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Various Oncothermia topics from the science and the practical application

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Editorial

Dear Reader,

The International Oncothermia-Symposium 2010 was a great success. Even now doctors are calling us to ask for details of the presented topics. Because of the high interest we are presenting you the posters of the event in this issue of the Oncothermia Journal.

Of course this is not all regarding the contents we prepared for you. I attended the WFCMS Conference in China in May of this year and I am happy that Prof. Dr. Clifford L. K. Pang (who is a member of our editorial board) gave permission to publish his results on “Status and Prospect on Contemporary Natural Medicine”.

The focus of the Onothermia method is the patient. We want to help increasing the patient’s quality of life and to extend the life time. Several doctors will be presenting presenting their great results with Oncothermia treatments in this year’s Oncothermia-Symposium. The abstracts will published in the November-issue of the Oncothermia Journal.

Our research and development division is working on a remake of our ECT device at the moment. A lot of interested doctors already asked for details. We will of course inform you about the status. Prof. Dr. Li from China submitted a detailed article about the possibilities of this therapy.

As in the last issue we want to introduce to you international clinics working with Oncothermia. This time we present the first Turkish clinic using Oncothermia and the medical practices of Dr. Peters, Dr. Langer and Dr. habil. Gregori from Germany.
We hope that you enjoy reading our Journal. If you have any wishes concerning the topics of our magazine or if you want to submit an article, please contact one of the Managing Editors.

Sincerely

Prof. Dr. András Szász

Lieber Leser,

Das Internationale Oncothermie-Symposium 2010 war ein großer Erfolg. Selbst jetzt, fast ein Jahr später, rufen Ärzte an, um nach Informationen zu den präsentierten Themen zu fragen. Aufgrund dieses Interesses präsentieren wie Ihnen in dieser Ausgabe des Oncothermia Journals noch einmal die Poster der Veranstaltung.

Natürlich haben wir aber auch noch weitere Themen für Sie: Ich habe an der WFCMS Konferenz in China im Mai dieses Jahres teilgenommen und freue mich, dass Prof. Dr. Clifford L. Pang (der ein Mitglied unseres Editorial Boards ist), sein Einverständnis gegeben hat, seine Ergebnisse über “Status and Prospect on Contemporary Natural Medicine“ zu veröffentlichen.

Der Schwerpunkt der Oncothermie-Methode ist der Patient. Wir möchten dabei helfen, die Lebensqualität des Patienten zu verbessern und die Lebensdauer zu verlängern. Auch in diesem Jahr präsentieren zahlreiche Ärzte auf unserem Oncothermie-Symposium ihre Ergebnisse mit der Methode. Die Abstracts zu den Vorträgen werden in der November-Ausgabe des Oncothermia-Journals veröffentlicht.

Unsere Forschungs- und Entwicklungsabteilung arbeitet an einer Neuauflage unseres ECT Gerätes. Einige interessierte Ärzte haben bereits nach Informationen gefragt. Wir werden Sie selbstverständlich über den Status der Entwicklung informieren. Prof. Dr. Li aus China stellt in seinem Beitrag die Möglichkeiten dieser Therapie vor.

Wie schon in der letzten Ausgabe möchten wir Ihnen auch in diesem Heft internationale Kliniken vorstellen, die mit Oncothermie arbeiten. Dieses Mal präsentieren wir Ihnen die erste türkische Klinik, die mit Oncothermie behandelt sowie die Praxis Dr. Peters und die Arztpraxen von Dr. Langner und Dr. habil. Gregori in Deutschland.

Wir wünschen Ihnen viel Spaß beim Lesen. Falls Sie Wünsche bezüglich der behandelten Themen haben oder einen Artikel einreichen möchten, kontaktieren Sie bitte unsere Redaktion.

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.

1. Selbstverständnis und Ziele

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.
- *Biologische Studien.* Mechanismen der Oncothermie, thermale oder temeperaturunabhängige Effekte, Ansprechen auf elektrisches Feld, bioelektromagnetische Anwendugen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologsche Effekte etc.
- *Oncothermie*-Techniken. Technische Entwicklungen, neue technische Lösungen.
- Hypothesen, Meinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen.

2. Submission of Manuscripts

All submissions should be made online at the Oncothermia Journal by email Oncothermia-Journal@oncotherm.org.

2. Manuskripte einreichen

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3. Preparation of Manuscripts

Manuscripts must be written in English, but other languages can be accepted by special reasons, when it has an English abstract.

Texts should be supplied in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be supplied in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be supplied in JPG format.

Manuscripts may be any length, but must include:

- *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.
- *Abstracts.* Abstracts should include the: Purpose, Materials and Methods, Results, Conclusions.
- *Test.* Unlimited volume.
- *Tables and Figures.* Tables and figures should be referred to in the text. (numbered figures and tables). Each table and/or figure must have a legend that explains its purpose without reference to the text. Figure files will ideally be supplied as jpg-file (300dpi for photos).
- *References.* Oncothermia Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3], [1-3]. The full references should be listed numerically in order of appearance, and presented following the text of the manuscript.

3. Manuskripte vorbereiten

Manuskripte müssen in englischer Sprache vorliegen. Andere Sprachen können in Ausnahmefällen akzeptiert werden, wenn ein englisches Abstract vorliegt.

Texte sollten in einem mit Microsoft Word für Windows (PC) kompatiblen Format eingereicht werden. Tabellen sollten in einem Word-kompatiblen Format eingefügt werden. Alle Graphiken (Illustrationen, Diagramme, Photographien) sollten im jpg Format vorliegen.

Manuskripte können jede Längen haben, müssen aber die folgenden Punkte enthalten:

- *Titelseite.* Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte. Es muss mindestens ein Autor ausgewiesen sein, dessen Email-Adresse und Kontaktdetails angegeben werden.
- *Abstracts.* Abstracts müssen enthalten: Zielsetzung, Material und Methoden, Ergebnisse, Fazit.
- *Text.* Beliebige Länge.
- *Abbildungen und Tabellen.* Abbildungen und Tabellen sollten im Text erläutert werden (nummeriert). Jede Abbildung / Tabelle muss eine erklärende Bildunterschrift haben. Bilder sollten als jpg verwendet werden (300 dpi).
- *Zitate.* Das Oncothermia Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

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5. Elektronische Korrekturfahne

Wenn die Korrekturfahnen fertig gestellt sind, werden die Autoren per Email informiert. Gedruckte Kopien werden nicht per Post versandt. Um Verzögerungen in der Produktion zu verhinden, müssen die korrigierten Texte innerhalb von 48 Stunden per Email oder Fax zurückgesandt werden.

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7. Advertising
The Oncothermia Journal accepts advertising in any languages, but prefers English at least partly. The advertising must have connection with the scope of the Oncothermia Journal and must be legally correct, having controlled values and true info.

7. Werbung
Das Oncothermia Journal akzeptiert Werbeanzeigen in allen Sprachen, wünscht aber die zumindest teilweise Gestaltung in englischer Sprache. Die Werbung muss eine Beziehung zu den Themen des Oncothermia Journals haben und der Wahrheit entsprechende Inhalte aufweisen.

8. Legal responsibility
Authors of any publications in the Oncothermia Journal are fully responsible for the material which is published. The Oncothermia Journal has no responsibility for legal conflicts due to any actual publications. The Editorial Board has the right to reject any publications if its validity is not enough controlled or the Board is not convinced by the Authors.

8. Haftung
Die Autoren aller im Oncothermia Journal veröffentlichten Artikel sind in vollem Umfang für ihre Texte verantwortlich. Das Oncothermia Journal übernimmt keinerlei Haftung für die Artikel der Autoren. Der redaktionelle Beirat hat das Recht,, Artikel abzulehnen.

9. Reviewing
The Oncothermia Journal has a special peer-review process, represented by the Editorial Board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of Reviewer will not be signed, her/his name will be handled confidentially. Papers which are not connected to the scope of the Journal could be rejected without reviewing.

9. Bewertung
Die Texte für das Oncothermia Journal werden vom redaktionellen Beirat kontrolliert. Um Konflikte zu vermeiden, werden die Namen des jeweiligen Korrektors nicht öffentlich genannt. Artikel, die nicht zu den Themen des Journals passen, können abgelehnt werden.

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Electrochemical Therapy of Tumors

What is Electrochemical Therapy（EChT）

Inserting electrodes (special produced by platinum) into tumor and connecting its with EChT apparatus, direct electric current arouse strong chemical reactions around electrodes and lead degeneration and necrosis of tumor cells. It is a new type method to treat tumor without surgical resection. The final result is caused by direct electric current inducing chemical reactions, so it is called EChT.

Historical note

The study of effectiveness of direct current on biologic tissues has a long history. In 1895, a physiologist tried to insert electrode into a dog's brain and gave D.C. stimulation on it, he found necrosis occurred in brain tissue around electrode. After that some other doctors have done a lot of experimental works about the reactions of biologic tissue for direct current.

However, the clinical application of this modality was initiated by the Swedish radiologist, Bjorn Nordenstrom. In 1983, he published a book in which he described his theory of biologically closed electrical circuits (BCEC) and the results of research for EChT on malignant tumors in animals based on this. He also reported the results of EChT on 20 lung cancer patients with 26 tumors in which he used the "skinny needle" he had developed for biopsy purposes as an electrode. Follow-up after 2 to 5 years revealed that 12 tumors had either disappeared or were markedly reduced in size.

But the real widely application of the technique has begun in China (China-Japan Friendship Hospital as the center of this application) after it was introduced to the country in 1986. The advantages of EChT include less injury, easy manipulation, safety and efficiency. It provides the chance of treatment for tumor patients to whom operation, radioand/ or chemotherapy is not indicated or ineffective.

Experimental studies on mechanism of EChT

It has been well established that tumor cells are more sensitive to certain changes in the environment than adjacent normal cells, which is the basis of application of radio-, chemotherapy, hyperthermia, microwave and laser therapy for treatment of tumors. Many pathological changes occurred in the tumor tissue when D.C. was act on it, such as pyknosis of nuclei, disruption of cell membrane, disappearance of mitochondria and coagulation and necrosis of nuclear protein

The publication of Nordenström's work for lung cancer aroused many researchers' attention and interest in this field. A number of scientists did animal experiments in order to make clear the mechanism of action, the indication of clinical application and improvement of the manipulation of the method. In animal experiments, histopathological studies have demonstrated that the killing effect of EChT on the tumor tissue surrounded anode area differs from that around the cathode area. The tumor tissue surrounded anode area showed necrosis of coagulation feature: cell structure was destroyed, pyknosis of cells, denaturation and coagulation of protein. While tumor tissue surrounded cathode area showed necrosis of liquefaction in nature: cell structure totally disappeared, water molecules accumulated due to the presence of positively charged sodium ions and large molecules of protein was swollen and dissolved.

Though the features of changes are different in anode and cathode areas, the killing areas of both electrodes are about the same, i.e. the radius of killing effect is 1 cm.

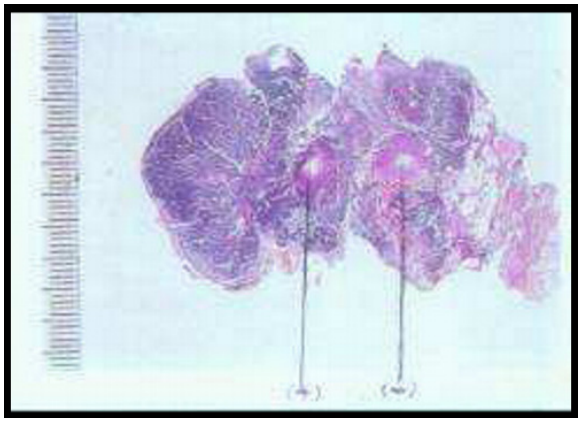


Figure 1. The killing effect of cathodes & anodes was similar

On the basis of large amount of animal experiments and clinical pathological examination, the mechanism of killing action of EChT has been confirmed as electrolytic effect of direct current.
The killing action of DC per se is limited only around the surface of electrode. To expand the killing effect are the substances resulted from electrolysis of water and electrolytes (NaCl and H_2O), i.e. NaOH and HCl diffused from around electrode to a certain distance. Na^+ ion formed by electrolysis will move toward cathode area and combine with OH- ion to form NaOH, which will result a strong alkaline (pH 12-14) environment. While Cl^- ion formed will accumulate around anode area and combine with H^- ion to form HCl, which is strong acidic (pH 1-2).

ELECTOLYSIS

pH12-14 pH1-2

↑ ↑

↑ ↑

NaOH ——— NaCl ——— **HCl**

↑ ↑

↑ ↑

$OH^- \leftarrow\leftarrow\leftarrow H_2O \rightarrow\rightarrow\rightarrow H^+$

The strong alkalinity and acidity are the main killing factors of the therapy. Hence, it is seen during the application of EChT there is large amount of foams oozed out from the periphery of electrodes releasing Cl_2 and H_2O_2.

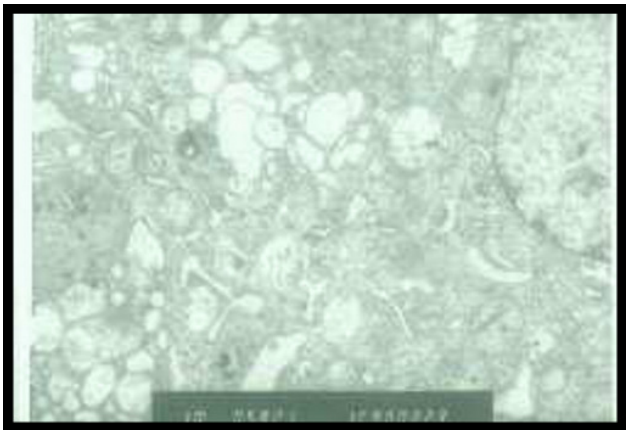
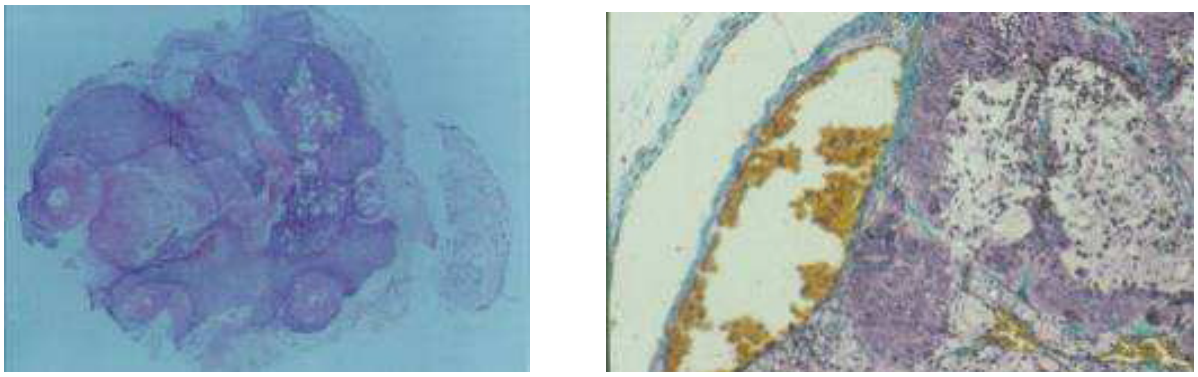


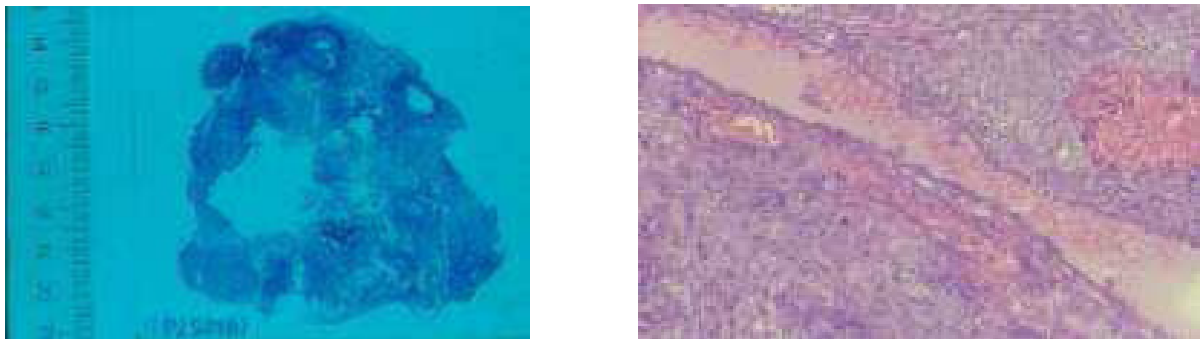
Figure 2. The figure of cancer cells disappeared and a mass of air bubbles came forth 10 minutes after EChT

The mechanism of EChT for treatment of tumors is summarized as follows:
(1) Electrolysis by direct electric current changes pH of environment which results in biological effect;
(2) Direct electric current could increase the permeability of cell membrane of tumor cells. Ions and Cl2 could go inside and kill tumor cells;
(3) Activity of enzymes in plasma was inhibited, proteins denatured, coagulated and necrosis occurred
(4) Electrolysis makes distribution of irons changed, which results in coagulatory necrosis around anode and edema around cathode



(low power lens) (high power lens)

Figure 3. The anode made tumor tissues dehydrated and carbonized protein coagulated and necrosis



(low power lens) (high power lens)

Figure 4. Cancer cells were dissolved and breakdown, congestion and edema of tissue were represented in the area of cathode

(5) Extensive embolism occurred in blood vessels in anode area.
Because severe edema in cathode area, microcirculation was damaged. Hence, the blood supply to tumor cells is interrupted
(6) White blood cells and T lymphocytes accumulated in anode area, which may be helpful to kill tumor cells. At the same time, the negatively charged tumor cells are adhered to anode area and metastasis of tumor cell are halted
(7) The damaged fragment of tumor cells by direct electric current could be the antigen to improve the immune system of the body

Clinical application and effectiveness of EChT to treat tumors
After the clinical applications of EChT to treat cancer reported by Nordenström in 1983, the China—Japan Friendship Hospital in Beijing took the lead to apply the method in clinical, and they have finished more than thousands operations for many kinds of tumors from then on.

Several years ago, we summarized the clinical effectiveness of 8641 cases of malignant tumors treated by EChT after long-term follow-up in 82 hospitals of China from 1987 to 2000 and 2069 cases of benign tumors treated by EChT in 16 hospitals from 1995 to 2000.

Malignant Tumors

Superficial tumors	(No.)	visceral tumors	(No.)
Skin	1058	Esophagus	1595
Breast	744	Lung	1113
Head and face	698	Liver	961
Throat	21	Prostate	20
Metastatic superficial lymph nodes	461		
Thyroid	350		
Vulva	337		
Melanoma	326		
Chest & abdominal wall	272		
Oral cavity	238		
Parotid	184		
Rhabdomyosarcoma	133		
Others	130		
Total	4391		3710

Table 1. The classification of 8641 cases

Age	No.	Male		Female	
		n	%	n	%
20~40	1284	765	59.6	519	40.4
41~60	4583	2901	63.3	1682	36.7
61~80	2485	1334	53.7	1151	46.3
> 81	289	181	62.6	108	37.4
Sum	8641	5181	60.0	3460	40.0

Table 2. The age and sex of 8641 cases

	No.	I		II		III		IV	
		n	%	n	%	n	%	n	%
Visceral	3710	40	1.1	820	22.1	1725	46.5	1125	30.3
Superficial	4931	910	18.5	2099	42.6	1413	28.7	508	10.3
Total	8641	950	11.0	2919	33.8	3138	36.3	1633	18.9

Table 3. Clinical stages of 8641 cases

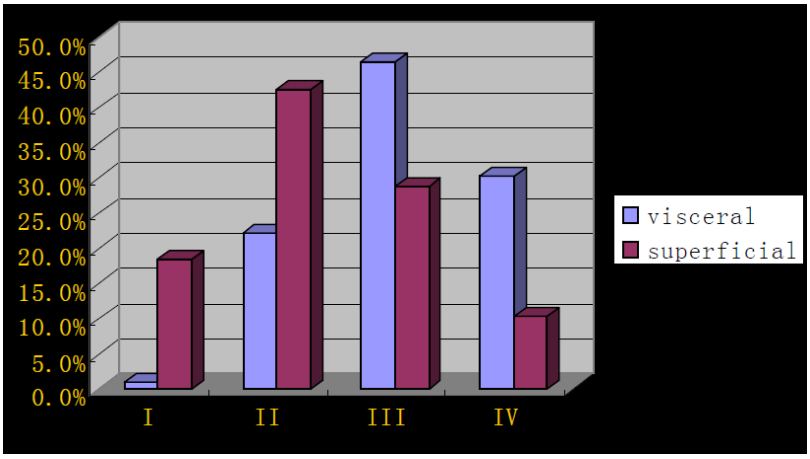


Figure 5. Clinical stage

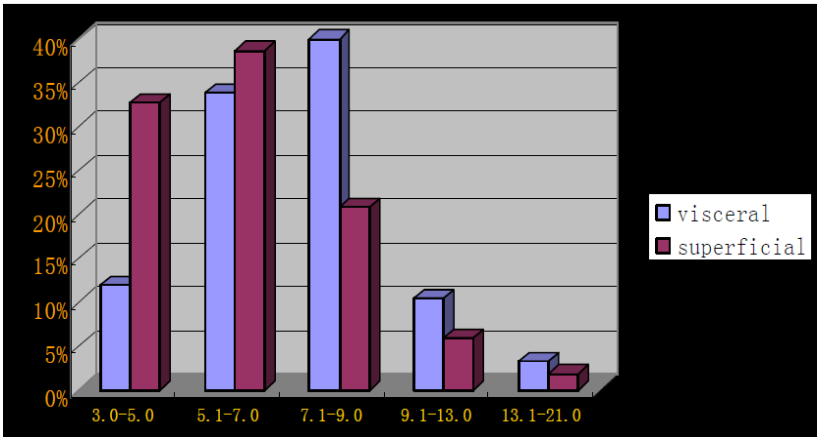


Figure 6. Tumor size

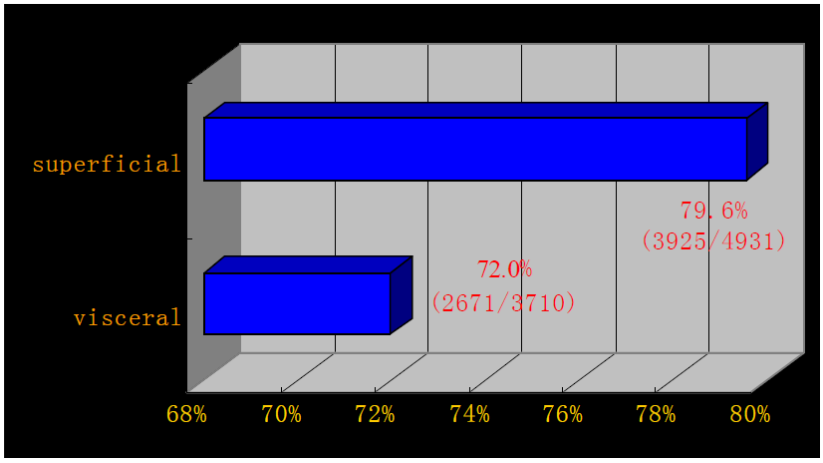


Figure 7. Clinical results treated by EChT (CR+PR ≈ 76.3%)

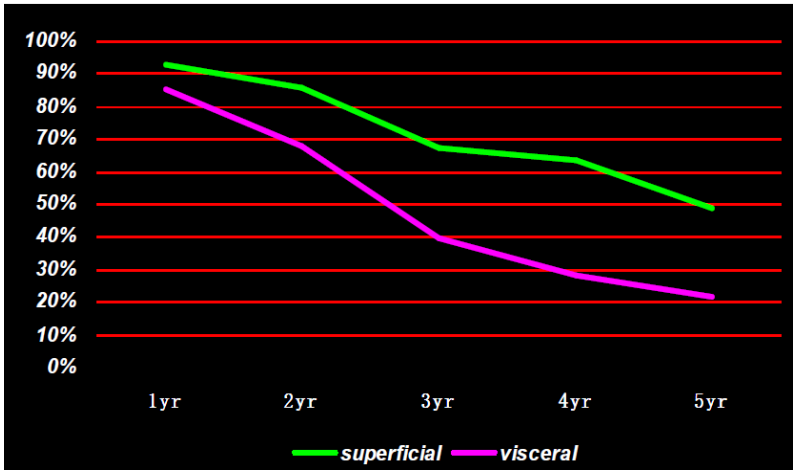


Figure 8. Survival rate

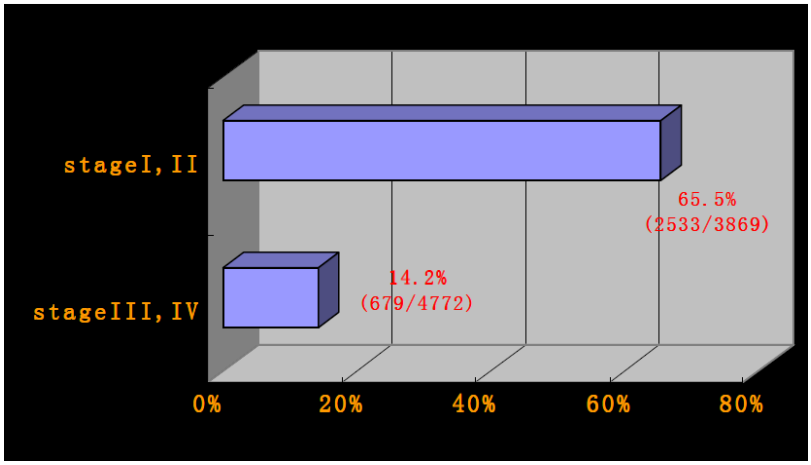


Figure 9. 5-year survival rate

Indications of EChT

When a cancer patient is not suitable for surgical operation and/or radio-、chemotherapy are not effective, EChT may show its special effectiveness.

The superficial tumors are well indications of EChT, such as cancer of head and face, breast cancer, parotid cancer, cancer of oral cavity, cancer of tongue, cancer of superficial lymph node, melanoma, rhabdomyosarcoma, cancer of vulva, cancer of penis, etc. Electrodes can be inserted accurately and arranged properly for those cases. Electric field for treatment can cover the whole cancer. Position and number of electrodes might be adjusted at anytime necessary.

EChT could have satisfactory result if other treatment is ineffective especially for late stage patients that have ulceration on the tumor (for example, local recurrence of operated breast cancer) which was not effectively treated in the past.

EChT can be a complementary method for surgical operation also. For the tumors which cannot be resection during thoracotomy (central type of lung cancer, mediastinal tumor), electrodes could be inserted accurately to treat tumor. It is the same for abdominal surgery and gynecological operation for cancers not being resection (liver cancer, kidney cancer, pancreas cancer, ovarian cancer, etc.). Symptoms could be relieved and there is effectiveness to certain extent.

Example cases:

Case 1. An abdominal surgery was tried to resect a liver tumor but failed. Before operation and CT scan.

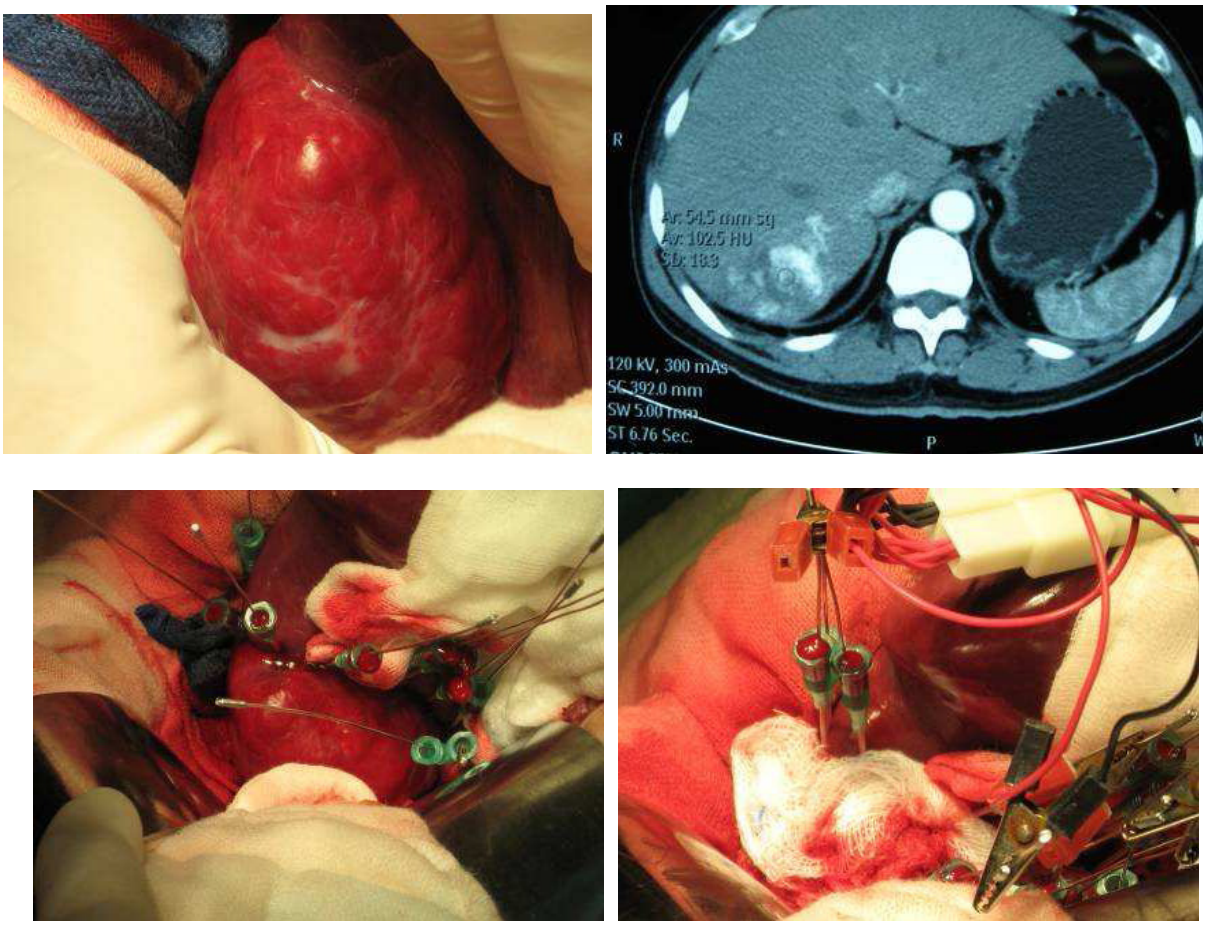
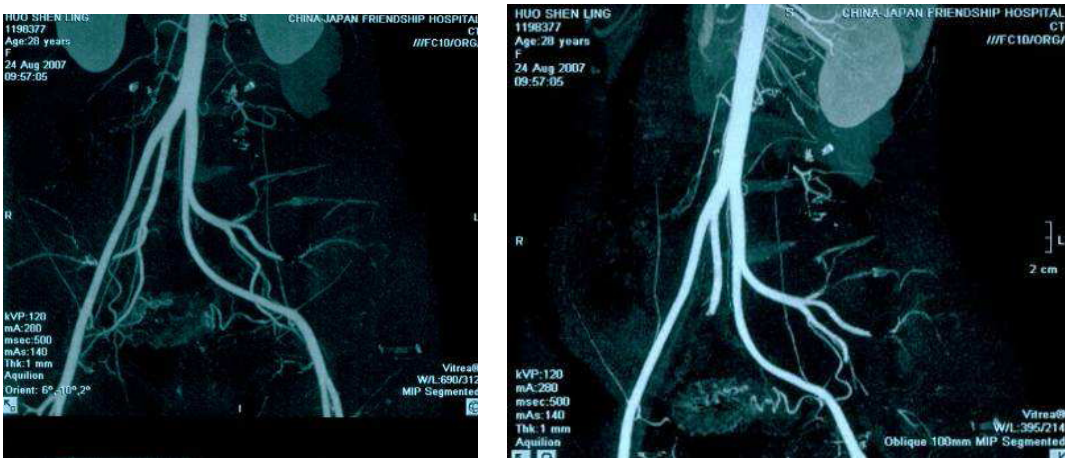


Figure 10. EChT was applied as a substitute treatment

Case 2. Tumor of post-peritoneum. F, 28ys. Tumor of pelvic cavity, CT scan showed the tumor 13X10X7cm. Left ureter was displaced to the other side. There is serious adhere between the tumor and surrounding tissue and the surgical resection was failed.



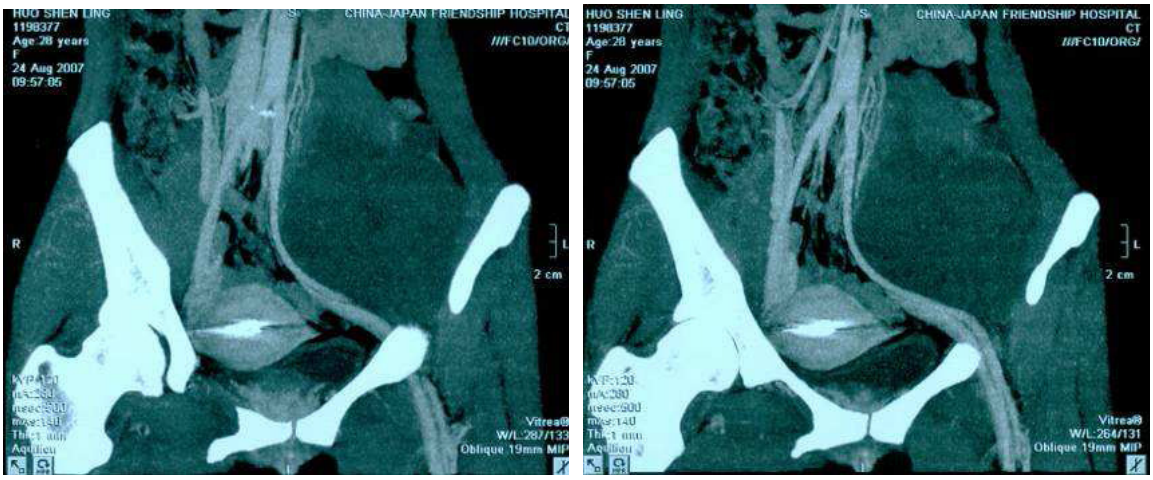


Figure 11. CT scan imaging

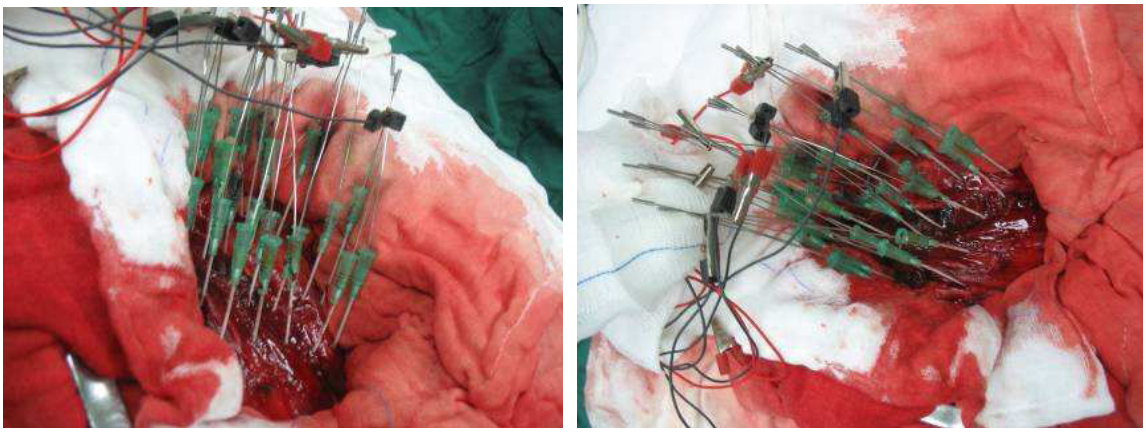


Figure 12. EChT was applied as a substitute treatment. Pathologic diagnosis: tumor of fusiform cell

Case 3. M,53ys. Left thoracic & abdominal tumor, 14X8X4cm. Both thoracic and abdominal cavity was opened but the tumor could not be resected. Pathologic diagnosis: neurofibroma.

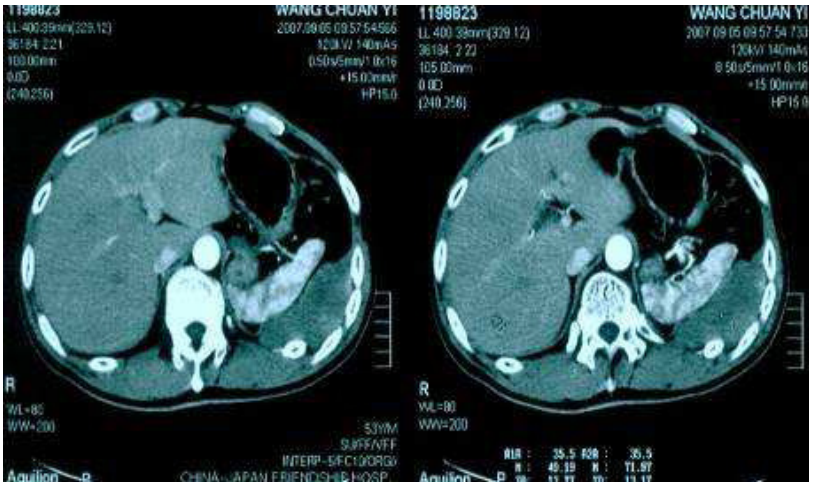


Figure 13. CT scan before EChT

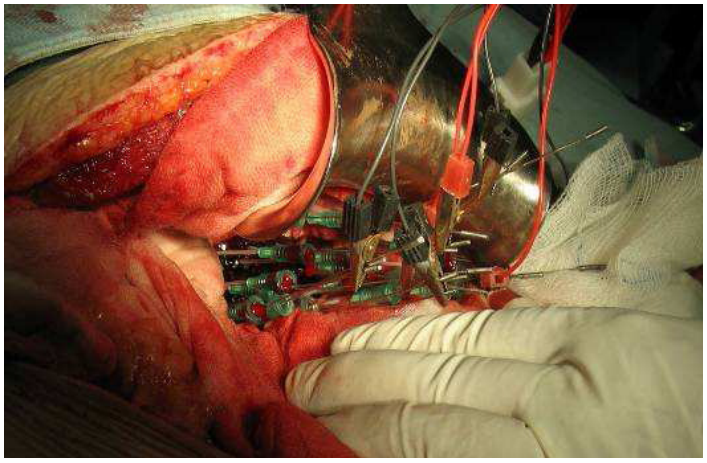


Figure 14. During EChT

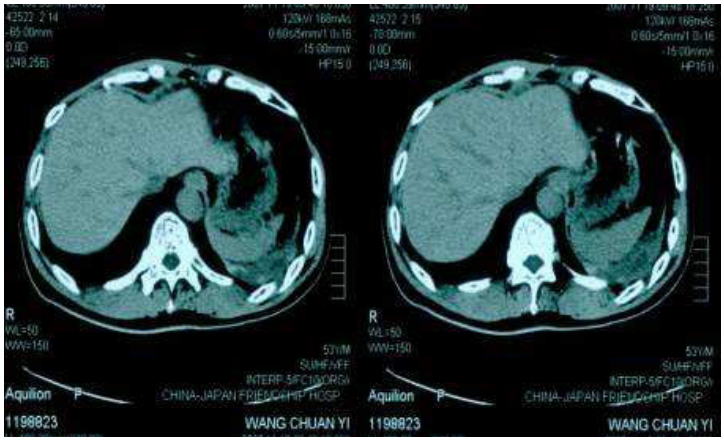


Figure 15. 13ms after EChT. The patient was followed up for 13 months and recovered well

Complications of EChT and its management

EChT is less traumatic, so even old or weak patients could accept this treatment. Slight fever, increase of WBC account after EChT might occur. It usually lasted for 3-5 days and return to normal automatically.

DC would not be harmful to patients when it is under 30V, EChT is also a save method since the voltage used is much lower than 30 V.

But if the insulation cannula does not arrange properly, surrounding normal tissue and skin damaged by electrode will happen. It can be cure spontaneously.

Manipulation of Electrochemical Therapy

1. Method of Treatment

(1) Selection of Instrument and Electrodes

Instrument: Computer controlled ZAY-B multifunctional instrument is used. It has two outputs with data storage and print function. Electric current, voltage and electric quantity needed could be pre-set. Alarm system would be started when short circuit or disconnection occurs.

Electrode: Electrode is made of platinum with 0.7 mm in diameter and 160 mm in length. It has high electric conductivity and better anti-erosive properties. Needles are coated plastic catheter for insulation to protect normal tissue against electric damage.

Figure 16. Electrochemical therapeutic apparatus and electrodes. Zay-B electrochemical therapeutic instrument and platinum electrodes. Made of China

(2) Manipulation

Cathodes are usually placed in the center of tumor and anodes in peripheral. However, both the cathodes and anodes could be placed one besides the other, alternately. Electrodes must be covered the whole tumor to avoid incomplete treatment. Insulating plastic tubes are used to protect normal tissue from injury due to electrolysis. Then electrodes are connected to the instrument to start treatment

The killing radius of each electrode is about 1.0 cm, the distance between two electrodes should be less than 1.5 cm. So the number of electrodes needed could be calculated according to tumor size.

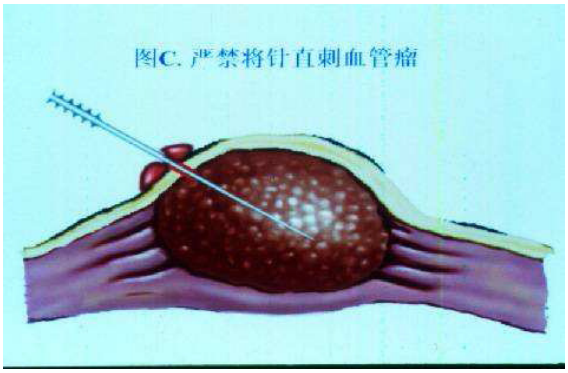


Figure 17. Incorrect method to insert a trocar into a hemangioma and induce in bleeding in the needle hole

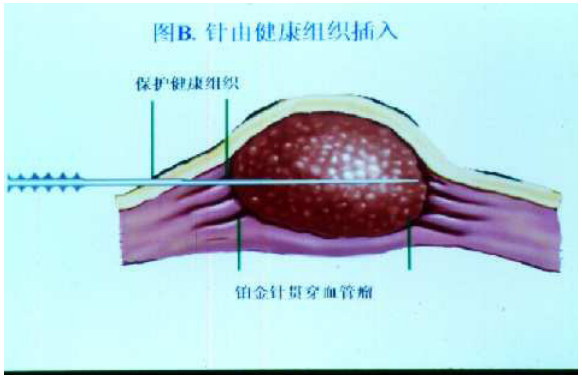


Figure 18. Correct method that trator is inserted into tumor through the normal tissue beyond the margin of tumor 2cm, bleeding is avoided and normal skin is protected

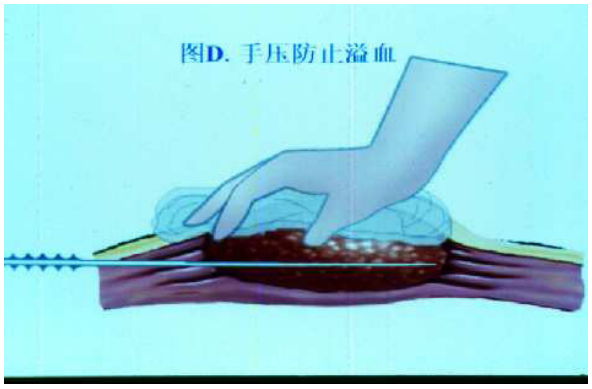


Figure 19. Pressing the hemangioma during EChT to extrude blood and necrotic liquid

There will be a rupture drop area of electric field between 2 electrodes when the distance of electrodes is over 2 cm. So 1.0~1.5cm will be the best choice of the distance between electrodes during EChT.

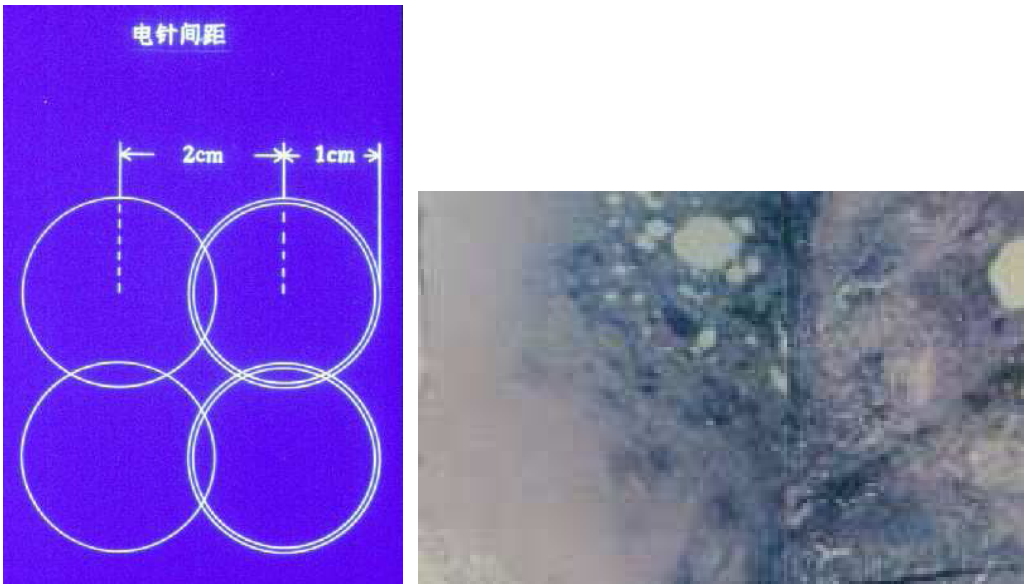


Figure 20. No remaining area left when the distance of electrodes was shorter than 2cm

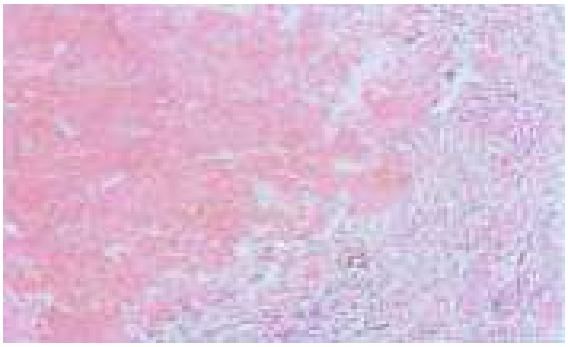


Figure 21. No cancer cells remained when the distance of electrodes is shorter than 2cm

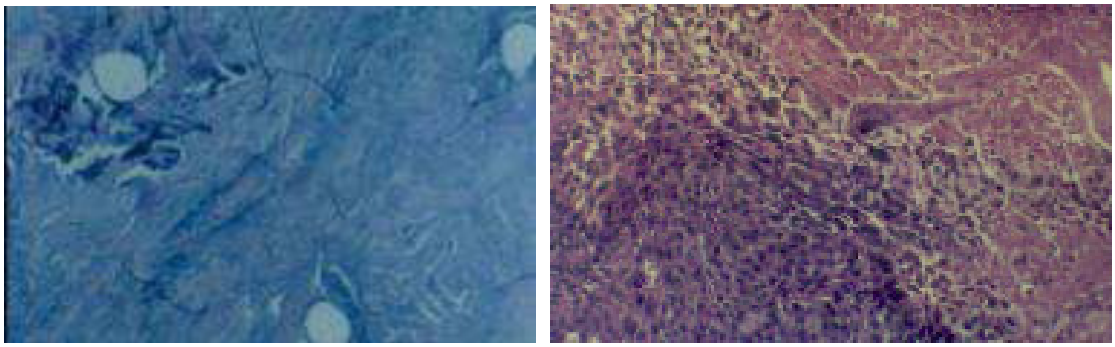


Figure 22. The distance of electrodes is over 3cm. Cancer cells can be found in the remaining area

(3) Requirement of electric current, voltage and electric quantity
Voltage usually used is 8—12 V and electric current is in a range of 80—180 mA. Electric quantity is determined by tumor size, usually 100 coulombs per 1.0 cm diameter of tumor mass.
(4) Duration of treatment
The concept of increasing electric current to high level in order to shorten treating time is wrong. That is because the action of EChT is electrolysis which needs time to perform the action. According to animal experiment, 4 V voltage and 20 mA is enough to have killing effect.

To improve the effectiveness of EChT for treating malignant tumors, following measures are recommended:
(A) For patients with advanced tumor who can not be treated with other therapies, EChT might relieve their sufferings and their life quality could be improved;
(B) For large tumor mass, more electrodes should be needed. If short circuit does not occur, the distance between electrodes could be reduced to 1.0cm in order to increase killing effect
(C) EChT might be combined with radio-chemotherapy, because EChT could make tumor cells more sensitive to radio-chemotherapy.
Positively charged anti-tumor agents, such as adriamycin and bleomycin, could be injected into tumor and moved toward cathode area to kill tumor cells.
(D) Chinese herbs could improve immune system and inhibit growth of tumors, and might be a supplementary treatment to be combined with EChT.

The future of EChT method
In 1987, Professor BJ Nordenström was invited to come to Beijing giving lectures on BCEC theory and demonstrated the use of EChT on malignant tumor. Following three years of animal and clinical practice in China, good therapeutic effectiveness has been achieved. It was approved as a new therapeutic method to be used and spread clinically by the Ministry of Public Health of China.
Over ten thousand cases of various kinds of tumors have been treated with EChT in China within nearly 20 years. It could be used not only for malignant tumors, but also for some benign tumors, such as venous malformations with excellent effectiveness.
The effectiveness of treating benign tumors is even admiring. EChT might be the best method, much better than surgical operation, to treat venous malformations with no bleeding, no scars left and no harm to the appearance and function. EChT was applied on breast hypotrophy and endometriosis in abdominal wall and satisfactory result has been achieved.

Typical cases

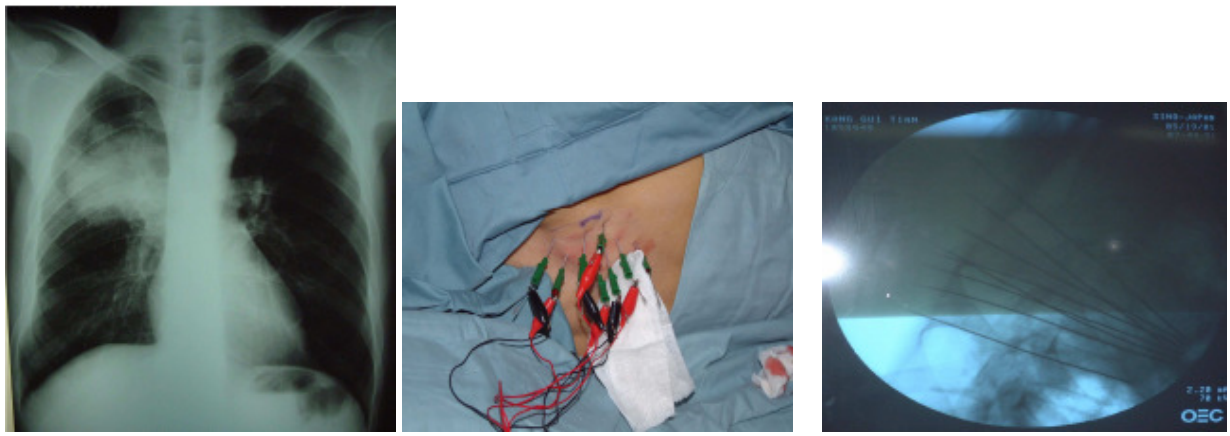
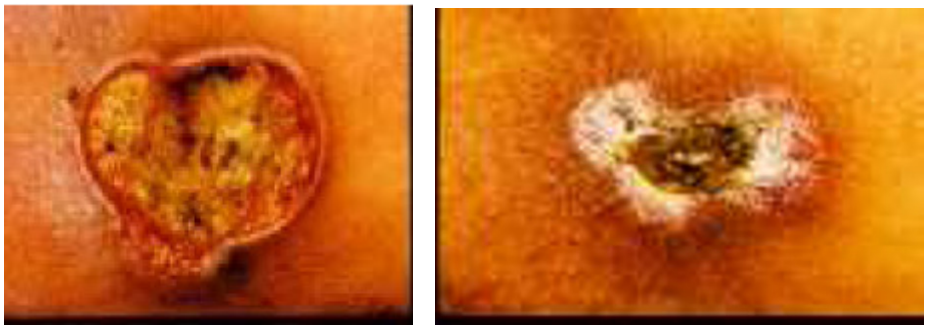
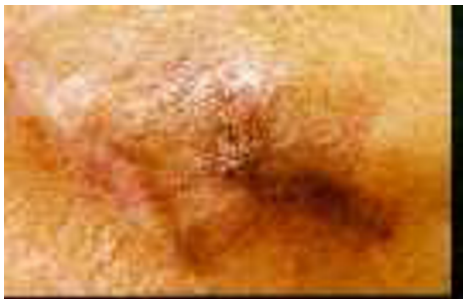


Figure 23. Right lung cancer. X-Ray film before EChT and during EChT

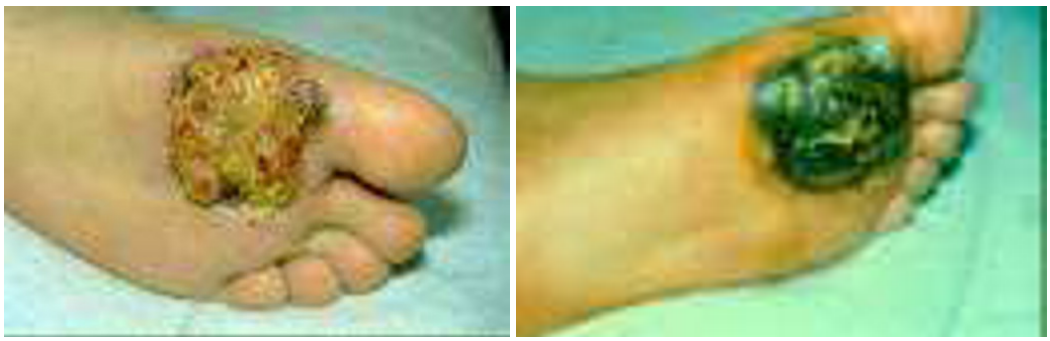


(Photo 1) (Photo 2)



(Photo 3)

Figure 24. Male, 42y. Cancerous ulcer in right thigh. 5.5x8.0cm. (Photo 1). After 2 times EChT (Photo 2). No recurrence through 6 years following up (Photo 3)



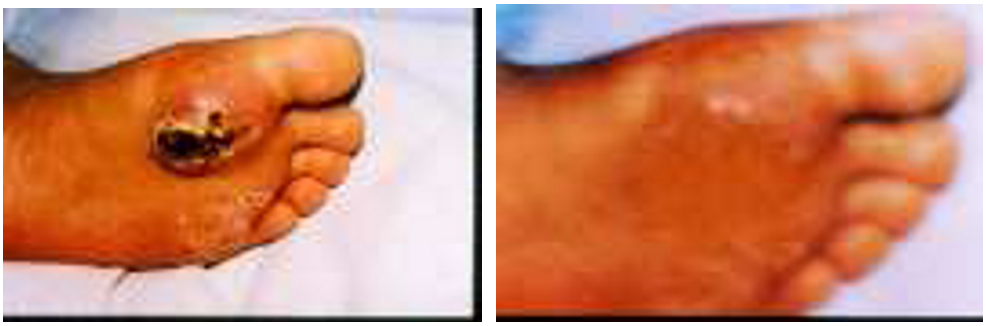


Figure 25. Male,34y. Melanoma in left foot. Recurred after surgical resected. The wound didn't heal up and the tumor grew to 4.5X5.0 cm. The wound healed 7 weeks after EChT and no recurrence developed through 4 years following up

Figure 26. M.30ys. Right upper limb soft tissue sarcoma recurred after 2 times surgery combing pulmonary metastasis, the tumor size:13X21cm. Before and during EChT

Figure 27. Tumor turned necrosis and fell off 5 days after EChT. The wound was healed 6 weeks there after. He died of lung metastasis after following up 20 months

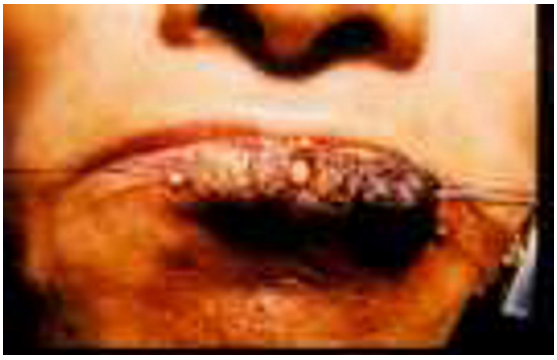


Figure 28. Male, 67y. Squamous cell carcinoma of low lip, 2.0x3.5cm. During EChT

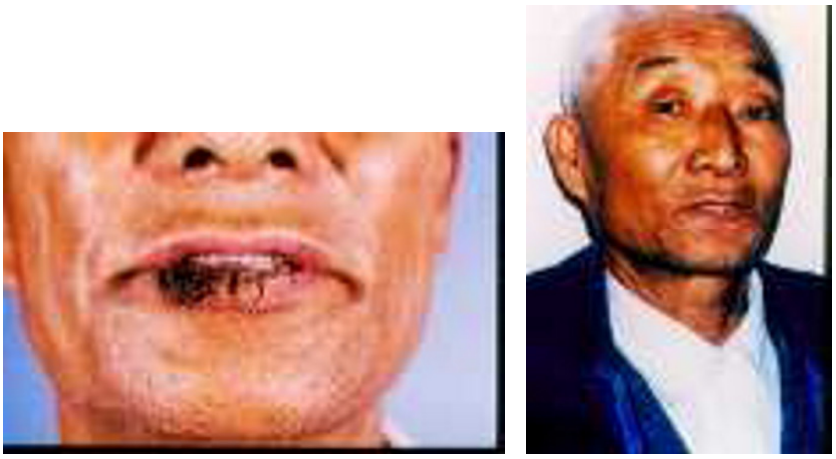


Figure 29. The tumor became necrosis and formed a scar after EChT. The photo showed a good figure of the patient 12 months after EChT

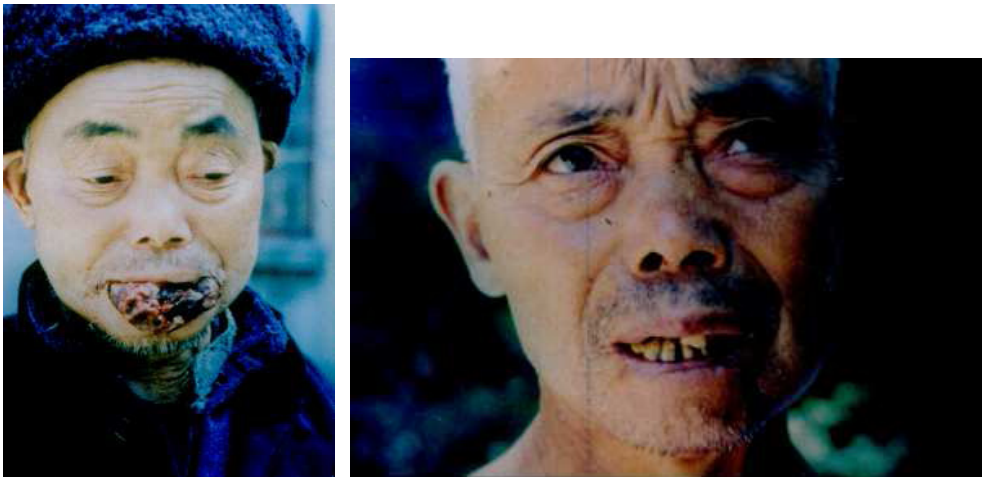


Figure 30. M,67y. Lower lip cancer of squamous epithelium, recurred after surgical resection, 2.0X3.5cm. Before and 1 year after EChT

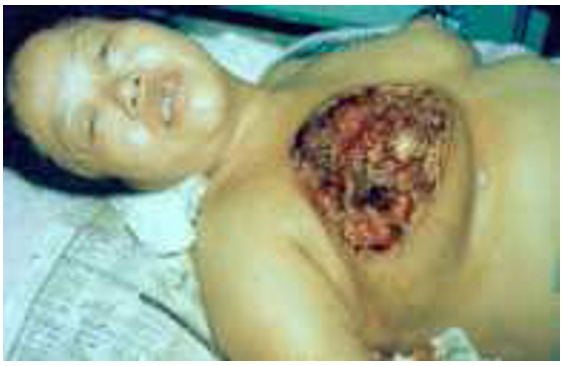
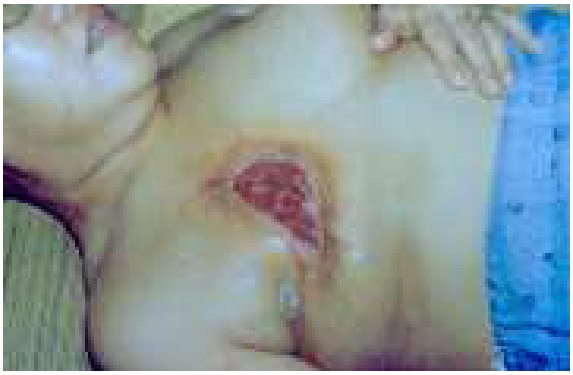
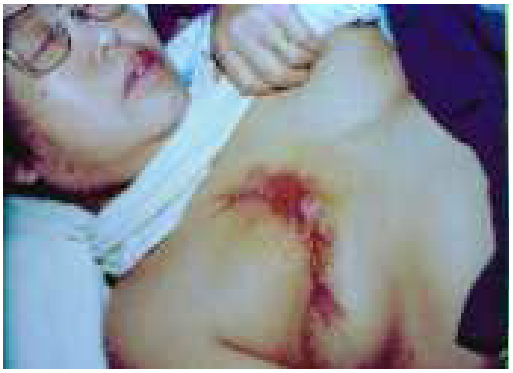


Figure 31. F. 52y. Local recurrence after resection of right mammary cancer. Carcinoma ulcer grew to 12´10cm

(photo 1) (photo 2)

Figure 32. The tumor necrosed and surface of wound obviously reduced 7 weeks after EChT (photo 1).The wound healed completely 9 weeks after EChT (Photo 2). (photo 1) (Photo 2)

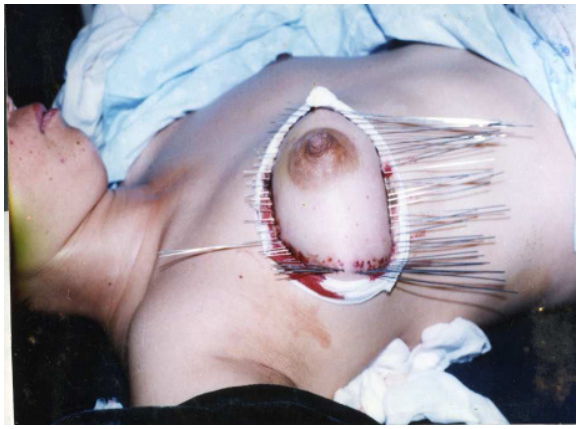
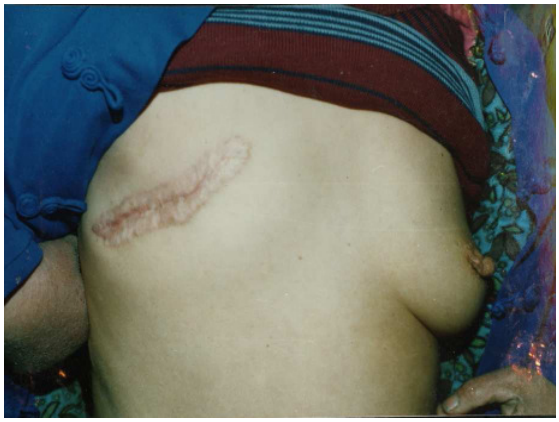



Figure 33. Breast cancer during EChT and 6 months after EChT

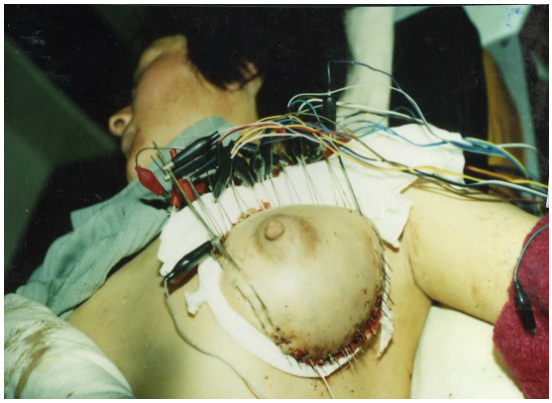
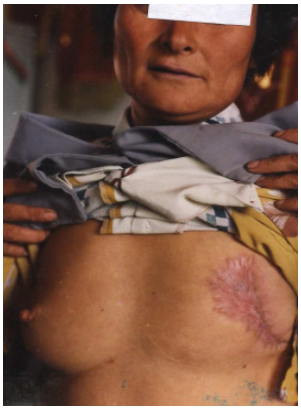



Figure 34. Breast cancer during EChT and 6 months after EChT

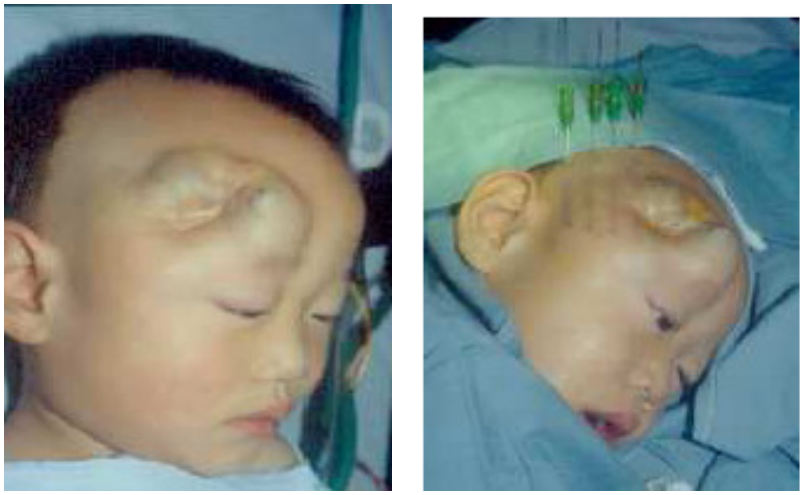


Figure 35. M.4y. Hemangioma in right forehead. Operation failed due to uncontrolled bleeding. The diameter was 7.8X9cm

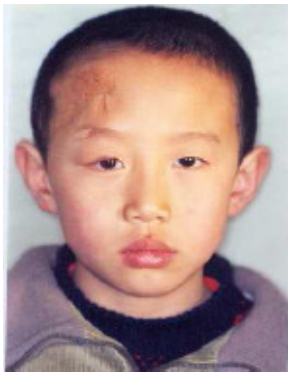
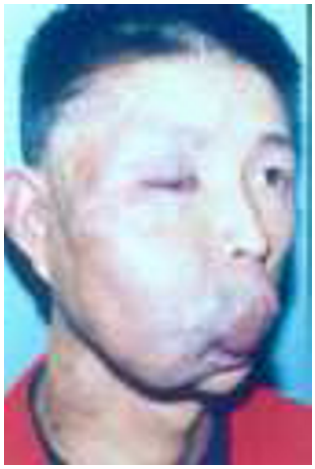
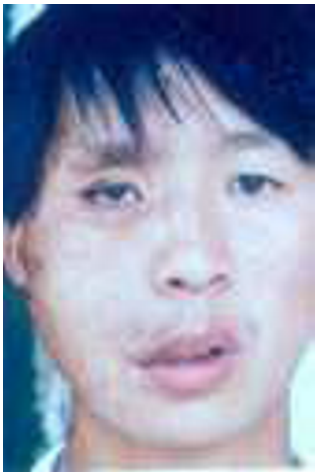


Figure 36. The tumor disappeared and no recurrence developed after 3 years after EChT



(photo 1)



(Photo 2)

Figure 37. M.32y. Huge venous malformations in maxillofacial region. Many therapies had been tried but all failed (photo 1). Photo 2 showed 1.5 years after EChT

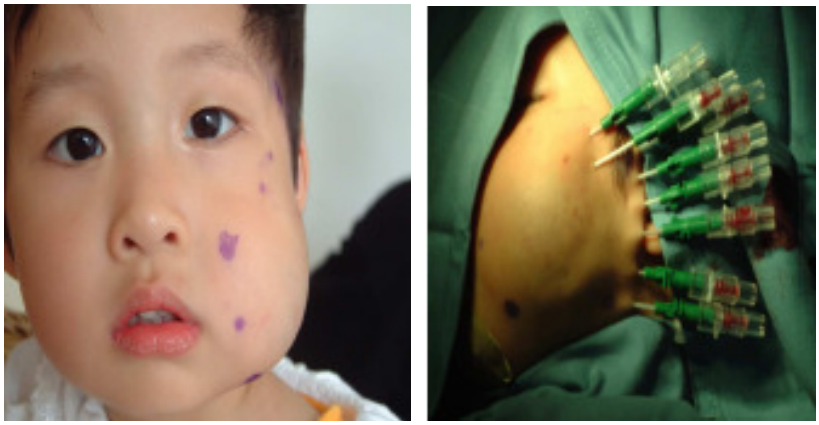


Figure 38. F.2y. Venous malformation in left maxillofacial region before and during EChT

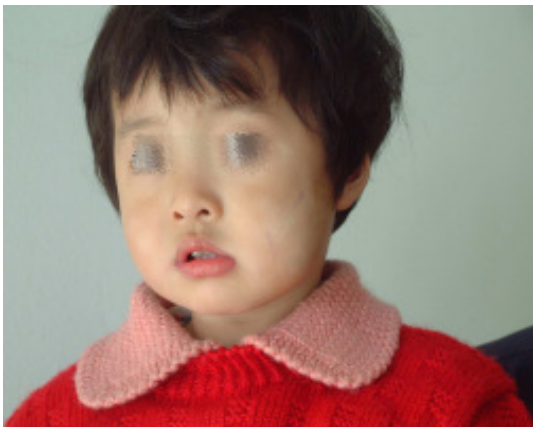


Figure 39. 2 years after EChT

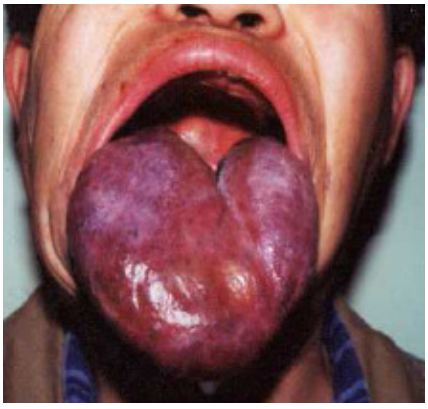


Figure 40. M.32y. Huge hemangioma in tongue. The tongue drop out of mouth and had a malfunction

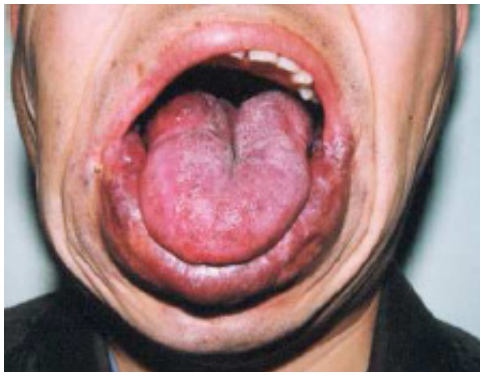


Figure 41. 1 year after EChT. Well function of tongue recovered

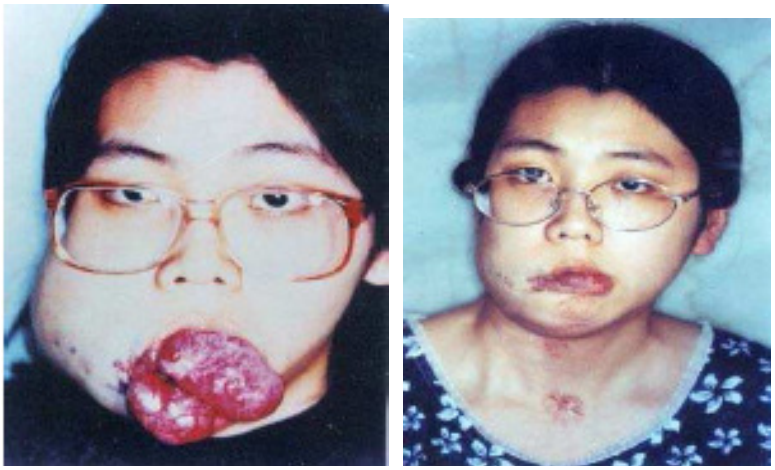


Figure 42. F.16y. Multiple hemangomas in right maxillofacial region tongue & lips. Speaking and foodintake were hindered. No recurrence for 3.5 years follow up after EChT. The well function of tongue and feature recovered

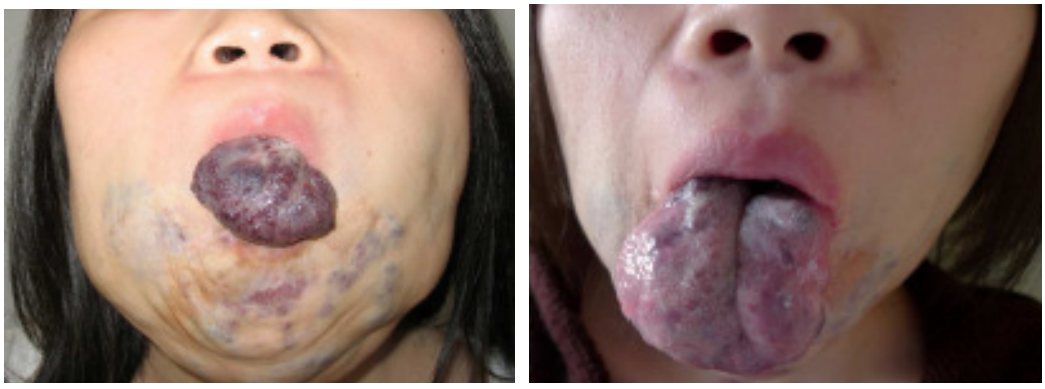


Figure 43. F, 20ys. Hemangioma of tongue before and after EChT

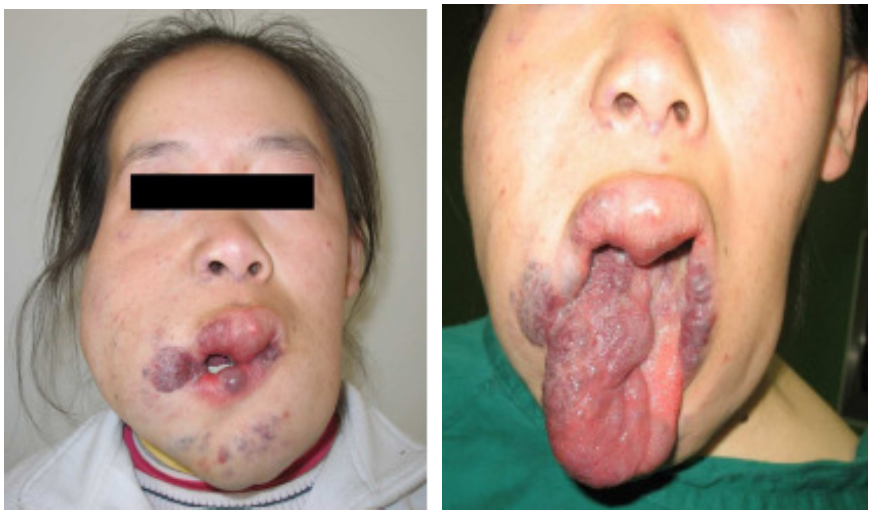


Figure 44. F,21ys.Maxillofacial & tongue venous malformation

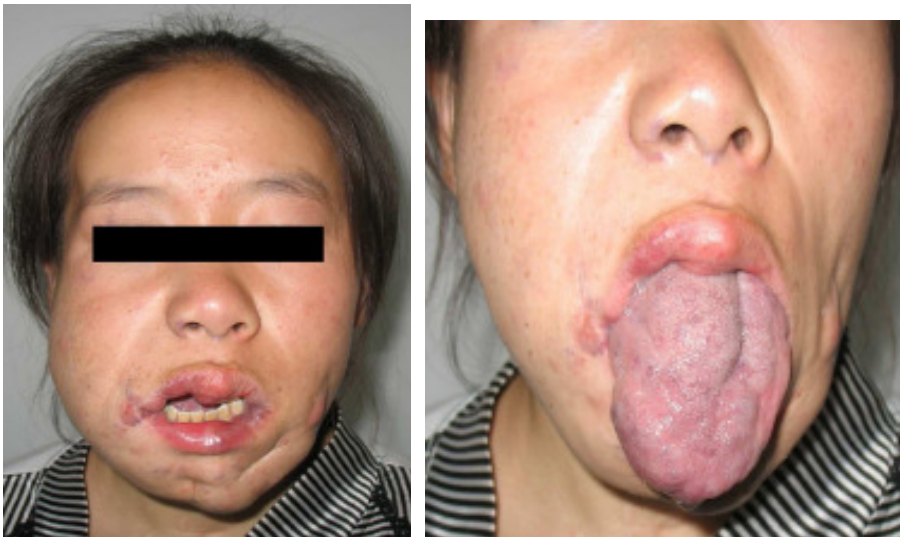


Figure 45. One year after EChT

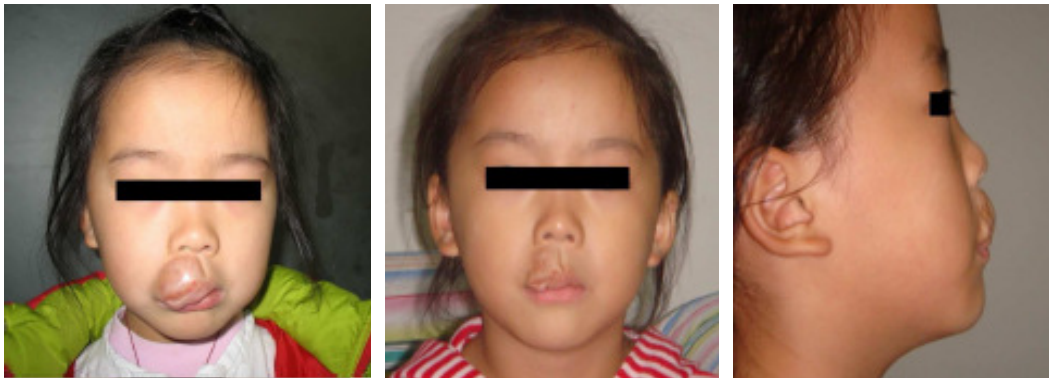


Figure 46. F.5ys. Up lip venous malformations reccurred after surgical resection. The photos show the patients' appearance before and after EChT

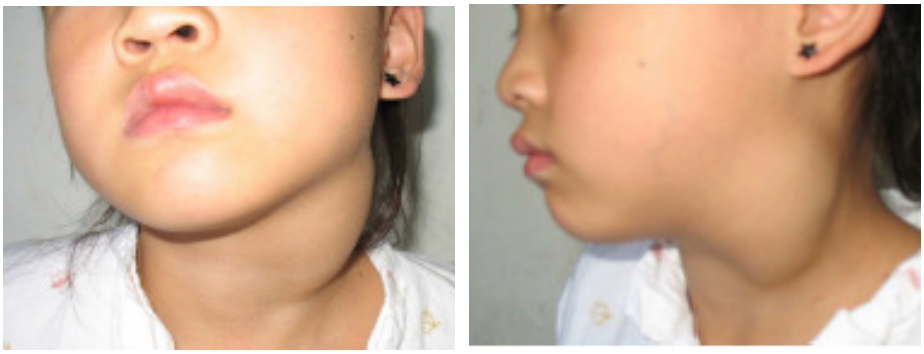


Figure 47. 7 years old girl with big vascular malformation of neck

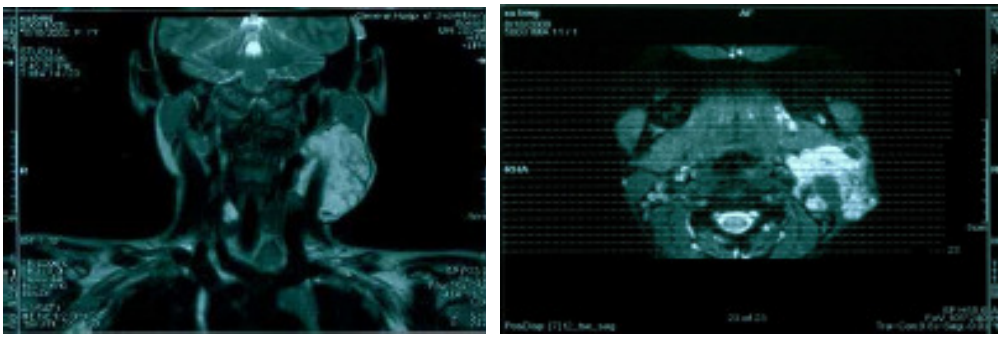
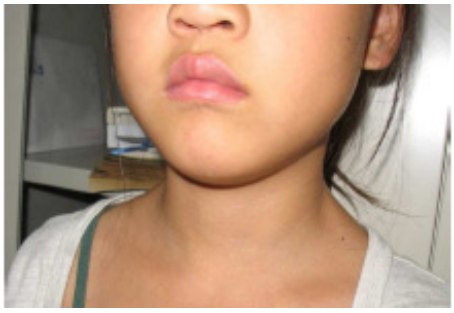


Figure 48. The same patient's MRI before treatment



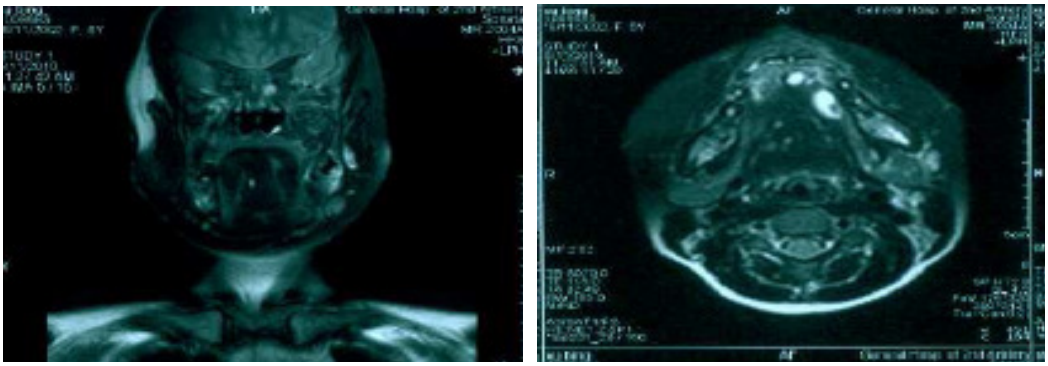


Figure 49. The same patient's appearance and MRI after EChT

Figure 50. M,20ys. Severe maxillofacial vascular malformations before EChT

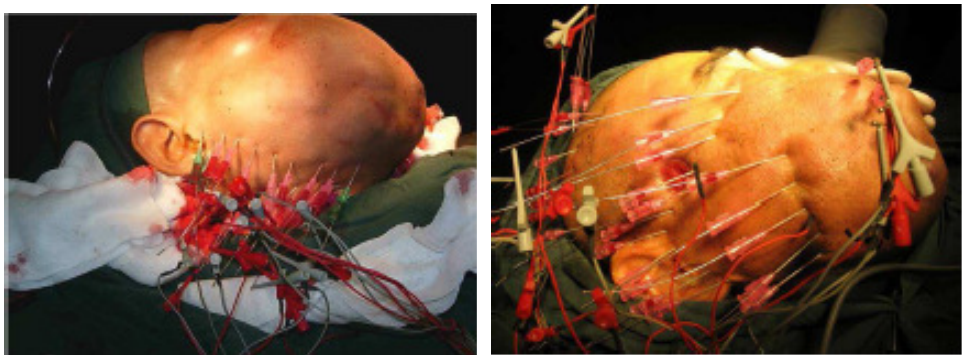


Figure 51. During EChT

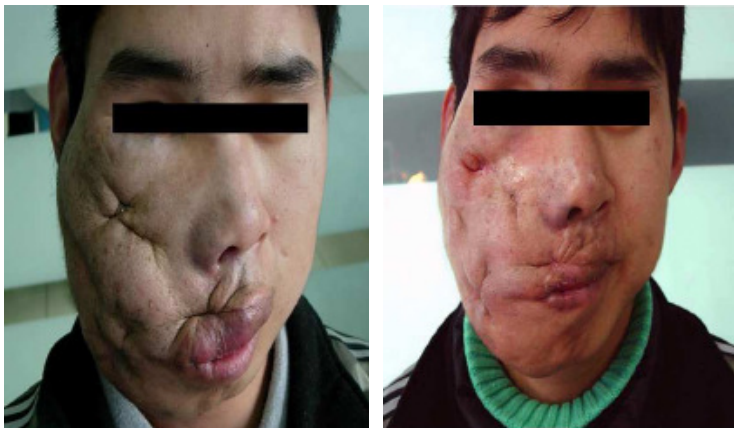


Figure 52. 1 year after 3 times EChT 3 times EChT and plastic surgery

Status and Prospect on Contemporary Natural Medicine

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Status and Prospect on Contemporary Natural Medicine

1. Concept of Natural Medicine

Natural Medicine has evolved along with human social evolution. It started by using primitive natural methods, natural medication and traditional health preservation methods, for disease diagnosis and treatment, rehabilitation, disease prevention, and health maintenance. Now, Natural Medicine has become an encompassing discipline of the medical field. However, the basic concept of Natural Medicine remains “human and nature in unison,” “mind and body in unison,” that is, the harmonious whole-body concept.

2. Definition of Natural Medicine

The definition of Natural Medicine consists of two parts. First, it exists in nature in a variety of substances and forms such as light, sound, water, electricity, air, soil, flowers and fruits, magnets, cold, heat, etc., that can be used directly or indirectly for human disease prevention and cure.
Second, Natural Medicine is based on the yin any yang theory, and the concept of whole-body balancing. It studies human body characteristics, and the organic nature of the diseases, both under natural laws. A variety of natural methods are then applied to restore human’s natural capabilities, and to mobilize the body’s life potentials, for achieving a balance between yin and yang. It takes full advantage of what natural environment provides, to stimulate the body to resist and cure diseases, and be rehabilitated.

3. The Practice Side of Natural Medicine Is Natural Therapy

The practice side of Natural Medicine is Natural Therpay. There is a diverse range of natural therapies that operate under the principle of Natural Medicine for preventing and curing diseases. Its characteristics are significantly different from surgery, synthetic chemical drugs, and radiotherapy, etc. In principle, this is a non-invasive and non-toxic therapy with virtually little trauma and pain.

4. Natural Therapies and Human Body’s Self Knowledge

Natural therapies have a wide scope of applications in the treatment of various diseases. They are generally simple, safe, effective, economical and practical, with little or no toxic side effects. Commonly-used natural therapies are such as acupuncture, scraping of the skin, massage, qigong, music, sound, water and light therapies. Natural therapies use the discipline and power of nature to regulate the body's imbalances and to restore the body's natural abilities. It's just common sense that we should avoid any treatment which can weaken the body's self-healing ability. Therefore, natural therapies do not rely on chemical drugs or surgeries, in order to avoid toxin accumulation, and body trauma.
The human being is a biological creature; the body has a fixed acid-alkaline balance that requires a discipline of essential nutrients, and metabolism. When the whole body is in a balanced state, it can perform its own functions including detoxification, immune defense and growth. But once the external factors negatively affect the metabolic balance and regulation of the body, it will result in diseases lf Natural Medicine professionals are able to grasp the disciplines of the human body, and utilize natural therapies in reasonable ways, they can re-balance the body back to normal. Going back to the basic concept of Natural Medicine we are reminded of "human and nature in unison," and "mind and body in unison."

5. Where Did Natural Medicine Come from?

The term "Natural Medicine" appeared as early as 4000 Bζin some ancient Indian medical literature. However, China is one of the birthplaces of Natural Medicine. It has the most comprehensive record of theoretical systems of natural therapies, and clinical treatments.

Theories of natural therapy originated in about 700 BC during the "Spring/ Autumn/Warring-Factions" period of China. It was then the initial Chinese Medical System was formed, the historical records of which include mineral spa bath, breathing exercise, "five-animal movement exercises;" tai chi, qigong therapy, and other natural therapies that are still being practiced by Asians and others today.

Natural therapies in the West originated in the 18th century called Western Alternative medicine. In 1991, the United States, Japan, Singapore and other countries formally proposed a theory of natural medicine or natural therapy. In its quoted view, "the human body in theory is in a wonderful balance, and it has self-healing capabilities. In the medical process, we should avoid any treatments which can weaken the body's self-healing ability. In addition, we cannot ignore the body's healing ability, and we cannot replace various self-healing ability of the body by various medical treatments." There we have it, the basic concept of Natural Medicine.

6. Problems Facing Natural Medicine

Due to historical, cultural and environmental differences, there are numerous theories of modern Natural Medicine. Hot springs, plants, diet, sleep, music, biofeedback, qigong, shiatsu, massage, exercise, acupuncture, Traditional Chinese Medicine (TCM) and other therapies are prevalent among many more others. Every therapy or method has its theoretical basis and followings. It is a fact that, despite Natural Medicine having a long history and documented contributions to human health, it has not been generally accepted by most patients and medical professionals. This problem is not only due to external forces, but also due to deficiencies in the field of Natural Medicine. Let me cite seven examples:

6.1 First, the lack of a complete scientific and theoretical basis in traditional Natural Medicine, non-standardized terms, and lack of innovation, all limit the development of Natural Medicine.

6.2 Second, Natural Medicine is generally classified as an experience-based medicine because its philosophies are totally different from chemical-based modern medicine. Natural Medicine is not recognized by the modern medical profession due to lack of modern medical evidences.

6.3 Third, Natural Medicine professionals are scattered all over the world. There is very little communication between them. They are fragmented, not within a unified system. The theories are difficult to promote, thus easy to be ignored.

6.4 Fourth, Natural Medicine training is seriously lagging. The little there is, very isolated and inward looking, results in virtually having no successors to champion it.

6.5 Fifth, in applying Natural Medicine, doctors and therapists lack scientific and standardized training and mentoring. Also they lack safe and formal processes, resulting in misunderstandings by other professionals, undermining the efficacy and reputation of Natural Medicine.

6.6 Sixth, natural medicine and pseudo-medicine boundaries are unclear since the beginning of ancient healing methods. Sometimes, practitioners deceive patients with over-the-top or mythical effectiveness of their therapies. The public has difficulty distinguishing them from the genuine, because these methods are often similar to natural therapies. Thus some people distrust even the true natural therapies wholesale, seriously affecting the reputation and development of Natural Medicine.

6.7 Seventh, the public do not have a deep understanding of Natural Medicine in the absence of promotion and education.

7. Short-Term Tactics for Dealing with the Problems and Challenges

Although Natural Medicine faces suspicion, exclusion and difficulties in promotion, Natural Medicine experts *(many of whom are present in this conference)* have the responsibility and obligation to improve the applications of natural therapies, and to cherish this common treasure of humanity, for the simple goal of improving human health. Our short-term objectives are, in short, to collect, sort, and promote each nation's natural methods of medical diagnosis and treatments. To that end, we must make unremitting efforts to do the following five tasks:

7.1.Carry out Frequent and Extensive Academic Exchanges

First, Specialty Committee of Natural Therapy (SCNT) is building a platform to expand its Natural Therapy organization and its general memberships. It will regularly carry out academic exchange activities, and promote natural therapy research exchange and cooperation throughout the world. It also aims to strengthen the theory of Natural Medicine in order to better inherit the essence of Natural Medicine.

7.2.Establish a Comprehensive Information Base on Natural Medicine

Second, establish a comprehensive information base on Natural Medicine. It is the crucial key to promoting the normalization and standardization of development and promotion of Natural Medicine. Through the standardized framework of Natural Medicine, the natural therapy research committee can expect healthy developments throughout the world. We hope that Natural Medicine experts worldwide can work together to collect and organize the scattered information on traditional natural therapies, and to discover and improve those with incomplete theoretical basis. And, we can make it more scientific, systematic, regulated and standardized for better promotion and acceptance. The discussion papers on the concept and contents of Natural Medicine and natural therapies in this conference are good attempts in this direction.

7.3.Set Standards for Evaluating the Effects of Natural Therapies

Third, despite natural therapies having broad applications and being effective, their evaluation criteria, adaptabilities and precautions are lacking, and need to be determined. In order to achieve better medical efficacies, we often need to use a variety of natural therapies in conjunction with each other. In light of this, we need to coordinate among a variety of natural therapies to define integrative applications. In order to better assess the efficacy of natural therapies, singly and/or integrative, we must develop evidence-based standards, recognizing both experiences and evidences. When we use evidence-based medicine to verify the efficacy of natural therapies, we can attain greater credibility and more rapid development opportunities.

7.4.Promote Natural Medicine

Fourth, promote Natural Medicine. The activities include:

- Promoting the features and advantages of Natural Medicine, and demonstrating its impacts.
- Studying each country's current development status of Natural Medicine, and absorbing the latest and matured research results.
- Promoting cooperation in scientific research of natural therapies, and proclaiming the achievements.
- Using modern scientific methods for data collecting, processing and analysis of the efficacy and side effects of natural therapies.

In so doing, Natural Medicine can finally be perceived as "simple," “f1exible," "non-toxic," "effective;' and "inexpensive;' etc. This will strengthen people's awareness of Natural Medicine, promoting it to all sectors of society. And with education, establish confidence in using Natural Medicine for disease prevention and control.

7.5.Establish Eligibility Criteria and Rating System for Natural Medicine Physicians

Fifth, we need to draft a Iist of eligibility criteria and a rating system to qualify natural medicine physicians. It is only through standardization that we can have an orderly development and promotion of natural therapists worldwide. We need to establish a qualification assessment agency for natural medicine physicians, establish an accreditation and rating standards committee, and train international personnel, so that Natural Medicine experts and researchers world-wide can develop to their potential.

8. Long-Term Prospects of Natural Medicine

Let us now see what long-term prospects Natural Medicine will have. Natural Medicine will cross over preventive medicine, c1inical medicine, rehabilitation medicine, nutrition, psychology, physics and other health care systems. We will have done major research on Natural Medicine, the results of which will allow us to better inherit, discover, sort, improve, innovate, interpret and share the theories and practices of Natural Medicine. In the future, we will develop and refine together to make Natural Medicine a medical system that has its own unique features. Although it originated from traditional medicine, it will have absorbed modern medical technologies, making it safe and effective. And, sometime, hopefully in my lifetime, the Western medical professionals will incorporate Natural Medicine with their medical profession and practice them both side by side.

9. Summary

Let me preface my summary by saying that in today's go-go-go non-stop world, the spectrum of diseases has seen a fundamental change. Cancers, cardiovascular and cerebrovascular diseases, diabetes and other chronic diseases of the liver and kidney, are now at the top of the spectrum. They can hardly be cured singly by using modern Western Medicine, which usually cures the symptoms but not the root causes. Chemical and drug-induced diseases are rampant. They have become topic-of-the-day in the medical world. So, people have a pressing desire to find a new medical method that does not rely on chemical drugs, which is safe and virtually without side effects, which can strengthen the body's immune system to fight diseases, and at the same time achieve the aim of disease prevention and cure.

The desire has lead to the recent phenomenon of "return to nature" and "return to basics" slogans of some nature-oriented people, which is good for Natural Medicine. At the same time, a number of safe and effective natural therapies are receiving greater and greater attention and recognition. Experts and scholars from all over the world continuously experiment with natural therapies to prevent and cure diseases. And, medial experts are endeavoring to find breakthroughs to solve all kinds of medical problems. In light of all these, I think the scientific and systematic study, exploration, organization, promotion and popularization of Natural Medicine is imperative. This is the heavy responsibility entrusted to us, and it has an important and far-reaching significance.

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

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

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

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

Introduction, objectives

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

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

Method

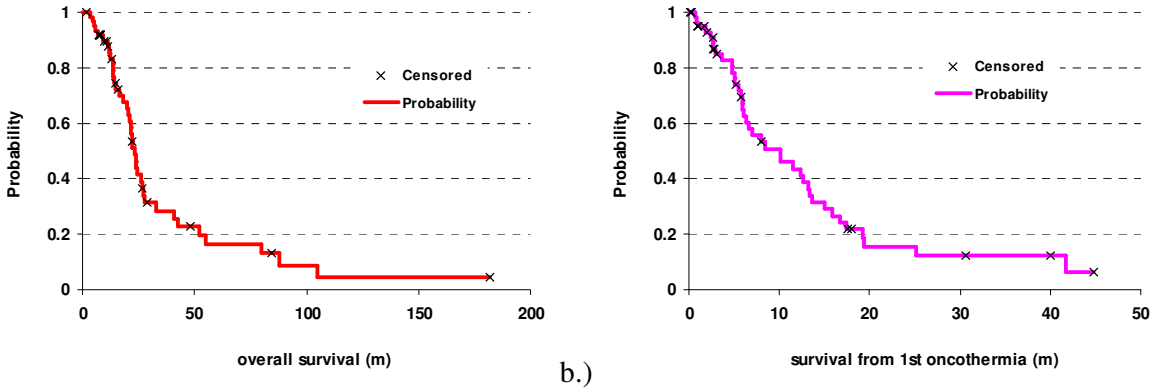
The provided results are obtained from an open-label, single-arm, monocentric, retrospective study. The involved patients are analyzed according to an intention-to-treat (ITT) schedule. Recruiting time was from April 1997 to August 2002, altogether 64 months. The primary endpoints of the study were the overall survival time (OS) and the survival time from the first oncothermia treatment (overall survival oncothermia treatment time, OSO). The dates of exitus were checked by the National Death Register, so the actual and accurate data were collected. The final check of the deaths was December, 2003. Inclusion criteria were: (1) Inoperable or sub-totally resected, or recurrent primary pancreas tumor, (2) progression after radio- and/or chemo-therapy, (3) Karnofsky Performance Score (KPS) > 40% and the inclusion was irrespective of the localization of the lesion in the pancreas. Patients started the oncothermia process in their late/advanced stages, where most of them had failed to respond to any of the applied conventional therapies.
Exclusion criteria were only the well-known contraindications of the oncothermia method (metallic implants or replacements in the treated area, missing heat-sense in the treated area, pacemaker or other field-sensitive implants in the patient).
The evaluation-methods were: descriptive biostatistics, log-rank survival tests (Kaplan-Meier plot), and comparison with large studies and databases and/or local historical data. Data were collected independently from two hospitals. One of them is the Peterfy Hospital, Budapest (PFY). It is a governmental hospital involved in the regular health-service network. The other is a private day-clinic (Htt-Med Polyclinics, Budapest, (HTT)), serving the patient only on a private, out-patient basis. The two trial-places were in information-contact, providing the treatments with the same practical conditions and guidelines.
The study had a couple of possible negative biases: (1) the treatment is paid or co-paid by the patients, who undergo it on a voluntary basis (intention-to-treat, ITT). All the process was under strict control by the oncologist who was responsible for the patient treatment till that time; (2) no randomized control arm exists; the trial is compared to available literature, large databases and to historical data. The reliability of the trial is checked by comparison of the independent hospital retrospective collections.
Nevertheless, the present study has a few possible positive biases as well: (1) patients are treated in their advanced stages, when other treatments had failed and/or are not possible; (2) the involved hospitals are engaged in the regular health-care system, they are not as well-equipped as the special institutes/universities; (3) the involved patients had no extra “trial-attention”.
The used device was EHY2000 (OncoTherm), capacitive coupled (oncothermia, OT). It works on 13.56 MHz, which is time-domain (fractal) modulated, with 40-150 W power absorbed by the tumor.

The treatment control was made by the absorbed energy [kJ], which was converted to the equivalent temperature [T]. The calculated average equivalent temperature in the tumors was above 40 ^{o}C in more than 90% of the treatment time. For further details of the method we would like to refer to ([18], [19], [20]) where it is explained in detail. The reality, the energy together with the increase of the temperature is basically used for the distortion of the structures, change of the chemical bonds and compensation of the physiological regulations [21], [22]. OT was performed in two/three sessions per week. Treatment time per session was 60 minutes. The power was gradually and linearly raised depending on the patient's tolerance from 40-80W to 100-150W. The applied average energy was 300 kJ/treatment (250-450). The applied applicators were 3.1 dm^2 and 7.1 dm^2, depending on the tumor volume.

Results

Hospital Peterfy (PFY) (n=61)

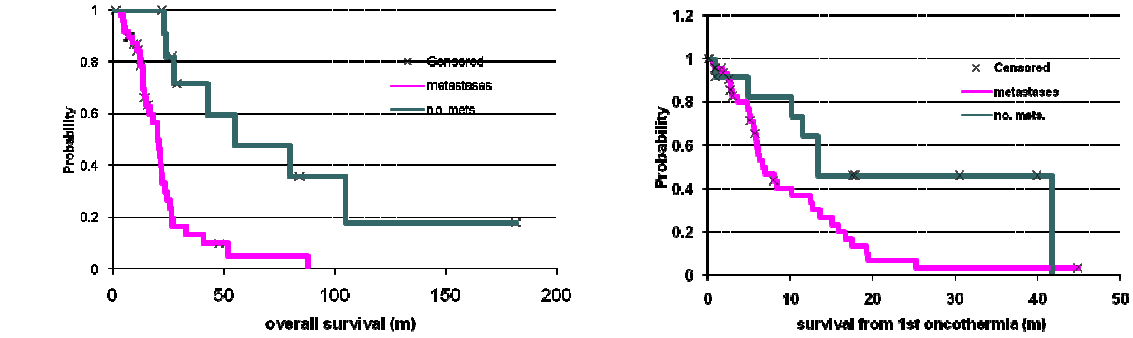
The age-distribution of n=61 patients was near to normal (p=0.82); no outlier was present. The median age was 58 y (38 - 77), the mean-age was 58.97 y (Std.err= 1.17). The gender distribution was 21/40 female/male (34.4/65.6 %). The ratio of the elderly (>68 y) patients were 21.3%.
Most of the patients (49, 80.3%) had distant metastases. They were heavily pretreated; everybody received at least one chemotherapy and 28% had surgery, 36% received radiotherapy.
The actual staging was made at the first diagnosis (44% was in advanced [WHO IIIb or IV] stages) and at the first oncothermia treatment (75% was in advanced stage).
The median of the elapsed time from the 1st diagnosis to the 1st oncothermia was 8m (0.4-172), while its mean was 16.3m (st.err.3.1). The elapsed time ratio to the overall survival was more than 50% (median 59.9%, [6.5-99.1], mean 59.4 [st.err.3.5]); the patients received their first oncothermia in the second half or their survival time.
The oncothermia treatment was provided twice a week, the treatment number was in average 8.1 (st.err.0.55) and its median 8 (2-23).
The Kaplan-Meier plots of the overall survival (OS) (median 16.4m, [1.7-181.9]; mean 25.6m, [st.err.3.8]) and the survival from the first oncothermia treatment (OSO) (median 5.7m, [0.1-44.9]; mean 9.2m, [st.err.1.3]) are shown in Figure. 1. For elderly patients neither the OS nor the OSO was different (p~0.68).



a.) b.)

Figure. 1. Overall (a) and oncothermia treatment time (b) survivals by Kaplan-Meier plot of the patients in PFY study

Naturally, the survival was significantly different for patients without or with metastases, (p=0.0003 p=0.031 for OS and OSO, respectively), see Figure. 2.



a.) b.)

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

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

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

The number of treatments does not influence the OS significantly (p=0.61), but the OSO (p=0.0023) and the follow-up time after the last oncothermia (p=0.01) well depends on the number of oncothermia treatments, see Figure 3.

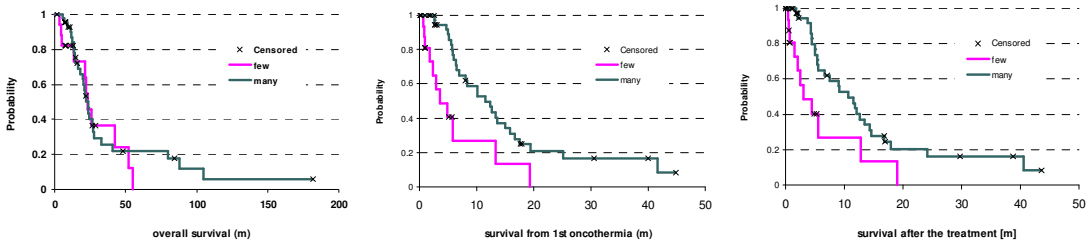


Figure 3. The various survival times for patients depending on the treatment session time. ("few" lower than the median number, "many" higher than the median number of the treatments).

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

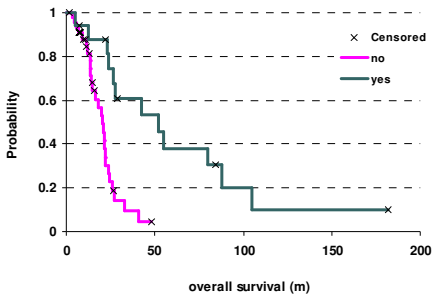
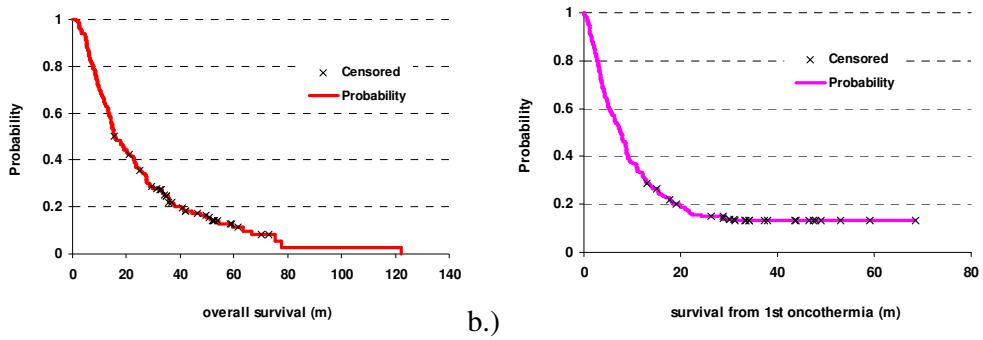


Figure 4. Effect of the pretreatment operation is significant considering the overall survival.

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

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

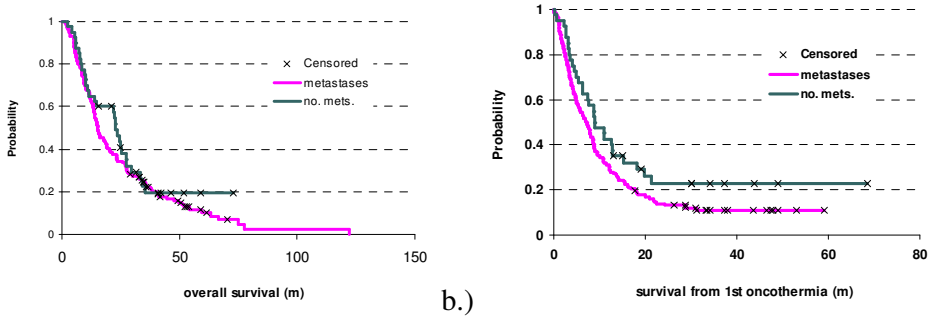
The age-distribution of n=197 patients was acceptably normal (p=0.59); no outlier was present. The median age was 57 y (16 - 84), the mean-age was 56.71 y (Std.err= 0.77). The gender distribution was 62/135 female/male (31.5/68.5 %). The ratio of the elderly (>68 y) patients were 20.3%.
Most of the patients (157, 79.7%) had distant metastases, (one two and three metastases were observed for 101, 43 and 13 patients, respectively). They were heavily pretreated; most of them (93.4%) underwent surgery and subsequent radiation-therapy (49%).
The actual staging was made at the first diagnosis (46.2% was in advanced [WHO IIIb or IV] stages) and at the first oncothermia treatment they were at a more advanced status.
The median of the elapsed time from the 1st diagnosis to the 1st oncothermia was 5.5m (0.2-111.3), while its mean was 10.6m (st.err.1.0). The elapsed time ratio to the overall survival was near 50% (median 45.4%, [1.6-96.7], mean 45.7 [st.err.3.9]).
The oncothermia treatment was provided twice a week, the treatment number was in average 7.9 (st.err.0.4) and its median 6 (3-40). The median treatment time was 60 min, (45-135) and the mean was 69.6 min (st.err.1.3), while the median equivalent temperature was 52 (43-59) and its mean was 51.4 (st.err.0.3). Note that the equivalent temperature is not the real temperature. It is the calculated value from the actual energy-absorption and the impedance, meaning of the actual destruction rate, which is as high, as would have been at the purely temperature oriented case.
The Kaplan-Meier plots of the overall survival (OS) (median 15.6m, [1.1-122.1]; mean 22.4m, [st.err.1.31]) and the survival from the first oncothermia treatment (OSO) (median 7.57m, [0.1-68.6]; mean 11.8m, [st.err.0.91]) are shown in Figure 5. For elderly patients neither the OS nor the OSO was different (p~0.37 and p~0.49, respectively).



a.) b.)

Figure 5. Overall survival (a), and survival from the first oncothermia (b) for the patients entered in the HTT study

The differences between patients without or with metastases in their OS and OSO were not significant (p=0.33 and p=0.07 for OS and OSO, respectively) Figure 6.



a.) b.)

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

The number of treatments significantly influences the OS (p=0.048) and the OSO (p=0.00046) and the follow-up time after the last oncothermia (p=0.0017) very much depends on the number of oncothermia treatments.

Interestingly, the surgical pretreatment was especially (p=0.0005) important for the longer survival either for OS (p=0.005) and OSO (p=0.016) (see Figure 7.), but the other pretreatments did not affect significantly neither the OS nor the OSO survival rates.

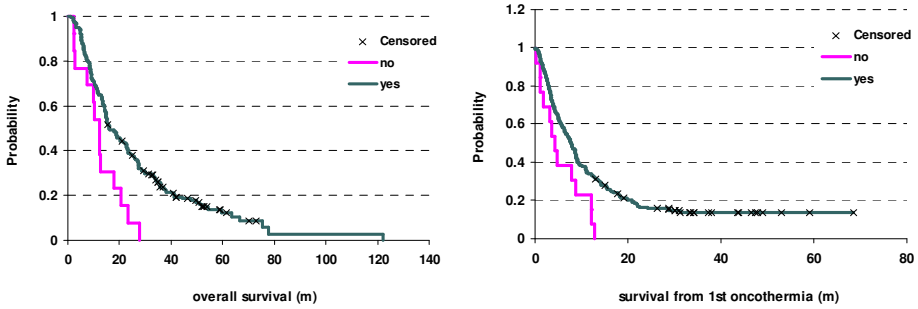


Figure 7. Effect of surgical pretreatments on the OS (a) and OSO (b) survivals

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

Comparative-analysis

The age-distribution of the altogether n=258 patients was near to normal (p=0.71); and no outlier was present. The median age was 57 y (16 - 84), the mean-age was 57.2 y (Std.err= 0.7). In the spectrum of the PTF a little shift to the elderly patients was present. The overall gender distribution was 83/175 female/male (32/68 %), and no significant difference could be measured between the places. The ratio of the elderly (>68 y) patients were 20.5%, (20.3 and 21.3% in PFY and HTT, respectively). The PFY/HTT patient ratio was 61/197 (24/76 %).
80% of the patients had distant metastases in both study-places (see Figure 8.) and half of them was in advanced stages at the first diagnosis of the disease (see Figure 9.). Patients were heavily pretreated (see Figure 10.), in PFY the chemo-therapy, in HTT the surgery was the most frequent modality.

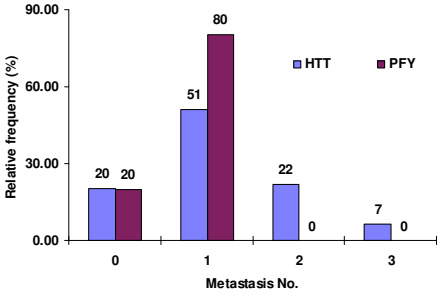


Figure 8. Comparison of metastatic cases

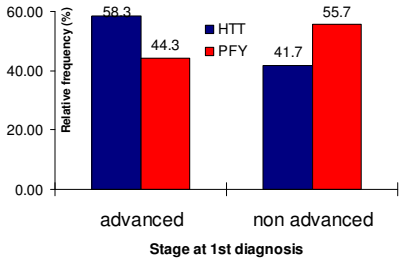


Figure 9. Staging differences

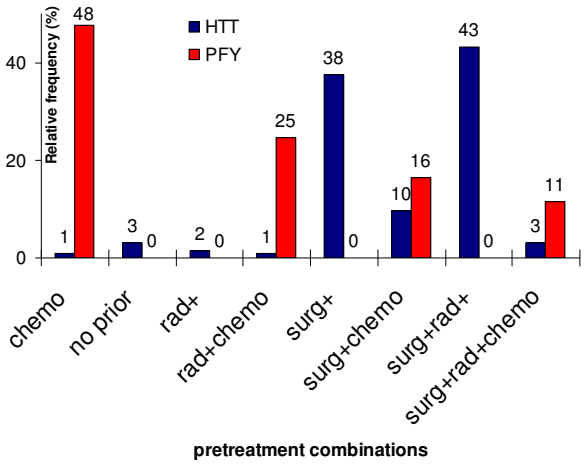


*Figure **Error! Bookmark not defined.**. Pretreatment combinations show the different emphases in the treatment strategies*

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

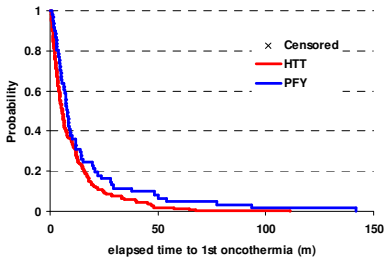


Figure 11. Elapsed time to first oncothermia is significantly shorter for HTT patients

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

The OS is significantly lower in HTT case (p=0.044) but in the OSO there are no significant differences (p=0.53). Survival after the treatment was not different in the two places (p=0.55). However, for elderly patients neither the OS nor the OSO was different (p~0.38 and p~0.86, respectively).
In both of the places most of the patients reported subjective improvement of their quality of life. No extra toxicity or safety problem was observed during the treatments.

Discussion

The above two studies were performed by the same guidelines but in entirely independent hospitals, with no overlap in medical personnel. The two retrospective data sets can be regarded as independent. The study of the expertise of the personnel in the two places was the same, their training was enough to make the optimal performance from the very start of the treatment.
The patients' pretreatments were mostly dominated by surgery and chemo-therapy in HTT and PFY, respectively. As well as the ETO was significantly different having earlier start of oncothermia in HTT, and surprisingly the OS was also significantly lower. Looks the patients treated by HTT were more advanced at their first diagnosis, (more metastases were detected) than the PFY counterparts, which explains the difference. Despite the difference in OS, the OSO does not differ significantly between the two places. The yearly survival rates could be regarded as identical (p>0.99) within the measurement error, (see Figure 12.). This could be indication of the oncothermia leveling action as well.

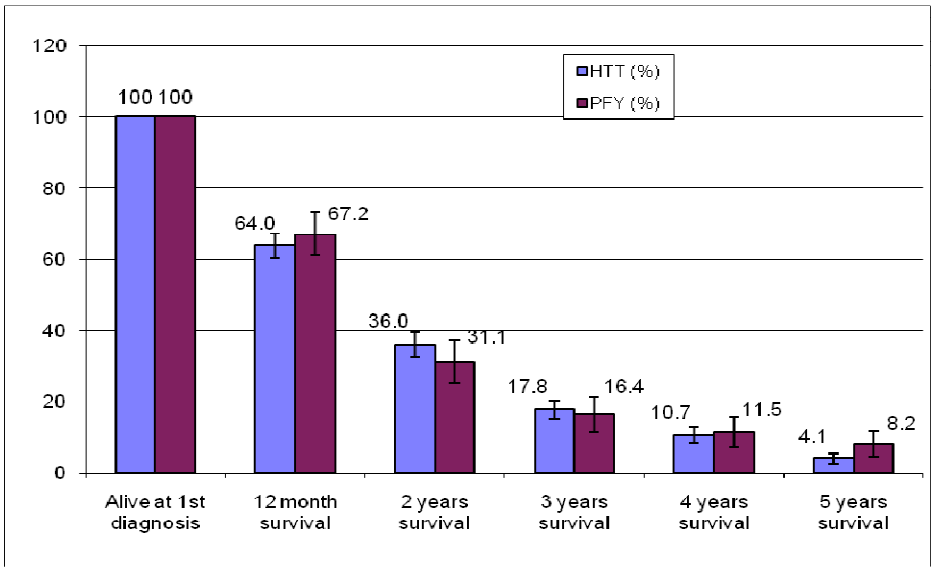


Figure 12. The yearly survivals of the patients in the two institutions. (no significant difference exists)

The results could be well compared to the available SEER [23] and Eurocare [24] data, see Figure 13.
The yearly survival rate is definitely much higher (significant) in the first three years than the database average. This result is remarkable taking into consideration the advanced patient-spectrum of oncothermia treated patients. The decrease of the difference by years is probably due to the very small influence on the longer survivals of the late-stage applied oncothermia for a short time. The most rapid cases are earlier in their stage to start oncothermia, so their overall survival is strongly influenced by the oncothermia treatment. This is supported by the fact that despite the significantly lower ETO the survivals are not notably different in the two institutions.

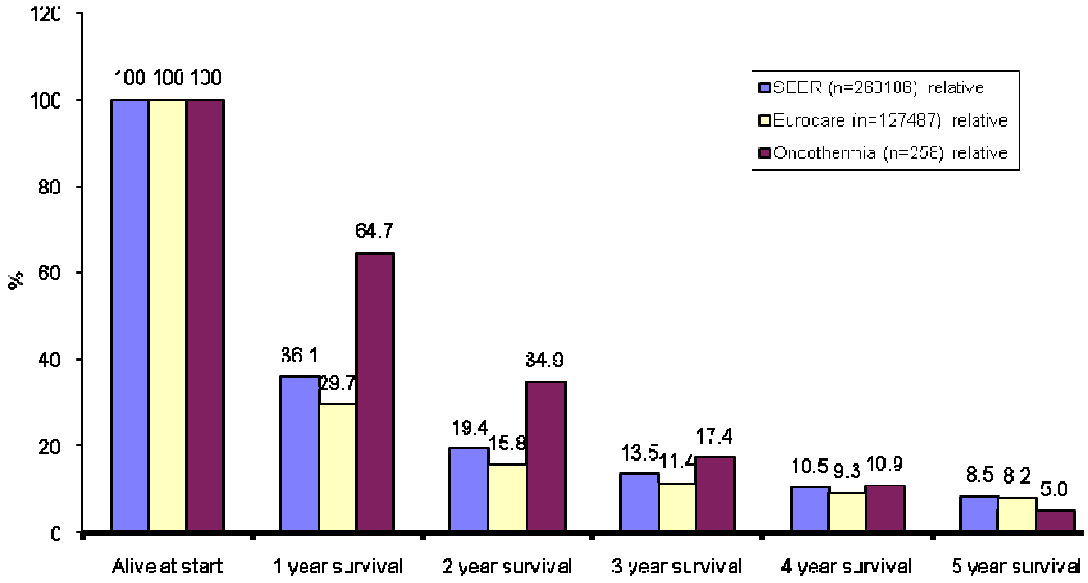


Figure 13. The comparison of the overall results with SEER and Eurocare data

We had collected a historical control (n=53) from the St.Borbala Hospital (Tatabanya, Hungary), for comparison. The data-set is the patients of one of the present authors (AD) who had worked at St.Borbala Hospital, so the comparison of his own data is feasible. The overall survival Kaplan-Meier plot shows significant benefit of the oncothermia (p=0.0046) Figure 14. (Median 15.8m (1-182) and mean 23.1m (St.err.1.3); for oncothermia and 14.0m (1-84), 18.5m (St.err.2.3) for the historical control.

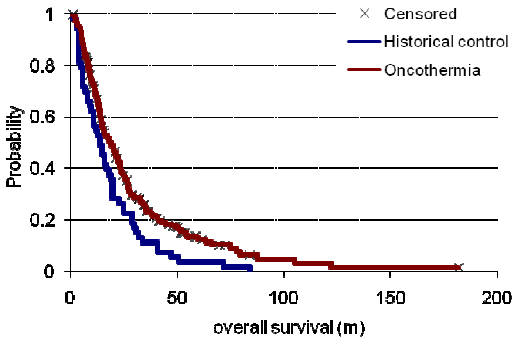


Figure 14. Kaplan-Meier plot for the historical and active arms in the study. The difference is significant

Conclusion

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

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

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

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

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

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Posters

These posters as well as the talks from the International Oncothermia-Symposium 2010 can be found on the following website:
www.io-symposium.com

A Case of Abscopal Effect in Metastatic Non-Small-Cell Lung Cancer treated with Radiation therapy and Oncothermia

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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.

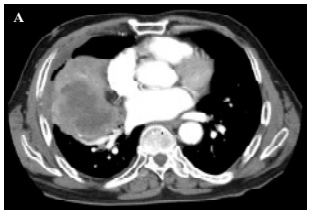
Poor performance status and/or multiple co-morbidities limit the treatment options for elderly patients. Their poor prognosis is commonly accompanied with a common refusal of cytotoxic chemotherapies even though adequate chemotherapy would be available with acceptable expected tolerance. In such cases radiotherapy can be considered as curative or palliative treatment option . The abscopal effect proposed by R.H. Mole in 1953, 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-macrophage colony stimulating factor (GM-CSF).

Case Report

A 72-year-old male patient was diagnosed with unclassifiable NSCLC by lung biopsy at other hospital in July 2009. The classification of the tumor at first diagnosis was cT2N2M0, stage IIIB (**Fig. 1**). 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. However, he still refused chemotherapy and together with his family members requested other possible treatment options. 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 Gy in 28 daily fractions for 5-6 treatments in a week (**Fig. 2**). It was followed by oncothermia after radiation 3 times a week. After 2 weeks of treatment, GM-CSF (250 microgram, Leukine®, USA) was administered subcutaneously once a day for 10days. 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 (**Fig. 3**) 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 combination attempt seemed to be more effective in immune response than radiotherapy alone. Further studies on the abscopal effect are necessary to evaluate action mechanism and the significance of cancer treatment option.



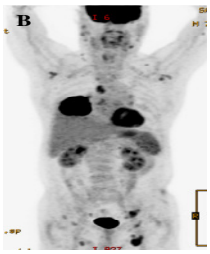
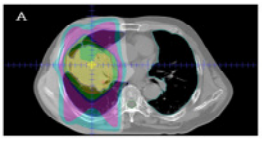
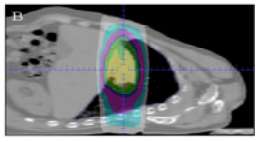
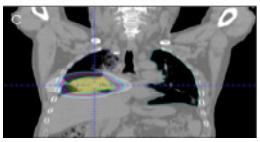


Fig. 1. CT chest scan (A) and whole body FDG-PET scan (B) of the patient. About 9.5 cm sized huge lung mass with central necrosis was detected in right lower lobe and the mass had a hypermetabolic walled cavity. Multiple metastatic lesions were also showed in both of neck, axillas, inguinal regions and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







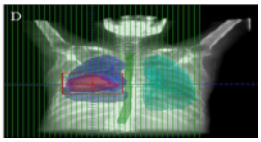


Fig. 2. Multi-leaf collimator (MLC) shaping surrounding target and radiation dose distribution in 3 directions for a patient with metastatic non-small-cell lung cancer. Scheme of the axial(A), sagittal(B) and coronal(C) images show the radiation dose distribution for lung mass of primary site. The isodose 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.

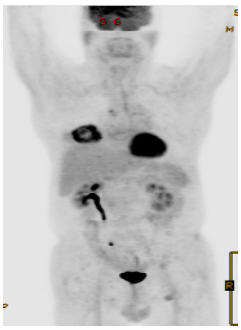


Fig. 3. FDG PET scan at the end of radiotherapy combining with hyperthermia and GM-CSF. The image shows excellent response in lung mass of primary site which was irradiated and complete remission in all metastatic lesions which were outside the radiation field.

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P-02 – Dr. Gabor Andocs, et al - Apoptosis induction with modulated radiofrequency (RF) hyperthermia (oncothermia) in immuno-defficient mice xenograft tumors (Review)

Apoptosis induction effect of modulated radiofrequency (RF) hyperthermia (oncothermia) in immunodeficient mice xenograft tumors

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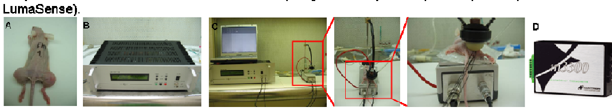
Introduction – objective of the work

Oncothermia method is more than twenty years serving the medical practices. It has successful applications either as a complementary therapy with the "gold-standard" modalities either as monotherapy, when no other possibility could be applied. The specialized animal-experiments had been started five years ago intending to clarify the basic mechanisms by in vivo scientific approaches. The complexity and interdisciplinary of the in vivo experimental series requested a wide cooperative scheme of various respected and honored research institutes and university laboratories. Our objective is to summarize the results of this intensive work and show the conclusions at the recent phase of the investigations.

Materials and methods

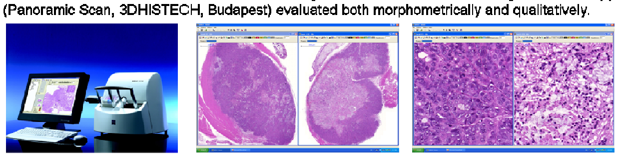
Immuno-defficient nude mice (BalbC/nu/nu) were used for xenograft and allograft models with HepG2, PC3, HT29, A431, GL261 cell-lines. The definite amount of cell-line suspension was injected to the femoral region of the 6-8 weeks old female mice and 18-20 days later the oncothermia treatment was performed, when the tumors were developed symmetrically in both sides on diameter 1-1.5 cm. The single shot treatment was identically performed for all the mice on their right lesion, while the left lesion was kept as untreated individual control to reduce the inaccuracies due to the individual variability of the animals.

Treatments were performed by highly specialized laboratory equipment (Lab-EHY, Oncotherm), optimized on mice dimensions, taking into account the physiology of the small animals, collecting all the important technical and biological parameters [1]. The impedance selection and automatic focusing which is well known in human clinical practices were applied in these experiments too [2]. The temperature of the tumors was controlled by high-accuracy fluoroptical system (Luxtron m3300, LumaSense).



Tumors satisfactory for treatment in mouse (A), Treatment device LabEHY-100 (B), Capacitive coupled electrode applicator for oncothermia of mice. (C), Fluoroptikal temperature measuring system (Luxtron) (D)

Slides of TMA tissue-multiblocks of the tumors of mice sacrificed in series of 0-72 h after the single shot treatment was stained by conventional hematoxilin-eozin (H-E) as well as by immunohistochemical methods and were digitalized and studied with digital microscopy (Panoramic Scan, 3DHISTECH, Budapest) evaluated both morphometrically and qualitatively.

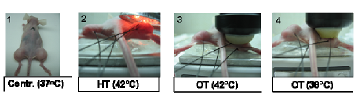


PanoramicScan device, its sample slide and the pattern from the digital microscopy software.

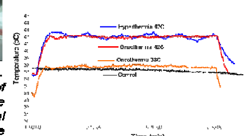
A subsequent series of our experiments were performed:

1. **Experimental phase:** Effect of oncothermia (single shot, 30 min, 42 C) on various tumor tissues were studied obtained from allograft and xenograft models. The investigated cell-lines were: HepG2 (human hepatocellular carcinoma), HT29 (human colorectal carcinoma) GL261 (mouse glioblastoma), A431(human epidermoid carcinoma), PC3 (human prostate carcinoma). Combined effect of chemotherapy (Mitomycin C) was studied in this phase also.

2. **Experimental phase :** Comparison of the efficacy of classical hyperthermia (HT) and of oncothermia (OT) with high number of experimental animals (four groups with 7-7 animals), using HT29 xenograft modell. We measured the effect of cell-killing independently from the temperature too. The effect was determined by digital quantitative analysis.

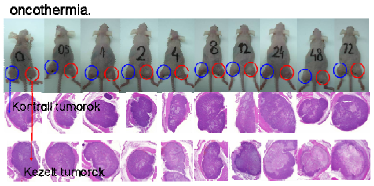


Experimental groups: 1. Untreated control, 2. Group of conventional infrared HT, 3. Oncothermia treated group, 4. The same as Group 3, but keeping the tumor on phyiological temperature. (This experiemnt was performed by intensive cooling of the tumor with the water-bolus of the electrode, limiting the temperature increase upto 38°C.



Representative pattern of temperature development measured in the center of the tumors during the treatments.

3. **Experimental Phase:** Effect of single shot 30 min oncothermia treatment was investigated immediately and 1, 4, 8, 12, 24, 48, 72 h after the treatment exploring the mechnaism of the oncothermia.



Experimental animals, and the full cross section of their tumors.

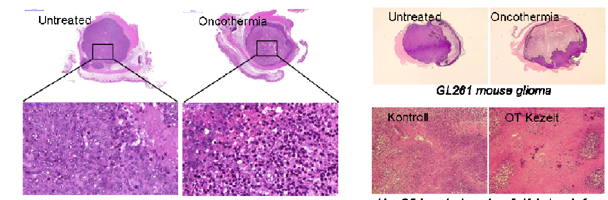
Based on morphological patterns we supposed the apoptosis is the dominant cell-killing mechanism. Based on this assumption we immunohistochemically measured the expression of p53 protein expression and also detected the apoptosis induced DNA fragmentation by TUNEL (Terminal deoxy-nucleotidyl transferase dUTP nick end labeling) The TMA slides collect 3-3 characteristic samples from every experimental tumors. The automatic immune-staining performed on the TMA blocks assured a standard antigen detection.

Leica Bond Max IHCH automata *TMA Master*

Results

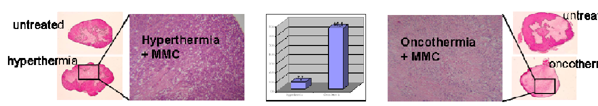
In its time development we observed the followings:

1.A, Oncothermia treatment made significant tumor distortion relative to the control in all the investigated tumors, irrespective its origin.



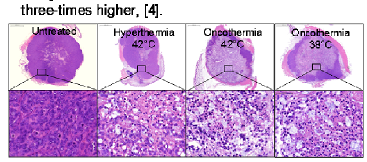
PC3 human prostate carcinoma *GL261 mouse glioma* *HepG2 humán hepatocelluláris karcinóma*

1.B, Significant improvement of the antitumor-effect of Mitomycin-C (MMC) was observed.

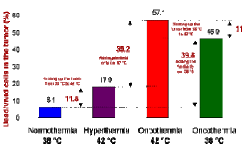


Complementary application of MMC with hyperthermia and with oncothermia on HT29 xenograft

2. Both the conventional hyperthermia and oncothermia have certain destruction of the malignant cells in the tumors in the studied cases, but the efficacy of oncothermia is almost three-times higher, [4].

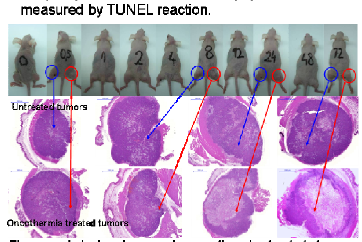


Morphological pictures of the treated tumors

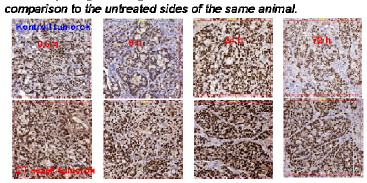


Quantitative analysis shows the significant differences between the treatments

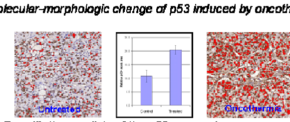
3. The documented cell-destruction is dominantly apoptotic. This is shown by the upregulation of the p53 protein, involved in the apoptotic-control, and also the certain fragmentation of DNA measured by TUNEL reaction.



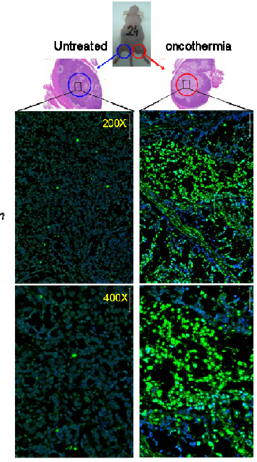
The morphologic changes in oncothermia treated tumors in comparison to the untreated sides of the same animal.



Molecular-morphologic change of p53 induced by oncothermia



Quantitative analisis of the p53 expression



DNA fragmentation after 24 h of the oncothermia treatment, measured by TUNEL, indicates the apoptotic cell destruction by oncothermia.

Conclusion

The applied mice models were suitable to study the effect of oncothermia on molecular level. The dominant role of apoptosis in the oncothermia cell-destruction is highly probable. Further investigations are in progress to study the mechanism of apoptotic induction and its connection with the cell-cycles as well as the role of the adherens and other cellular connections.

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Are we able igniting natural processes to kill cancer cells?

Dr. Nora Szasz[1], Dr. Gabor Andocs[2,3], Dr. Oliver Szasz[1,4], Dr. Lajos Balogh[3], Dr. Linda Muller[5], Dr. Nora Meggyeshazi[5], Prof.Dr. Andras Szasz[1,4]

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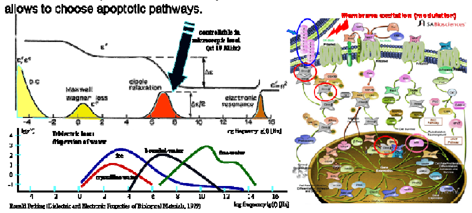
Objective

Long-time living ancient paradigm is eliminating the tumor cells by drastic, artificial effects (resection and necrosis) in the actual lesions. Original idea of the very first interventions in oncology had favored the necrosis by elevated temperatures in the local area. The original hyperthermia (HT) concept used the consequences of the definite high temperature in the tissue and in the physiology reactions. Oncothermia method (OTM) is a modern heir of this ancient thinking. However it changed the paradigm, emphasized more the natural physiological and biophysical-chemical processes instead of the temperature which anyway has many complications in local applications. OTM uses well-controlled modulated radiofrequency (RF) current-flow through the target tumor [1]. Temperature dosing has problems on the control and the selection of the malignancy [2], so OTM definitely uses special non-temperature dependent effects [3] avoid the normal temperature spreading promoting undesired blood-flow by the time, as well as selectively and effectively acting to eliminate the tumor [4]. OTM applies electric field to modify the natural processes, which is a well-established research area, [5]. Our present article summarizes the possible explanations of the natural OTM mechanisms, focusing on the way to proof the actual hypotheses.

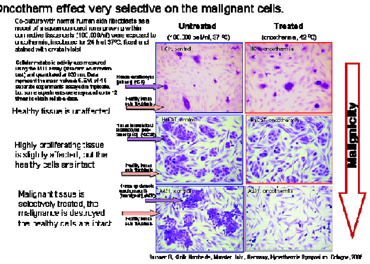
Method

We performed various experiments studying the natural factors of the cell-destortion effects by OTM. A highly specialized experimental setup (EHY110, Oncotherm, Germany) was used for in-vitro and in-vivo experiments, having single shot treatments in every cases. Effects were studied histomorphologically (HM) and immunhistochemically (IHCH) by various antibodies with digital microscopy system (MiraxView, 3D Histech).

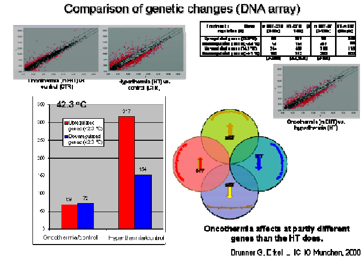
The polarization conditions are effectively approached in frame of β-dispersion of the aqueous electrolytes. The dose is measurable on the ignited chemical effects [4] instead of the temperature. This makes possible the membrane excitation, which allows to choose apoptotic pathways.



Oncotherm effect very selective on the malignant cells.



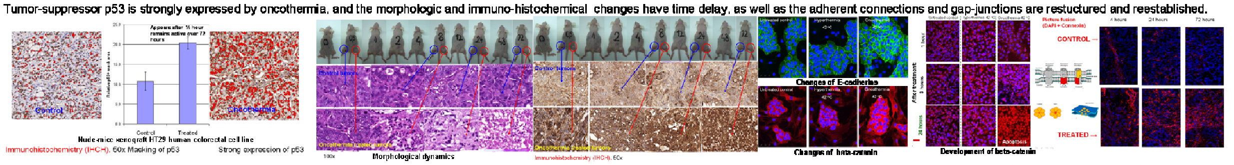
Comparison of genetic changes (DNA array)

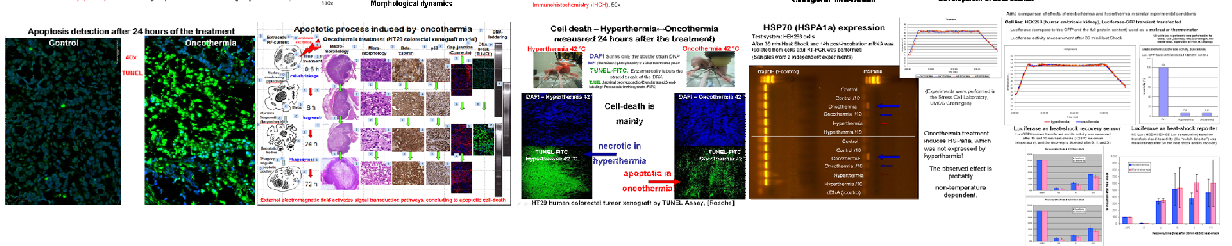


Results

Experiments show a definite time delay of tumor-destruction. The effect of OTM immediately after single shot is weak by both the HM and IHCH experiments. However, the elapsed time shows accelerated development of the cell-killing. This not immediate effect suggests the action of natural processes, which we measured. Reestablishing the adherent connections (E-cadherin) and its signal pathways (beta-catenin, p120 catenin) can be measured by IHCH, and cells start to shrink (instead of swelling expected by necrosis). Appear a definitely enhanced expression of p53 protein. After longer time in vivo (4-24 h) observable the expression of connexins (gap-junctions), and nuclear relocaliztion of beta-catenin starts, which is finished after 72 hours of the treatment. During this development apoptotic bodies could be observed.

Tumor-suppressor p53 is strongly expressed by oncothermia, and the morphologic and immuno-histochemical changes have time delay, as well as the adherent connections and gap-junctions are restuctured and reestablished.





Conclusion

Oncothermia probable ignites natural apoptotic processes selectively in the tumor.

Oncothermia is the only process, where the synergy of the most modern biophysics (fractal physiology [6], [7], [8], [9]) is used, and applied to gain the natural processes with the hyperthermia (thermal conditions). Oncothermia is the only process which uses the synergy of the electric field and thermal processes. Oncothermia solves such technical problems, which were blocking the stable applications. This rigorous approach could be only the basic of the wide acceptance and the reimbursement from the Krankenkasse. Oncotherm focuses by automatisms (see below) not necessary to change the sizes of the electrodes to have focusing (which is anyway a rough volume-emphasis, and not a real focus).

Oncothermia solves the selective deep action on cellular resolution [10]. The main idea is connected to the electric field effect of cancer, worked out by the Karolinska Institute, Sweden [11]. The effect of electric field is a hot topic in science, [12], [13], [14], [15], [16], used in other treatment modalities also [17]. Oncotherm company was one of the firsts who constructed treatment unit, and shown it to the medical community, [16]. The results were amazing, [19]. Oncothermia development was a non-invasive application of the electric field. The method was rapidly developing and clearly proven [20]. The electric field effect is widely applied on lower frequencies also [21], [22], [23] and a clinical trials of other electric-field methods are also in progress [24], [25].

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Booster for all medication processes

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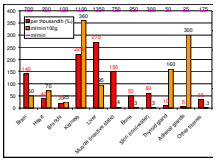
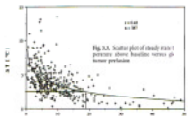
Objective

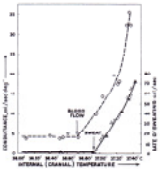
One of the problematic point of the medication its targeting. The systemically administered drugs are distributed in the whole body by the blood, irrespective its origin by i.v. infusion, orally taken or getting by muscular injection, rectal suppository, skin-addicted, inhalations etc. However the delivery and the in-situ effect of the given drug to the target is a crucial point of the treatment. This is also the main point of the personalization of the drug-administration in every medial actions and especially important in the oncology, where the toxicity is an effective danger. Objective of our presentation is to introduce the device, which is devoted to help in this line of the problems: the chemo-booster.

Method

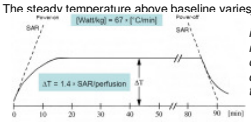
The drug in all systemically administered cases delivered and distributed by the blood-stream. The task to increase the drug-concentration in a given volume is increasing the blood-flow in the targeted area. The higher temperature could activate the microcirculation of the capillaries (capillary filtration capillary pressure, etc), increasing the micro vascular perfusion, local tissue oxygen, nutrients, and phagocytes to the area being targeted. It could also regulate the cell cycle by changing calcium ion binding.







The steady temperature above baseline varies by the washout perfusion. [1]



The sudomotor and vasomotor responses to the stimulus of internal temperature were plotted simultaneously, to show the relative positions of their thresholds and the coordinated action of the two phenomena. No significant further decrease of conductance was observed as temperature dropped below the threshold of active vasodilatation. [2]

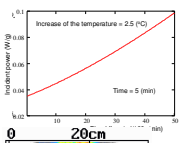
SAR: specific absorption rate [W/kg]
ΔT: steady state temperature elevation [°C]
perfusion [ml/100g/min]

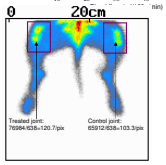
increases pretty linearly with the heat-input (I) [1] as:

$$\Delta T = \frac{60I}{kS_t}\left(1 - e^{-kt}\right) \qquad \left[k = \frac{Fp}{100\lambda}\right]$$

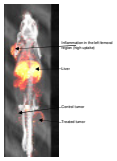
Eq.4.

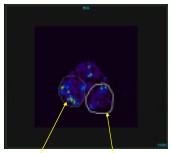
where S = specific heat of the tissue [J/g/K]; F = tissue-blood-flow [ml/min/100g]; λ = ratio of absorption ability of heat in tissue and blood; p = density of the tissue [g/ml]; I = heat input rate [W/g] of the tissue; ΔT = increase of the temperature in the tissue [K]; t = time [min].

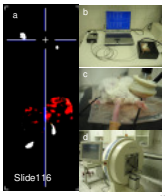




A healthy beagle dog was measured by the radiopharmaceutical (400 MBq 99mTc-HAS) injection, to see the blood-perfusion differences comparatively in joints. The result shows a perfusion enhancement of 16.8% in the oncothermia treated joint





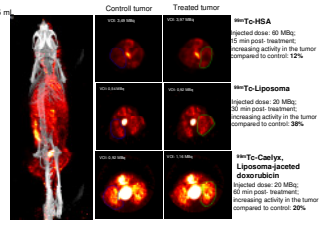


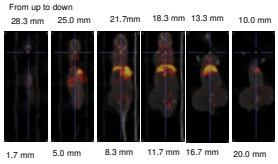
The measurement of the mice-tumor with symmetrical control. (a) the result in a depth (slide 116), (b) the experimental arrangement, (c) the mice under the treatment, (d) the SPECT tomography

MicroCT-SPECT Radiopharmakon: ^{99m}Tc-signaling

Treated tumor 1.16 mL **0.70 MBq (Increased uptake by 46%)**

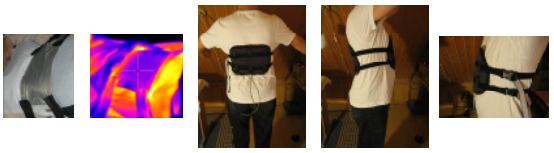
Control tumor: 1.15 mL **0.38 MBq**





Results

A small device had been developed to heat up the full volume under the electrode in full depth. It has no treating effect like oncothermia had (it has no cellular selection or focusing), it is a simple local heater in depth. The heating is generated by the Joule-loss in the body, and makes vasodilatation there. The vasodilatated volume has higher blood perfusion which delivers more drug (and more oxygen) to the target, and relatively deprives it form the other areas of the body. This is a drug-boosting in a requested volume, but it does not make any more selection. The temperature range is 37-39oC, which is optimal for boosting function. The booster works not only by the vasodilation but also could be combined by the pharmacokinetic parameters of the given drugs, activating the chemo-reactions and the reaction rates by the higher temperature in the targeted volume. Its application covers a wide range of diseases. For example it could be used for rheumy, goat, pain-management, arthritis, dermatology, muscle spasms, sport supports, gynecology, allergy, rhinitis, common cold, pediatric ear diseases, nerve healing, bone Healing (unsure of any published clinical studies that are proven), cosmetics (like adipose problems, cellulites, acnes, blisters, etc.), support of the general rehabilitation process. It has a little curative effect on wound healing as well.



The electrode heats up the tissue but itself remains cold after 60 min treatment.

Remarks: It is a deep-heat for blood-circulation gain. The usual heaters heat the surface, and vasodilatate the subcutan capillary-bed. This negative effect for drug-targeting, because the drug could be concentrated on this area instead of the target. The booster makes the heating deep by Joule-heat of the current flowing through the targeted volume.

Following actions also could be generated:

1. increased fibroblastic activity and capillary growth
2. increases the nutrition concentration in the volume
3. increases the metabolic activity in the volume (higher quantity of nutrition, oxygen and higher local temperature)
4. synergically increases the field-dependent effects, (optimizes the membrane excitation and helps activating the signal pathways, etc.)
5. increases the effects on the blood-structure in the volume,
6. increases venous and lymphatic flow
7. changes in physical properties of tissues
8. increases tissue extensibility
9. possible changes in enzyme reactions
10. increases the heat- and field-stress reactions (mainly the developments of heat-shock-proteins, HSP)

Further actions are:

1. Muscular relaxation
2. Edema reduction
3. Lymphedema reduction
4. Treatment of venous stasis ulcers
5. Assists in removal of cellular debris and toxins
6. Alters diffusion rate across the cell membrane
7. Increases intramuscular metabolism
8. Superficial wound healing
9. Analgesia – pain relief, pain-killing device
10. Could help the analgesic drugs to be activated

Technical parameters:

1. It is a heating device in depth, not focusing, heats the full volume
2. Its frequency is 6.78 MHz
3. It has ultra-light, super-flexible, multi-purpose and multi-use electrodes
4. It has no modulation
5. It is 8 kg, and 40W power

Conclusion

The newest device from Oncotherm Company is not for oncology alone. This universal small device could be indispensable support for the actual treatments by various medications, and could be essential for the personalization processes.

This is not a curative device! This helps for personalizing and targeting every medicaments administered systemically, irrespective which disease is treated. The treatment is provided by the medication, the booster makes its personalization.

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P-05 – Prof. Dr. Andras Szasz - Brain glioma results by oncothermia

Brain glioma results by oncothermia

Szasz A.

Department of Biotechnics, St.Istvan University, Hungary, & Oncotherm GmbH, Troisdorf, Germany

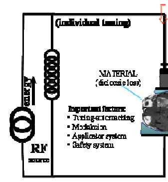
St.Istvan University

Objective

None of the established state-of-the-art treatments in malignant primary brain tumors, especially in glioblastoma multiform (GBM), could show effective or commonly accepted curative potential until today. The editorial question of JAMA [1] in 2005 is actual even now: "Where to go from here?" Our objective to show a feasible way to go, summarizing the results obtained till now made by modulated electro-hyperthermia (oncothermia) in various clinics in EU.

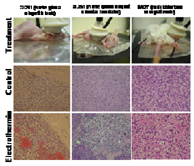
Method

Data are collected from GBM and anaplastic astrocytoma (AA) published observational studies. The method is transcranially applied modulated RF-current capacitive coupled at 13.56 MHz carrier frequency, (Oncotherm, EHY2000+) described in details elsewhere [2]. The applied protocol was unified step-up heating, 40-150 W RF-power with water-bolus cooling. Treatment is applied in combination with chemo- and/or radio-therapy or used as monotherapy if the conventional therapies fail.

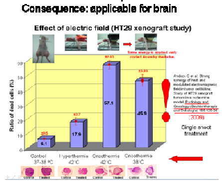


Specialties of the method

Detailed laboratory experiments had proven the efficacy of oncothermia on brain-glioma cell-lines



It is effective on low temperatures also
Consequence: applicable for brain



Due to the low temperature it is applicable near the eye

Easy to manage the treatment

Results

Study 1 Prospective single-arm Phase I/II study, [21], [22];

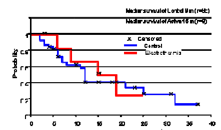
(Neurology Clinic, Regensburg University, Germany) Investigators: Prof.U.Bogdahn & Prof.P.Hau. Electrothermia is NON TOXIC (even by high dose escalation). It could stabilize the state of patients in highly advanced cases (n=15).. Examples:

Patient: RE-013-4, 49y, male, Anaplastic Oligoastrocytoma, WHO II, 2 resections (partial), 3 relapses. **1st therapy:** Radio Tx **2nd therapy:** PCV (Procarbazine, CCNU and Vincristine) **3rd therapy:** Temizolomide (Temodal); **4th therapy** Nimustin(ACNU) + **Electrothermia**, Cycles of ACNU: 3 Cycles of electrothermia 3, Sessions of electrothermia: 50, (5w); **Karnofsky** score at **start**: 70 **Karnofsky** score at **end** 60, **Best performance: STABLE DISEASE (SD)**

Patient: RE-014-4, 49y, male, Glioblastoma multiforme, WHO IV, 2 resections (partial), 3 relapses. **1st therapy**: Radio Tx + Temizolomide (Temodal)/PEG-Dox, **2nd therapy**: Epothilone **3rd therapy**: Temizolomide (Temodal)/Int.; **4th therapy**: Nimustin(ACNU) + **Electrothermia**, Cycles of ACNU: 2, Cycles of electrothermia 3, Sessions of electrothermia: 56, (5W); **Karnofsky** score at **start**: 80, **Karnofsky** score at **end**: 80, **Best performance: STABLE DISEASE (SD)**

Study 2 Prospective double-arm Phase II study, [23].

Prospective, double arm brain glioma study (control arm n=36, active arm n=9) study for advanced primary brain tumors (gliomas WHO IV) was done in Nurnberg (Klinikum Nürnberg-Nord, Nürnberg, Germany, Investigator: Prof. Dr. H. Renner) Trimodal therapy was applied: radiotherapy (50-60 Gy), chemotherapy (Temodal) and electrothermia (3-12x; 60 min). The median survival was measured on control-arm as 9m, while in the active electrothermia arm it was 15m

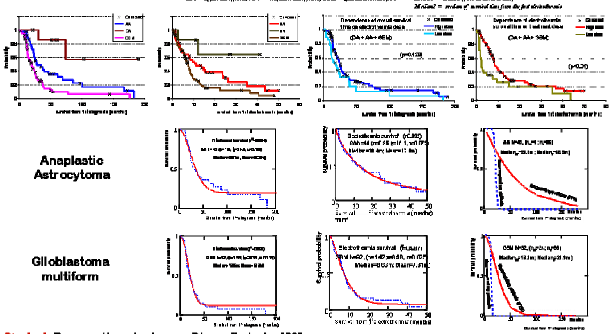


Study 3 Retrospective single-arm Phase II/III study was performed (n=140) [24].

Retrospective, single arm brain glioma study for advanced primary brain tumors was done (in all cases the "gold standards" were failed)

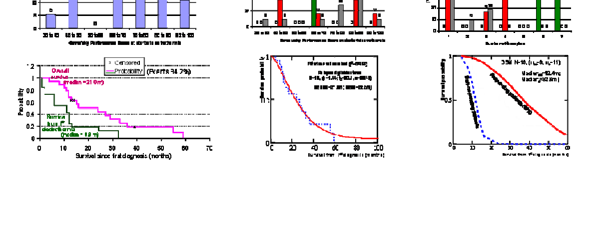
WHO grade	# Pts.	Median1 [m]	(min.-max.) [m]	Median2 [m]	(min.-max.) [m]	Average1 [m]	(St.dev.) [m]	Average2 [m]	(St.err.) [m]
DA	8	39.2	22-180	11.6	1.1-41	73.0	18.3	15.5	5.2
AA	40	25.8	3.6-183	8.1	1.4-50	43.9	7.0	13.4	2.0
GBM	92	16.0	1.4-170	0.1	0.3-46	23.0	2.5	8.0	0.9

DA = diffuse astrocytoma, AA = anaplastic astrocytoma, GBM = glioblastoma multiforme; *Median1 = median of overall survival time*; *Median2 = median of survival time from the first electrothermia*

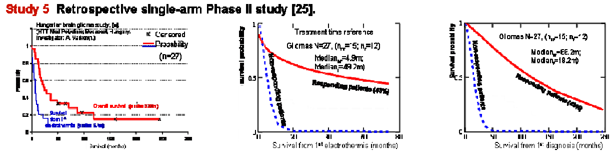


Study 4 Prospective single-arm Phase II study, [26].

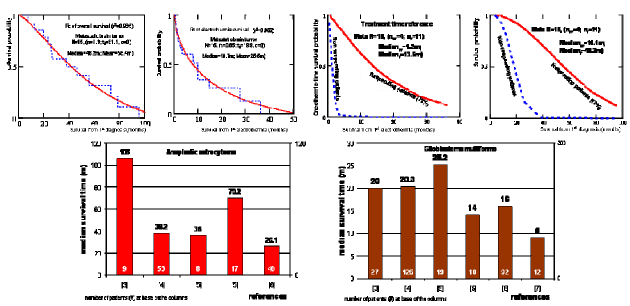
ACNU combination (60 mg/m2), which was used for safety (Phase I; dose escalation) trial had been used in Phase II as well for recurrent glioblastoma (n=19) (Klinik St.Georg, Bad Aibling, Germany, Investigator: Dr. F. Douwes, [19]). The quality of life of patients was measured by standard Karnofsky Performance Score, (KPS). The obtained median of overall survival was 21.8m (average survival 25.5m) while the median survival from first electrothermia was 8.8m (average survival 13.5m), Fig. 24. The local clinical response had no complete remission and 58% of the patients were in progressive disease (not responding on electrothermia). The ratio of responding patients is 59% (failing 41%) calculated by the parametric selection. This difference could be caused by the relatively short follow-up in the trial.

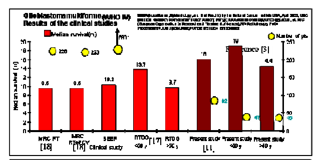


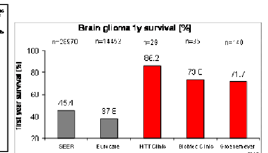
Study 5 Retrospective single-arm Phase II study [25].

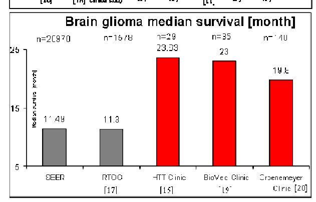


Study 6 Retrospective single-arm study for metastatic brain tumors (n=15) [27]









SEER (Surveillance, Epidemiology, and End Results) by the National Cancer Institute USA, April 2000; **EUROCARE** Statistical database of cancer in the European Union **MRC** (Medical Research Council, Brain Tumor Working Party); [10]; **RTOG** (Radiation therapy Oncology Group, [17]; **EORTC** (European Organisation for Research and Treatment of Cancer) [16]; **RT** = Radiotherapy, **PCV** = Procarbazine + CCNU(Lomustine) + Vincristine, **TMZ** = Temizolomid

Toxicity

A well designed Phase I study shows the safety of the method [8]. The dose escalation has no extra hazard even in very frequent applications.

Conclusion

The results are strongly indicating the feasibility and the benefit of the oncothermia showing a valid treatment potential and safe application. Oncothermia is a potential way to escape from the present impasse situation and treat brain gliomas successfully. Performing prospective, randomized clinical trials in the future is mandatory.

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Clifford Hospital — Non-Toxic Integrative Cancer Treatments

As a large modern general hospital, Clifford Hospital is the first JCI (Joint Commission International) accredited Chinese hospital, a National Grade "Triple-A" Hospital and a "Famous Traditional Chinese Medicine Hospital" of China. It has been accredited by JCI three times. The JCI accreditation surveys are carried out once every 3 years.

Bestowed the titles of National Education Base for Preventive and Curative Cancer Treatments, and Reputable TCM Oncology Center of Guangdong Province, Clifford Hospital Oncology Center achieved breakthroughs in medical treatment, utilizing modern techniques such as hyperthermia, chelation, medical ozone therapy and traditional therapies including Chinese Medicine, acupuncture, herbal cuisine, psychotherapy, medical Qigong, music etc, combined with the latest advanced medical procedures which are radiotherapy and chemotherapy of international standard, argon-helium cryoablation, gamma knife, photodynamic therapy, bio-targeted therapy, stem cell immunotherapy, genetic therapy and others. For different needs at different periods of cancer prevention, treatment, recovery and remission, individualized protocols are made by medical experts in Joint Case Conference according to the patient's specific conditions so as to strengthen the patient's immune system, prolong the patient's life and improve the patient's quality of life.

Doctor Pang and specialists of varying fields hold Joint Case Conference to make the individualized treatment protocol.

National Education Base for Cancer Treatments

Reputable TCM Oncology Center of Guangdong Province

Over 30 international oncologists participate in Joint Case Conference, providing individualized protocols.

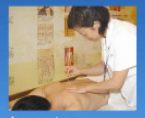
Dr. Clifford L. K. Pang, M.D.
Pioneer in the Non-Toxic Integrative Cancer Treatments
Founder and CEO of Clifford Hospital

Dr. Pang has rich clinical experience in Non-Toxic Integrative Cancer Treatments for cancers of the liver, stomach, intestine, thyroid and breast and others, with success in curing over 1,000 patients with various cancers. He has published several medical works including A Study of Non-Toxic Integrative Cancer Treatments.

Over 20 advanced procedures are available for cancer prevention, treatment, recovery and remission.

Over 1,000 cancer patients were cured without cancer metastasis and recurrence for many years.

Hyperthermia



Acupuncture

Medical Ozone Therapy

Traditional Chinese Medicine Syndrome Differentiation and Treatment

Minimally Invasive Interventional Therapy

Chelation Therapy

Local Hyperthermia (Hungarian Local Hyperthermia Machine, Onco Therm EHY-2000)

Dietetic and Herbal Cuisine Therapy

祈福医院
CLIFFORD HOSPITAL

Joint Commission INTERNATIONAL

国际肿瘤绿色综合疗法中心

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Hyperthermia

Local Hyperthermia (Hungarian Local Hyperthermia Machine, Onco Therm EHY-2000)

Cancer

Traditional Chinese Medicine	Immunocyte Therapy
Bio-Targeted Therapy	Nutritional Therapy
Psychology Therapy	Body-Alkalization Therapy
Medical Qigong	Interventional Therapy
Gene Therapy	Stem Cell Therapy
Radio Frequency Ablation	Hyperthermia
Medical Ozone Therapy	Chelation
Acupuncture	Argon-Helium Cryoablation.

International-Standard chemotherapy and radiotherapy
International-Standard surgical procedures

Over 1,000 cancer patients were cured without cancer metastasis and recurrence for many years.

Oncology Center of Clifford Hospital

We propose non-toxic integrated cancer therapies to help the overall recovery of body and mind. It breaks the limitation of mono anti-cancer treatment and maximally improves the therapeutic effect, so as to prevent metastasis and relapse of cancer, improves patient's quality of life and prolongs their life span.

祈福医院
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国际肿瘤绿色综合疗法中心

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P-07 – Dr. Nora Meggyeshazi, et al - Clinical studies and evidences of modulated RF conductive heating (oncohtermia) method

Clinial studies and evidences of modulated RF-conductive heating (oncothermia) method (Review)

Meggyesházi N.(1), Szász A.(2)

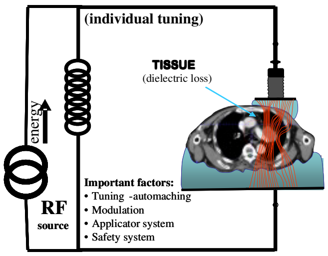
(1) *I. Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary.*
(2) *Biotechnics Department, St. István University,Gödöllő, Hungary*

Objective

Modulated RF-conductive heating (oncothermia) has twenty years experience in the clinical practices. The presently working more than 100 devices produce enormous number of treatments and collect a strong experience forming a consensus in the treatment. Present a comprehensive summary of clinical studies made by oncothermia. Compare the data and make possible statistically significant statements.

Method

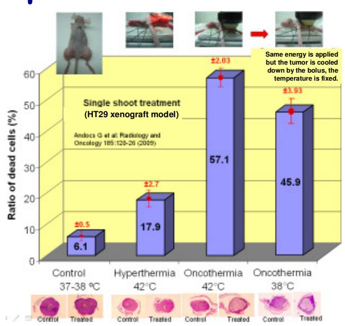
The treatment method is capacitive coupled at 13.56 MHz carrier frequency modulated RF-current, (Oncotherm, EHY2000+) [1]. The applied protocol was unified step-up heating, 60-150 W RF-power with water-bolus cooling. (The technique is described elsewhere [1].) Treatment is applied in combination with chemo- and/or radio-therapy or used as monotherapy if the conventional therapies fall. These lines of treatments are mostly determined by the individual, personalized treatment-decisions, usually without having help from any evidence based statistical approvals. Present data are collected from observational studies, except some of brain and colorectal cancer trials.



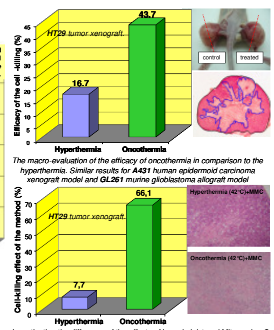
We compared the collected data of the same localizations and same protocols from various clinics. They common significant difference from the databases is a kind of statistical evidence.
To make objective evaluation we had special considerations:

- Evaluate the available data also by parametric statistical methods (Weibull-distribution), mining the information in long treatment processes, where oncothermia was only a fraction of the overall treatment-time
- Compare the first year survival rates with the large international databases
- Compare results of clinics in the same patient groups and same oncothermia protocol,

Specialties of oncothermia



Comparison of the effects of hyperthermia and oncothermia on identical temperature 42 C. To reduce the deviation by bio-variability all animals had their own control which was evaluated together with the untreated animals as well. (Each group had seven animals.)



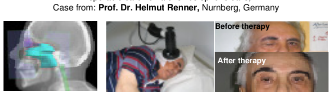
*The macro-evaluation of the efficacy of oncothermia in comparison to the hyperthermia. Similar results for **A431** human epidermoid carcinoma xenograft model and **GL261** murine glioblastoma allograft model*

Investigating the difference of the effects of i.p. administered Mitomycine-C. The cellkilling is relative to the control tumor on the same animal. B)Hemalaun-eosin stained microscopic images of tumor samples

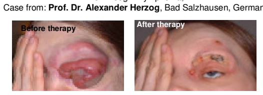
Possibility to treat sensitive areas

It is effective on low temperatures also Consequence: applicable for brain [16] or other sensitive organs.

Inoperable carcinoma of sinus sphenoidalis,
Case from: **Prof. Dr. Helmut Renner,** Nurnberg, Germany

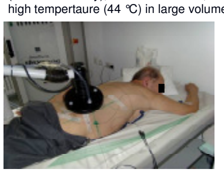


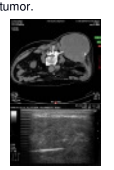
Non-Hodgkin lymphoma,
Case from: **Prof. Dr. Alexander Herzog**, Bad Salzhausen, Germany

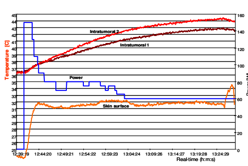


Temperature

Intratumoral in situ temperatrure (**Klinikum Nord, Nürnberg, Germany), Prof. Dr. H. Renner)**
Patient: FP, male, 87y; **Tumor:** Weichtel sarcoma on the right side of the back, **Primer diagnosis:** 12/07
CT-guided biopsy; **Histology:** Malignant fibrotic histiocytoma G3; **Therapy:** curative, Radio-Thermo-Therapy (Double-modality); first Oncothermia, afterwards radiotherapy, Dosis 22 Gy, 6 Fractions, Result: Reaching high tempertaure (44 ℃) in large volume tumor.







Toxicity

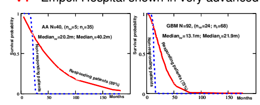
A well designed Phase I study shows the safety of the method [2]. The dose escalation has no extra hazard even in very frequent applications for such sensitive organs like brain gliomas.

Clinical results

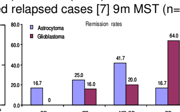
We summarize only the localizations, which results are pure with conventional methods

Brain studies

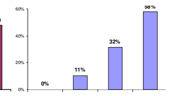
I. ASCO (2003) [3] the MST for AA 106m (n=9) and 20m (n=27) for GBM patients,
II. ASCO (2008) [4] 38.2m (n=53) and 20.3m (n=126) for AA and GBM respectively,
III. Witten-Herdecke University published [5] 70.2m (n=17) and 25.2m (n=19) as well as [6] 26.1m (n=40) and 16m (n=92) data for AA and GBM MST, respectively.
IV. HTT-Med MST results [5] were 36m (n=8) and 14m (n=10) for AA and GBM, respectively.
V. Empoli Hospital shown in very advanced relapsed cases [7] 9m MST (n=12) for GBM.



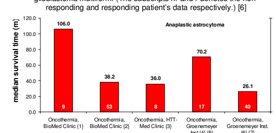
The parametric fit of responders of Anaplastic astrocytoma cases and glioblastoma multiform. (The subscripts nr and r denotes the non-responding and responding patient's data respectively.) [6]



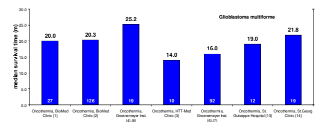
Local responses for AA (n=53) and GBM (n=126) in the study [4]



Phase II trial for recurrent glioblastoma (n=19), [17]. (ACNU combination (60 mg/m2)

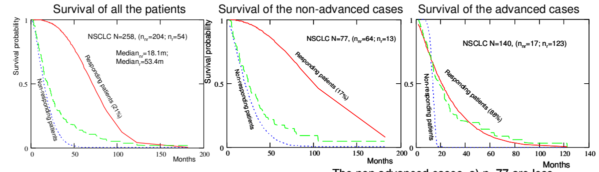


Results of median survival time for advanced anaplastic astrocytoma in different, independent clinics using the same oncothermia protocol.

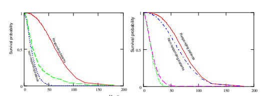


Results of median survival time for advanced glioblastoma multiform in different, independent clinics used the same oncothermia protocol.

Non-small-cell lung cancer study



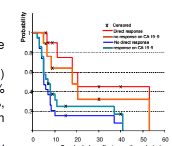
The non advanced cases a) n=77 are less responding than the advanced ones b) n=140 [18]



The distribution together with the historical control (n=311) only slightly differs from the distribution without the control group (n=258), showing the well controlled study comparison [18]

Pancreas studies

I. ASCO (2002), [8], the first year survival (1yS) 41.7%, while the subsequent years are: 20.6%, 13.5%, 9.4%, 4%, with MST 10.8m.
II. ESHO (2003), DEGRO (2004) [9], [10], the 1yS in HTT-Med (n=73) 52.1% (MST=12.7m), and in Peterfy Hospital (n=26) 46.2% (MST=12.0m). In the subsequent years were 31.5% &15.4%, 16.4&11.5%, 9.6&3.8% and 2.7&3.8%, which data are higher than expected from the large databases
III. Results were repeated in six different clinics in two countries significantly improving the achievements of the conventional treatments shown in summary [11]. In addition to the above two more clinic showed its 1yS: Veramed (n=42) 52.4% and Nurnberg Nord (n=13) 46.2%



The prognostic value of CA-19-9 tumor-marker in the present pancreas study. The survival is significantly separated to responders and non-responders on CA-19-9. (The tumor-market is a little more optimistic, but not significantly.) [18]

Metastatic liver studies

I. The colorectal liver metastasis was the topic of four different studies on liver [12],
II. ASCO (2007) [13], MST was 20.5w, 50% presented evidence for increase well being.
III. ICACT [14], had shown definite benefit for 25 patients (n=30) by oncothermia
IV. ESHO (2005) [15], had shown in second line treatment 80% response rate.

Conclusion

The results are strongly indicating the feasibility and the benefit of the oncothermia showing a valid treatment potential and safe application. Our results conclude the feasibility of the oncothermia and despite of the high-line treatments shows evidences by the parallel studies in the various clinics. Performing prospective, randomized clinical trials in the future is mandatory. A well designed Phase I study is shown in our other We concentrate on the results of anyway complicated diseases, like brain gliomas, pancreas carcinoma, metastatic liver from colorectal carcinoma. In glioma cases a prospective study (Regensburg University, [2]) had shown the safety of the oncothermia treatment. The efficacy results are everywhere significantly better than any of the data in public databases (SEER, Eurocare): paper [8].

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Abbreviations

Databases: SEER (Surveillance, Epidemiology, and End Results) by the National Cancer Institute USA, April 2000; **EUROCARE** Statistical database of cancer in the European Union;

Evaluation: CR = Complete Remission, **PR** = Partial Remission, **NC** = No Change, **SD** = Stable Disease, **PD** = Progressive Disease; **MR** = Major Response (CR+PR); **MST** = Median Survival Time;

Diseases: AA = Anaplastic astrocytoma, **GBM** = Glioblastoma Multiforme, **NSCLC** = Non-small-cell Lung Carcinoma,

Subscripts: "**r**" – Responders; "**nr**" – No Responders.

Societies with their common abbreviations: ASCO, ESHO, DEGRO, ICACT,

Successful co-administration of electrohyperthermia and bevacizumab in non-small cell cancer: A case presentation

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1.Clinical Oncology Dept. "B", National Institute of Oncology, HungaryBudapest
2.Oncotherm Ltd, Paty, Hungary

Introduction

Non-small cell lung cancer (NSCLC) exceeds in number the 85% of all malignant lung cancers. In metastatic disease the principle goal is to prolong survival with the least toxicity keeping in mind the importance of patients' quality of life.

Bevacizumab **(Avastin®)** has been accepted as first line treatment in combination with platinum based chemotherapy and maintenance therapy in NSCLC. Bevacizumab can be added safely to several chemotherapeutic agents, however there is no data on co-administration with thermotherapy. No robust evidence exits about the beneficial effect of loco-regional thermotherapy on overall survival, but it can be used successfully in symptom palliation.
Electrohyperthermia is a form of thermotherapy using electromagnetic field.

Medical history

- In the 64 year old male patient a solitary lung lesion was captured by screening chest radiograph.
- **2008 February**

  The lesion was diagnosed as stage III/A lung cancer and a right upper lobectomy was made.

  Pathology result: adenocarcinoma, pT2 (3,8cm), pN1 (1/1), vascular invasion

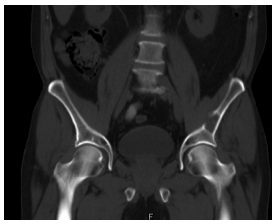
  He rejected adjuvant chemotherapy.
- **2009 June**

  one mono-localized (left hip bone) osseal metastasis was proved with unequivocal and consistent results of CT, MRI and bone scan

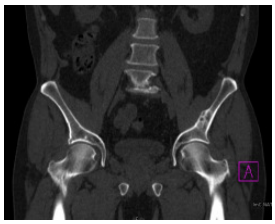
First-line treatment

- **2009 July- November**
  - 6 cycles of bevacizumab (7,5 mg/ttkg) + paclitaxel (175 mg/m^2) + carboplatin (400 mg/m^2) 3 weekly + zoledronic acid (4 mg 3 weekly)
  - Result:: stabile disease
- **From November 2009**
  - Bevacizumab (7,5 mg/ttkg) maintenance therapy + zoledronic acid (3 weekly)
  - Loko-regional elektro-hyperthermia (Oncothermia, OT)

    given OT three times a week with the maximal tolerated dose of 70W (EHY 2000®, Oncotherm Ltd, Paty, Hungary, 20 cm electrode)
  - The treatment is still ongoing, no > grade 1 adverse reaction emerged
  - Serial MRI imaging shows the lesion diminished in size



Metastasis in left hip bone Augustus 2009



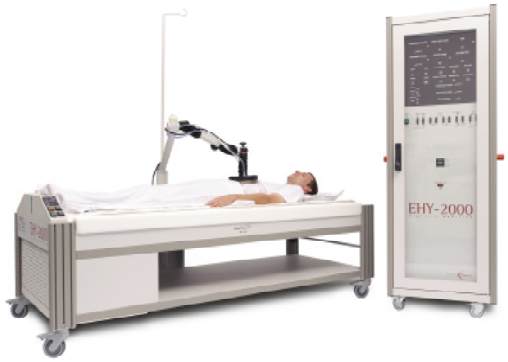
Regression May 2010

Oncothermia

Oncothermia is a loco-regional deep hyperthermia using the EHY-2000 device. It is a rapidly developing adjuvant treatment modality in cancer therapy.

Principles of oncothermia are direct continuation of the classical hyperthermia with addition of the modern technological and bioelectromedical knowledge. Its main goal: to maintain focused energy absorption in extracellular fluid in the malignant lesion and selectively destroy the cellular membrane of tumor cells. One of the realization of oncothermia principle is the device EHY2000. It uses the impedance selection to focus the absorber energy, and with the modulated electric field partly activates membrane connected pathways of apoptosis as well as partly babblings and destroys the membrane of malignant cells.[3].

The effect of oncothermia is synergistic with irradiation and several chemotherapeutic agents. There is some evidence that it may facilitate immun-defence mechanisms, alleviate pain and ameliorate way of feeling.



Conclusion

The expected 5 year survival-rate of advanced NSCLC is around 2%. This relatively small efficacy of the present oncotherapies explains the intensive search for new , new therapeutic modalities.

In the present time platinum-based doublet and concomittantly administered bevacizumab can ensure the longest overall survival.

In this case oncothermia did not compromise the efficacy of bevacizumab and its co-administration was safe, having no extra side effects by its complementary application.

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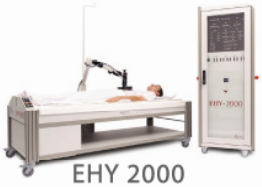
P-09 – Mr. Balazs Acs, et al - Development and Designing in Oncotherm Group

Development and Designing in Oncotherm Group

Mr. Balázs Ács | Production Manager, Oncotherm Ltd.

The current design and devices:



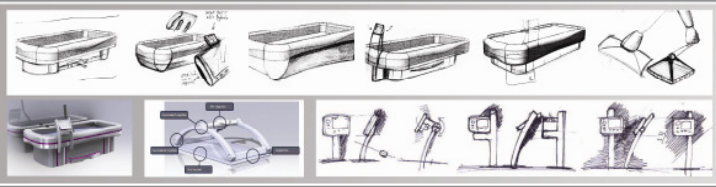
EHY 2000

EHY 2010

EHY 3010

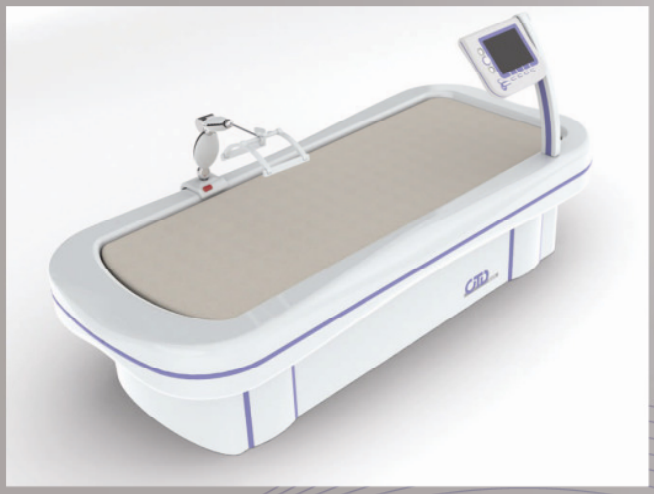
Birth of a new design:

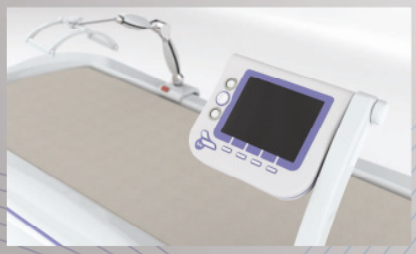
What happens when we start a plan?
First of all we talk about what the goal is: a new design, a redesign, a correction on the basis of customer suggestion, etc.
When we make a new design, we start with some drafts:



Next generation in Oncotherm:

The next generation Oncotherm product is coming in the end of 2011.





Future plans:

For more: www.oncotherm.com

P-11 – Dr. Henning Saupe, et al - Effect of rouleaux formation of erythrocytes in blood of patients treated by oncothermia

Oncothermia effect on rouleaux-aggregation of erythrocytes

Henning Saupe (1), Christian Buttner (1) & Gabor Andocs (2)

(1) Arkadia Klinik, Kassel, Germany

(2) Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene Budapest, Hungary

Objective

Observation and explanation of rouleaux phenomenon induce permanent debate started from its discovery. The aggregation of erythrocytes is a prominent feature in humans and other species "athletic" species [1]. In vitro studies have shown that aggregation of blood increases as shear rate decreases. Aggregation also depends on hematocrit and the concentration of macromolecules in the plasma or suspending medium [2], and in the presence of high molecular weight polymers, such as plasma proteins or dextrans, aggregate to form rouleaux and rouleaux networks [3]. However, the circumstances in which aggregation occurs is not well understood. Correlations of aggregation parameters with C-reactive protein and fibrinogen was proven in unstable angina, acute myocardial infarction, and bacterial infection [4] as well.
Our aim in this paper is to describe the systemic observations of blood samples before and after oncothermia, trying to clarify the oncothermia effect on blood.

Method

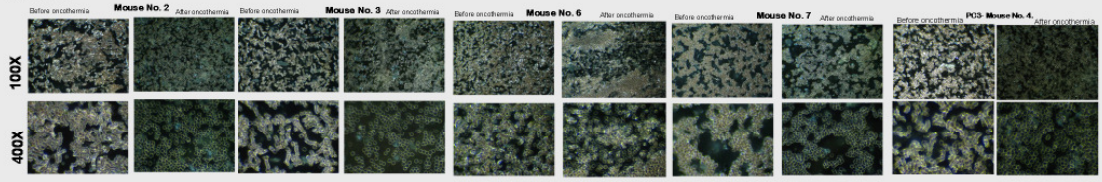
Blood samples of nude mice were studied before and after oncothermia treatment. The mice (Balb/C nu/nu) were xenografted by human HT-29 colorectal carcinoma cell-line in their both femoral regions symmetrically hetrotopic subcutaneous. The electrode was the most modern flexible arrangement, the applied power spectrum and the temperature plot are shown on the figures. The set of mice (ten animals) and the treatment device are shown for reference. Oncothermia treatment was done on mice for 30 minutes, single shoot reaching and keeping constantly 40 C in the tumor, while the other tumor (always the left one) was not treated, was studied as reference (modelling a not treated distant metastasis on the animal.)

Blood samples from voluntary humans also was collected. The human donors had suffered various malignant diseases. Blood samples of mice were carefully collected from tail's venue (venipuncture in tail vein) of mice under anaesthesia. The human samples were obtained from finger capillaries. Samples of venous blood from humans were collected also for comparison. The individual blood-collection was made immediately before and immediately after oncothermia treatment, as well as systemically performed in subsequent treatments in humans. Samples were promptly (freshly) measured by dark-field microscopy (slide-holder table was not heated). The pictures were archived by high resolution photo- or video-techniques.

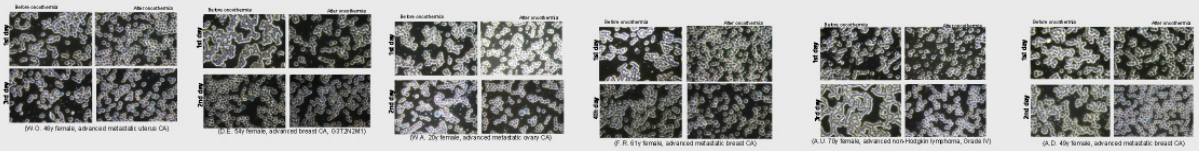
Results

Before the treatments the rouleaux formation of blood samples characteristically was observed in majority of the human individuals and 40% of the investigated animals. In all the cases, when the rouleaux formation was shown, oncothermia treatment has changed the roulleaux groupping, and the samples were mostly free of erythrocyte aggregates. These phenomena were independent of the treatment localization and also from the venous or arterial origin of the blood sample, and were observed both in humans and mice.

Mice



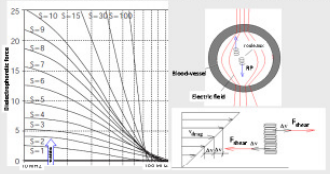
Humans

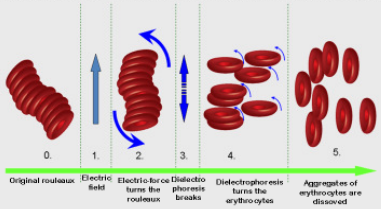


Discussion

The distortion of the erythrocyte aggregates could be well discussed by the action of the **dielectrophoretic forces.** The rouleaux are dielectric particles in aqueous electrolyte. The inhomogeneous field polarizes it together with its host matrix – the electrolyte. The polarization creates different charges in the ends of the rouleaux-chain, as well as in the electrolyte (Fig..). The movement of the RP depends on the charge values in its ends and in the host electrolyte.

Rules –
Dielectrophoretic force has some specialties in 13.56 MHz region [8]
1.maximal polarization exists in the axis of the rouleaux,
2.the dielectrophoretic force grows with the length of rouleaux,
3.the rouleaux fixes its direction from low filed-strength to high one,
4.the maximal polarizing direction in short rouleaux is radial.





The effect of oncothermia based on the rules above. The long rouleaux directs itself to the field-direction (rule 1.), and move from the cork-flow to the shear flow region (rule 3.). This tendency is gained by the length of rouleaux (rule 2.). In the region of shear-flow (Newton's flow) the middle of the rouleaux move with speed v_{drag}. Consequently its ends have opposite drag-forces and on this way the shear destroys the long rouleaux, (see Fig. . The satisfactorily small parts of the destroyed rouleaux turn perpendicular with their axis to the outside filed, so they have no further distortions (rule 4.).

Conclusion

In blood specimens where the rouleaux formation of the erythrocytes were observed, oncothermia dissolved the aggregates. Measurement of the oncothermia effect on rouleaux phenomena could lead us a simple control of the treatment efficacy, but our present data are not eligible for definite conclusions.

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P-12 – Dr. Oliver Szasz, et al - Effects far from equilibrium in electromagnetic heating of tissues

Effects far from equilibrium in electromagnetic heating of tissues

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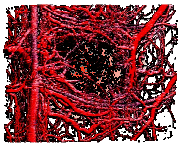
Objective

One of the very first treatment "technologies" for oncology is the regional heating of the tissues and body-parts, (hyperthermia, HT). This long history was not enough to be accepted as conventional treatment, facing mostly skeptic opinions among the oncology experts. The main reason is its controversial results and poor control, the missing of appropriate selective, controllable safe deep heat-delivery. Constrained balance of physiological feedback and the sophisticated transport network with very heterogenic tissue structures block applying the simple heating practices. This situation requests definite bioengineering tasks as well as new paradigm for the medical applications. The modern heating technologies based on electromagnetic interactions made a huge step ahead in this complex field, but not enough yet to solve some crucial problems in deep heating [1]. The commonly applied microwave and high radio-frequency (RF) radiation is challenged by the magnetic and capacitive heating techniques, applied lower frequencies. oncothermia method (OTM), heats by the dielectric loss in the various body electrolytes and makes possible to select between the tissues and concentrate on the malignant cells. Due to the constrained RF-current conduction of oncothermia, the complex impedance determines the actual flow-direction of the current. This could distinguish by the microscopic heterogeneity in the treated tissue [2]. The main problem is the temperature, which would like to equalized by time in the heated area, and steadily heats up the full environment in wider and wider range, supplying the tumor for growth. We need energy-input which can be focused and has no physiologic control. This is which oncothermia had introduced.

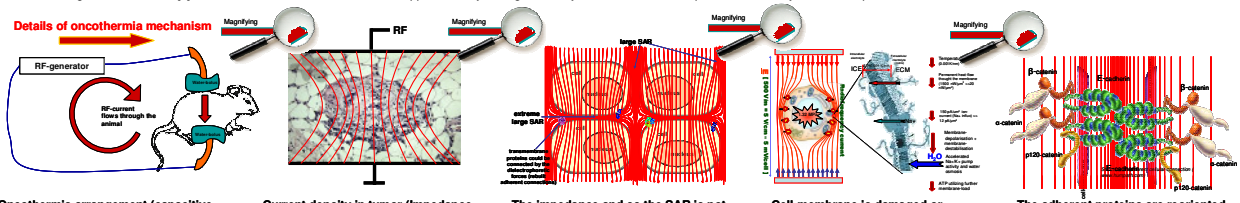
Oncothermia solves the problem: selectively forces various pathways of apoptosis by electric field



By time the temperature equalizes in the area, the heat is conducted away

Method

The relatively low frequency RF-current dominantly flows in the extracellular electrolyte. The energy absorption creates a temperature gradient through the cellular membrane, which drives non-equilibrium processes by constrained heat-flow through the membrane, [3]. The ion- and mass-flows could be well approached by Onsager's theory in the frame of non-equilibrium thermodynamic description.



Oncothermia arrangement (capacitive coupling) [oncothermia]
Tumorous experimental animal is a part of the electric circuit, well controlled, unharmed, anesthetized.

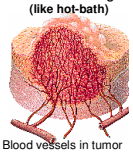
Current density in tumor (Impedance selection)
Low impedance of tumor focuses the RF-current and its energy in the highly proliferating volumes

The impedance and so the SAR is not homogeneous
The extracellular electrolyte has lower impedance and higher current density, more absorption

Cell-membrane is damaged or modified to more permeable
The temperature gradient is a driving force of non-equilibrium effects (Onsager's cross-flows)

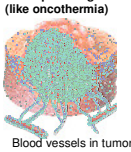
The adherent proteins are reoriented and connected
The adherent connections and many "social" pathways are reconstructed for function

Surface heating (like hot-bath)



Blood vessels in tumor are the heat sources

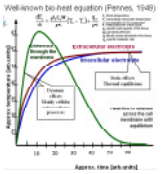
Deep heating (like oncothermia)

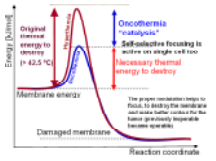


Blood vessels in tumor are the heat sinks (!)

The actual realization of oncothermia is capacitive coupled heating, using the constrained conduction of 13.56 MHz RF [5], amplitude modulated by time-fractal pattern [6], which is not limited by the thermal-energy [7].

In vitro and *in vivo* experiments were accomplished on identical 42 °C reference temperature by conventional hyperthermia and oncothermia methods, respectively. The experimental systems are *in vitro* cell-lines (HT29, B16, HepG2, A431) and their *in vivo* xenografts in nude mice. The changes of the adherent connections the cell membrane-associated effects (activation of the apoptotic signal transduction pathways, heat shock protein mediated stress-responses) were studied *in vitro*, while the cell-destruction mechanisms were investigated *in vivo*.





Results

Synthesis of HSP-s additional extracellular and membrane HSP70 appears through the more permeable membrane
$T_o + \Delta T$, $\Delta T \approx 0{,}01$ °C/10 nm ≈ 10^6 °C/m, Temperature-gradient driven processes
Thermo-electrical current ≈ 150 [pA/μm²] (Na^+ influx), normal ≈ 12 [pA/μm²] Na^+ efflux}, drastically decreases the membrane potential, destabilizes the membrane
Thermo-mechanical pressure ≈ 1320 kPa, (electro-osmotic effect, rigid tumorcell membrane), water-pressure
Heat flow ≈ 1.5 [pW/μm²] (at 1 [K/s]), (metabolic heat-flow ≈ 0.002 [pW/ μ m²], destroys the ordered membrane
Rectifying effect leads a positive feedback to gain the temperature and the pressure in the membrane.
Specific absorption rate of water is high in the membrane (Beta dispersion, ~10 MHz).
Membrane associated apoptotic pathways are activated (E-cadherin, beta-catenin, p53 expression)

Oncothermia paradigm avoids from high temperature, because:
- Temperature heats up the vicinity of the tumor, it can not kept locally focused
- Temperature increases the danger of burn of healthy parts in depth (mistocusing, conduction, etc.)
- Temperature request the increase of the safety-cooling on the skin
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely
- Temperature increases the blood-flow in the region, in consequence increases the dissemination
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemopenetration into the tumor (vasocontraction or blood-vessel blockage in the tumor)
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo-reaction rates (vasodilatation in the healthy tissues)
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient

In oncothermia the temperature is not a correct dose control, because:
- Moderate temperature avoids the natural contra-regulation effects
- Temperature does not exceed the systemic physiological limit (42 oC)
- Tumor selection is solved by non-temperature dependent way (electric concept)
- Focus is to be fixed to the tumor, moves together with the natural body movements (impedance control)
- Selection is solved on cellular level suppress the dissemination of the malignant cells
- Cellular connections (adherent connections, gap-junctions) of malignant cells are reestablished to avoid the further dissemination
- Cellular communications (social signal) is reestablished to promote the natural (programmed) cell death for malignant cells
- Possibility of the cellular molecular exchange (gap junctions) is reestablished to promote the normal function of the cells.
- The "master switch" (p53 gene) is activated promoting the natural way of various cell killing pathways
- Cell-membrane permeability is increased to express the HSP on the outer membrane signalizing the cell malignancy for the systemic immune actions.
- Cell-membrane is excited to ignite various communication pathways in the cells.
- Electric field blocks the positive feedback loop of tumor-supporting injury currents

Oncothermia avoids the static approach
Measurement of intensive thermodynamical parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra-regulatory effects. (This concept however, became the main request of the classical hyperthermia approach in its guidelines.)
The forced equilibrium increases the heat-flow to the blood-stream, which is an effective cooling media trying to block the static concept.
The heat-flow to blood supports the positive feedback loop of the basic-acidic electrolyte balance, and promotes the intensive growth of the tumor by addressed oxygen delivery.
Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead its elimination. (These processes like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc.)
Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy.)

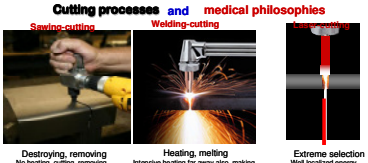
Oncothermia works with entirely dynamic (natural) processes
Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, does not constrain it for false defense.
Control of oncothermia is natural, always fitted to the actual conditions (changes of the electrolytes determines its actions).
No considerable heat-flow to the blood-stream by oncothermia, no gain of the positive feedback of electrolyte balancing-loop
Thermal gradients make dynamism in a very local area of the cll-membrane of malignant cells. The applied selection focuses on this thermal non-equilibrium.
The relatively slow "step-up" heating keeps the non-equilibrium stable for long time for action
The slow heating up does not create considerable physiological contra-actions,
The slow heating makes the healthy tissue adapted to the growing temperature
The slow temperature change does not generate high stress and following sterss reactions
The applied electric field makes at least three time more effective cell killing than the temperature does.
The applied fractal modulation makes possible selecting and supporting the natural processes to activate the natural healing mechanisms and reestablish the healthy "social signal' between the isolated cells, promoting the anti-malignancy collectivity
Complete relaxation could be supported by relaxing music, video or sound effects during the treatment

Oncothermia is f personalized
Oncothermia is mainly regulated by the patient's tolerance
Oncothermia control based on thermal sensing of the patients, for safety and for efficacy reasons. Safety is avoid burning the tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient natural defending/protective system.
Oncothermia uses natural processes to cure, understanding and using these needs thinking doctors and their understandings
Oncothermia acts of natural physiology regulation, which needs understanding of the processes
Oncothermia needs permanent dynamic approach, follow-up well what is happening during the treatment.
Step-up heating is the basic treatment approach, which requests permanent care on the process
The effect of the activated natural processes are not acting immediately. To have a control treatment-by treatment is essential.
The patient's well being during and after the treatment is necessary side of the well conducted protocol
Complete relaxation could be supported by relaxing music, video or sound effects during the treatment

Conclusion

The non-equilibrium thermodynamics makes OTM feasible to go over the difficulties of the problem of the selective deep-heating. With this new paradigm OTM could be a candidate in the branch of modern therapies in medical practice. OTM could be applied in various biomedical fields where the selection and the drug-targeting as well as the personalized treatment are important requests.

Cutting processes and medical philosophies



Destroying, removing
No heating, cutting, removing by mechanical work
Philosophy of Surgery
Removal, wound
Optical orientation

Heating, melting
Intensive heating far away also, making deformation and reallysing in the material
Philosophy of Hyperthermia
Burn-out, necrosis
Thermal orientation

Extreme selection
Well localized energy consumption, very precise
Philosophy of Oncothermia
Activation of apoptosis
Modulated electric field

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Evaluation of single-arm studies of oncothermia

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Objective

Oncothermia survival studies are problematic due to the missing control arm. This is a problem is general, when the treatment targets advanced, mostly refractory, relapsed malignancies in high treatment lines, when the only way is the sequential treatment. Usually the care in high line treatment (or in terminal phase) has very limited evidence based possibilities, its medical decision-making processes are usually well tailored to the individual patients [18], [19]. In these cases evidences have to be shown when randomized controlled trials are not possible, [20]. The sequential trial [1], [2], [3], is well known, and applied frequently in the case of small trials [4]. The sequential trial (like the oncothermia) is applied for the same patient in sequences, In this approach the development of the patient is measured and documented. Our objective to show how the evaluation of the single-arm study could be realistic enough to be evidence based.

Method

The basic of the idea of the data-separation is the appropriate parameterization of the non-parametric Kaplan-Meier survival pattern by poly-Weibull fit. However we have some qualitative assumptions:

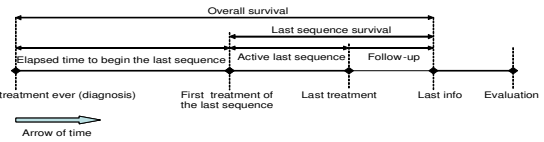
- Patient starts the new sequence when the previous had not (or had not satisfactory) result.
- The new sequence gives positive addition (no worsening of the patient's stage due to the applied therapy in the actual sequence).
- The new sequence does not block the possibility of subsequent sequences, the patients will not be excluded from the possible other therapies by the actual one.
- The effect of the new sequence affects the survival curve, so the studied Kaplan-Meier plot includes the information.
- The sequence is medically controlled at least on the same way, as were done in pervious therapies. No uncontrolled "side therapies" are in use.

Studying the median of a survival curve alone disregards the real success measurable at the end of the study. Correcting this "mistake" the average (mean) of the distribution is considered.
The mean is more affected by the "tail" of the distribution, so it gives more accurate idea on the cure-rate. The median is more responsible for the information how quick the loss of the patients, while the mean has more part on the information how long the effect of the high-success patients. Both are important for characterization, the time-scale and the shape of the distribution are independent parameters. The distribution curve must be characterized at least by two parameters. These two parameters are the mean and the median, supposing to characterize the non-parametric distribution, and so in fact this is a hidden parameterization of the Kaplan-Meier plot. Best mining of the data would be when the non-parametric Kaplan-Meier survival plot could be parameterized. Description of survival curves by parametric distribution function was a long time effort, could be approached by fitting the parametric Weibull (Avrami) curves [21], [22], [23], [24], [25], on the actual probability function. The universal applicability of the Avrami function was recognizes much earlier, [26], [27], [28].
Using the Weibull distribution function to approach the survival curve parametrically is theoretically and practically established for clinical applications, [25]. Fitting the measured Kaplan-Meier survival curve (*KM(t)*) by a function *S(t)* composed by two Weibull functions (with parameters denoted by superscripts *(R)* and *(NR)*), describing the responders and non-responders by a composite ratio *C*, respectively. Application the parametric Weibull distribution function approaching the survival curve for clinical applications is established theoretically and practically, [5], [6], [7], [8]. It is used for a long time for survival description in gerontology [9], [10] and in oncology [11] as well.

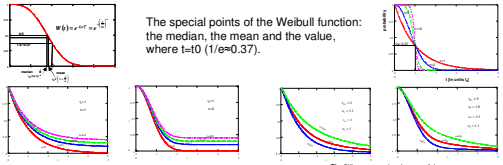
$$KM(t) \approx S(t) = (1-C)e^{-\left(\frac{t}{t_0^{(R)}}\right)^{n^{(R)}}} + Ce^{-\left(\frac{t}{t_0^{(NR)}}\right)^{n^{(NR)}}}$$

Sequenced trial is well known, and applied frequently in the case of small trials [29].
However we have some qualitative assumptions:

1. Patient starts the new sequence when the previous had not (or had not satisfactory) result, This condition is generally valid, no reason start new therapy when it works satisfactory. (In some cases due to psychology or other factors anyway could be abandoned a successful therapy, but we assume it is less than 5% of all the treatments.)
2. The effect of the new sequence affects the survival curve, so the studied Kaplan-Meier plot includes the information. (Example: when the effect is improving the quality of life but does not affect the survival, the sequence cannot be studied by survival curves.)
3. The sequence is medically controlled at least on the same way, as were done in pervious therapies. No uncontrolled "side therapies" are in use.



The time-sequences of oncothermia studies. The time between the first ever treatment and the first oncothermia is complex, having numerous pre-treatments. It is regarded here as one step



The special points of the Weibull function: the median, the mean and the value, where t=t0 (1/e≈0.37).

The Weibull function when a definite ratio of the patients is cured

The fitting curves at various c-values

By these assumptions we study a split of the original cohort distribution splitting it to two groups: responding and non-responding patients. The Weibull approach [15] is divided it into two different distributions [16], [17], composed linearly, one whom the treatment had no or minor influence and one where the treatment was effective. The weighted addition of the curves reconstructs the original. The "inclusion criteria" for the patients to oncothermia treatment is when the "gold standards" are not eligible. These criteria could be checked by study the elapsed time to the first oncothermia from the first diagnosis. The time from the first diagnosis to the first oncothermia has to be a cohort (when the inclusion of the patients to oncothermia had identical criteria) consequently it has to be characterized by single-Weibull parametric formulation.
The process is performed at oncothermia survival first (five parameters is considered to the best fit: the two Weibull curves t_0 and n for each, and their composite ratio C, (ratio of the non-responders) which fixes the patients by their numbers into two groups, (equation 45.). The residual will be automatically obtained from this fit, which is nothing else only the value of the survival-fit at the maximal survival time [$S^{(OT)}(t_{max})$].

The same composite ratio is applied for overall survival also:

$$S^{(OT)}(t) = (1-C)\exp\left[-\left(\frac{t}{t_0^{(R)}}\right)^{n^{(R)}}\right] + C\exp\left[-\left(\frac{t}{t_0^{(NR)}}\right)^{n^{(NR)}}\right] \qquad S^{(EL)}(t) = (1-C)\exp\left[-\left(\frac{t}{t_0^{(R)}}\right)^{n^{(R)}}\right] + C\exp\left[-\left(\frac{t}{t_0^{(curc)}}\right)^{n^{(curc)}}\right]$$

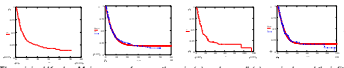
Results

The evaluation of the Kaplan-Meier plot by parametric distribution works well in the practice. Patients responding to the treatment are well distinguishable from the responders, and on this basic the overall survival benefit can be evaluated. The significance level depends on the number of patients, but over 25 patients it usually fits better than 95% confidence. We evaluated numerous single-arm clinical trials, showing the efficacy of the study. The evaluation was well correlated with the independently measured other parameters as well as the criteria of start of oncothermia also shows stable reference distribution.

$$S^{(start)}(t) = (1-C^{(start)})\exp\left[-\left(\frac{t}{t_0^{(R)}}\right)^{n^{(R)}}\right] + C^{(start)}\exp\left[-\left(\frac{t}{t_0^{(NR)}}\right)^{n^{(NR)}}\right]$$

Further control could be given by study the historical control of the pancreas treatment from the same investigator (n=34), who did the oncothermia treatments. The Weibull decomposition fit produces statistically identical curves, no possibility to detect any significant differences in decomposition, it is a cohort. Comparison of the non-responders in overall survival and the control group shows remarkable correspondence this supports again the validity of the decomposition.

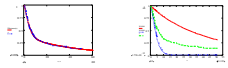
Let us study an actual example of the pancreas trial (n=99), [12].



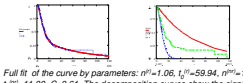
$$W^{(curc)}(t) = c + (1-c)e^{-\left(\frac{t}{t_0^{(curc)}}\right)^{n^{(curc)}}}$$

The original Kaplan-Meier curves for oncothermia (a) and overall (c) survivals and their fits. The parameters are n=1.14, t_0=6.34, c=0.18 and n=1.38, t_0=13.74, c=0.17 for oncothermia and overall survivals, respectively

Better fits could be achieved by parametric decomposition of the survivals. The decomposition significantly divides the cohort of advanced, inoperable pancreas cancer patients on two subgroups (responders and non-responders) in oncothermia survival.. Keeping the *C* composite parameter, the fit and decomposition of the overall survival is available.

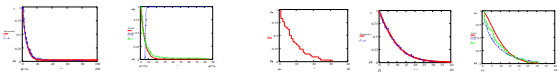


Full fit (a) of the curve by parameters by (45): $n^{(r)}$=0.95, $t_0^{(r)}$=43.13, $n^{(nr)}$=1.34, $t_0^{(nr)}$=4.75, C=0.61. The decomposition curves show the significant difference of responders (39%) and non-responders (61%)



Full fit of the curve by parameters: $n^{(r)}$=1.06, $t_0^{(r)}$=59.94, $n^{(nr)}$=1.67, $t_0^{(nr)}$=11.00, C=0.61. The decomposition curves show the significant difference of responders (39%) and non-responders (61%) [Applied the same ratio as in oncothermia survival]

The "inclusion criteria" for the patients to oncothermia treatment is when the "gold standards" are not eligible. These criteria could be checked by study the elapsed time to the first oncothermia from the first diagnosis. The time from the first diagnosis to the first oncothermia has to be a cohort (when the inclusion of the patients to oncothermia had identical criteria) consequently it has to be characterized by Weibull parametric formulation, where the two distributions are close, or $C^{(start)}$ is small. Indeed, fit and decompose) the curve of elapsed time from the first diagnosis to the start of oncothermia, the definite dominance of one single curve. This shows our "inclusion criteria" is really valid cohort-forming condition.

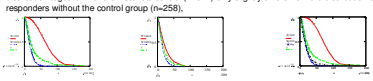


Full fit of the curve by parameters: $n^{(r)}$=1.17, $t_0^{(r)}$=5.51, $n^{(nr)}$= -14.02, $t_0^{(nr)}$= 6.00, C=-0.021. The decomposition curves show the absolute dominance of a single Weibull distribution, (its modification is 2.1%.)

The Kaplan Meier survival curve of the historical control and its fit by two Weibull functions. Parameters: $n^{(r)}$=1.47, $t_0^{(r)}$=10.76, $n^{(nr)}$= 0.83, $t_0^{(nr)}$= 7.19, C=0.50. The decomposition curves are statistically identical

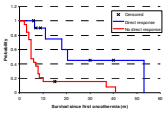
Comparison with the historical control

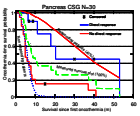
The same could be observed in other study (non-small-cell-lung-cancer [NSCLC]) [13], where the distribution together with the historical control (n=311) only slightly differs from the distribution of non-responders without the control group (n=258).



The Kaplan-Meier plot of single arm study (n=258) of non-cell-lung cancer and its decomposition, (C=0.79.4,) and decomposition of the historical control (n=53), from the same investigator (C=0.55,) and their comparison

Other prospective study [14],had measured the local clinical response and the survival time in the same trial. The direct response (CR+PR) shows good, significant correspondence with the parametric separation.
Significant correspondence of the measured and calculated separation of the patient's survivals by their local response.





Conclusion

Parametric evaluation of Kaplan-Meier non-parametric distribution works well for single arm studies. The single parameter reference of the Kaplan-Meier (median survival) is unsatisfactory; the two parametric Weibull distributions describe the situation much more exactly.

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EWHA WOMANS UNIVERSITY

HISTORY OF HYPERTHERMIA AND ELECTRO-TREATMENTS

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Department of Gynecology, Ewha Women's University, Mok-Dong Hospital, Seoul, Korea
St.Istvan University, Department of Biotechnics, Budapest, Hungary

Objective

Our objective to show the long historic development of the hiperthermia and the electromagnetic therapies directly to the present: to the oncothermia.

Ancient approach of heat-therapy

Hyperthermia is ancient treatment. Started with the early ancient cultures The beginning had sacral & cultural rules, centering on the Sun ((like God)in Egyptian philosophy).

Fire (like the highest value of substances in Greek Philosophy).

Start of MEDICINE - Hippocrates (BC 460 – BC 370)


First mentioning of hyperthermia (Edwin Smith Surgical *Papyrus*)


The oldest medical Handbook: Tablet with pharmaceutical description from Nippur Late 3rd millennium BC.


Beliefs on GOD SUN



Greeks philosophy – the FIRE

Those who cannot be cured by medicines, can be cured by surgery. Those who cannot be cured by surgery can be cured by fire(hyperthermia). Those who cannot be cured by hyperthermia, they are indeed incurable.

Heat was applied to locally affected parts of the body and to its entirety by means of hot water, steam, sand, and mud baths. Natural hot air caverns connected with volcanic sources were utilized. BC 5 C, Egyptian priest/physician Imhotep infected tumors before surgically removing them.

Ancient fever therapies

Later, Hippocrates had ideas as to the significance of fever, and modern concepts as to its possibilities. "Give me the power to produce *fever*, and I will cure all disease," (BC 460-BC 370, Hippocrates)

"If indeed any were so good a physician as to be able to produce *fever*, it would not be necessary to look for any other remedy in sickness." – (A.D.450, Rufus of Ephesus)

"Heat acts well in eye diseases which are without pain and lachrymation. It is good for all sorts of ulcers but principally those due to cold." The techniques of heat application included wet fomentations, dry packs, steam baths, hot air baths, and sun bathe.- (BC 42 – AD 37, Aurelius Cornelius Celsus)

Middle ages

Arabian medicine
- Feet, and neck tumors, such as burning or boiling water
- Ablation technique is used burn out the tumor

European medical development
17-19 Century, advances in medical research and technology in a philosophical debate as a progressive step in scientific approaches

An engraving by Jacques Lainet (Paris, 1659) - the combination of mercury and heat for the treatment of syphilis.

In Japan, thermal springs were used for the treatment of all forms of syphilis, arthritis, rheumatism, acute genitourinary infections, and respiratory, digestive, nervous and ocular diseases.

1595, **Galileo Galilei** thermometer is invented. It is applied for enabling scientific instruments for heat

1611, **Sanctorius** , thermometer is applied first ever for clinical use

Herman Boerhaave (1668-1738) is the founder of electric medicine having an interest in the physiology reaction of heat and temperature. Animal experiments: to investigate the impact on the animals oven heated up to 73 ° C.: Dogs and cats died within 28 minutes, Sparrow in 7 minutes.

"I would be the greatest physician if I could *produce* intermittent fever as easily as *suppress* it."

Sir Clifford Allbutt (1868) introduced the clinical mercury thermometer

William Cullen of Edinburgh (1710 – 1790) "An elevated temperature of the body was a paralytic symptom due to depression of a natural influence on heat production."

Modern history

Fever Clear and scientific concepts of beneficial metabolic activity and nutrition of human genders, and to understand the connected neurophysiology. These investigations gave some innovative medical discovery which were initiated by the actual conditions bacteriologist use the fever to heal the disease, while clinicians should fight against it due to the inflammatory response (to the destruction of foreign agents), they must lower the body temperature avoid the damages (mainly brain). Physiologist Johann von Muller, surgeon Billroth, and the pathologist Virchow were pionering fever is an increase of *oxidative processes* due to stimulation of the central and peripheral nervous system

1866, W. Busch (Germany) Patients with soft tissue sarcoma in the neck alone decreased after suffering a high fever. Similar experiences have been reported from United States and Europe use fever like hyperthermia in practice

1935, Warren: introduced physical hyperthermia in cancer treatment. 32 patients with hopeless cancer was successfully treated using diathermy or radiant energy reaching the rectal temperature 41 ° C. The cure rate was very high, and who was not cured the survival time seemed to be elongated by 1-6 months. Nikola Tesla, von Zeynek, Nagelschmidt and others were investigated the "diathermy" trying to increase the thermopenetration and concentrate the heat in the depth of the body.

William Coley, (1862–1936) 1893 mixture of killed bacterial infusions (*Coley's Toxins*) The toxins induce fever reaction, and this heat treatment stimulates the immune system to attack and kill the cancer-cells. it was applied for soft tissue sarcomas, lymphomas, osteosarcomas, Ewing's sarcomas, and malignant melanomas, cervical, ovarian, testicular, renal, breast, and colorectal carcinomas

Julius Wagner-Jauregg (1857-1949) 1917 It is found that the malaria vaccination is effective for the treatment of paralytic dementia. He had a Nobel Prize in 1927 as a founder of heat therapy

Heat-therapies today

Modern electro-heating devices, continuing the ancient idea: heating and control the temperature

BSD-Medical | Thermotron | Brucker | Alba

The classical paradigm has classical controversies: the temperature control and action makes difficulties. A new paradigm is necessary. This was the synergy with electrotherapies.

Development of electro-therapy

1891 d'Arsonval high frequency current flowing in the human body becomes the prototype of provide electrothermal treatment

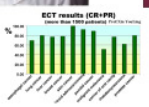
Started a new era of electro-medicine all over the world

Guillemot WH: Electricity in Medicine (Robman Ltd. London, New York, 1906)

High popularity expected "final solution" for diseases.

Electrotherapy in combination with immunotherapies was pioneered by **Dr. Rudolf Pekar**, developing how the body could defend and fight against cancer.

Björn E. W. Nordenström Biologically Closed Electric CircuitsClinical, Experimental and Theoretical Evidence for an Additional Circulatory System. New ideas on the bioelectric interactions


ECT results (CR+PR)

Dr. Xin Yu-Ling, Head of Thoracic Surgery at Friendship Hospital in Beijing, China (first two photos) and his staff have administered many ECHT treatments. The Cancer Center of P.L.A., Nanjing Ba-Yi Hospital, Nanjing, China (third and fourth photos) also treats cancer patients using ECHT.

Oncothermia - synergy of heat and electro therapies

First steps (1988-1990) ECT systems, working on galvano effect, modified Nordenstrom's idea. The modification is the integration of the time-fractal fluctuations (fractal physiology approach)

Basic synergy steps (1990-1993) EHY systems, uniting the locoregional hyperthermia with the ECT therapeutic modality.

Extreme approach (whole body hyperthermia) (moderate and extreme infrared heating including the fractal modulation on 960 nm radiation.

Intraluminar applications (PCT systems) Applied mainly for prostate treatment, including also the first application for benign tumors by oncothermia

The modern oncothermia working in wide range of applications. It could be applied in cases when other therapies fail.

The renewed intraluminar system

The research unit

The booster continues the traditions

Conclusion

The ancient approach is vivid. Its unification with the updated modern scientific and technical achievements it is on the way to became the standard therapy, the fourth "column" of the oncotherapies.

History of oncothermia and their devices

Ms. Constanze Feisskohl[1], Ms. Janina Leckler[1], Mr. Balazs Acs[2], Dr. Oliver Szasz[1,2]
(1) Oncotherm GmbH, Troisdorf, Germany
(2) Oncotherm Kft. Paty, Hungary

Objective

Oncothermia concept was found when the company was established, however the way of realization is a long process, having various steps forward and sometimes dead-ends. Our objective to show the history of oncothermia through its devices, giving a picture how stable development was achieved by the years, and conclude with a lesson how to go further.

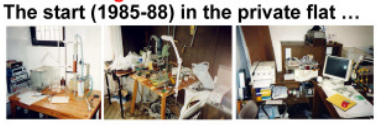
Description

The university spin-off in 1988 was based on a biophysical idea. The medical value was added with the first device in use. This was the "Ducat" device, (started to work in 1989 at Clinic St. Georg, in Bad Aibling, Germany). This was a galvano-device, which was on exhibit in the first Congress of ECT knowledge in Beijing, China in 1991. The next step was a non-invasive device the very first EHY (1992) and parallel was further developed the galvano technique. (ECT) which reached the German GS approval in 1994. The first EHY2000 was produced in 1994 and reached the CE sign (first ever in the category of hyperthermic oncology according to European medical device Directive) from TUV Munich, Germany in 1998. In the meantime the first intraluminar device (PCT) was developed on the same theoretical basis like the previous devices, and was in clinical probe in 1995, and the first whole body hyperthermia (WBH) was also parallel developed and tried in 1997. (its moderate version (MSH) was launched in 1999.) In 2001 a venture capital was invested to the company, and Oncotherm GmbH was established in Troisdorf in 2002. The first device for this company was developed and launched in 2004 (EHY2000plus). The first multi-local device (EHY3000 series) was shown in 2008, and soon, less than a year later, the first very modern intraluminar devices (EHY1000 series) were placed on the market. Parallel with the oncological hyperthermia Oncotherm had developed very unique devices for special use. For a special request a device for asthma treatment (REY) was developed in 2000, and for laboratory use (in vivo and in vitro applications) a high preciosity device series (LabEHY series) was launched in 2006. This was extended with a special temperature measuring device (EHYTS). A non-treating (non-curative only complementary) small device was developed in 2009 (ChemoBooster), which is for boosting any chemotherapy efficacy. Our new field the andrology, and the first probe device had been appeared in 2010 (AndroTherm).

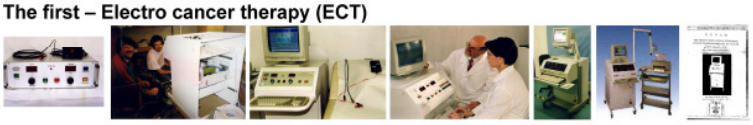
All the developments from the beginning had ideas of fractal physiology and such modulation!

Medical challenge: modulated electric field application

The start (1985-88) in the private flat …



The first – Electro cancer therapy (ECT)



Medical challenge: Non-invasive solution

The first – non-invasive solution – Electro-hyperthermia (EHY)

Technical challenge: The electrode optimizing (electrode construction is a key element of the proper treatment!)

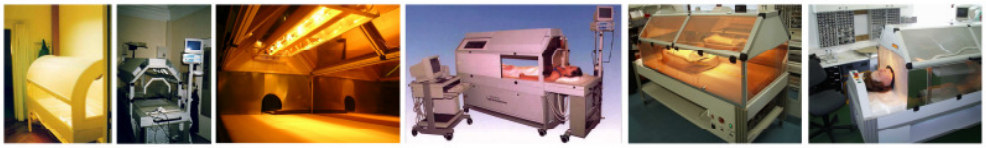
Technical challenge: The shielding & electromagnetic compatibility

Challenge with invasivity again – ICT

New medical challenge: distant metastases – whole body hyperthermia (WBH)

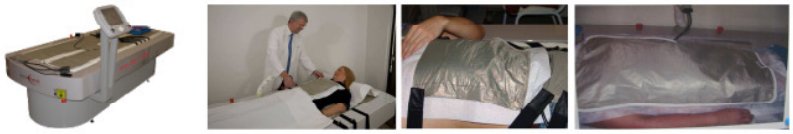
The extreme solution

The moderate (fever) solution (MSH)



Laboratory needs (LabEHY)

Revolutionary solution for distant metastases – multilocal treatment



New medical challenges:

Personalization of other therapies (Booster)

Andrology requests

Medical challenge for intraluminar application

Conclusion

Oncotherm company and its method is based on stable scientific, medical and technical knowledge with specially developed details for the actual tasks in every devices. Our long time expertise made possible developing a completely new technology and reaching the present status: **Oncothermia is maturated for acceptance!**

P-17 – Dr. Frank Breitkreutz – Hyperthermie – Was müssen Krankenkassen und Beihilfe zahlen?

Die Erstattung hyperthermischer Therapien durch die gesetzlichen Krankenversicherungen

Dr. Frank Breitkreutz[1]

[1] Rechtsanwälte Dr. Breitkreutz & Kollegen, Potsdamer Platz 11, 10785 Berlin, (www.dr-breitkreutz.de/hyperthermie)

Einleitung: Nach § 27 Abs. 1 SGB V haben gesetzlich Krankenversicherte einen Anspruch auf Krankenbehandlung, wenn diese notwendig ist, eine Krankheit zu heilen, ihre Verschlimmerung zu verhüten oder Krankheitsbeschwerden zu lindern. Dabei müssen die Qualität und die Wirksamkeit der Leistungen dem allgemein anerkannten Stand der medizinischen Erkenntnisse entsprechen und den medizinischen Fortschritt berücksichtigen (§ 2 Abs. 1 Satz 3 SGB V).

Neue Behandlungsmethoden dürfen in der vertragsärztlichen Versorgung ausschließlich dann zu Lasten der gesetzlichen Krankenkassen (GKV) erbracht werden, wenn der Gemeinsame Bundesausschuss (GBA) eine positive Empfehlung abgegeben hat, unter anderem zum therapeutischen Nutzen, der medizinischen Notwendigkeit und der Wirtschaftlichkeit (§ 135 Abs. 1 Satz 1 SGB V). Dieser Grundsatz darf allerdings nach einer grundlegenden Entscheidung des Bundesverfassungsgerichts dann nicht mehr gelten, wenn der Betroffene an einer lebensbedrohlichen Krankheit leidet, für die schulmedizinische Behandlungsmethoden nicht vorliegen und es ernsthafte Hinweise auf eine positive Beeinflussung des Krankheitsverlaufes durch eine „Außenseitermethode" gibt. In diesem Fall ist auch eine (noch) nicht positiv bewertete Behandlungsmethode zu Lasten der GKV zu erbringen.[1]

Rechtslage bei der Hyperthermie: In einer Stellungnahme aus dem Jahre 2005 äußerte der GBA, dass nach dem derzeitigen Erkenntnisstand - mangels ausreichend validierter Daten - die Einführung in die vertragsärztliche Versorgung (noch) nicht empfohlen werden könne.[2]

Da es insoweit an einer positiven GBA-Bewertung im Sinne von § 135 Abs. 1 Satz 1 SGB V fehlt, sind hyperthermische Therapien nach den o. g. Grundsätzen des BVerfG nur dann zu Lasten der GKV abrechenbar, wenn sie zur Therapie einer lebensbedrohlichen Erkankung vorgenommen werden, für die schulmedizinische Behandlungsmethoden nicht (mehr) zur Verfügung stehen und wenn es ernsthafte Hinweise auf eine positive Beeinflussung des individuellen Krankheitsverlaufes gibt.

Aktuelle Rechtsprechung: Die Rechtsfortbildung zur Leistungspflicht bei hyperthermischen Behandlungen befindet sich aktuell noch in einem sehr frühen Stadium. Seit der grundlegenden „Nikolaus"-Entscheidung des BVerfG im Jahre 2007 wurden lediglich 10 gerichtliche Entscheidungen publiziert, wobei sich stattgebende und ablehnende Entscheidungen in ungefähr gleicher Anzahl gegenüber stehen:

Erstattungspflicht angenommen:	Erstattungspflicht abgelehnt:
▸ Mamma-Ca., nach 2 Jahren Knochen- und Lebermetastasen; Hyperthermie unterstützend zur zytostatischen Therapie (SG Stuttgart 2010[3])	▸ Gutartige Prostatavergrößerung; Patient lehnte operative Entfernung ab, zog hyperthermische Behandlung vor **Ablehnungsgrund**: keine Lebensbedrohung (LSG Bayern 2009[6])
▸ (inoperables) Pankreas-Ca., Hyperthermie unterstützend zur zytostatischen Therapie (SG Münster 2010[4])	▸ Glioblastome multiforme; Teilresektion und 12 Monate Temozolomid; „stabiler" Tumorbefund **Ablehnungsgrund**: Standardtherapie verfügbar; fehlende Heilungsaussicht durch Hyperthermie (SG Würzburg 2010[7])
▸ Mamma-Ca., nach gravierenden Nebenwirkungen Chemotherapie komplett abgesetzt; nunmehr Kombination von Hyperthermie und dendritischen Zellen (SG Augsburg 2007[5])	▸ Ovarial-Ca., OP – Chemotherapie; nach 2 Jahren Metastasen in der Milz; Patientin lehnte weitere zytostatische Therapie ab und unterzog sich hyperthermischer Behandlung **Ablehnungsgrund**: Standardtherapie verfügbar (LSG Bayern 2008[8])

Schlussfolgerungen: Die GKV ist zur Kostenübernahme onkologischer Hyperthermie-Behandlungen verpflichtet, sofern im Einzelfall keine allgemein anerkannte Behandlungsmethode zur Verfügung steht und sofern mit einer spürbar positiven Einwirkung auf den Krankheitsverlauf gerechnet werden kann. Dies wird insbesondere dann der Fall sein, wenn das Malignom nach den schulmedizinischen Leitlinien nicht mehr kurativ therapiert werden kann und die einschlägige hyperthermische Studienlage einen signifikanten klinischen Effekt belegt.

Bibliographie:

(1) BVerfG vom 29. November 2007 (1 BvR 2296/07)
(2) Beschluss-begründung zur Änderung der Anlage III - Nicht anerkannte Untersuchungs- und Behandlungsmethoden" der HWI-Richtlinie vom 19. Januar 2005
(3) Sozialgericht Stuttgart vom 05. Februar 2010 (S 8 KR 7849/09)
(4) Sozialgericht Münster vom 26. August 2010 (S 11 KR 108/06)
(5) Sozialgericht Augsburg vom 27. Dezember 2007 (S 12 KR 413/07)
(6) Landessozialgericht Bayern vom 22. Oktober 2009 (L 1 KR 279/07)
(7) Sozialgericht Würzburg vom 29. Juni 2010 (S 6 KR 369/08)
(8) Landessozialgericht Bayern vom 12. Februar 2008 (L 5 KR 82/06)

P-18 – Ms. Anett Gallne-Valyi - Introduction of the international quality management system: OncoTherm Group

Introduction of the international quality management system: OncoTherm Group

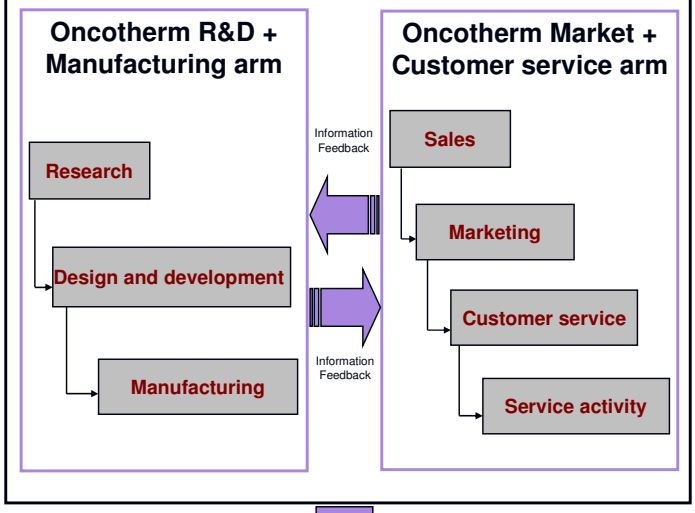
Anett Gállné-Vályi
Quality Manager of Oncotherm Group

OncoTherm Group

Common Quality Management System based on:

- **ISO 9001:2008** Quality Management System. Requirements
- **ISO 13485:2003/AC:2009** Medical Devices. Quality Management Systems. Requirements for regulatory purposes
- **93/45 EEC** Medical Device Directive (MDD)

Therefore we have a common quality system based on the concerning ISO standards and MDD, which provides that our processes are working in a well-controlled way and we advert all requirements/demands coming from our customers and from the national, international regulations.



Approval by TÜV Süd (Munich, Germany)

Oncotherm System (OS) =
Oncotherm Device (OD) + Oncotherm Method (OM)

„Product of Germany, Made in EU by German approval"

Conclusion:

The OncoTherm Group is a marketing method which is in synergy with the devices and jointly presented on the market as a system. There is a 21 years hard work, experience and knowledge behind the OncoTherm System which certifies that this system has stood the test of the time.

OncoTherm Group doesn't follow the practice of the large globalized European companies who are transferring the manufacturing outside Europe. We do everything in Europe and proud on that high level production culture which is represented by our 21 years old company.

Objectives of the presentation:

- Show the basis of the permanent improvement of the efficacy of oncothermia combined with high quality and complete safety for the users and patients.
- Keeping up the trust of our users and potential customers

Basic points:

- ✓ Oncotherm devices are prepared by team-working of highly qualified experts
- ✓ This unification of the German medical and constructive knowledge with the general European manufacturing culture based on the concerning requirements
- ✓ Oncotherm solves the globalization requests inside of the EU, strengthening its reputation and good-will
- ✓ Oncotherm established a perfect cooperation between the research, medical knowledge, marketing, manufacturing and services
- ✓ Oncotherm operates in the frame of strict common German quality management systems based on the below mentioned aspects:
  - Our devices are distributed for over fifteen countries worldwide, using the German medical knowledge and practical expertise.
  - Most medical feedbacks are coming from the smart German physicians from more than hundred oncothermia installations in the country. This is a good input for the research, design and development as well as an important help of the manufacturing and controlling channels.
  - Feedback from the service activity and the customer service is an integrative part of the company's progress. These pieces of information directly and permanently improve oncothermia method and its devices.
  - Oncotherm manufacturing facilities are organized reacting flexible and quickly on the market demands and challenges.
  - The oncothermia methods are in the focus of our marketing policy. The devices are serving this state-of-art methodology, giving effective weaponry in the hand of the medical staff for fighting in the war against cancer. This marketing strategy requests integrative and tight cooperation with research, design and development amalgamated by interdisciplinary approaches of modern technical and medical knowledge.

Oncothermia marketing and manufacturing arms are working like an integrative unit that makes us strong and effective on the market.

Our quality management systems are satisfying the highest European medical standards. The production process of the devices has ISO13485 medical standard and it is approved by **TÜV Süd Product Service GmbH (Munich, Germany),** who also certifies our products according to the European Medical Device Directive (medical CE-mark).

The business processes have also the highest standard (ISO9001) granted by the **TÜV Süd Management Service GmbH (Munich, Germany),** vouching for the standardized available processes to satisfy oncothermia users and potential customers.

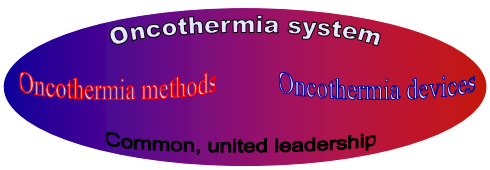
TÜV Süd as the largest Notified Body for medical devices in EU justifies the operation of our quality management systems and keeps it well-controlled to fulfill every necessary European requirements .

CE 0123

Integrity:

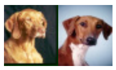
We don't sell only a device but an **OncoTherm System** which consists of **OncoTherm Device** and **OncoTherm Method**.

Full process is controlled by unified overall leadership and unified overall quality system!



P-22 – Dr. Lajos Balogh, et al - Oncological and non-oncological applications of electromagnetic hyperthermia (Oncothermia®) in the veterinary clinics – 2 years of experience

Oncological and non-oncological applications of electromagnetic hyperthermia (Oncothermia®) in the veterinary clinics – 2 years of experience.



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Introduction

Loco-regional hyperthermia in oncology has ambivalence discretion in the medical community. The extremely long history of the method as well as the supposed universal ability to complement all the existing traditional methods is not enough to prove its efficacy. The central point of the non univocal acceptance and the mixed feelings is the some-times unsuccessful selective heat-delivery into the deep-seated tumors. The selectivity could be enhanced by electric field. Theoretical considerations showed the problem of the temperature dose-concept, and it is shown, that the thermal energy does not limit the electromagnetic effects through the membranes. Advantageous thermal and induced non-thermal effects of electromagnetic hypertermia (EHT, Oncothermia®) in human medicine is in use for decades. Surprisingly there are much less references about the veterinary utilities.

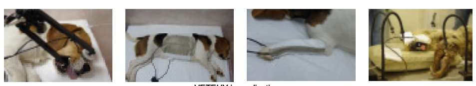
Our objective was to check the clinical utility of electromagnetic hypertermia as a single modality and in combinations in veterinary patients.

Materials and Methods

Dogs and cats affected by either primary or recurrent neoplasias referred to the National "F.J.C." Research Institute for Radiobiology and Radiohygiene (NRIRR) from April 2008 to June 2010, were included. Initial work-up consisted of a physical examination, hematology and serum biochemical profile. The diagnosis was confirmed, if not properly performed before referral, through a core biopsy or a cytological evaluation of the lesion and, if enlarged, of the regional lymph nodes. Eligibility criteria included the following: non-resectable, measurable tumors (measured by digital caliper, x-ray or ultrasonography, or scintigraphy, or CT, or PET/CT) and the surviving expectation of at least 1 month, no other antitumoral or corticosteroid or non-steroidal antiinflammatory treatments or surgery within 2 weeks of entry to trial, malignant primary tumor, with or without metastases to the regional lymph nodes, and without macroscopically evident (x-ray, or ultrasound, or scintigraphy, or CT or PET/CT) distant metastasis and/or other life-threatening metabolic diseases.

We applied EHT with capacitive coupled modulated 13.56 MHz radiofrequency method (oncothermia OT). OT was provided for different canine and feline oncological patients (altogether more than 64 cases) as a single treatment (6/64), and in a combination with fractionated Cobalt irradiation (51/64) or with medical treatments (7/64). Dog patients suffering in other chronic diseases (4 osteoarthroses, 2 heart insufficiencies, 2 epileptic, 2 non-healing skin abscesses) were also co-treated with local (or regional) OT so that the original, non-eligible medical treatments were not changed.

VETEHY



VETEHY in application

Results

Single OT in oncological diseases resulted significant tumor size decrease 2 out of 6 cases, 3 stable disease and 1 progression of disease. Cobalt irradiation followed by OT resulted 5/51 tumor-free status, 42/51 partial remissions, 3/51 stable disease, and progression of disese in 1 case. Chemotherapy boostered with OT resulted 2/7partial remission, 3/7 stable disease, and 2/7 progression of disese in late stage, metastatic cases. Side effects eg.: erythema (2 cases), necroses (2 cases) occurred at the learning phase of technique, later on we could prevent this side effects with the constant superficial and deep temperature control in or patients. OT proved to be useful in all the non-oncological diseases and no side effects, contraindications were remarked.

Summarized results of treatments

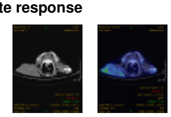
Treatment methods	Tumor-free status	Partial response	Stable disease	Progression of disease
Oncothermia alone	0 / 6	2 / 6	3 / 6	1 / 6
Oncothermia + Cobalt irradiation	5 / 51	42 / 51	3 / 51	1 / 51
Oncothermia + chemotherapy	0 / 7	2 / 7	3 / 7	2 / 7

•In other non-oncological chronic diseases (4 osteoarthroses, 2 heart insufficiencies, 2 epileptic, 2 non-healing skin abscesses) oncothermia boostered medical treatment showed improvement in clinical symptoms on the base of owner's and handling veterinarian's observations.

Case I., a complete response

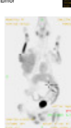
Animal:
name: Perdi
rass: Mixbreed
sex: spayed female
colour : black
age: 10 years
Dg.: Reciduving mammary carcinoma merged with axillary lnn metastases

Photo of the tumor

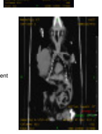


CT and ^{18}FDG PET/CT sagittal images of the axillary region

Before treatment: 24x16x8 cm huge, cystic tumor mass in the axillary region.



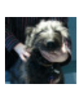
Whole body ^{18}FDG PET scan before treatment

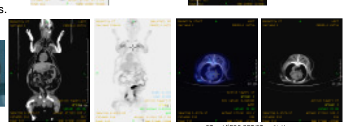


Whole body Ct before treatment

Treatment:
6 x 30 minutes local oncothermia followed by immediate 6 x 4.5 Gray Cobalt irradiation. Monday-Wednesday-Friday schedule, 2 weeks.

After treatment:
No visible/palpable tumor-mass only scarr-tissue (citologically proven) is seen in the dog . The dog has been considered tumor-free 6 months after completing the therapy.





Whole body CT after treatment

Whole body ^{18}FDG PET scan after treatment

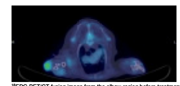
CT and ^{18}FDG PET/CT sagittal images of the axillary region ater treatment

Case II., a complete response

Animal:
name: Tomi
rass: Mixbreed
sex: male
colour : yellow
age: 7 years
Dg.: Mastocytoma Grade III in the elbow region

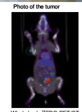
Tomi before treatment

Photo of the tumor

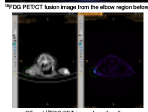


^{18}FDG PET/CT fusion image from the elbow region before treatment

Before treatment:
2x3 cm (in diameter) large primary skin tumor



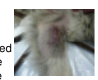
Whole body ^{18}FDG PET/CT fusion image before treatment

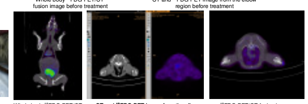


CT and ^{18}FDG PET image from the elbow region before treatment

Treatment:
6 x 30 minutes local oncothermia followed by immediate 6 x 5 Gray Cobalt irradiation. Monday-Wednesday-Friday schedule, 2 weeks.

After treatment:
No visible/palpable tumor-mass only mild side effects of non-controlled oncothermia is seen in the dog . The dog has been considered tumor-free 6 months after completing the therapy.





Whole body ^{18}FDG PET/CT fusion image after treatment

CT and ^{18}FDG PET image from the elbow region after treatment

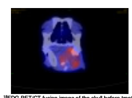
^{18}FDG PET/CT fusion image from the elbow region after treatment

Case III., a partial response

Animal:
name: Muki
rass: Mixbreed
sex: male
colour : yellow
age: 8 years
Dg.: oral (non-pigmented) melanoma

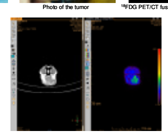
Muki before treatment

Photo of the tumor



^{18}FDG PET/CT fusion image of the skull before treatment

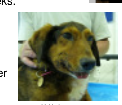
Before treatment: 6 x 6.5 x 5.3 cm locally invasive, ulcerating malignancy in the mouth



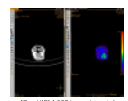
CT and ^{18}FDG PET image of the skull before treatment

Treatment:
6 x 30 minutes local oncothermia followed by immediate 6 x 5 Gray Cobalt irradiation. Monday-Wednesday-Friday schedule, 2 weeks.

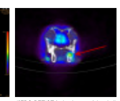
After treatment:
Considerably smaller (28% of pretreatment tumor volume) has been detected after completing the treatment. The dog is however not tumor-free but living a normal life 3 months after completing the therapy.



Muki after treatment



CT and ^{18}FDG PET image of the skull after treatment

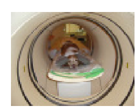


^{18}FDG PET/CT fusion image of the skull after treatment

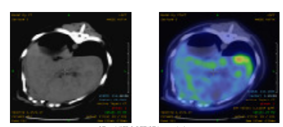
Case IV., a non-responding patient

Animal:
name: Angie
rass: Breton spaniel
sex: spayed female
colour : brown-white
age: 9 years
Dg.: pancreas exocrin carcinoma with multiple abdominal metastases

PET/CT examination



Before treatment: Primary tumor lis a 2x 3x 3 cm lexocrin pancreas carcinoma with multiplex abdominal metastases.



CT and ^{18}FDG PET/CT images before treatment

Treatment:
6 x 30 minutes local oncothermia followedby carboplatin infusion and doxorubicin injection , 10 days.

After treatment:
The dog was initiated for oncothermia + chemotherapy carboplatin and doxorubicin based protocol) but 10 days ater she was euthanized on the request of owner and because of progression in symptoms. Many small multiplex metastases was found all around the surfaces of intraabdominal organs.

Ex vivo macroscopy immediatelly after euthanasia

Conclusion

We concluded that local and regional OT could be a useful tool as a single antitumoral modality but even more clinical utilities could be reached in a combination with radiotherapy or with chemotherapy. OT could be advantageous in the treatment of a variety other chronic diseases too. Further pro- and retrospective clinical studies needed to implement this novel technique into veterinary medicine.

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P-23 – Prof. Dr. Andras Szasz, et al - Oncothermia combination with traditional Chinese medicine: network approach

St.Istvan University

ONCOTHERMIA COMBINATION WITH TRADITIONAL CHINESE MEDICINE: NETWORK APPROACH

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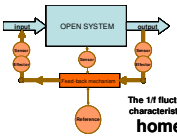
Objective

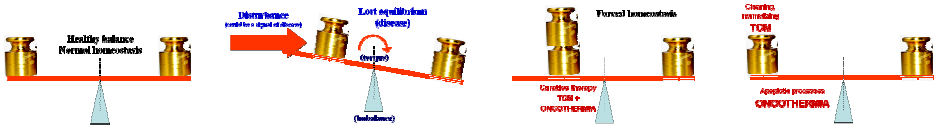
Acupuncture and their connective pathways the meridians are ancient Chinese knowledge but it is not understood yet in details [1] . Request of the stable homeostasis of the complex organisms is demanding interdisciplinary approach and new paradigm for the topic. The detecting and reconstructing the deviation 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 [2]. This technique [3] is well proven from the laboratory level to the clinical applications [4]. Our aim is to synergize the TCM with OTM on the common basis of equilibrium demand; and use the recognition of the deviations from the complex harmony of the organism or its part for selection to act properly.

Method, research proposal

An extended network approach was presented in the topic [5], 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 ([6], [7], [8], [9]), fractal physiology ([10], [11], [12], [13]), and the bioscaling ([14], [15], [16]). Oncothermia widely using these new scientific results [17], [18]; as well as the resonance phenomenon is studied and used in the light of a new theory [19], and special vector-potential theory [20], [21], [22] helps to complete the method. The problems of the thermal limit in the deep-seated tissues is theoretically [23] and experimentally [24] 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 living system is energetically open, its stability is a stochastic equilibrium, called homeostasis. Both the TCM and oncothermia has proven actions to reestablish the natural homeostasis.



Oncothermia promotes the natural processes and in this meaning has coherent aims with TCM philosophy and especially with the acupuncture. The main proven effects of acupuncture are the pain-reduction and general analgesia, and reduction of the side effects of cytotoxic drugs and other side effects of the aggressive therapies. These factors could be good complementary facilities of the TCM and oncothermia methods.

The best, hypothetical cooperation of the methods however is on the field of immune-reactions.

Numerous published data show the immune-effect of acupuncture & many evidences we have in oncothermia on the natural apoptosis and abscopal effect (immune assisted hypothesis)

Acupuncture – humans

Immuno-action	References	Effect/action
Macrophages	25, 30	promoter
Neutrophils	25, 32, 34	promoter
Neutrophils	33	no effect
NK-cells	25, 30, 40, 41	promoter
Lymphocytes	25, 30	promoter
Lymphocytes	45	suppressor
Immunoglobulins	48, 49	suppressor
Immunoglobulins	50	promoter
Immunoglobulins	51, 52	no effect

Electro-acupuncture – humans

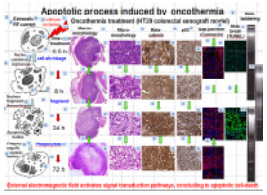
Immuno-action	Reference	Effect/action
NK-cells	42	no effect

Acupuncture – animals

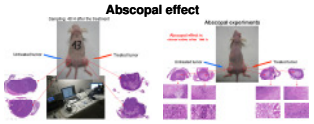
Immuno-action	References	Effect/action
Macrophages	29	promoter
Neutrophils	31	promoter
NK-cells	37	promoter
Lymphocytes	37	promoter
Immunoglobulins	53	promoter

Electro-acupuncture – animals

Immuno-action	References	Effect/action
Macrophages	26, 27	suppressor
Macrophages	28	no effect
NK-cells	35, 36, 38, 39, 43	promoter
Lymphocytes	44, 46	suppressor
Lymphocytes	47	promoter
Immunoglobulins	44	suppressor



Abscopal effect

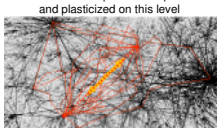


Oncothermia effect far away from the treated lesion.
(a) No immediate effect (48h is not enough to activate the immune processes).
(b) The effect is characteristic after 168 hours of the single shoot treatment (40 °C).

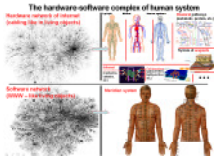
TCM diagnostic phenomena and actions for tumor

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

The meridian system can be explained by network approach, and the action of acupuncture explained and plasticized on this level



The "hardware" of meridians based on the general networks in the body.



Conclusion

Recognition of the distortions in the healthy tissue have some common principles and possibilities in TCM and OTM.

The synergy of the ancient knowledge and the high-tech state-of-art of the medical knowledge could be established with this research.

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P-24 – Prof. Dr. Gabriella Hegyi, et al - Oncothermia combination with Traditional Chinese Medicine: Proposal on Chinese Herbal Medicine approach

Oncothermia combination with Traditional Chinese Medicine: Proposal on Chinese herbal medicine approach

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Objective

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, 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]. 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 herbal medicine of TCM (Chinese Herbal Medicine CHM) and oncothermia.

TCM history sketches

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.

Method

TCM Diagnosis (Basic Principles)

- ✓ Holism, complex approach of the living system and its environment
- ✓ Identification of patterns & conditions (seeking root causes of disease)

Supporting Vital Qi & Cultivating the Root in TCM

- Nourish Qi & Yin/Blood.
- Tonify Spleen & Kidney.
- Tonify Liver & Kidney.

Expelling Pathogenic Factors in TCM

- Soothe Liver & regulate Qi.
- Invigorate Blood & Transform Blood Stasis.
- Transform Phlegm & dissipate clumps.
- Clear Heat & resolve Toxicity.

TCM Etiology

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

TCM Treatment (Basic Principle)

- Same disease, many patterns
- Many patterns, same disease
- According to person, time & place

TCM Pathology

- Yin-Yang imbalance
- Disharmony of Qi & Blood
- Dysfunction of Zang-Fu organs
- Resultant local manifestation of Toxic pathogenic factors.

Effects of TCM Treatment – Western Perspective

- 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.

TCM Asserts

- Vital Qi can strengthen the patient's resistance to infection & enhance cell-mediated immunity.
- Surgery damages Qi & Blood and affects the functioning of the Zang-Fu organ. This manifests as depletion & damage of Qi & Blood, disharmony of Ying Qi & Wei Qi & disharmony of Spleen & Stomach.
- Treatment is aimed at reducing the possibility of recurrence & metastasis & creating an appropriate condition for future radiotherapy or chemotherapy.

Cancer and TCM0

Combining TCM & Western Medicine in Surgery, Chemotherapy & Radiotherapy

The Role of TCM in Cancer Treatment Strategies

- Supporting Vital Qi & Cultivating the Root.
- Dispel Pathogenic Factor.

TCM in reducing the side-effects & increasing the effectiveness of Radiotherapy & Chemotherapy:

- ✓ Enhance the overall results of the treatment & prevent local constriction & recurrence.
- ✓ Reduce toxic reactions & adverse side-effects.
- ✓ Improve hematopoiesis, protect renal & hepatic functioning.
- ✓ Reduce gastro-intestinal side-effects.
- ✓ Alleviate radiation pneumonitis, proctitis & cystitis.
- ✓ Reduce vomiting.
- ✓ Increase immune function & raise long-term survival rates.

TCM will:

- ✓ Supplement Qi & nourish Blood.
- ✓ Fortify the Spleen & harmonize the Stomach.
- ✓ Enrich & supplement the Liver & Kidneys.
- ✓ Relieve toxicity & transform Phlegm.
- ✓ Clear heat & resolve toxicity.

Before Surgery

Goal

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

TCM will:

- ✓ Supplement Qi & nourish Blood.
- ✓ Fortify the Spleen & augment Qi.
- ✓ Enrich & Supplement the Liver & Kidneys.

After Surgery

Goal:

- ✓ Reduce the possibility of recurrence & metastasis.
- ✓ Create an appropriate condition for future radiotherapy & chemotherapy.

TCM will:

- ✓ Tonify Qi & Blood.
- ✓ Harmonize Ying & Wei Qi.
- ✓ Harmonize Spleen & Stomach.

TCM Treatment of Tumors

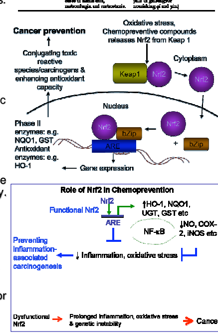
- Phlegm-Damp - Transform Phlegm & Dispel Damp.
- Liver Qi Stagnation – Sooth Liver & Regulate Qi.
- Blood Stasis – Invigorate Blood & Transform Blood Stasis
- Heat Toxicity - Clear Heat & Resolve Toxicity
- Spleen/Kidney Deficiency - Tonify Spleen & Kidney
- Qi & Yin Deficiency (Qi & Blood Deficiency)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

TCM Diagnosis of TumorsPhlegm-Damp

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

Effect of Ginseng on tumor-suppression [8]

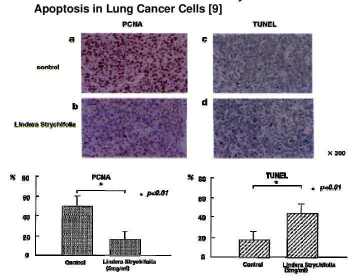
Actions	Indications	Chinese medicine products
To replenish the primordial qi	Collapse due to prostration of primordial qi, exhibiting extremely cold limbs, sweating, vertigo and shortness of breath.	*Shenfu tang* - decoction of ginseng and *Aconiti Lateralis*; [illegible] - decoction of ginseng for treating yang-exhaustion.
To nourish the spleen and stomach	Spleen and stomach qi deficiency complicated by dampness, exhibiting weakness of limbs, emaciation, indigestion, vomiting or diarrhoea, fullness in the epigastrium and chest.	*Shenling baizhu san* - powder of ginseng, *Poria* and *Atractylodis Macrocephalae*; *Jianpi wan* - pills for strengthening the spleen.
To promote the production of body fluid	Impairment of both qi and yin, exhibiting lassitude, shortness of breath, excessive perspiration, dry throat, thirst, also for long-standing cough due to lung deficiency.	*Shengmai yin* - liquid of ginseng, *Radix Ophiopogonis* and *Fructus Schisandrae* for restoring the pulse.
To invigorate the spleen and nourish the heart	Disorders involving heart and spleen deficiency, exhibiting palpitation, amnesia, insomnia, poor appetite, fatigue, also for cases of [illegible], metrorrhagia and metrostaxis.	*Guipi wan* - ginseng pills for invigorating spleen and nourishing the heart; *Renshen yangrong wan* - pills of ginseng for nourishing qi and yin.



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 [10]

TCM diagnostic phenomena and actions for tumor						
Qi & Yin/Blood Deficiency: Qi & Yin	Qi & Yin/Blood Deficiency: Blood	Blood Stasis	Heat Toxicity	Spleen /Kidney	Phlegm /Damp	Liver Qi Stagnation
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				

Extracts from the Roots of *Lindera strychifolia* Induces Apoptosis in Lung Cancer Cells [9]



Immunohistochemical staining of PCNA and TUNEL in LL-2 cell s.c transplanted in mice. 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). Photographs show the typical immunohistochemical appearance in tumor tissues from mice of control (a and c) and *L. strychifolia* extract (5.0 mg/ml) treated mice (b and d). Cell proliferation and apoptosis were detected using anti-PCNA antibody (a and b) and a modified TUNEL method (c and d), respectively. Graphs show change in PCNA-positive and TUNEL-positive cell number in the tumor tissue. Values represent the means ± SD.

Proposal

There are various CHM 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 [5]. Synergetic effects of the OTM and CHM is expected due to the well targeted tumor-tissue by OTM in combination with the effective CHM like Tongyou-sum plant. Also the effect of ginseng and its Nrf2 cancerpreventive 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 OTM 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 OTM and TCM is extremely huge. We are ready to work out the European alternative of the "East meets West in cancer care collaboration" [6] on the basis of the widely applied TCM evidences [7].

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P-25 – Prof. Dr. Andras Szasz - Oncothemia Concensus

Oncothemia Concensus

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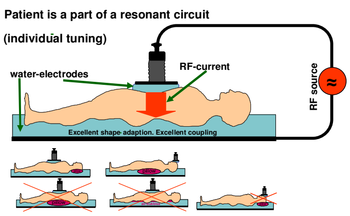
Objective

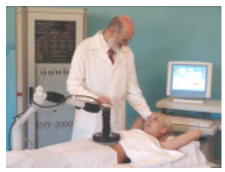
Oncothermia became a widely used and popular method in over 15 countries of the world. It is not a "gold standard" yet, but it is on the way to reach its stable and important position as a "fourth column" among the main oncotherapy modalities. It has wide-range applicability for every solid tumor in all possible localization, irrespective its primary or metastatic form. It could be applied together with all the known oncotherapy methods, and it is applicable in higher lines of the therapy protocols, even in the refractory and multirelapsed cases as well. Its applicability contains the curative and palliative approaches as well as it is well personalized to provide the optimal available treatment for the given case. Our objective is to propose a convention for various treatment conditions, to make a frame of the protocols which has to be filled up by the actual and well personalized details.

Method

A comprehensive book [1], and numerous scientific and technical papers were published on oncothermia, [2], so the technical basis is stable. Oncothermia has collected during its 21 year existence a massive expertise and large data-collection, which are the basic of any convention for treatment protocols. The main factors to fix a personalized protocol are (1) kind of the complementary treatment, [decisional basic is the protocol of the "gold standard" therapy], (2) kind of the tumor entity, (3) kind of the personal status (4) physiological factors of the patient. The most frequently applied bimodal treatments are the oncothermia combined with chemotherapy or radiotherapy.



Easy to use, convenient to lay



Oncothermia works on **conduction principle**. RF-current flows through the patient from one electrode to the other one. Electrodes are flat-metals, both under water pillow: one is in the bolus; one is under the water-mattress. Water is a transmitter of the RF-current, making possible a good fit of the human body to the flat metals. Both water-electrodes (the water-bed and the water-bolus) are parts of the highly sophisticated electric circuit and not only a matter of convenience. The well-constructed device **does not radiate**, the RF-energy flows in a controlled way to the constrained directions, the current delivers the energy where the malignancy is. Both electrodes are active, current flows through them in all the frequency periods.

Oncothermia is a **personalized, non-toxic treatment.** Oncothermia, in most of the cases, is applied when the conventional cancer therapies fail, when the applied therapies need resensitizing or their substitution is necessary. Oncothermia efficacy is focused on patient-centered values: **survival time and quality of life**. Oncothermia can be applied as triple- or quadruple-modality (radio-chemo-thermo-therapy and additional to surgery (adjuvant or neo-adjuvant) as well as some supportive therapies (vitamins, enzymes, etc.) can be given alongside. Oncothermia is a versatile treatment for various solid tumors, its applicability is not limited to specialties, its universal applications could be easily fitted to all the "gold-standards" as well as it could be a good complementary support for other oncotherapies too.

Results

Oncothermia consensus for TREATMENT

1. Apply only in combination (exception if the conventional treatments are not applicable)
2. Treatment time is 45-90 min (average is 60 min)
3. Treatment frequency 2-3 times a week (sometimes everyday low-dose for blood-perfusion)
4. Treatment number 4-12/cycles (average 5.8)
5. Treatment cycle follows the combination (average is 2.3)
6. Step-up heating, gradually increased power, (follow the adaptability of the patient)
7. Give time to adapt the modulation (in case of sensitive organs like the brain)

Oncothermia consensus for SAFETY

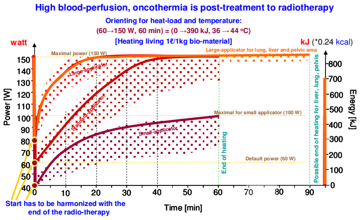
- Physician and/or trained clinical staff must be in duty and monitor permanently the treatments!
- The treatment needs extra care, when the patient has reduced thermal sensitivity!
- Treatment is prohibited when the patient is unconscious!
- Treatment is prohibited when patient is under deep-sedation or anaesthesia!
- Treatment is prohibited in case of patient, who isn't able to communicate with physician!

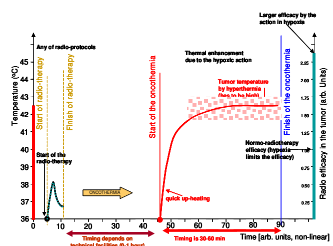
Oncothermia consensus for PRACTICE

- If the patient has inclination to epilepsy, the physician has to take extra attention!
- Make pause of the treatment at rearranging and/or positioning the applicator!
- Clear away all metallic or magnetic pieces from the patients before treatment!
- Check the well filled electrode bolus, do not work with air-bubbles!
- Control the frame of electrode out of touching the skin!

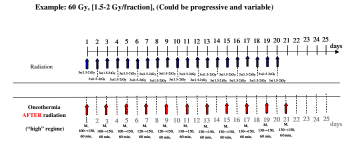
Protocols for combination with radiotherapy (RT) has to consider the blood perfusion of the tumor. When the tumor has adequate blood-perfusion than due to its high oxygen content it is sensitive for RT. In this case RT has to be applied first, immediately following by oncothermia with the highest tolerable power. This combination process is repeated every second day, (while the fractionated radiation could be on its own protocol every day). Oncothermia follows RT immediately (in 30 min range). In case of low blood-perfusion oncothermia has double role: increases the blood-flow to sensitize the RT and supports the cell-killing mechanisms. Fractionated RT follows oncothermia in this case in everyday application. In case of chemotherapy oncothermia has to be started when the highest chemo-perfusion is expected in the tumor-lesion to support the chemo-infiltration and the chemo-metabolism in the tumor. All the protocols have to be fitted to the request of the tumor-localization, and its duration has to be actualized by the stage and the progress of the cancer.

High blood-perfusion, oncothermia is post-treatment to radiotherapy



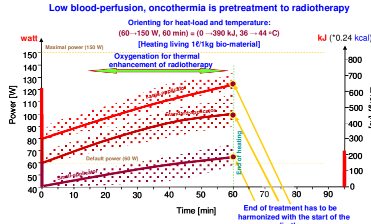


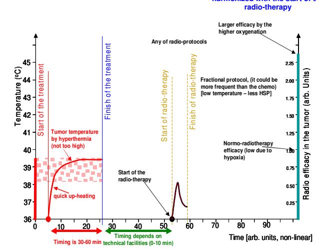
Example: 60 Gy, [1.5-2 Gy/fraction], (Could be progressive and variable)



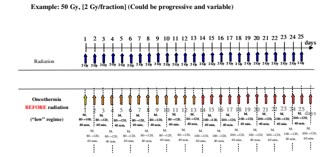
high blood−perfusion the radiotherapy efficacy is expected high, its primary application is desirable. Oncothermia has to be applied afterwards with the highest tolerable dose to achieve the maximal result!

Low blood-perfusion, oncothermia is pretreatment to radiotherapy



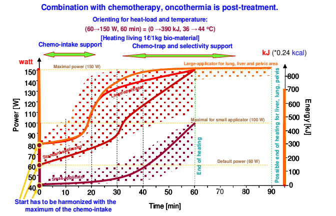


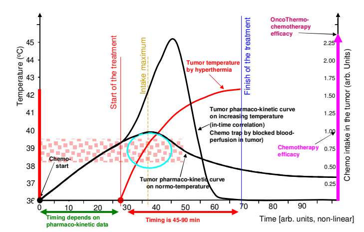
Example: 50 Gy, [2 Gy/fraction] (Could be progressive and variable)



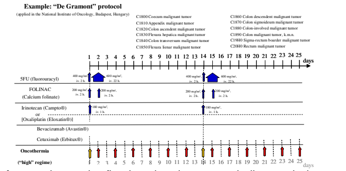
low blood−perfusion the radiotherapy efficacy is expected low. The primary application of oncothermia is desirable, with low power making the oxygenization effective. Radiotherapy has to be applied afterwards.

Combination with chemotherapy, oncothermia is post-treatment.





Example: "De Gramont" protocol



Chemotherapy has to be fitted to the chemo-metabolism and pharmaco-kinetics of the actually applied drug. Oncothermia has to be applied before or during the chemo treatment. Administering the chemotherapy after the hyperthermia could decrease the chemo-intake of the tumor, due to the fact that hyperthermia blocks the neoangiogenetic blood-flow.

Best performance of the combination can be achieved, when the oncothermia is performed at the time when the given drug has the highest chemo-dose by the tumor. These kinetic data of the actual drug are usually provided by the producer.

References

[1] Szasz A Szasz N, Szasz O. (2010) Oncothermia – Principles and Practices, Springer Verlag, Heidelberg http://www.amazon.com/Oncothermia-Principles-Practices-Andras-Szasz/dp/9048194970

[2] Szasz A (2006) Physical background and technical realization of hyperthermia. In: Baronzio GF, Hager ED (eds) Locoregional Radiofrequency-Perfusional- and Wholebody- Hyperthermia in Cancer Treatment: New clinical aspects, Ch 3, Springer Science Eurekah.com, pp. 27-59. http://www.springer.com/west/home/biomed/cancer?SGWID=4-125-22-150459762-0&detailsPage=ppmmedia%7CotherBooks&seqNo=0&CIPageCounter=CI_MORE_BOOKS_BY_AUTHOR0

P-26 – Prof. Dr. Woong Ju, et al - Oncothermia in Gynecologic Oncology (Experience of the EWHA Womans University Hospital, Seoul)

EWHA WOMANS UNIVERSITY

Oncothermia in Gynecologic Oncology

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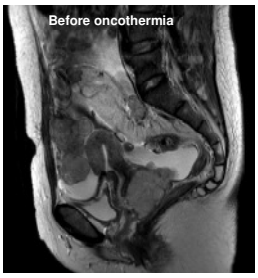
Objective

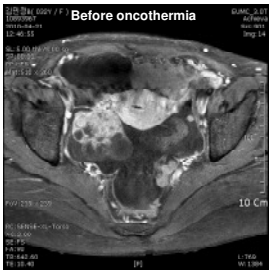
Ewha Womens Hospital intensively uses oncothermia for gynecological malignancies. The time for the application of the new technology is not enough to present statistically evaluable number of patients in cohorts, so our objective is reporting only an interesting case, having multiple primer metastases.

Method

We apply for the treatment the EHY-2000 oncothermia device with variable electrode sizes. A treatment cycle contains 10 sessions in average, made 2-3 times a week, having at least a day between the treatments. Every session was performed in duration of 60 min. Patients of advanced uterine cervix and ovary tumors are treated. Oncothermia was applied complementary to various chemotherapies.

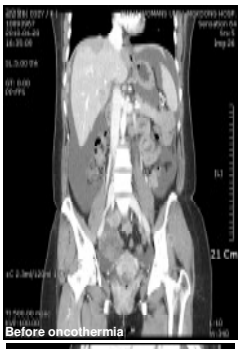
The case which we show is advanced patient (EOv, 32 y), diagnosed in April of this year. Past history was three years ago a cesarean section, with medical history: DM/HTN/Tb/Hepatitis (-/-/-/-). No family history was registered. The uterine cervix punch biopsy was positive: adenocarcinoma, as well as the cytology of the ascetic fluid was also positive for adenocarcinoma. The images (CT, MRI, PET) show large ovarian mass, suspected double primary cancer (uterine cervix and ovary). The peritoneum had serious ascites, (probable carcinomatosis peritonei with unilateral Krukenberg disease). From April to June was treated with oncothermia and three times with neoadjuvant chemotherapy (Genexol+ Carboplatin). Patient was operated in August. Uterine cervical mass and bilateral, ovarian mass - invasion to vagina and peritoneum DDx). Primary uterine cervix cancer with carcinomatosis peritonei with bilateral Krukenberg disease. Double primary cancer of uterine, cervix and both ovary with carcinomatosis peritonei

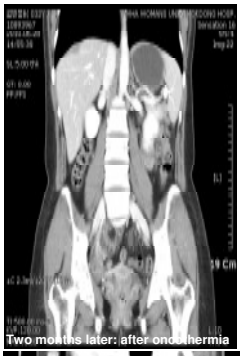


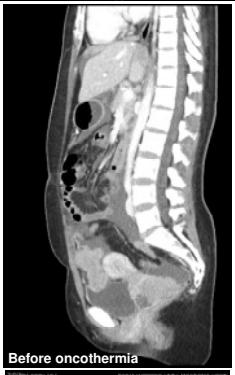


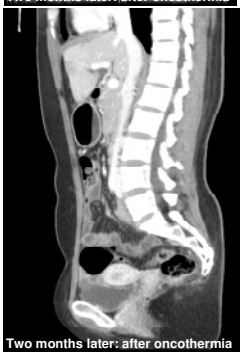
Results

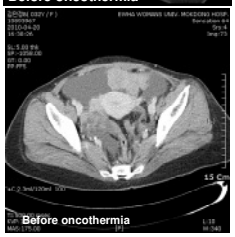
Before oncothermia treatment | **After oncothermia treatment**

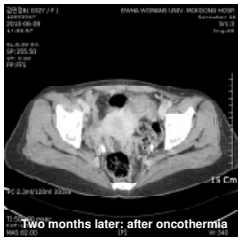






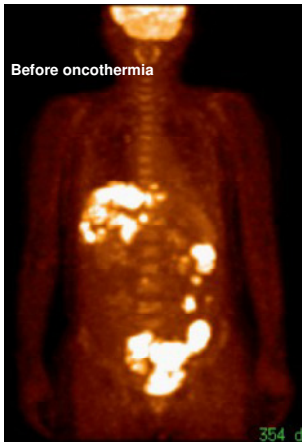


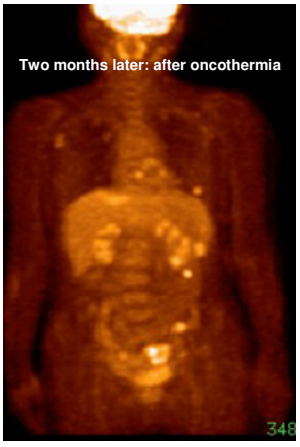




Diagnosis in June shows curative improvement: Decreased extent of mass in uterine cervix and in right ovary. Improvement of hepatic metastasis in both lobes of the liver with residual lesion.
Improvement of peritoneal carcinomatosis with residual lesion. PET shows impressive improvement of cure. The operative results in August showed the pelvic cavity with a vengeance 4*3*3 cm3 a nodular mass with a thick wall of the right ovary was observed in peritoneum, omentum, rectal serosa findings necrotic nodular mass. Abnormalities are not visible on the left ovary. The CA-125 and CA-19-9 tumor-markers had been normalized.

Positron Emission Tomography (PET)





Conclusion

Oncothermia treatment is looks feasible to treat advanced gynecologic malignancies. For evidences perspective, randomized studies, and measuring the overall survival as end-point is desired.

Oncothermia treatment for small-cell-lung carcinoma

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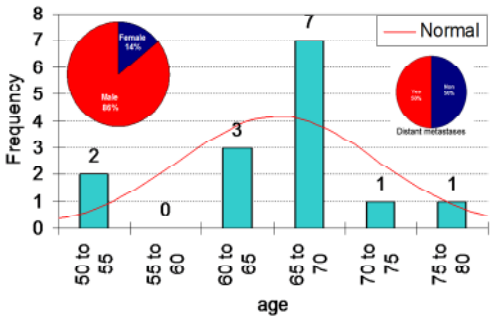
Objective

Small cell lung carcinomas (SCLC) were studied combined with various chemotherapies. This is a running study, we present only interim results. Our objective was to obtain reliable data of SCLC treatment with oncothermia.

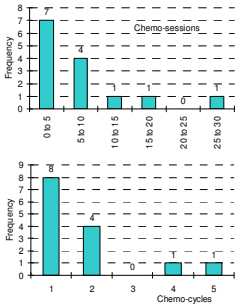
Method

The treatments were provided with device EHY-2000, using the electrode of 30 cm diameter.

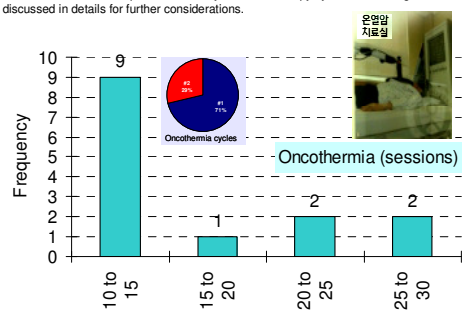
Data of the patients (n=14) are registered and evaluated retrospectively. The average age of patients is 64.4 y (50-77, St.Err.: 1.94), having 12/2 male/female ratio. Ten patients had only one oncotherapy cycle, while four got two cycles. Seven patients had distant metastases two of them multiple, involving their brain. Some cases are discussed in details for further considerations.



Characteristics of the patients included in the study. (Patients included till now only. The study is in progress, patients are recruiting.)



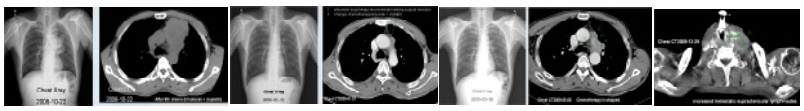
Patients are heavily pretreated



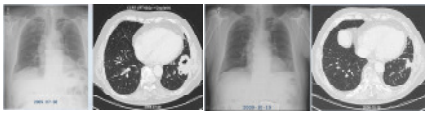
The oncothermia was applied mainly in one cycle. One cycle was 12 sessions in average. The treatments were provided two-three times a week, with one day off in between.

Case reports

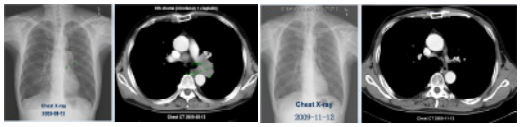
The local clinical response is impressive, shows shrinking of tumor in ten cases while tumor growth was observed in two and no change in two cases as well. The interim results for survival shows median survival 7.5 m, (1-30) with mean survival of 10 m (St.Err.:2.35). The Kaplan-Meier plot is shown. Case reports well demonstrate the efficacy of the oncothermia as complementary treatment for SCLC.



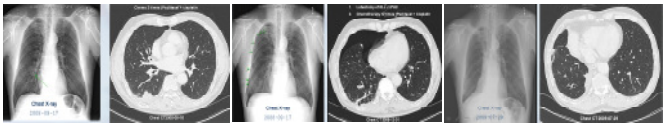
Patient: #6268041, 54y, male, Symptoms:breathing problems, neck nodes. Diagnosis: Non-small cell lung cancer, (Oct. 2008)+ metastases in head-cervix. Histology: Adeno-carcinoma, Treatments - Results: Chemotherapy: 6x Irinotecan+Cisplatin; Result (1): progressive disease (PD). Oncothermia: (3 times a week.) + chemotherapy (Etoposid+Cisplatin). Result (2): Good partial remission (PR) → progression again (8 months progression-free-survival, [PFS]) → Lymph-node invasion



Patient: #6317068, (KBO) 76 y, male, Diagnosis: Squaomus cell lung cancer, N3 lymph node involvement Treatments - Results: CCRT, Chemotherapy: Cisplatin; Radiotherapy: 63 Gy, fractioned); Oncothermia: (3 times a week.) Result (1): progressive disease (PD)



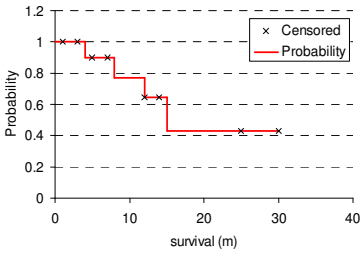
Patient: #6328645, (O) 67 y, male, Diagnosis: Small cell lung cancer (SCLC), Histology: Squaomus cell lung cancer, (Aug.12. 2009.) Treatments - Results: Chemotherapy: 6x Irinotecan+Cisplatin; + Oncothermia: (3 times a week.) Result: Good partial remission (PR) (Nov. 12. 2009)

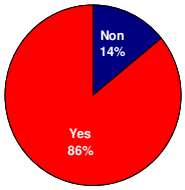


Patient: #6261847, 67 y, male; Symptoms: Blood tinged sputum (Sep. 17.2008) Diagnosis: Squaomus cell lung cancer, pleural seeding Treatments - Results: Chemotherapy: 3x Placlitaxel+Cisplatin; Result (1): progressive disease (PD). Lobectomy of RLL and IPHC (intraperitoneal hyperthermic chemotherapy), + Chemotherapy 12x Placlitaxel+Cisplatin; + Oncothermia: (3 times a week.) (Dec.01. 2008). Result (2): Stable disease (SD) → follow-up: Stable disease (SD); (July 29, 2009)

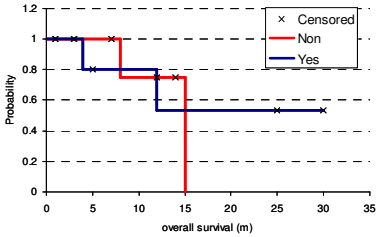
Interim study-results

The local clinical response is impressive, shows shrinking of tumor in ten cases while tumor growth was observed in two and no change in two cases as well. The interim results for survival shows median survival 7.5 m, (1-30) with mean survival of 10 m (St.Err.:2.35). The Kaplan-Meier plot is shown. Case reports well demonstrate the efficacy of the oncothermia as complementary treatment for SCLC.





Local response



Survival with distant metastases

Conclusion

Oncothermia treatment has feasibility to treat SCLC. For evidences a perspective, randomized study, and the overall survival end-point is desired. The study continues, and further evaluation is in progress.

Oncothermia treatment of lung carcinomas

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Objective

Advanced lung carcinomas were studied. Oncothermia was combined with various chemotherapies and radiotherapy. Our objective was to obtain reliable data of lung-cancer treatment with oncothermia.
Results are interim, the study is in progress.

Method

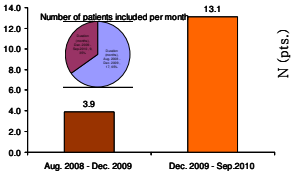
Study was started in August 2008, and was sequentially evaluated in December 2009 (n=66) and September 2010 (n=118), retrospectively.

Number of patients till September 2010: n=118 (70/48 m/f)

Oncothermia was provided with device EHY-2000, 60 min in all sessions, using electrode of 30 cm diameter.

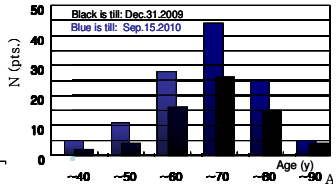
In first period 54.5% in the second one 64.4% was in advanced stages, and additionally 21.2% and 33 % had recurrence or metastases, respectively. The other stages were only 24.2% and 9% in the investigation sequences respectively.

Inclusion criteria: Recurrence after resection lung surgery and/or advanced stage lung cancer (IIIb or more), and/or inoperable (unsuitable for surgery)

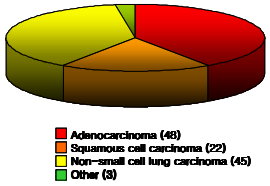


Distribution of patients by ages

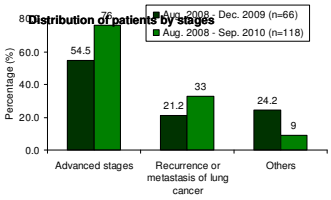
Average age: 62.9 ± 11.1years old (range; 29 ~ 86 years)



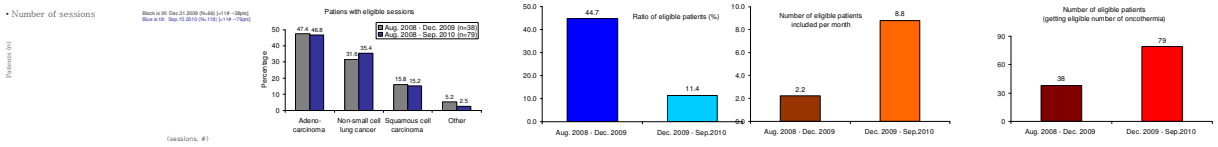
Distribution of patients by tumor-character



Distribution of patients by stages



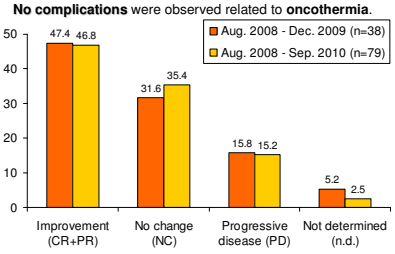
We studied only the cases with eligible number of sessions, excluding those who had not such number (less than 12 sessions) of the treatments. Numbers of included patients are n_i=38 and n_i=79, respectively.

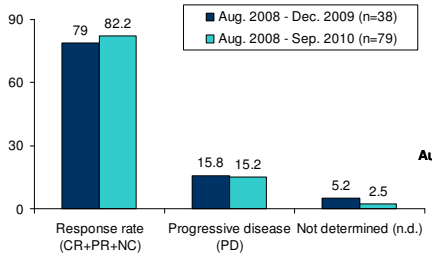


Results

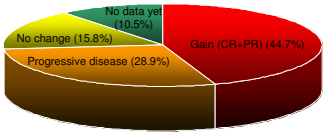
We had measured the local clinical response only, the survival analysis could be done later. The local data shows improvement (CR+PR) 47.4% and 46.8%, NC 31.6% & 35.4%; PD 15.8% & 15.2 %; n.d. 5.2% & 2.5% in first and second sequences of the study, respectively. Regarding the advanced and relapsed cases, the overall local response-rate (CR+PR+NC) is 79% and 82.2%.

No complications were observed related to **oncothermia**.





Aug. 2008. → Dec. 2009



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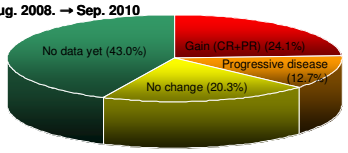
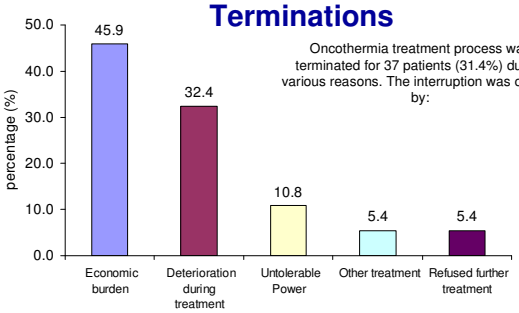


Terminations

Oncothermia treatment process was terminated for 37 patients (31.4%) due to various reasons. The interruption was caused by:



Conclusion

Benefits	Disadvantages
• Easy to treat. • No vomiting, no body weakness, no hair loss no complications. • Effective pain-reduction	• The expensive cost of treatment • Does not seem to work immediately • Shortness of breath due to pleural effusion at the attitude is difficult to lay

Oncothermia treatment has feasibility to treat advanced and relapsed cases of lung-cancer. For evidences a perspective, randomized study, and the overall survival end-point is desired. The further work is in progress.

St.Istvan University

Personalization of oncothermia

Dr. Andras Szasz, Dr. Gyula Vincze, Dr. Szasz Oliver
Department of Biotechnics, St. Istvan University, Budapest, Hungary

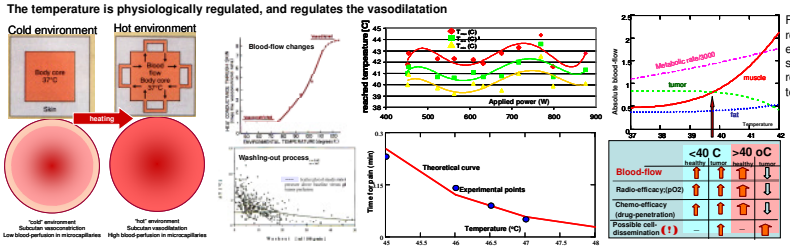
Objective

Dosing of oncothermia is based on the energy delivery to the targeted tumor [1]. This energy is well focused on cellular level [2], and makes the dose of energy optimal for cell destruction [3]. The personal feedback of the patient is the important control of the process; the patient became the primary sensor of the treatment protocol. This gives good safety records and low toxicity and side effects for the patients, however the objective dose is not equal for them. We know it well, that the dose is an important factor, the too low is ineffective, the too high is toxic. Our objective is investigating the personalized feedback in point of view of the objectivity of the dose.

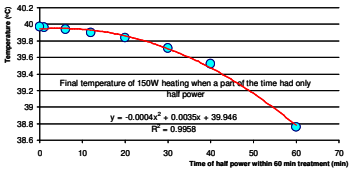
Method

The objectivity of the treatment is definitely depends on the radiofrequency current and its gained voltage on the given impedance on the tumor. This current is well regulated by the skin-conductance and by the connected physiological changes. The inconvenient feeling of RF-heating defines a pain-limit, which depends on many objective and individual factors. A good approach is regarding the nerve-cell sensitivity objective (the cellular processes are well unified), and regarding the personal differences as influence of physiological factors. The main factor for heat-sensitivity is the blood-perfusion and blood-flow in the subcutaneous layers where the heat-sensing nerves are located. The high blood-flow is an effective heat-exchanger, cools the given volume, and the nerves tolerate higher energy-flow through the layer. The high blood cooling is not only the facility to have higher energy-flow, but also getting more current through the volume. The higher current density excites the nerve-sensing, and the feeling again an overheating, requests down-regulation. In the case of low blood-perfusion the current is small, so the nerves can tolerate more intensities than anyway. The crucial point is the surface heat-regulation, which has to be carefully done by the electrode systems. When the surface temperature kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. A detailed mathematical model is worked out for this regulation mechanism, and applied in oncothermia treatment.

The temperature is physiologically regulated, and regulates the vasodilatation



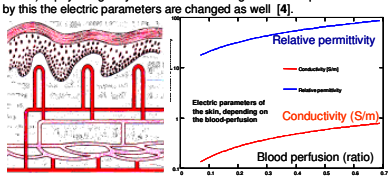
Furthermore the step-up heating is important not only avoid the inconveniences, but regulate the adaptation mechanisms. Healthy cells can be adapted to the electric/heat-stress, while this adaptation is much less in the malignant lesions. The step-up heating supports the physiological selection and makes the contrast of the reaction definite. The start at low-power does not considerable influence the final temperature.



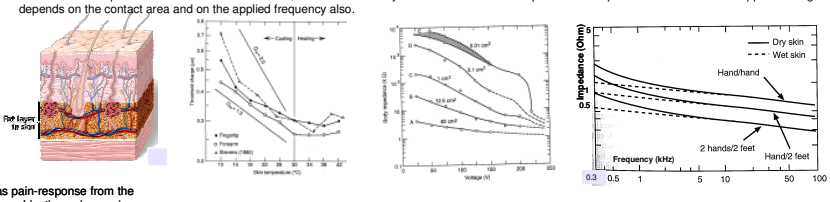
Other factor is connected to the psychological interaction with the treatment process also. In any protocols, when the temperature is described as a dose, when the required temperature can not be achieved than of course it is forced by the power, so the incident energy is not limited in this case. Oppositely, if the patients can not tolerate the prescribed power (and required temperature), than a lower one is applied in their cases. The pain in the body depth is independent from the temperature sensing nerves, the pain there has other mechanisms, which are not part of the prevention of damage (like the temperature sensing), but sensing the actual damage itself. Consequently blocking the surface heat sensors is a high risk factor, which is never made in oncothermia therapies.

Bioelectromagnetic considerations

The energy is transmitted through the skin. The skin (as described above) is physiologically controlled and changes its blood-perfusion and by this the electric parameters are changed as well [4].

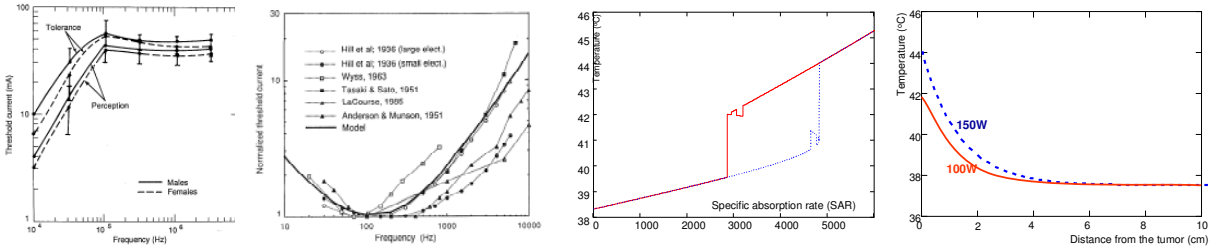


The subcutan adipose tissue is an electric blockade, and its conductivity decides the current transport at a fixed power transmission. The applied voltage depends on the contact area and on the applied frequency also.



Only the temperature has physiological blood-flow response, the current has pain-response from the skin. This pain tolerance is constant (saturated) at 13.56 MHz. This allows an objective pain sensing by the current, which depends on the thickness of the adipose layer. This creates a negative feedback signal: when the fat is thick, the temperature grows and make a temperature pain limit which by step-up heating increases the blood-flow by vasodilatation. The current in this way grows, but when the blood-conductance became too high, the pain from current will limit the process again, and contros the personal merit, which is pretty objective due to the saturation of the current sensing.

The physiological effects (temperature and non-temperature dependent bioelectromagnetic interactions) cause a hysteresis of the heating by the provided specific absorption rate, and makes different the step-up and step-down heating. The effect of the side-heating is small, no disturbance in healthy tissue is expected.



Conclusion

Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. The synergy of the technical and psychological regulations makes objective dose control for oncothermia processes, keeping the energy dose in the curative range.

The personalized oncothermia-dose is objective.

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Oncothermia research support by LabView-based data-aquision systems

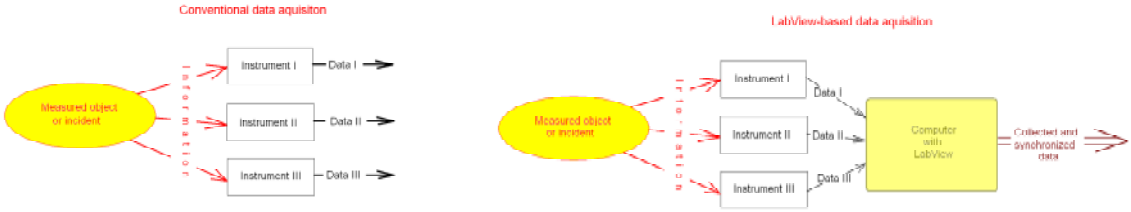
Skrihár Gábor
Development engineer, Oncotherm kft.

The necessity of integrated data-aquisition systems

The aim of all scientific experiment and measurement is to collect information about the measured object or incident. On the field of research it's especially important to acquire all of measurable information during the the experiments, because often we don't know exactly, which of the parameters will give us new and useful informations. But in a lot of cases the data aquisition could be quite difficult, because:

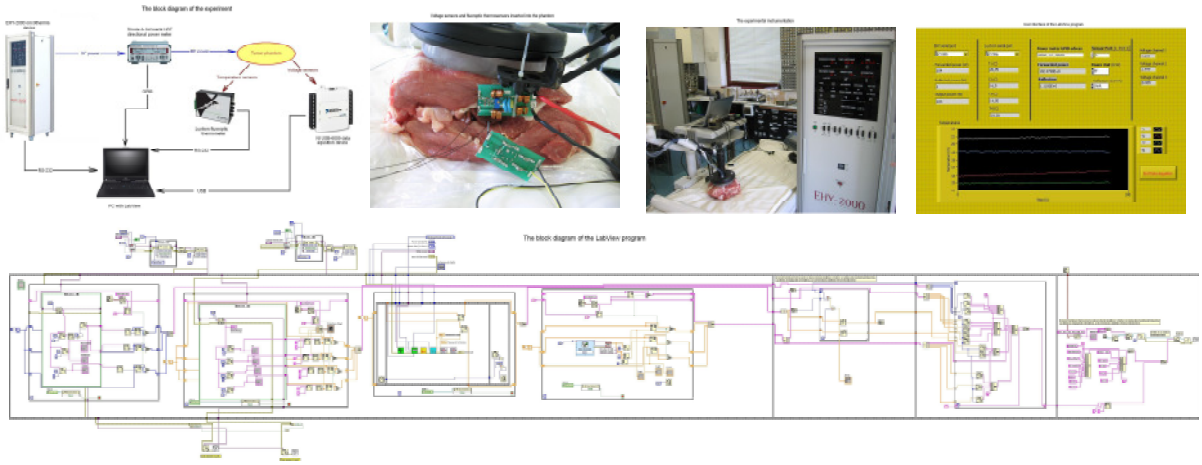
- If during the measurement more instrument is used, the simultaneuos and continuous observation all of them is not possible.
- A lot of instruments don't provide built-in data aquisition and storing
- Although some instruments have this functions, it could be difficult to synchronize the data acquired by various instruments.

The solution of this problems is such a data collection system, that in real-time collects and synchronises all of the information, that the used instruments provide during the measurement and than stores them into a common database, allowing the common processing of them. By this way the efficinency of the scientific research could be greatly increased. For us at Oncotherm is a priority to make more efficient our R&D activity, so we started to develop integrated data-aquisition systems to support our research projects.
The main element of this systems is the LabView program suite, which is developed especially for data-aquistion and instrument control and is provided by National Instruments. The main task of LabView is to control the the NI's own DA units, but the products of the most important instrument manufactors are controlable by the suite too. During our projects we use both NI instruments and the instruments of other manufacturers (Tektronix, Rhode&Schwartz) too.



The instrumentation of an experiment

The key factor of destroying the tumor cells is the quantity of the current flowing through them. By maximizing the current int he tumor the efficiency of the therapy can be maximized too. During the propagation of the electromagnetic wave in cable, the formation of current-maximum points is unavoidable. There was a concept, that by changing the tuning of the EHY-2000 device (to tune not to the perfect 1.00 SWR) that points can be moved along the cable – into the tumor The aim of the introduced experiment was to decide if that concept is right or not. For the experiment a body and tumor phantom was used, which was built up by a beef kidney inserted into a pork thigh.
The data aquisition system assembled to this experiment consisted of the following instruments and provided the following informations:
EHY-2000 oncothermia device: the forwarded, reflected and useful powers transmitted by serial port
Rhode & Schwartz power meter: the forwarded power)to check the power meter of the EHY-2000) and the SWR by GPIB protokol
Luxtron fluoroptical thermometer: this four-channel device gives us information about the temperature changes of different parts of the tumor during the threatment. It transmits the collected data by serial port.
National Instruments USB-6009: this DA device was used to collect and transmit the data of the voltage sensors
By using the data provided by the reviewed instrumentation we got a clear picture about the electrical and heat effects of the various tuner settings, which gave important informations about the correctness of the concept..



Other possible usages

The data-collecting systems always follow the demands of the current research projects, capitalizing the flexibility of the LabView-based DA systems. On the grounds of our experiences until now we have more possible applications of LabView-based data-aquisition systems. The most importants of them are:

- LabView-LabEHY: LabEHY is a hyperthermia device specially developed for in vitro and in vivo experiments. Our ambition is to controll the device by a LabView-based surface using an NI device built into the instrument. This solution will give us the oppurtunity to monitor all of the inner activities of the instrument and control the device by various ways – for example by using the output data of other devices for the automatic contol of the LabEHY.
- Production support: automated testing of our products by LabView-based instrumentations.

By realising these conceptions we can improve both the effectivity and the speed of our R&D projects and improve the quality of our products, so we are comitted towards these ways.

P-31 – Dr. Oliver Szasz - Success of Oncotherm

Success of Oncotherm

Dr. Oliver Szasz
CEO of Oncotherm Group, Troisdorf, Germany, Dr.Szasz@oncotherm.de

Objective

Oncotherm company became this year 21 years old. It has started its life in the Universities. The ideas were formulated as a part of the surface science in Glasgow (Scottish Surface Centre, Strathclyde University), followed by a spin off form the Eotvos University Budapest in 1988. The first contacts with Germany were established almost immediately. Dr. Douwes (St.Georg Klinik, Bad Aibling), asked the human medical applications of the till that time only theoretically formulated ideas. The actual requests of the clinical use formulated by Dr. Douwes were successfully performed, starting with galvano-therapies, and continuing to the basic of the presently well known oncothermia method. The company is certified in all aspects by the rigorous German TÜV services having the CE and the ISO approvals for the products and production processes, respectively. The German approval is combined with the high-quality manufacturing in Hungary, following that traditional line which other typical German products (like Audi, Bosch, Mercedes, etc.) does. Our objective to show the market success of the company.

Method

Our marketing aim to keep the full developing and manufacturing process in the EU. Oncotherm does not follow the large multinational companies making their productions outside of the Community. We are committed to show the high-level of the famous German medical knowledge, ("MED in Germany") together with the well-known traditions of the German products: we are engaged for the best quality, for the immediate application of the newest research results, and for the highest reliability of the method.
Oncotherm sells not simple devices. We are selling a method of ONCOTHERMIA, we are selling our high level expertise, which is supported by scientists and medical practitioners, smart and engaged doctors, diligent and precise nurses.
Oncotherm in its own is a company which would like to give the best instruments to the hand of professionals supporting them in their responsible and important everyday work.
Oncotherm developed all the parts and details according to the optimal harmony technically together and with the users. We had chosen the way when did not bought ready parts and units, mounting them together, but step-by-step developed own units to offer the best for the actual tasks.

APPROVALS, CERTIFICATES ("Production of Germany, manufactured in EU")
Product: CE certificate, TÜV Product Service, Munich, Germany (largest notified body in EU) (TÜV - Technische Überwachungs-Verein, Technical Monitoring Office)
Marketing, sales: ISO9001, approved by TÜV Management Service, Munich Germany
Manufacturing: ISO 13485, approved by TÜV Product Service, Munich, Germany
EMC: German Accreditation Office (Deutscher Akkreditierungs Rat, DAR)
Additional approvals: China, Russia, Ukraine, S.Korea, Canada (TÜV America)

The strong commitment and philosophy of Oncotherm opened new dimensions of hyperthermia treatments, and it is based on 3E+3S concept:

Efficacy principles

3E

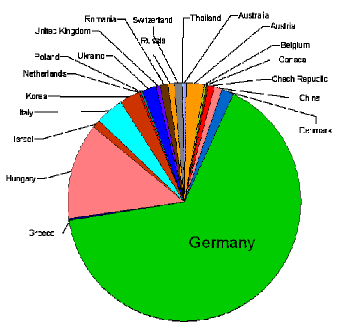
1. **efficacy** by large energy absorption with electric field assistance,
2. **efficacy** by cellular self-selective focus realized by modulated RF-current,
3. **efficacy** by distinct improvement of the survival rate and by unambiguous increase of the quality of life

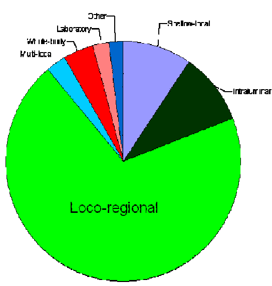
Safety principles

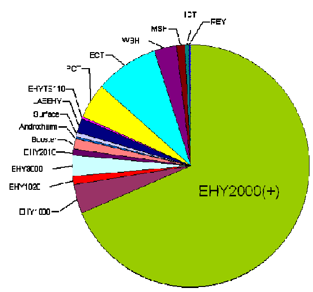
3S

1. **safety** for the patient with optimally personalized energy-absorption, based on the enduring control of the RF current through the patient,
2. **safety** for the treating medical personnel with high electromagnetic standards, making possible to use oncothermia even in dwelling-houses,
3. **safety** for your quiet daily work by the solid scientific, biomedical and clinical proofs.

Results







262 devices in 21 countries
(some are out of our control
actively controlled ~200 devices in 17 countries)

17 types of devices in 7 categories were developed during the history of oncothermia.

Shallow-local	ECT, ICT, Surface
Intraluminar	PCT, EHY1000, EHY1020
Loco-regional	EHY2000+, EHY3000, EHY2010, FEY
Multi-local	EHY3100
Whole-body	WBH, MSH
Laboratory	LABEHY, EHYTS110
Other	Booster, Androtherm

Conclusion

New paradigm is necessary for hyperthermia in oncology Necessity of oncothermia

Hyperthermia contradiction (1): "The biology is with us while the physics is against us" (J.Overgard, [1])
Oncothermia changes the paradigm (1): "The biophysics is with us"

Hyperthermia contradiction (2): "The biology and the physics is with us while the physiology is against us" (S.Osinsky, [2])
Oncothermia changes the paradigm (2): "The fractal physiology is with us"

Hyperthermia contradiction (3): "Reference point is needed!" (J.van der Zee, [3])
Oncothermia changes the paradigm (3): "Back to the gold standards, use the energy instead of temperature"

Oncothermia is a personalized, non-toxic treatment which supports the natural processes (apoptosis, immune reactions, conditional effects, etc.) to be a helper of electro-hyperthermia actions. Oncothermia is a new paradigm of the modern oncotherapies.

Oncotherm understood the update demands of the modern oncology:

Personalized treatments
Demand and conditions is important
Preventive and follow-up procedures
Oncothermia is a convenient treatment for all the demands

Non-toxic treatments
Minimal toxicity with maximal benefit
High selectivity, local actions
Oncothermia is non-toxic, local and depresses the toxicity of others also

Increase of the quality of life
Low QoL with long survival is not satisfactory
QoL has a great economic importance also
Oncothermia is an ideal method to increase the QoL

Increase of the survival time:
It is the most important factor, it is ranked before the clinical results
It is not enough if a method offers only clinical success-rates
Oncothermia together with the clinical successes is definitely a tool for longer survival

Economic points
The cost/benefit ratio is frequently counted
Financial background of the medical treatment is an important issue
Oncothermia is a cheap and easy to use method, low contraindications and complications

Acknowledgement

Oncotherm workers feel themself like a violin-maker does: trying to produce the best violin ever, making innovation as much as possible, and dreaming about a nice concert. **BUT we never make concert. The concert is given by the oncothermia users.**

Oncotherm is deeply indebted for the capable and clever physicians using oncothermia, we are thankful for talented supporters and users, and gramercy for researchers and scientists who are all helping oncothermia on the way of further developing and reaching new heights to help the suffering patients and win the war against cancer.

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P-32 – Ms. Constanze Feisskohl, et al – The customer is king: The marketing concept of the Oncotherm Group

The customer is king:
The marketing concept of the Oncotherm Group

Ms Constanze Feißkohl[1], Ms Janina Leckler[1]

(1) Oncotherm GmbH, Troisdorf

CONCEPT AND MARKETING TOOLS

The focus of our work is informing doctors from all over the world about the method and possibilities of Oncothermia. We are dealing with oncothermia as a complex method and not simply market and sale of devices.

Our driving force is to help the suffering patients. Only when the doctors see and accept the complementary treatment option of Oncothermia, the patient can be helped by us. Physicians who are applying oncothermia are not only passive users, they are active helpers to build up the next development step for their better services and for wider possibilities of the oncothermia method. We are building up the future together with all the oncothermia users.

Through different actions we are trying to offer the best possible service and support for our customers, mainly by keeping them informed on scientific results and backgrounds.

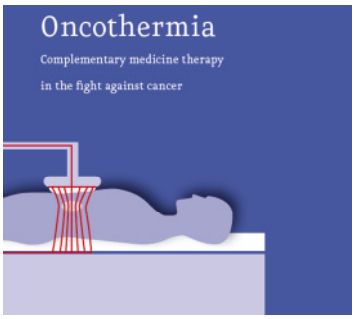
Our different tools include for example publications, website, newsletters, events, brochures, patient information and so on present our successful synergy of professional technique and the science.

The Menu of our new Website: www.oncotherm.org

Our newsletter is sent out monthly and informs the customers about news in science, the company and on events and new developments

The yearly organized Symposium is also a tool to inform about the method and support the customers with new studies and scientifical results

New brochure design



CONCLUSION

Oncotherm works with a professional marketing concept based on the needs of our customers and their own „customers“, the suffering patinets. Our aim is to make the method more prominent to help patients and to support the doctors using the oncothermia method. Oncotherm knows very well: we are united community with our customers, regarding them our partners in recognising the demnds and introducing it in the permanent development of the oncothermia method. Oncothermia devices can not fulfill their intended prospective without our smart and active partners who are the complete medical personal applying everyday the method and using the oncothermia skills to win the war against cancer.

Institute for Hyperthermia and Immunotherapy IWIT, Vienna 14 Years Experience in locoregional and whole body hyperthermia

Kleef R, Kekic S, Hadcic D, Rigler W, Pecher O.

BACKGROUND

The IWIT is the leading Institute for Hyperthermia in Austria

- > 17.000 h of whole body hyperthermia
- > 5.000 Treatments with locoregional Hyperthermia
- Largest center to successfully combine oncological and non-oncological treatments

Conditions treated

- Autoimmune diseases, Allergies
- Chronic Infections
- Chronic fatigue Syndrome, Burn Out, SAD
- Pain Syndromes
- Cancer

PURPOSE AND HYPOTHESIS

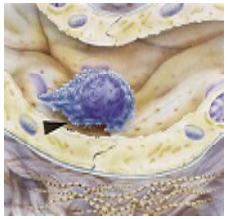
Whole Body Hyperthermia

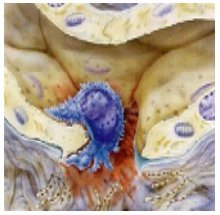
Whole Body Hyperthermia – the carefully monitored creation of artificial fever – is one of the most promising therapeutic strategies in physical medicine in use today. The central mechanisms of hyperthermia are the regulation of the matrix reaching deeply into the body's core and the modulation of the immune system. Healthy individuals benefit from increased stress resistance levels and deep regeneration effects.

Locoregional Hyperthermia in cancer therapy is combined with cytostatics, radiation or immunotherapy. Cytostatics whose effect will be amplified by the produced heat are especially apt for treatment. Amongst others Cis-Platin, Mitomycin, Bleomycin and Epirubicin are known to have this effect. Also a combination with radiation seems to be reasonable. The radiation therapy affects all cells that are well-supplied with oxygen, while hyperthermia increases oxygen partial pressure in tumor cells.

MATERIALS AND METHODS

Pleiotropic & Complex Effects of Hyperthermia
- Immunological Effects -at fever-range Temperature

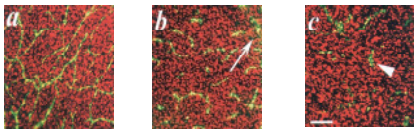




- Emigration & Migration (Expression: ICAM-1, L-Selectin ↑; ELAM-1 ↓)
- Chemotaxis ↑
- Cytokine-Induction (IL-1,-2,-6,-12, TNF-ß, NO, CSF)
- Activation of Effector Cells (NK, MO, DC, CTL)
- HSP-Expression (chaperones, HSP-TAA-complex)

Anti-angiogenic effect of heat

a. Large control tumor
b. Hyperthermia (44°C, 60 min) disrupted 25-50% of the blood vessels in the small tumor.
c. The anti-vascular activity was more potent (is more distinct) in larger tumors

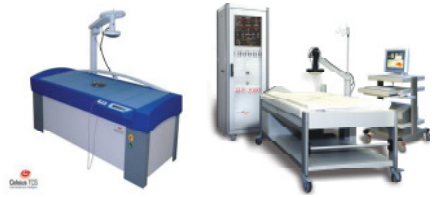


Eikesdal, HP et al.: Int J Hyperthermia 2002; 18:141-152

RESULTS

Locoregional Hyperthermia

In **locoregional hyperthermia** the application of hyperthermia with external **plate electrodes**, is employed with radio short waves 13.56 MHz which invade about 12cm into biological tissue. There is a distinction between **direct** and **indirect** effect. The **direct** effect relates to the tumour cell itself. It has an influence on protein metabolism, energy metabolism as well as on the character of the cell membrane. The **indirect** effect relates to the attached tumour cells as a whole, i.e. disturbances of the micro circulation.



CONCLUSIONS

Summary of Basic Research in HT
- Increased **blood perfusion** at mild and moderate T
- **Immunological** effects at fever-range T
- **Synergism** with radiation, antineoplastic agents, antihormones, and immunomodulators
- Induction of **apoptoses** at T > 40°C
- **Antiangiogenetic, molecular and genetic effects**
- Reduction of **drug-resistance**
- Induction of **necrosis** at T > 45°C

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