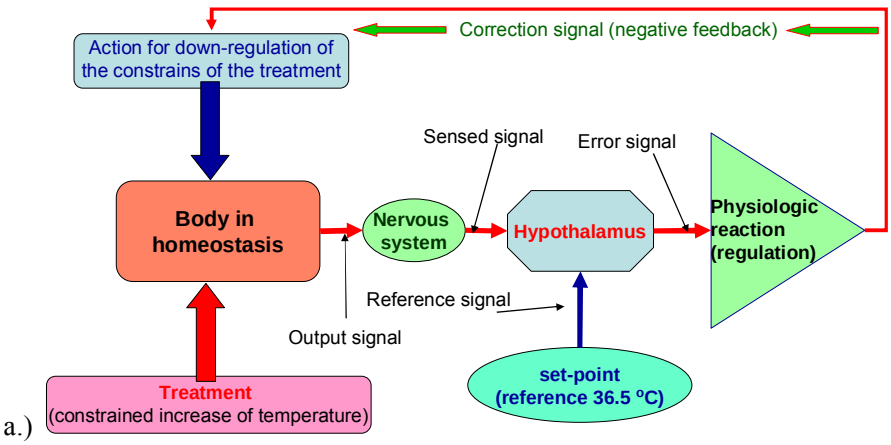


Figure 4. Oncothermia acts differently. It helps the natural feedback loops for natural corrections, and not makes constraints, which induces immediate correction effects form the body by negative feedback protection mechanisms.

The natural therapy helps the homeostatic control, consequently the physiology does not work against this action. The main task is to direct the physiology in the standard way, and act on such normal line. The positive feedback loops (the avalanche effects), which may destroy the normal homeostatic equilibrium, has to be stopped by the therapy.

Let us see an example, the hyperthermia treatment. When the set-point in hypothalamus is normal for temperature regulation, the body controls the physiological actions (like sweating, subcutan capillary blood-flow, heart-rate, etc.) and tries to suppress the effect of the external heating. However, when the set-point is adjusted, the complete physiological reaction-set helps the temperature increase in natural way, (see Figure 5.) **[19]**.



a.)

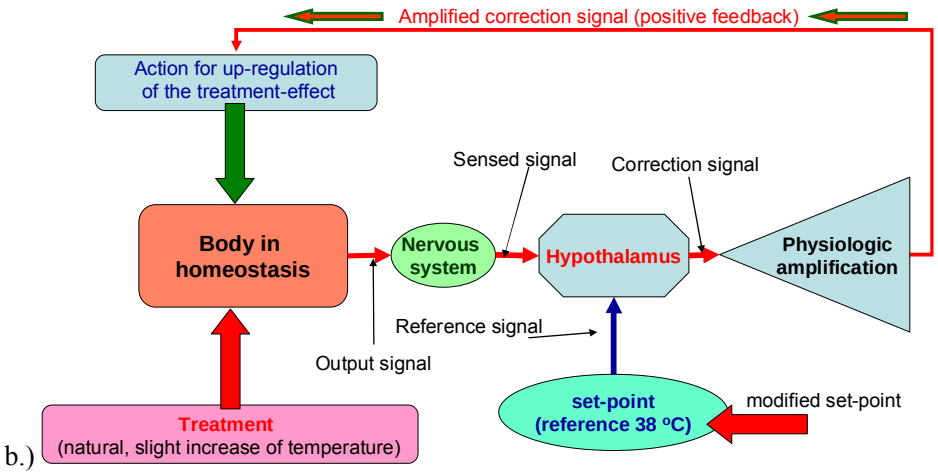


Figure 5. A schematic example of the constrained and natural effects. (a) The constrains in a heat treatment gains negative feedback, the homeostatic regulation works against, tries to down-regulate the effect. (b) By adjusting up the set-point (e.g. natural fever), the homeostatic regulation will upregulate the parameters, helping the natural treatment. (This example is systemic, but the local blood-flow and many locally controlled physiologic parameters work in the same way.)

Due to the negative feedback control the processes are self-controlling, seeking to a definite equilibrium. Resulting of this process no high accuracy of the constrain control is necessary.
The homeostatic control is the basic of the fractal physiology, which is applied in oncothermia as essential mechanism, induced with the fractal fluctuation on the modulation of the carrier frequency [21]. This special selection is based on self-organizing behavior of the bio-materials, which is a well-known and widely investigated topic in science [22] and especially in biology [23], as well. The above shown proliferation homeostasis works on the renewing of the cellular system, but one cell has to be annihilated giving place for the new-born one keeping the complete function in equilibrium (homeostasis). The equilibrium of this complex system could be described by fractal physiology [24], [25], [26], [27] and bio-scaling [28], [29], [30]. This complexity is mirrored in the four dimensional description of the living state [31], which is valid in all the scales of the life [32]. It is proven, that the entropy in homeostasis is constant in all scales of the complex system [33].
The complex network of the regulating pairs with opposite actions is the basic of the Traditional Chinese Medicine (TCM) philosophy too (Yin-Yang pairs). The complexity means that the system can not be simple additionally composed from their parts, the parts alone do not carry the function, which they have in the complete complex system. The couplings and interactions between the controlling pairs could explain the multi-functional behavior of the tuning a single controlling pair, so the consequences of one external retuning of the balance could lead to various results.

Network control of the homeostasis

The mesenchyme, which is 25% of the human body, has important role forming homeostasis of the organism [34]. It is a loose connective tissue with undifferentiated type [35]. The pink-noise with entropy $S_E=1.8$ characterizes the homeostasis like an intensive parameter. This intensive is valid for every physiologic signals and for all the organs, the $S_E=1.8$ is an universal constant for the living body.
The cellular functions like supplies and filtering are mediated by the mesenchyme, which represents a transmitter between the blood-capillaries and the cells. The mesenchyme is a ground substance matrix for the cells, it is an ordered set of meshwork of connective species like highly polymerized hydro-carbonates, gucosaminoglycans, ologasacharid-chans connected to proteins, proteoglycans, and structure-glycoproteins, meshing by the dendrites of cellular glycocalix and by the extracellular matrix.

Mesenchyme has a trimodal function: cellular, humoral and neural. The cellular function makes the chemical equilibrium of connective tissue together with reticuloendothel cells. The humoral function controls the transport processes through the capillaries and lymph-network. This transport mechanism ensures the communication with far away systems. The neural function is responsible for the functional connection with all other parts of the organism. The three levels are different in their ranges: the cellular is local, the humoral is mesoscopic and the neural is global (systemic) interaction in the body. Due to the slow transport processes, the humoral effects are slow, while the neural is speedy.

The information control is effective by assistance of the neural system, of the cellular transport (hormones, enzymes, apoptosis, "social" signals) and of the humoral by blood and lymph transports too. The cell is the quickest to react. All the controlling mechanisms are operation by a pair of opposite signals: up- and down-regulation the actual process. This is valid in all the time-scales having numerous pairs to form the physiological signals. The three levels are connected with each other by the mesenchyme.

The homeostasis is determined by the equilibrium of the large number of opposite pairs. As example, we describe the proliferation homeostasis. There is a mechanism, which replaces the aged, harmed or too stressful cells. This process, which again the equilibrium of the opposite driving forces, stabilizes the final size of the organs. The opposite processes are the annihilation (apoptosis driven by the programmed cell death) and creation (cell division driven by growth factors). The two sides are in equilibrium in healthy state. When this equilibrium vanishes, the system works faulty, that is the illness. When the apoptosis starts to dominate that could be an autoimmune disease, when the creation determines the process, tumor is the result. The complexity of the system (which characterized by the number of the opposing pairs) is the basic of the proper work, allows the system accommodating properly to the environmental challenges. The acting signal-pairs are connected and coupled to each other, forming a unified complex system.

The deterministic way of the control can not be enough accurate and stable, with appropriate processing velocity, so the process is not deterministic. There are a crucial role of the random processes also to make the control optimal, not use unnecessary accuracy and waste energy to control the system. The aim of the homeostasis is safeguard the cellular functions, assure the constant life-conditions for these smallest units. The environmental parameters must kept in a tolerable band, the fluctuations of the actual values must not go over a definite limit for a longer time. These thresholds keeping the average of the parameters constant in time, but due to the given band-width the deviation also must be fixed (see Figure 6.).

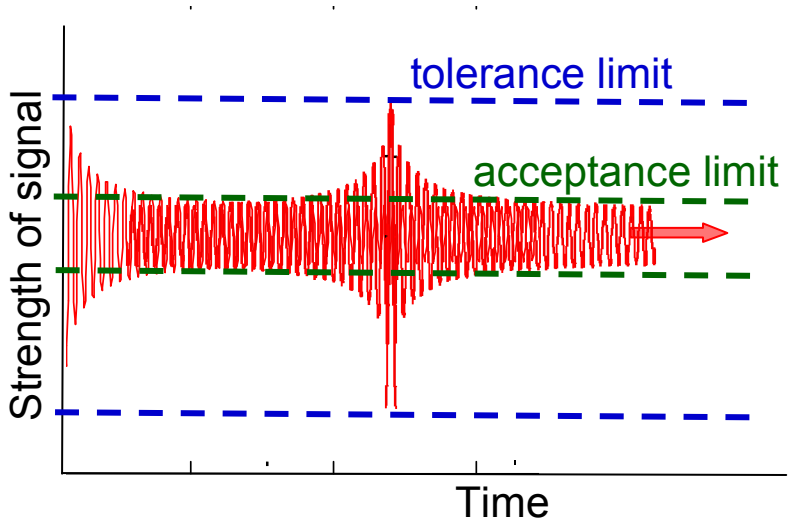


Figure 6. The fluctuations must be in the definite range keeping the control properly. Consequently the average has to be always fixed in time, and the random fluctuations remain in the band for a long-range of the time.

The structure of fluctuations is essential in this stochastic process. The mesenchyme is the coupling media of the action networks constructing the homeostasis. The mesenchyme is a crossing field of the homeostatic actions working like hubs for various and numerous actions. Modifying the hubs, the homeostatic control could be changed. Three main effects could act:

1. The mesenchyme over-controls. In this case the signal has to be down-regulated, purging is active [36].
2. When the signal is too low, it must be up-regulated, which is the tonization **[36]**.
3. The signal is correct, but its deviation is too large. Than a homeostatic entropy has to be produced at the hubs, **[36]**.

The human quantum generator

The human body comprises 10^{14} cells, [37] and a singular cell is composed of several millions of giant molecules. The average quantum activity of the human body: $1.45*10^{27}$ photon/cm^3/s, [38]. The human body radiates not only in the thermal emission range (3 – 10 μm), but it emits microwaves in millimetre wavelengths with high intensity as well [39], [40]. Moreover, the radiation is active even in the X-ray range: decay of the radioactive isotopes (^{40}K) could be observed [41]. The most frequent chemical processes belonging to each wavelength of the spectrum can be seen on the Figure 7.

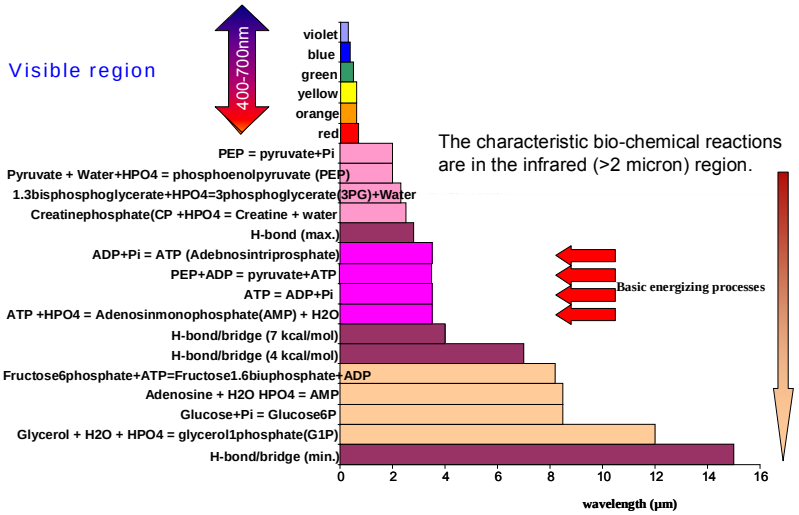


Figure 7. Typical processes of the infrared spectrum in living objects

The utilization of food in accordance with the calometric measurements has 49-50% efficacy. However, if the human organism were a heat engine then the efficacy (calculated the best [42] case) would be:

$$\eta = \left(1 - \frac{T_{ambient}}{T_{body}}\right)100 = \left(1 - \frac{300}{310}\right)100 \cong 3\% \qquad (1)$$

Consequently the human organism is not a heat engine, the photons are produced by combustion. All of these facts indicate the human body is not a simple thermal radiator. On the other hand, the human organism comprises highly specialized units: energy generation and its consumption is not necessarily taken on the same place in the body. The main energy-carrier producers in the cells are the mitocondria. Mitochondria produced ATP, is the carrier of the free-energy in the cellular processes, produced $2 \cdot 10^{26}$ ATP molecules/day [43]. The evolution of energy takes place by the well known hydrolysis of ATP to ADP. The conserved energy carrier is the ATP which energy is converted to instant photon radiation at its hydrolysis. Consequently the energy is carried by these

photons in subsequent steps. ATP transports the energy dominantly by diffusion while the photon makes radiative transmission. In the case of radiation, the photon is absorbed by the actual processes (ionic-pumps or other molecular "motions") or freely travels and damped after a short length. By absorption its energy transforms into thermal molecular vibrations. Its utilization is inefficient in the human organism (it is not thermal engine). There has to be a secondary energy distribution system, which transports the energy in the non-thermal form. Therefore, the highly developed organisms invented a highly efficient method for the production and transportation of photons or related energy "bags" like solitons [44], [45], [46]. These interactions have a long-range coherence [47], and defined on the dielectric matter [48]. For these processes we have to exclude the possibility of the frequent energy-carrier transformation, and also the energy distribution in the form of photons is supposed. If the energy was transmitted by photon carrier, namely, by radiating electromagnetic field, suitable boundary surfaces (waveguides) have to exist; otherwise the energy diffuses, and will be absorbed. Hence, there we suppose the existence of schemes in the advanced organisms like humans transmitting the energy in the form of electromagnetic waves.

Considering that the ionic conductivity of the human organism is relatively low and the frequencies of the transmitted photons are high, [49], consequently, the boundary conditions have to be satisfied by high dielectric constant. The wave conductors therefore have to be dielectric feeder lines of high polarizability, with extraordinary dielectric properties [50].
Because of the complexity of the human organism photons of different frequencies (e.g. see Figure 7.) are produced. The simultaneous transport, distribution, unification of several photons and the avoidance of not wanted frequencies is possible through the energy transport of solitary-waves, by soliton carriers, [51]. In consequence we guess the antennas and feeder transmission-lines are special means carrying soliton-energy in biological systems, involved in the "social control" [1] of the system.

On the other hand, the good efficiency requires an energy distribution where every "user" gets the photon of adequate energy. This assumes a distribution system according to the frequency and absorption process according to the resonance. All these can be complied also by the transport of soliton carriers. Within the energy distribution system there are subnetworks separated by the frequencies, and evidently those users connect to the system – specialized in this way – which requires the photon on the actual frequency. In consequence there are meridians in the human organisation specialized by frequencies.

Cancer and TCM

TCM works as diagnostic as well as treatment facility in malignant diseases. Its diagnostic phenomena cowers many acupunctural points to measure the balance of the various sub-networks in the complex human body (see Table 1.). The diagnosis of tumors is based mainly on

- Phlegm-Damp
- Liver Qi Stagnation
- Blood Stasis
- Heat Toxicity
- Spleen/Kidney Deficiency
- Qi & Yin Deficiency (Qi & Blood Deficiency)

TCM diagnostic phenomena and actions for tumor						
Qi & Yin/Blood Deficiency		Blood Stasis	Heat Toxicity	Spleen /Kidney	Phlegm /Damp	Liver Qi Stagnation
Qi & Yin	Blood					
Ren Shen	Nu Zhen Zi	Dang Gui	Bai Hua She She	Ren Shen	Gua Lou	Chen Pi
Xi Yang Shen	Ji Xue Teng	Chuan Xiong	Jin Yin Hua	Dang Shen	Zao Jiao Ci	Ju Ye
Dang Shen	Ze He Che	Dan Shen	Ye Ju Hua	Bai Zhu	Fa Ban Xia	Zhi Ke
Huang Qi	Gui Ban Jiao	Chi Shao	Lian Qiao	Fu Ling	Bai Jie Zi	Fo Shou
Bai Zhu	Xuan Shen	Yi Mu Cao	Ban Bian Lian	Huang Qi	Dan Nan Xing	Chuan Lian Zi
Fu Ling	Sha Shen	Yue Ji Hua	Ban Zhi Lian	Shan Yao	Shan Ci Gu	Xiang Fu
Huang Jing	E Jiao	Ling Xiao Hua	Chong Lou	Gan Cao	Zhe Bei Mu	Xiang Yuan
Shan Yao	Dan Shen	Tao Ren	Pu Gong Ying	Rou Gui	Ting Li Zi	Qing Pi
Dang Gui	Da Zao	Hong Hua	Zi Hua Di Ding	Rou Cong Rong	Qian Hu	Zhi Shi
Bai Shao	Zhi He Shou Wu	Ji Xue Teng	Yu Xing Cao	Yin Yang Hua	Xing Ren	Mu Xiang
Gou Qi Zi	Long Yan Rou	San Qi	Ban Lan Gen	Tu Si Zi	Cang Zhu	Yan Hu Suo
Shu Di Huang	Gan Cao	Ru Xiang	Bai Jiang Cao	Bu Gu Zhi	Fu Ling	Da Fu Pi
		Mo Yao	Huang Qin	Ba Ji Tian	Huo Xiang	Yu Jin
		San Leng	Huang Lian	Gou Qi Zi	Pei Lan	Da Dou Zi
		E Zhu	Haung Bai	Nu Zhen Zi	Yi Yi Ren	Ba Yue Zha
		Pu Huang	Ku Shen	He Shou Wu	Che Qian Zi	Da Hui Xiang
		Ma Bian Cao	Shan Dou Gen	Shu Di Huang	Jin Qian Cao	Chen Xiang
		Hu Zhang	Long Dan Cao	Huang Jing	Bi Xie	Hou Po
		Zhong Jie Feng	Shi Shang Bai	Zi He Che	Tong Cao	Ding Xiang
		Xi Shu	Tu Fu Ling	Shan Zhu Yu	Zhu Ling	Bai Dou Kou
		Shui Hong Hua Zi	Bi Xie	Sheng Di Huang	Mu Gua	Mei Gua Hua
		Liu Ji Nu	Zhi Mu		Du Huo	Gou Qi Zi
		Niu Xi	Da Qing Ye			Jiu Xiang Chong
		Zao Jiao Ci	Ma Chi Xian			
		Gui Jian Yu	Bai Tou Weng			
		Chuan Shan Jia	Ren Gong Niu Huang			
		Tu Bie Chong	Ya Dan Zi			
		Shui Zhi	Tian Hua Fen			
		Meng Chong				
		Xue Jie				
		Shi Lian Chuan				
		Wu Ling Zhi				

TCM diagnostic phenomena and actions for tumor						
Phlegm /Damp	Liver Qi Stagnation	Blood Stasis	Heat Toxicity	Spleen /Kidney Deficiency	Qi & Yin/Blood Deficiency	
					•Qi & Yin	•Blood
•ST 40	•PC 6	•SP 6	•SP 6	•ST 36	•SP 6	•DU 14
•SP 4	•LI 4	•LI 4	•LI 4	•UB 20	•ST 36	•UB 39
•LV 2	•ST 36	•SP 10	•SP 10	•UB 21	•KD 3	•UB 17
•SP 9	•UB 40	•UB 17	•SHI XUAN	•REN 12	•KD 1	•SP 10
•LU 10	•LV 3	•LI 11	•LI 1	•SP 6	•UB 23	•UB 23
•HT 3	•UB 22	•UB 40	•LU 11	•PC 6	•UB 18	•REN 4
•SJ 5	•ST 44	•LU 5	•LI 11	•SP 4	•LV 3	•DU 4
•LI 4	•LV 14	•ST 36	•UB 40	•LV 13	•KD 6	•DU 15
•LI 11	•GB 34	•UB 20	•LU 5	•SP 10	•REN 6	•UB 11
•UB 20	•ASHI	•LV 3	•ST 36	•UB 23	•LI 11	•KD 3
•UB 13		•ST 44	•LV 3	•DU 4		•ST 36
•SJ 10		•LV 14	•ST 44	•REN 6		•UB 20
•ASHI POINTS		•GB 34	•LV 14	•REN 4		•SP 6
		•REN 14	•GB 34	•LV 3		•LV 3
		•UB 22	•DU 14			•REN 6
		•DU 20	•UB 22			•PC 6
		•XI CLEFT POINTS	•ASHI			•UB 18
		•ASHI				•UB 21

Table 1. The diagnosis facilities of TCM in classical homeostatic balance measurement

The treatment facilities are also very large making again a good synergy basis of oncothermia and TCM. The TCM treatment of tumors concentrate on the

- Phlegm-Damp - Transform Phlegm & Dispel Damp.
- Liver Qi Stagnation – Sooth Liver & Regulate Qi.
- Blood Stasis – Invigorate Blood & Transform Blood Stasis
- Heat Toxicity - Clear Heat & Resolve Toxicity
- Spleen/Kidney Deficiency - Tonify Spleen & Kidney
- Qi & Yin Deficiency (Qi & Blood Deficiency) – Tonify Qi & Yin/Blood

The TCM has special role in cancer treatment strategies by supporting Qi and dispeling pathogenic factors.

The combination of TCM with Western medicine could be active in all the "gold standards; in surgery, in chemotherapy and in radiotherapy. It could be applied before surgery, aiming the

- Improve the body's ability to withstand surgery.
- Reduce post-operative complications
- Control the development of the disease.
- Benefit postoperative rehabilitation.

TCM makes status applied before surgery as

- supplementing Qi and nourish blood.
- fortifying the spleen & augment Qi.
- enriching and supplementing the liver and kidneys.

TCM can be applied after surgery also. Its goal in these cases is double:

- Reducing the possibility of recurrence and metastasis.
- Create an appropriate condition for future radiotherapy and chemotherapy.

These goals are in complete correspondence with the goals of oncothermia, so again the synergy is actually ready. TCM will do the after surgery applications:

- Tonifying Qi and blood.
- Harmonizing Ying and Wei Qi.
- Harmonizing spleen and stomach.

Furthermore of the surgery combinations, TCM is reducing the side-effects and increasing the effectiveness of radiotherapy and chemotherapies by:

- enhancing the overall results of the treatment
- preventing local constriction and recurrence.
- Reducing toxic reactions and adverse side-effects.
- improving hematopoiesis,
- protecting renal and hepatic functioning.
- Reducing gastro-intestinal side-effects.
- alleviating radiation pneumonitis, proctitis and cystitis.
- Reducing vomiting.
- Increasing immune function
- raising long-term survival rates.

It is again the complete synergy with oncothermia, offering huge number of possibilities apply these methods in synergy.

Immune basic of synergy of Oncothermia with TCM

Acupuncture and their connective pathways the meridians are ancient Chinese knowledge but it is not understood yet in details [53]. Request of the stable homeostasis of the complex organisms is demanding interdisciplinary approach and new paradigm for the topic. The detecting and reconstructing the deviation from the normal balance of the homeostasis is the basic principle of TCM. The Chinese herbs, the physical (mechanical or electromagnetic acupuncture, acupressure) and mixed forms of heating and diffusion-therapies (moxa therapies) approaches are pointing these problems, and solving it with ancient methods. Oncothermia method (OTM) uses also the deviations from the normal homeostasis for selecting the tumor cells and on this basis ignite natural processes to eliminate them from the system, reestablishing the communication harmony between the cells [54]. This technique [55] is well proven from the laboratory level to the clinical applications [56].

The questions from the quantum generator considerations above directly addressed: what is the wave conductor and how is it fed? Evidently, this can be propagating antennas only, namely, antennas distributed in the whole organism that collect the photons and conduct them to the feeder line. Obviously, these have to be broadband antennas to be found everywhere in order to absorb the least possible photons. The components of the network to be found everywhere are the vascular, lymphatic and nervous system. These have a function of collection and distribution. (The resonance effect of subtle propagating waves is experimentally proven in Escherichia coli bacteria system, [57]). Certain co-acting parts of the bio-systems can be regarded as meridians. There is no necessary identify any anatomical structure with this network. Therefore, it is not a separately

specialized network transporting any material, but each living organism could have such a transmission network. (The acupuncture can be used in the veterinary medicine as well, [58].)

The single synergistic parts are connected forming a coherent network [59]. There are connection points where the solitons branch-off or join. These co-acting units – as they are formed from three subsystems – get to the surface of body at certain places, [60]. It is remarkable that these conductions to the skin surface have mostly similar physiologic structure [61], identified as acupuncture points.

If we intervene at these points physically, on the one hand, we are able to couple out or in energy in the system, on the other hand, we can influence the shape of solitons (consequently, the spectrum of photon energy). This method is used by the acupuncture therapy, since, if we carry out the coupling in or out of energy in the points of the suitable meridian then we are able to influence the energy exchange. Next, we are going to examine how are the co-acting units established and what is the system model.
Between the acupuncture points to be found on the same meridian the electric resistance is lower than between the points outside, [62], [63].

There are points where the concurrent clusters of the circulatory, lymphatic and nervous systems being in synergy get together to the surface of skin **[61]**. Their structure is very similar. Moreover, these points are different from the other points of skin surface regarding their physical properties. The different features are as follows: lower electric impedance, carbon dioxide production, infrared radiation [64].

The lower impedance follows from the wave-conduction property. It is evident that the wave propagates in the range of lower wave resistance. The intensive infrared eradiation indicates the feeder-line nature and its loss. The feeder line emits here the inevitably dissipating energy. The intensive infrared radiation makes the cells of skin surface to have a higher metabolism level. Probably, this is the reason of the higher CO_2 emission. It can be imagined as well that we might speak about a simple control of energy emission as the carbon dioxide is an infrared reflector. Long time ago we did not wear clothes, therefore, we had a very sensitive energy-emission control system in which the acupuncture points – forming the part of the system – operated as intensive emission places. The emission was controlled in these by means of carbon dioxide production, namely by a chemical process. We may conclude this part: energy distribution system has numerous points through which the energy system can be controlled very exactly and sensitively.
An extended network approach was presented in the topic [65], and we would like to continue our research on this basis. The in silico studies will have their roots from the network analysis together with the modern fluctuation theory for complex living organisms (fractal-physiology) was developed in the last decades to study this complexity: like self-organization ([66], [67], [68], [69]), fractal physiology ([70], [71], [72], [73]), and the bioscaling ([74], [75], [76]). Oncothermia widely using these new scientific results [77], [78]; as well as the resonance phenomenon is studied and used in the light of a new theory [79], and special vector-potential theory [80], [81], [82] helps to complete the method. The problems of the thermal limit in the deep-seated tissues is theoretically [83] and experimentally [84] solved, so it has no any barrier for the wide investigations in synergy experiments. TCM involves electro-acupuncture and laser acupuncture, which are similar in their electromagnetic (conductive) approach to oncothermia effects. We studied the network control in acupuncture and connected it with the fractal physiology approach, used essentially in oncothermia applications. The network is recognized as scale independent and so well generalized for all the living structures.

The outer connection points for this control are probable the acupunctural points. The living systems are energetically open, they are strongly connected to their environment. The special material exchange in the acupunctural points (CO_2 development [85], temperature differences [86],

potential differences [87]), as well as the change of the size [88] of the acupunctural point support the assumption that these connections are controlling hubs in the complex system.

The stimuli of the acupunctural points (controlling the active fluctuations in the homeostatic band) could be achieved by various methods, like invasive needles, like electric or laser stimuli or mechanical pressure. We do not know yet the actual local processes induced by the stimuli, but probable the mechanical and electric factors make the disturbance which promotes the natural correction system to reestablish the homeostatic equilibrium. Probable there is no single effect could be named for action, but various local disorders are conflicting, like micro-wounds making injury current, like micro-bleeding inducing platelet-derived growth-factors (PDGF), like forced cellular apoptosis and replacing division, etc. Irrespective of the realized ways of the action, the acupuncture is probable giving enough disturbances to rearrange the structure of the local hub for finding the homeostatic equilibrium again by self-organizing way. This is much similar to the process, when we give mechanical vibration for a bowl of cherries to arrange itself to a lower energy status with self-organization way (see Figure 8.). The stimuli are active till the micro-disturbance exists [89], **[36]**. There are examples for the stochastic disturbance inducing self-organized processes in the bioprocesses.

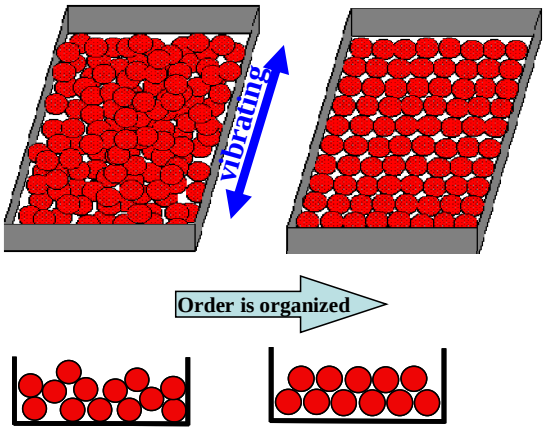


Figure 8. Mechanical self-organization by vibrative disturbance.

Forming the secondary, ternary and fourth structures of proteins operated by self-organizing way [90], and one of the functions of stress-induced proteins (heat-shock proteins, HSP) is providing such disturbances for the stress-unfolded portents where the molecules could find the lower energy state forming their normal structure again [91].

There are many well proven effect to show the immune action of TCM, which could be well harmonized and supported by the oncothermia immune simulative and immune activation effects. The classical needle and newer electro-acupuncture of humans (Tables 2. and 3.) and on animals (Tables 4. and 5.) show the proofs

Immune action	**Effect/action**	**References**
Macrophages	promoter	[92], [93]
Neutrophils	promoter	[94], [95], **[92]**
Neutrophils	no effect	[96]
NK-cells	promoter	[97], [98], **[92], [93]**
Lymphocytes	promoter	**[92], [93]**
Lymphocytes	suppressor	[99]
Immunoglobulin	suppressor	[100], [101]
Immunoglobulin	promoter	[102]
Immunoglobulin	no effect	[103], [104]

Table 2. Immune effects of acupuncture in humans

Immune action	Effect/action	References
NK-cells	no effect	[105]

Table 3. Immune effects of electro-acupuncture in humans

Immune action	Effect/action	References
Macrophages	promoter	[106]
Neutrophils	promoter	[107]
NK-cells	promoter	[108]
Lymphocytes	promoter	**[108]**
Immunoglobulin	promoter	[109]

Table 4. Immune effects of acupuncture in animals

Immune action	Effect/action	References
Macrophages	suppressor	[110], [111]
Macrophages	no effect	[112]
NK-cells	promoter	[113], [114], [115], [116], [117]
Lymphocytes	suppressor	[118], [119]
Lymphocytes	promoter	[120]
Immunoglobulin	suppressor	**[118]**

Table 5. Immune effects of electro-acupuncture in animals

These facts are also in complete harmony of the oncothermia immune stimulation and absocpal effects. The herbal supports of the TCM offers also a great synergy potential. Many herbs applied in TCM are immune supporters and trying to rebalance the lost homeostatic control. One of the most known herbal application is the ginseng, which effect of Ginseng on tumor-suppression was shown as connected to Nrf2 [121] in prevention (see Figure 9. and 10.). The nuclear factor (erythroid-derived 2)-like 2, (Nrf2), is a transcription factor that in humans is encoded by the NFE2L2 gene. [122]. NFE2L2 induces the expression of various genes including those that encode for several antioxidant enzymes, and it may play a physiological role in the regulation of oxidative stress. The proven stimuli of the Nrf2 is a very promising possibility of the TCM and oncothermia synergy.

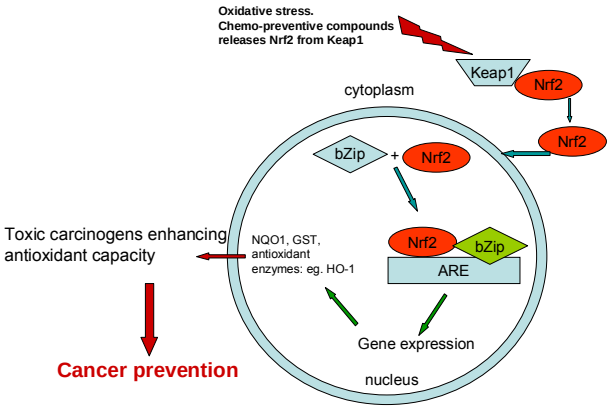


Figure 9. Cancer prevention way by Nrf2

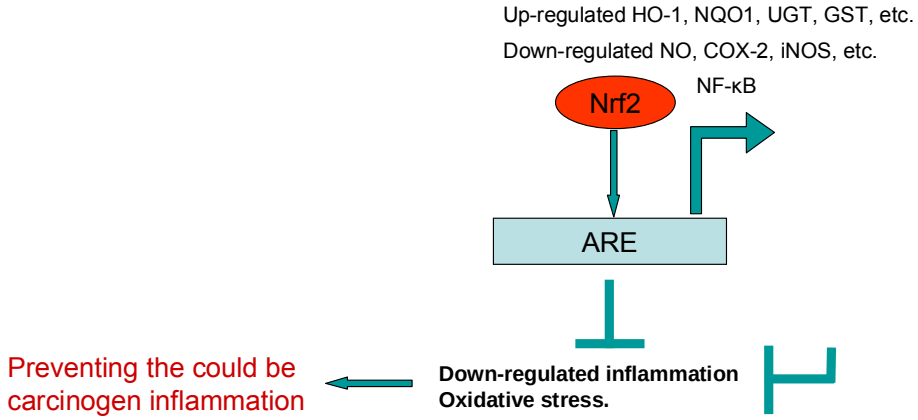


Figure 10. The role of Nrf2 in chemoprevention. When Nrf2 has a dysfunction, that makes prolonged inflammation and oxidative stress, leading to genetic instability, and at the end to cancer

Extracts from the Roots of *Lindera strychifolia* Induces Apoptosis in Lung Cancer Cells, which was experimentally investigated by immunohistochemical staining of PCNA and TUNEL in LL-2 cell s.c transplanted in mice [123]. At 1 week before transplantation of LL-2 cancer cells, mice received *L. strychifolia* extracted solution daily until the end of the experiment. At 35 days after *L. strychifolia* treatment, tumors were resected and examined histologically (n = 11/group). The typical immunohistochemical appearance (PCNA and TUNEL) in tumor tissues from mice of control and *L. strychifolia* extract (5.0 mg/ml) treated mice well shows the difference. Cell proliferation and apoptosis were detected using anti-PCNA antibody and a modified TUNEL method, respectively. Change in PCNA-positive and TUNEL-positive cell number in the tumor tissue PCNA control 50% dropped to 20% ($p<0.01$), and TUNEL control increased from 20% to 50% ($p<0.01$).

Proposal

There are various TCM substances acing palliative or curative on tumorous diseases. For example of pain reduction the "Senecio palmatus". For curative treatments special moxibustion techniques with various complex mixture of herbs could be applied [124]. Synergetic effects of the oncothermia and TCM is expected due to the well targeted tumor-tissue by oncothermia in combination with the effective TCM like Tongyou-sum plant. Also the effect of ginseng and its Nrf2 cancer preventive action with oncothermia is investigated, and genarlly the apoptotic possibilities for various TCM herbs. The effect of synergy will be investigated by in silico, in vitro and in vivo experiments, using special oncothermia device for laboratory use (EHY110, Oncotherm). The latest histomorphological and immunohistochemical methods will be used for evaluation,; mainly concentrating on p53 tumor-suppressor protein and the apoptotic pathways, including beta-catenin. Protocols of clinical studies will be worked out on the basis of the experimental results.

Potential of the synergy of high-tech oncothermia and TCM is extremely huge. We are ready to work out the European alternative of the "East meets West in cancer care collaboration" [125] on the basis of the widely applied TCM evidences [126].

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Komplexe Probleme kann niemand allein lösen. Eine Gruppe von Ärzten und Therapeuten mit unterschiedlichen Spezialisierungen und Schwerpunkten ist leistungsfähiger als ein nur auf sich selbst gestellter Arzt. Diese Erkenntnis hat die Praxisklinik Dr. Schuppert in Bonn für ihr Konzept genutzt: Im Ärzteteam der Praxisklinik sind die Erfahrungen aus vielen unterschiedlichen Fachgebieten vertreten, ohne dass dabei der Blick auf die ganzheitlichen Zusammenhänge verloren geht.

Das Angebot umfasst umfangreiche und moderne schulmedizinische sowie naturheilkundliche Diagnose- und Therapieverfahren. Mit einem breiten Spektrum wird ein großer Teil medizinischer Fachbereiche abgedeckt. Das erspart dem Patienten unnötige Wege, Wartezeiten und Doppeluntersuchungen.
Die Krankheitsgeschichten und alle Ihre Untersuchungs- und Behandlungsdaten sind für jeden Arzt und Therapeuten aus der zentralen EDV direkt abrufbar. Besprechungen der Fachgebiete untereinander sind von Tür zu Tür jederzeit ohne Probleme möglich.
„Je ganzheitlicher die Therapie, umso größer ist die Aussicht auf Behandlungserfolg", so die Philosophie von Dr. Schuppert und seinem Team.

Chronische Krankheiten, Schmerzen, Krebs, „sich nicht wohlfühlen", all das beeinträchtigt die Lebensqualität. Die Ursachen hierfür zu finden ist daher die zentrale Aufgabe. Im Anschluss an ein ausführliches, intensives Erstgespräch wird gemeinsam mit den Patienten ein individuelles, auf sie und ihr Krankheitsbild abgestimmtes Therapiekonzept erstellt.
Dabei werden immer die Zusammenhänge der Beschwerden aus den verschiedenen Bereichen des Körpers berücksichtigt. Abhängig vom Krankheitsbild entscheiden die Ärzte gemeinsam mit ihren Patienten, welche schulmedizinische und/oder naturheilkundliche Behandlung am effektivsten ist.

Die Schwerpunkte der Praxisklinik Dr. Schuppert sind:

- Allgemeinmedizin und Naturheilkunde
- Innere Medizin und Kardiologie
- Onkologie und Ganzheitliche Krebstherapie
- Akupunktur und Traditionelle Chinesische Medizin
- Gynäkologie
- Osteopathie
- Psychotherapie und energetische Medizin
- Schmerztherapie
- Allergologie
- Ursachendiagnostik
- Präventive Medizin, Check-up-Untersuchungen

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Tagesklinik „Erzgesund“ Zentrum für Zelluläre Bioregulation & Anti Aging Burkhardtsdorf, Germany

Frau Dr. med. Gabriela Röder ist Fachärztin für Allgemeinmedizin und absolvierte zusätzlich vertiefende Ausbildungen im Bereich der Naturheilkunde wie z.B. die Zelltherapie nach Prof. Landsberger.
2005 hat Frau Dr. Röder die Tagesklinik „Erzgesund“ gegründet, deren Fokus zunächst ausschließlich auf die biologische Krebstherapie gerichtet war. Seit Oktober 2011 führt Frau Dr. med. Röder die Tagesklinik als Zentrum für zelluläre Bioregulation & Anti Aging. Hierbei verfolgt sie das Prinzip einer konsequenten Verknüpfung von Schulmedizin mit den Erkenntnissen der Naturheilkunde, der traditionellen chinesischen Medizin und der Energie- und Informationsmedizin.

Das diagnostische und therapeutische Konzept der Tagesklinik charakterisiert folgende Schwerpunkte:

- Vor jeder Behandlung steht eine umfassende Diagnose mit modernsten ***Diagnoseverfahren*** mit dem Ziel, die Ursachen von Regulationsstörungen zu lokalisieren.
- Die Ursachen aller Erkrankungen beruhen primär auf einer Störung der ***zellulären Bioregulation.*** Aus diesem Grund werden in der Regel im ersten Schritt der Behandlung die Fähigkeit zur Verbesserung der Bioregulation und die Anhebung des Energieniveaus therapeutisch mit unterschiedlichen Methoden eingeleitet. Mit diesem therapeutischem Schritt wird die ***„Therapiefähigkeit“*** der Klienten entscheidend verbessert.
- Im zweiten Schritt kümmert sich das Klinikteam intensiv um die Ursachen der individuellen Befindlichkeitsstörungen, mögliche Störherde und Blockaden und deren therapeutische Auflösung. Dafür stehen modernste ***therapeutische Gerätesysteme, Mittel und Methoden der Naturheilkunde*** und der ***traditionellen chinesischen Medizin*** zur Verfügung. Bei Bedarf wird auch mit einer ganzheitlich orientierten Zahnarztpraxis zusammengearbeitet.

Natürlich ist dies nur ein Leitfaden. Nach einer umfassenden Diagnose erhält jeder Klient einen individuellen Therapieplan, denn die persönliche Einbindung in die Therapieprozesse hat oberste Priorität. Dem Klinikteam ist es wichtig, bei den Klienten eine Veränderungsmotivation zu erreichen. Denn diese sind selbst der Schlüssel zur Heilung.
Chronische Krankheiten entwickeln sich langsam, und es braucht Zeit, sich wieder zu erholen. Das Team der Tagesklinik Erzgesund unterstützt und begleitet seine Klienten.
Auf dieser Basis hat Frau Dr. Röder neue Therapiestrategien entwickelt, insbesondere für die biologische Krebsbehandlung
- auch unter Einbeziehung des Oncothermiegerätes EHY-2000 -, für die Behandlung von Borrelliose, die Behandlung von Herz- Kreislauferkrankungen und die so genannten Zivilisationserkrankungen.

TAGESKLINIK ERZGESUND
Zentrum für Zelluläre Bioregulation & Anti-Aging

XXXI.
Conference of the International Clinical Hyperthermia Society (ICHS)

October 12th-14th 2012
Hotel Marriott
Budapest, HUNGARY

At the last ICHS annual meeting in Tbilisi, Georgia in September 2011 Prof. Dr. András Szász was elected as new president of the ICHS. He will take over all responsibilities for the society and will host next year's conference. The event will take part in Budapest, Hungary and will he held together with the 2nd International Oncothermia-Symposium. We will inform you about the progress of the organizing and information about talks regularly.
Please send us your abstracts for talks and posters as soon as possible! We are looking forward to all speakers and participants!
Company sponsoreships are possible. Please contact Ms. Janina Leckler (leckler@oncotherm.de) for detailed information.

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Phone: 0049 (0) 2241 31992 0

Dear colleagues,
dear members of the ICHS,
dear Oncothermia-users,

Hyperthermia started to be an integrative part of the oncotherapies. Our society is one of the oldest in this field. Since its establishment ICHS has represented the best traditions of the oncological hyperthermia, uniting the best national and international efforts to reach the wide acceptance of this complementary treatment.
Like in most other areas of life international communication is getting more and more important in the medical field.
Let us exchange our experiences, get to know new approaches of hyperthermia in oncology, let us seriously and openly discuss new ideas. Our society has preferred direct debates, has protected explicit and frank opinions for medical approaches for building up a better, safer and successful oncology treatment. Our main concern is to help the suffering patients with a longer survival and a high quality of life.
I invite you to our conference to continue our traditions and strengthen hyperthermia as a stable weapon in the war against cancer!
Yours:

Prof. Dr. Szasz Andras
ICHS President

www.hyperthermia-ichs.org
www.io-symposium.com