Review Article

Oncothermia: Emerging Therapy in Oncology

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Abstract

The healing effect of heat was already mentioned in the advanced cultures of the old Egypt (2400 B.C.), but only the medical professionals of the Greek Antique used this therapeutic approach consistently, acknowledged it and called it over-warming (in Greek: Hyperthermia). Oncothermia is a new paradigm which entails the generation of temperature gradient by self-selection absorption of electric field energy based on the bio-impedance selection and modulated radiofrequency electric current to produce lethal heat flow between the extra- and intracellular matrix of the tumor cell membrane. It provides synergies with other traditional treatment modalities. The spread of this technology worldwide is a strong evidence to support it, based on palliative pain control and prolongation of survival in many solid tumors e.g. liver, pancreas, brain, prostate and lung when other therapies fail.

Keywords: Oncothermia, Cancer, Deep Electro-Hyperthermia, Conductive Hyperthermia, Modulated Radiofrequency Electric Field.

Introduction

"Give me the power to produce fever and I heal every illness", said Parmenides, Greek physician, 540-480 B.C. Hyperthermia is the oldest treatment of cancer in medicine. [1, 2] There is a plethora of literature devoted to the efficacy and the power of hyperthermia in oncology, [3- 10] The method is discussed in text-books of radiotherapy[11] and general oncology. [12] Despite these tremendous efforts, hyperthermia is not generally accepted as a conventional therapy. The problem is its controversial performance, addressing many questions and raising doubts. This is exactly what happened in a cervical cancer study where the results were very promising, [13] and a control study [14-16] was disappointing. The explanation may be simple: a reference point was missing. [17] Oncothermia solved this issue with remarkable clinical results.[18]

Change of Paradigm

The controversy of hyperthermia has originated from the complications of the deep heating and the selection (focusing) of the heat-effect. These challenges were based on bio-physical and engineering problems. Developing oncothermia from biophysics, solved such technical problems.
Challenging points in conventional hyperthermia:

- Making the focus artificially has numerous problems, because the malignant tumors have no real boundaries.
- The problem is even more complex to see the technical complications of the focusing in depth of the human body. For safety, the process must avoid creating hot-spots, and has to eliminate the natural and other body-movements (e.g. breathing, position-changes, etc.) of the patients, as well as avoid the overheating of the surfaces, when the energy penetrates in to the body.

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- The smearing of the focused temperature by time due to the heat-exchange flow with the environment of the targeted volume, and equalizing the temperature in the neighborhood.
- There are many theoretical problems of the heat-effects on the tumor and healthy tissues e.g. the induction of various Heat Shock Proteins (HSP), promoting hypoxia, helping the dissemination of the malignant cells to the blood-stream, etc.

The idea of oncothermia solves the selective deep action on cellular resolution. It uses the electric field to select and destroy the malignancies. The electric field uses in medicine evolved with the discovery of electricity at the turn of the nineteenth century i.e. fulguration, electrocautery. [19, 20] A detailed theory was worked out by Nordenstrom B. at the Karolinska Institute, Sweden. [21] The effect of electric field is anyway a hot topic in science, and used in other treatment modalities, [22, 23] and used in other treatment modalities. [24] Oncothermia development in the early 1990s acquired rapid momentum with clear indications of proven value. [25]

The modern fluctuation analysis (fractal-physiology), the resonance phenomenon, the hypoxia study and the special vector-potential theory support the concept of oncothermia, [26-29] The possible side-effects of the scattered radiation were studied for safety issues. [30]

Oncothermia is based on the paradigm of a definite energy dose control replacing the single temperature concept. Synergy of deep heat delivery and the electric field can affect cell-killing by avoiding the high temperature which cannot be kept in a local area for a long time, and can work at low temperatures as well. [31-33]

Technical Considerations

Two basic principles.

1. The malignant cells have autonomy. They are in permanent competition with others for nutrition. The active ionic exchange of the malignant cells is more robust compared to their healthy counterpart. This allows the introduced current to find the optimal path, which goes through the best conduction way. So the current goes self-selectively to the malignant cells. [32]
2. Naturally, the absorbed energy increases the temperature similar to the case of ionizing radiation in order to damage the DNA, and the chemical bonds and rearrange the structure. If we have a fatty dish after a dinner, we could wash it with large volume of very hot water, instead if we add a detergent we can reduce the water temperature, and make the job easier, and not waste energy with large volume of hot water. To raise the temperature alone in the tissues is not safe so we need to deliver it to the target specifically to the place where we want to do the destruction (like the ionizing radiation does). What is the target? It cannot be the cellular interior (nuclei and DNA) because by non-ionizing radiation needs again high temperature, and the initial problem is not solved. The target is the cellular membrane. If we keep the current in the extracellular matrix then the energy heats up only this electrolyte, and a heat-flow starts from the extra- to intra-cellular regions through the membrane. This heat-flow accompanied by different ionic flows and water transport, changes the Hodgkin-Huxley equilibrium, the membrane became more transparent, and eventually destroyed [31]. The transparent membrane also could be helpful to kill the malignant cells, because large concentration of the intracellular HSP will be expressed extracellularly, which has direct effect on apoptosis and stimulation of the systemic immune reactions.

In oncothermia, no artificial focusing needed for selectivity, and no isotherms in space and time has to be controlled. Both effects are solved with a directed electric field. It is a well designed capacitive coupling on 13.56 MHz free-frequency. It is controlled by the changes in the impedance and the absorbed energy, which both are accurately measured. It is similar to the RF-ablation hyperthermia, where the temperature is not measured, the effects are controlled by the

measured impedance of the tissue. The power is ranging from 30-150 W, which is far enough for heating up the tumour over 42 ºC in a well controlled manner. Less than 20 W is enough to heat up a 5 cm diameter tumour from 36 ºC to 44 ºC at 3 minutes.

Oncothermia requires technically two definite effects: selectivity and cell-killing. It is selective by the higher conductivity and higher permeability of the extracellular matrix of malignant tissue. The higher ionic concentration in the more active cellular environments and different physiological conditions (see Positron Tomography (PET)), allow even spatial resolution by this effect Electric Impedance Tomography (EIT) and Current Density Image (CDI). *In vitro* experiments, the healthy fibroblast remains intact, while the aggressively malignant melanoma cells are destroyed. Oncothermia is based on the modulated electric field effect, which works in synergy of the classical temperature-based hyperthermia concept. In preclinical conditions (*in vivo* and *in vitro*) many measurements were done in animals and there are many interested users who tried up till now the temperature development by the method, which is a complex, invasive measurement approach.

The constrained thermodynamic transport effect destabilizes the cell membrane, increases its permeability and lead to its bobbling and distortion. These high efficacy factors favor oncothermia over hyperthermia. It also produces higher concentration of HSP in the outer membrane in the extracellular matrix. The higher HSP concentration in the vicinity of the malignant cells together with the changes of the adherent connections between the cells induces apoptosis. Change of adherent connections (E-cadherin and β-catenin) are also indicators of the gain of the social signals promoting the apoptosis. Remarkable change could be observed on beta-catenin dynamic development by time after the treatment on HepG2 human hepatocellular carcinoma cell-line. This considerable change after 24 hours of the treatment is sharply different from hyperthermia on the same temperature, and supports other observations of the non-temperature dependent processes. The sudden regrouping of the beta-catenin and its enrichment at the cell-nuclei could be an indicator of apoptosis. [34]

Clinical Experience

Oncothermia is a complementary therapy, applied together with all the "gold standard" therapies like surgery, and radiotherapy to improve blood flow and oxygenation, also applied pre and post-radiation therapy, and with chemotherapy boosting drug delivery. The new therapies i.e. immuno-therapies, dendritic-cell treatments, stem-cell treatments, gene-therapies, virus-therapies, etc. are all applicable with oncothermia. Its application as monotherapy is only possible when the gold standards failed (resistance, kidney or liver failure, blood count problem, etc.). In this case, it is a palliative method. In most of the cases, oncothermia is applied in high line treatments due to the possible satisfaction of the gold-standard therapies in first- second- and even third-line. The fourth line application of oncothermia is general, no contraindication could be listed due to the stage of the patients. Oncothermia could be applied in all the tumor-kinds, including the central nervous system, lung and liver.

It is commonly used for solid tumors like lung, liver, pancreas, brain, gastrointestinal, gynecological, etc. [35, 36]

We compared the 1st year survivals rate on a huge number of patients which showed good results in all the registered sites. [37] The retrospective analyses in independent clinics show coherence in the success, and definitely and significantly higher survival time than the large databases.

Very successful application is for brain gliomas.[38-41] The obtained data were significantly higher than the data of the large international databases. A dose escalating Phase I clinical study was performed at the Neurology Clinic, University of Regensburg, showing the safety when applied to the brain. The safety of the treatment could be shown by the spectacularly

documented near-eye case, when the tumor disappeared by the oncothermia treatment, while the eye remained unhurt, intact from the treatment (Fig 1). [42]

The registered oncothermia data in brain glioma when compared with large international databases, (Fig. 2).

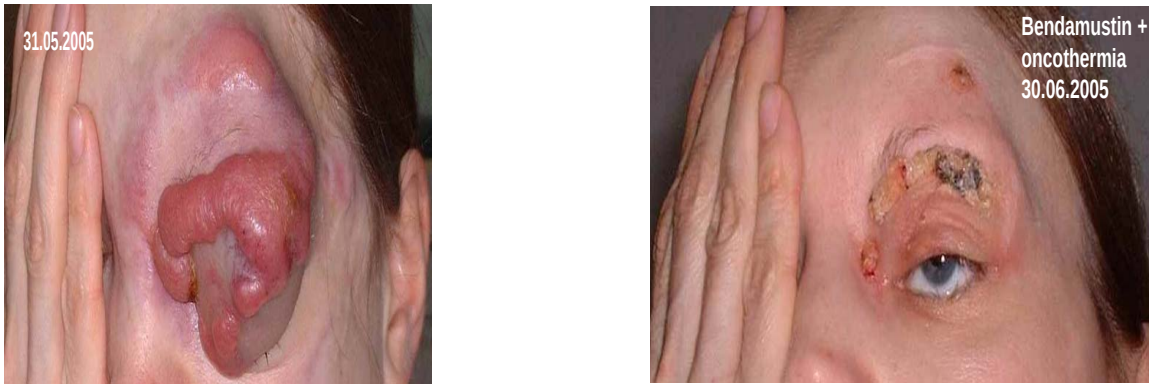

Figure (1): The near-eye treatment (38 y, female; Non-Hodgkin Lymphoma, combination with chemotherapy "Bendamustin").

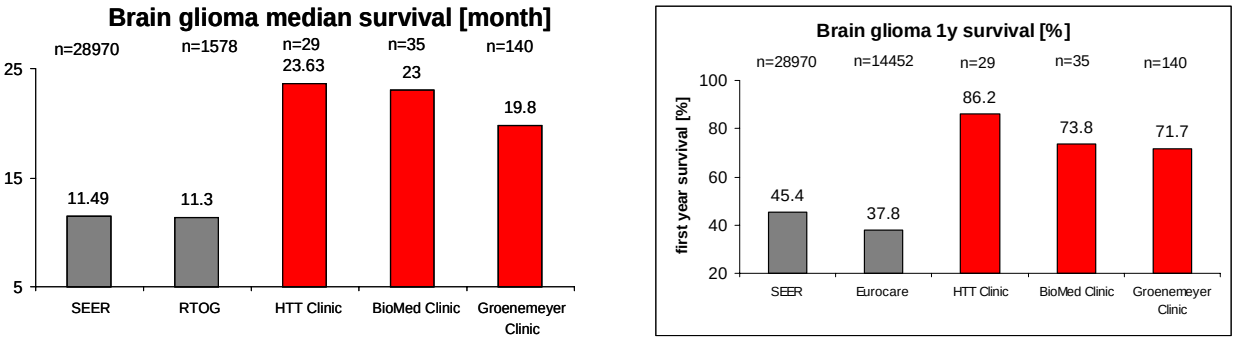

Figure (2): The median and first year survival comparing oncothermia with SEER and RTOG results.

The metastatic liver tumor is a very complicated issue due to the effective cooling of the large blood flow and the sensitivity of the organ due to the chemo-toxicity from previous treatments. Colorectal liver metastasis which had failed chemotherapy in advanced cases showed observable response to oncothermia monotherapy, Fig.3, [41] in addition to hepatocellular carcinoma. [43]

Pancreatic carcinoma is a rapid and aggressive disease, and not too many conventional hyperthermia results can be found in this location. [44] Oncothermia results presented in ASCO. [38, 40] Results were repeated in six different clinics in two countries (see Fig. 1), with statistically significant results.

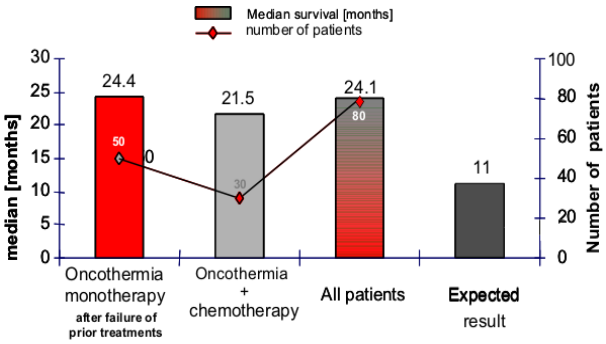

Figure (3): Colorectal cancer liver metastases retrospective clinical study, (n=80).

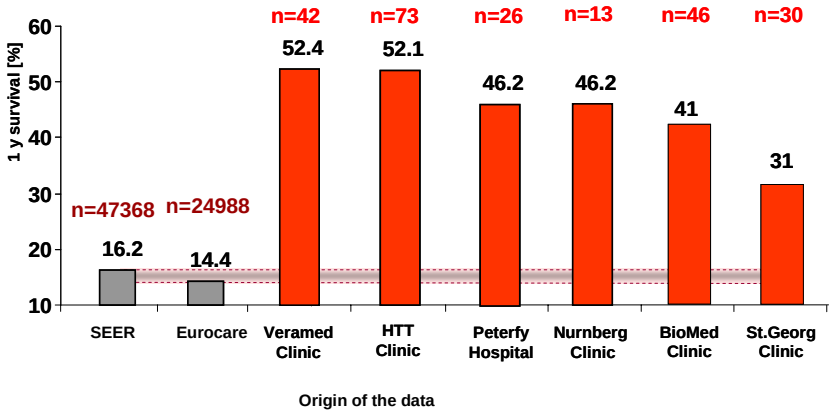

Figure (4): Comparison of six independent oncothermia clinics with the SEER and Eurocare databases.

The lung is also a complicated organ for hyperthermia because of the permanent cooling-ventilation of the breathing. Oncothermia, due to the non-equilibrium approach, is an excellent treatment for that as well, Figure 5.

Also, remarkable effects were published on bone tumors [45] using oncothermia.

The oncothermia challenge is its small fraction only of the overall survival. Oncothermia is applied when other treatments fall, consequently the patients with long overall survival could not have observable life-prolongation, even if oncothermia was effective. The aggressive disease with short survival is a chance to indicate the efficacy. For these reasons, we compared the 1st year survivals rate only (see Fig 1. and Table 1.). In this sense, oncothermia is indicated as a feasible, effective method.

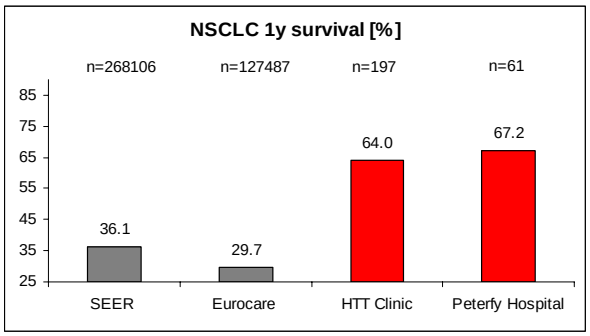

Figure (5): Comparison of oncothermia results with large databases on NSCLC.

The device works over 100 places actively, over

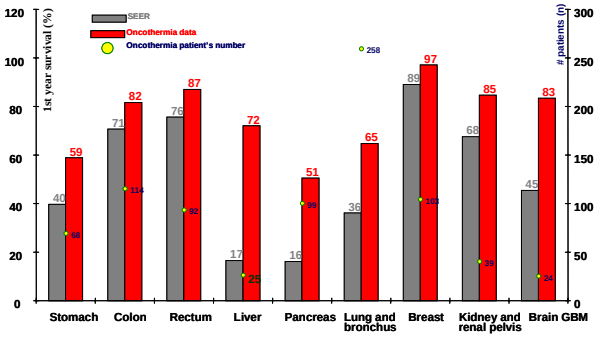

Figure (6): Comparison of the first-year survival rates of various cancers with the large databases.

Improvement of the first-year survival percentages of oncothermia (advanced patients) compare to SEER and Eurocare data weighted average.

Table (1): Additional effect (surplus on best databases in the world) are shown in the 1st and 2nd year survivals. Only increase of the survival could be registered.

#	Localization	Patient number			Oncothermia (+%)	
		SEER	Eurocare	Oncothermia	1st year	2nd year
1	Brain glioma	28970	14452	140	90.63	50.38
2	Colo-rectal	242920	127406	218	20.5	5
3	Esophagus	18302	18231	12	34	67.7
4	Ovary	39383	22929	27	51.1	40.7
5	Corpus uteri	68271	22509	9	15	0
6	Kidney	38270	23683	39	22.2	15.3
7	Liver	12696	9041	25	250.9	221.7
8	Lung	268106	127487	258	96.7	98.1
9	Pancreas	47368	24988	99	230.53	336.71
10	Prostate	243451	82190	18	5.4	0.8
11	Soft-tissue	11256	5011	16	29.5	37.5
12	Stomach	42813	43082	68	47.3	14

The differences of the classical, temperature

15 countries of the world. Oncothermia is twenty years on the market, having permanent development following the state-of-art. No serious toxicity or side effects were reported during this long period. Minor adipose burns were happen in about 3% of all the large number of treatments. (Presently more than 100.000 treatments in a year are provided with the method). Patients report less side effects from the conventional treatment if oncothermia is complementarily applied. They report furthermore a better quality of life and improved well-being.

Comparison of Oncothermia with Other Hyperthermia Methods

The primary challenge of the oncological methods is the selectivity. Classical hyperthermia is selective only by the chosen focused area. Oncothermia however is selective on the cellular level, could eliminate the malignant cells in the transition volume as well as finds the disseminated cells in the area as well. This means it is more effective for the malignant cell killing, without destroying the healthy cells.

All oncological methods are challenged by their reproducible control. Chemotherapy uses mg/m^2 radiotherapy J/kg units. The classical hyperthermia controls the temperature as the average energy of the given volume, measures in ^{o}C. Oncothermia controls the deposited energy into the given volume. The energy control makes possible to use normal dose-parameter like J/kg. The control of this dose is non-invasive and its accuracy is the same as the dose-control of the classical therapies. All of the oncological methods have a treatment concept for dose-determination. All the methods apply the maximal tolerable dose, including the oncothermia as well. There is a strict limit however: the safety, which is measured by toxicity of the dose. Oncothermia measures the safety also by this way, determining the maximal available energy going through the skin-area, measured in J/m^2.

controlled hyperthermia and the oncothermia is summarized in Table (2).

Table (2): Comparison of main parameters of classical hyperthermia and oncothermia.

	TEMPERAURE CONTROLLED HYPERTHERMIA	DOSE CONTROLLED HYPERTHERMIA (ONCOTHERMIA)
	SAFETY	
Parameter	temperature (^{o}C)	energy (kJ/m^2)
Technical	invasive or MRI	power-meter
Challenges	hot-spots (volume)	hot-fat (surface)
	QUALITY-GUIDLINE	
Parameter	special temperature (CAM43,T_{90})	conventional (kJ/kg)
Technical	space distribution	power-measurement
Challenges	give proper dose	give proper dose
	CONTROL, REPRODUCIBILITY	
Parameter	Focus by temperature	self-selective
Technical	Physiology & movements relevant	Physiology & movements irrelevant
Challenges	cylindrical	shape-keeping

Oncothermia could be used for such malignancies, where other classical hyperthermia methods are unable to manage: brain malignancies, head and neck malignancies, extended liver-, lung-, breast- and gastric-malignancies. These advantages are summarized in Table (3).

Table (3): Comparison of main treatment areas of classical hyperthermia and oncothermia.

Localization	Treatment possible	
	Radiational	Oncothermia
Brain	no	yes
Head&neck	no	yes
Esophagus	partially	yes
Stomach	yes	yes
Pancreas	yes	yes
Liver (&mets.)	partially	yes
Colo-rectal	yes	yes
Prostate	yes	yes
Kidney	yes	yes
Urological	yes	yes
Soft-tissue	yes	yes
Bone	partially	yes
Gynecological	yes	yes
Lung	partially	yes

Oncothermia is energy-dose oriented, and uses this parameter to control properly the processes. However, the temperature grows of course by the energy deposition, which could be measured also by independent invasive local or non-invasive MRI measurements.

The cost/benefit ratio is better for oncothermia, because its price is lower, its installation does not need shielding, no huge place and special arrangement is necessary. Oncothermia has very low energy-consumption and low number of operation personal. The effective engagement time of the device pro patient is much lower than the other hyperthermia methods, due to the easy treatment preparation and use. Summarized in Table (4).

Table (4): Comparison of cost/benefit ratio of classical hyperthermia and oncothermia.

Cost/benefit ratio	Hyperthermia	
	Radiational	Oncothermia
Shielding	needed	not needed
Place	special	regular
Energy consumption	3-4 kW	one kW
Operation personal	3	1
Preparation time for one patient [min]	60	5
Places of installation	large hospitals	any places
Attenuation depth (penetration on 1/e)	2-5 cm	14-18 cm
Energy absorption efficacy	~ 10%	~ 50 %
Intended area of use	trunk, mainly pelvic	every body-parts

The risk/benefit ratio for oncothermia is low. The toxicity is negligible, all together <10%. (Note the patients are in most advanced cases, usually in third line when the oncothermia starts for them.) The risk of the misfocusing and hot-spots in the depth is impossible, due to the self-selective system. The risk of the patient movements during the relatively long treatment (which is the main origin of the misfocusing) has no role in oncothermia, because of the self-selection. Contrary to the largely radiative hyperthermia systems, the electromagnetic radiation is so low at using oncothermia that the device is certified to be applied in living areas (flats) also, so the risk for the using personal is in fact does not exist; summarized in Table (5).

Table 5: Comparison of risk/benefit ratio of classical hyperthermia and oncothermia.

Risk/benefit ratio	Hyperthermia	
	Radiational	Oncothermia
Observable toxicity [%]	~ 70	< 10
Hot spots	possible	impossible
Surface burn	possible	possible
Misfocusing	possible	impossible
Patient's movement compensation	not exists	automatic
Shielding	necessary	not needed
Environmental radiation near by	high	negligable
Energy absorption efficacy	~ 10%	~ 50 %
additional temperature measurement	needed	not necessary

Oncothermia has difference not only from the classical hyperthermia methods, but definitely from the other hyperthermia processes, using electric field (capacitive coupling) as well. The main points are characteristic:

1. Oncothermia uses moderate power to keep the temperature controllable low. The high power will heat the volume [temperature is smeared with time] and no focus control is available. For this oncothermia has special surface control. (It is patented method.).
2. Oncothermia uses conduction heating, not simple capacitive, it is "impedance coupling". When the electrodes have distance (moved a little or air bubbles) the tuning immediately recognizes, and stops the treatment. This is necessary because if the impedance conduction is not proper enough, than the field effect does not work optimally.
3. Oncothermia uses modulation on the carrier frequency. The carrier frequency is only the "transmitter" and the real cell-killing info (for natural apoptosis) is in the modulation. (It is patented method.)
4. The electrodes have special arrangement (patented construction) to make the field effect optimal.

Systemic adverse events of oncothermia include erythema, fat burn and transient fever. The average temperature change was 1.3 °C and maximum was 2.5 °C which all were restored in 1 hour. In addition, some mild to severe fatigue has been noticed in some patients.

Conclusion

Oncothermia has introduced a new paradigm to hyperthermia, solving the historic enigma and controversies of hyperthermia methods in oncology.

It has been proven to be complementary to other treatments. In fact, it enhances the beneficial effects of chemotherapy and radiation. Even a tumor which was resistant to chemo and radiation therapy initially, will respond again following hyperthermia treatment.

The best results are expected in pelvic tumors e.g. frozen pelvis which has exhausted all forms of therapy. In brain tumors where all other modalities had failed. In the elderly who cannot tolerate other conventional therapies. Patients who are having renal or liver disease with poor tolerance to chemotherapy. It is considered an addition to palliative care in treating cancer especially stage IV diseases.

We are convinced that oncothermia has become the fourth modality of the "gold standards" in the armamentarium of cancer therapy.

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الأونكوثيرميا: استخدام الحرارة كعلاج مستعجل في الأورام

مروان العكشة

مستشار أمراض الدم، عمان، الأردن

الملخص

ذكر التداوي عن طريق استخدام الحرارة في ثقافات متقدمة منذ مصر القديمة حوالي عام 2400 قبل الميلاد، وقد استخدم الأطباء اليونان هذه الطريقة العلاجية على الدوام وكانت تدعى في اليونانية إحداث الاحترار Hyperthermia.

الأونكوثيرميا Oncothermia هو النموذج الجديد الذي ينطوي على جيل من الانحدار في درجة الحرارة عن طريق امتصاص الانتقاء الذاتي لطاقة الحقل الكهربائي على أساس المقاومة للتيار الكهربائي المعدَّل للموجات اللاسلكية لإنتاج تدفق حراري قاتل بين المصفوفة خارج وداخل غشاء خلايا الورم. ينتج عن ذلك تحفيز لجهاز المناعة بحيث يقوم بمهاجمة الخلايا السرطانية المنتشرة في مناطق أخرى من الجسم. وهذه التقنية لا تتعارض مع غيرها من طرق العلاج التقليدية، كالعلاج الكيماوي والشعاعي. وإن انتشار هذه التكنولوجيا على نطاق العالم هو دليل قوي على فعاليتها من حيث السيطرة وتلطيف الألم بالإضافة لإطالة أمد البقاء على قيد الحياة في العديد من الأورام الصلبة ، مثل أورام الكبد والبنكرياس والدماغ والبروستاتا والرئة عندما تفشل العلاجات الأخرى.

الكلمات الدالة: الأونكوثيرميا، الأورام السرطانية، إحداث الاحترار، العلاج الكيماوي والشعاعي.