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Oncothermia: New Method of Tumor Therapy

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Abstract

Oncothermia is a kind of hyperthermia in oncology. Its efficacy is successfully proven for different advanced cancer localizations, frequently when other therapies fail. Clinical studies and results show its advantages in oncology. Oncothermia is a self-selective process to concentrate the energy on malignant cells targeting their cellular membrane, using the temperature gradient to generate heat-flow between the extra- and intracellular electrolytes, acting to ignite apoptotic processes from outer signal-pathways. Synergies of oncothermia with some chemotherapy were observed, having more efficacy than in the conventional heating combinations. Experiments and clinical results showed the higher benefit of the oncothermia when compare with the results of classical hyperthermia activity at same level of temperature. This paper will review the literature and illustrates the difference between oncothermia and hyperthermia treatment. It will also highlight the effectiveness of oncothermia treatment for different types of tumor. Oncothermia is widely used in numerous clinics and hospitals enjoying definite clinical benefit on elongation of the survival time accompanied with good quality of life.

Keywords: Oncothermia, clinical applications, clinical studied cancer, tumor, hyperthermia, electric-field, electromagnetic radiation, electromagnetic field.

Introduction

Hyperthermia is an age old therapy which originated from Egypt. This age old tradition has been revived by the discovery of electromagnetic energy without causing significant toxicity, absorption of electromagnetic energy directly or indirectly promotes tumor destruction with different favorable physiological and cellular effects. Oncological hyperthermia is the combination therapy, providing synergistic effects with most of classical treatments. Recent books on radiology and oncology have dedicated a part of its topic on hyperthermia, with no surprise there are large number of books discussing this, it's also be discussed and referred in different books and high-ranked clinical journals. [1, 2].

In medical literature hyperthermia has varieties of definition which all involves high temperature and differ only in localization which ranged from cellular to whole body heating. Hyperthermia is involves over heating of a particular affected tissue [3,4].

Hyperthermia involves energy transfer mechanism which regulates and causes changes in the energy flowing in the tumor region. The modern conventional traditional oncological hyperthermia methods [1] use non-ionizing electromagnetic radiation [3]. The changes, however, could have both the directions, the accelerated growth and promoted dissemination is also an option together with the opposite: to suppress of the tumor growth, destroy the malignant cells. Due to the opposite possibilities the method and the technique of the energy-transfer have crucial role.

The controversial results of the causes of hyperthermia therapy is technically challenging the deep heating to medical and technical personals [6,7]. How deep-seated tumors can affected by energy? Selection between malignant and non-malignant normal areas? How to enhance the effect of hyperthermia on malignant area and avoid changes in normal areas? How to reduce or prevent irritation / toxicity to normal cells? How to produce reproducible dose and control the medical treatment? The answers are delivered by oncothermia.

Oncothermia had formulated a new paradigm, [4] trying to make it clear "What is against the acceptance of hyperthermia?" [5]. It is no question: hyperthermia is a thermal medicine. The heating, the energy absorption in the living tissue and in consequence the rise of its temperature is the basic mechanism of hyperthermia. Oncothermia is definitely hyperthermia, it uses thermal

effects in its action. The temperature in nano-ranges could be even higher than what the local non-invasive hyperthermia methods usually produce.

Oncothermia [6], is a kind of oncologic hyperthermia using well selective electromagnetic effect [7] for the cancer-cells. Oncothermia adopts low-radio frequency to modulates the electromagnetic effect of the methods of traditional oncology with significant applications [8].

Preclinical Studies

Using specific difference among the tumor cells and healthy cells, oncothermia overcomes all the challenges posed by hyperthermia in oncology [9], by using electromagnetic way [10]:

1. Applying mechanism like self selective in which current goes self-selectively only to the affected malignant cells (in this case the focus would be automatic). [11].
2. The method of oncothermia modifies the distribution of energy, to optimize the selective distribution and avoids the homogeneous heating of the area. It targets the cell membranes by affecting the extra-cellular matrix and heating up their electrolyte thus initiate heat flow from extra-to intra-cellular compartments through the membrane becomes more transparent, and destroyed [12].

These points are realized, and this procedure is called modulated electro-hyperthermia or oncothermia [13]. Oncothermia was designed after considering many theoretical considerations for idea work. Application of oncothermia is also supported by fractal-physiology) studies or fluctuation analysis. [14].

To understand the effect of oncothermia alone and compared with traditional methods of heating some preclinical experiments has been conducted. The experimental setup allowed maintaining conditions identical for both methods of heating, heating in conventional manner and in the form of oncothermia. Onchothermia experiments (in-vivo and in-vitro) were performed by a laboratory device specially developed for such purposes.

Oncothermia is a selective process in which the extracellular matrix of the cancerous tissue has higher conductivity and allows radiation [15]. It is well documented in the literature [18] that oncothermia selectively destroys the malignant melanoma cells (A431 cell line) without affecting the normal fibroblast. [16].

The changes in heat transport across plasma membrane induce bobbling and distortion in the membrane [12]. These are high efficacy factors favoring oncothermia over its temperature-equivalent hyperthermia counterpart.

The setup was configured to provide fine temperature control, which is responsible for heating, maintaining the temperature and dynamic cooling. Temperature changes lead to induction of shock protein. The characterization by the temperature like average was validated by luciferase transient transfected HEK293 cell lines [17].

The broken adherent connections (E-cadherin and β-catenin) could be reestablished by oncothermia allowing the “social signals” and so promoting the apoptosis [18].

In the study of effect of oncothermia in human hepatocellular carcinoma (HepG2 cellline), a significant changes in dynamic development of beta-catenin was observed after 24 hours of the treatment [19]. Apoptosis is an indicator of the sudden regrouping of beta-catenin and its enrichment in the cell nucleus [21]. Proteins conditions of apoptosis induction by the external signal are shown in the mRNA level [22] and in protein level [23].

It has been shown, that the apoptotic process by excitation of the cytoplasmic membrane is caspase independent in majority [19], and the upregulation of death receptor TRAIL-R2 (DR5) together with FAS and FADD proteins has definite role in it [20]. AIF nuclear translocalization was observed at 14-24h, which again well corresponds with the caspase-independent signal transduction [21]. The mitochondrial pore formation (BAX) was associated with cytochrome C release, which is generally the “point of no return” of the apoptotic process [22]. The DNA fragmentation of late apoptotic process was obviously shown by a massive TUNEL positivity developed at 24-48h post-treatment.

At the same temperature in hyperthermia necrosis is preferred whereas in oncothermia apoptosis was more likely as observed by detecting double strain of DNA (DAP) staining and by measuring the enzymatic labeled strain break of DNA (TUNEL- FICT). The results indicate that in-vivo and in-vitro correlation. The outstanding tumor targeting can be proven by the temperature measurement in the cancerous and the neighboring tissues.

In vivo effect was proved by the Xenograft tumor-models. The model was obtained by inoculation of Human colorectal carcinoma cell-line (HT-29) subcutaneously, into the thigh region of nude mice with 6 x 10^6 cells into the thigh of nude mice. 18 Days after the tumor inoculation the experiments were conducted. Animals which developed tumors symmetrically and of approximately the same size were included in the study.

Local classical hyperthermia and oncothermia were used in the study. Fluoro-optical method was used to control and accurately measure intra-tumoral temperature.

Mortality rate after treatment was calculated by morphological criteria comparing the different modalities of treatment on basis of pathological changes and by distinguishing area of intensive proliferation from other areas showing necrotic, dead cells. Changes in tumor area of animals that of control and treated regions were compared and analyzed statistically. Statistical significant difference was observed. (Fig. 1).

Figure 2 depicts the comparison and histological evaluation of hyperthermia and oncothermia combined both methods with mitomycin-c (MMC) single dose chemotherapy in vivo at tissue and cellular level. Nude mice having HT29 human colorectal carcinoma cell line derived xenograft tumor model was used. Animals (2 each) of hyperthermia (42ºC) and oncothermia (42 ºC) were treated with 3 mg/kg mitomycin-C (half an hour prior the treatment).

The effect of temperature was investigated [23]. The same temperature application of the two thermal treatments was tried together with the only field application (cooled back) case (Fig. 4.). Figure 4 indicated the advantage of oncothermia where the electric field has significantly higher synergistic effect on cell-killing process (Fig. 4) .

Clinical studies

Oncothermia is a method realizing the above effects in personalized manner [24], utilizing the energy liberation and consequent heating at the immediate vicinity of the outer cell-membrane of the tumor cells. Numerous in-silico, in-vitro, in-vivo and preclinical experiments take precedence of the clinical applications, and the method is in fact applied worldwide [25]. Several clinical studies are reported which shows the efficacy of hyperthermia in oncology. Interesting results were observed with the irradiative as well as with capacitive hyperthermia, with some serious troubles.

In year 2000, what seems a breakthrough was recorded [26] in cervical carcinoma, which is a serious condition, using combination of hyperthermia with radiotherapy. But, later the results could not be reproduced [27]. The optimum temperature required for activity could not be optimized [28]. The definite problem is always to find optimum energy required for targeting and treating the tumor [31, 32].

The efficacy of hyperthermia in oncology was shown in results of many clinical studies, but the drawback in some of these studies are shown in difficulties of comparing with controls and sometimes the unrepeatability as mentioned cancerous clinical studies of carcinoma of cervix [29] [30]) [31].

Oncothermia can be applied in cases when conventional heating has definite complications or even contraindication. These are the near-eye applications, the bleeding, inflammatory cases and the sensitive organs (like brain) in advanced conditions (like large intracranial pressure). There are multiple case reports showing unique possibilities of oncothermia in these cases above. For example, the case of a 67 years old patient who had an inoperable squamous epithelium carcinoma in sphenoidalis sinus causing right opthalomology, treated with radiation and oncothermia. The results is a complete remission of the tumors. This is a case of near eye application [32].

Another example: a case report of a male patient of 54 years with carcinoma of esophagus carcinoma, treated with chemotherapy, surgery 50Gy-radiotherapy were not effective, the condition progressed to dysphagia (blocking the food-passage), Then treated with 6 oncothermia [33]. The condition showed improvement and then, after 12 treatments there was complete regression of the tumor.

Several research papers and clinical data published indicates the utility of oncothermia. In retrospective, study of results of using oncothermia in human, including reviews and research papers, most of these studies were single arm, open label studies for treating people suffering from advanced stages, where the traditional methods of treatment had failed. It includes inoperable and progressive malignancies after fasted chemo- and radiotherapies. Exclusions were only the well-known contraindications of hyperthermia: after organ-transplant (due to the massive immune-suppression), pregnancy, missing communication ability, missing temperature sensing on the treated area, etc. High attention and exclusive care is necessary in cases of electric implants (like peacemaker) or large metallic implants (like hip-replacement or skull-cover), patients with epilepsy, with high sensitivity for electric fields or other personal problems or comorbidities.

Some case show erythema (<8%), at site of treatment but no subcutaneous toxicity or other side effects, when there is a conventional treatments (radiotherapy and/or chemotherapy), patients show the usual toxic effect. Most patients reported less pain than before with feeling of being better

In the retrospective studies of collection of cases one obvious negative drawback appear, that is the lack of controls and there is a bias in selection of cases according to voluntary decisions. In these studies the end points were to compare the survival rate to be compared with conventional treatments.

The treatments were made on a voluntary basis for ITT population, which was negative bias as well. Positive bias was the selected very advanced patient-population. Also positive is the missing "trial psycho-attention" and the entirely regular treatment conditions (no extra care is given). The primary endpoints of the studies were always the survival rate, which was evaluated by regular descriptive biostatistics and log-rank survival test.

Most cases that were included in studies using oncothermia in treatment of brain, lung, liver, pancreas, g.i.t, vaginal and testicular tumors and these form a vast data. The retrospective data are compared to the large databases (Seer [34] and Eurocare [35]), having possibility to see the position to the best available data in a huge average.

The clinical studies of oncothermia cover various lesions [25]. Average number of patients in the studies is 53, by lesions 116. Maximal patient number in a study (Phase III) was 311 (NSCLC) [36]. The average oncothermia enhancement ratio (ratio of the median survival of responders to non-responders) was 5.1. Some special results are published for gliomas [37, 38, 39, 40, 41]; for hepatocellular carcinoma (HCC) [42]; for liver, (metastatic of colorectal origin) [43, 44]; for bone metastasis from NSCLC [45]; for pancreas [46, 47]; for cervix [48], for ovary [49]; for prostate [50], for soft-tissue sarcoma [51], for biliary carcinoma [52]. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages.

Though the survival rate of cases treated by oncothermia is very low but still this is better than the classical treatments. Mostly oncothermia was applied after failure of other treatments.

The efficacy of onchothermia is indicated, when it has some benefit in cases where the disease is aggressive with short survival. For these reasons Szasz and Dani, have compared the 1st year survival rate only (see Fig 5). In this sense oncothermia is indicated as a feasible, effective method [53].

The median of overall survival time is also gained in most of the localizations despite of the only advanced cases in oncothermia treatments, (Table 1.).

Studies of using oncothermias in brain tumors specially in brain-gliomas were reported in papers presented in Conferences like ASCO [54], ICACT [55], ESHO [56], ICHS [57], ICHO [58], and others [40, 59]. The results seem to indicate a significantly higher survival rates in comparisons with other treatment and also age-adjusted survival is higher.

Oncothermia is found to be exceptionally good in the complicated situations, which arose due to cooling of large blood flow and chemo-toxicity from previous treatments in metastatic liver tumors. Published results indicates that oncothermia is exceptionally good for colorectal liver metastasis as well [40, 60, 61, 62].

Concerning liver tumors, oncothermia was not expected to be very effective due to complicated situation and cooling of large blood flow through it but experimental studies on condition o colorectal metastasis to the liver indicated that oncothermia was successful.

The sensitivity of the liver during chemotherapy in advanced cases (if other treatments were unsuccessful chemotherapy) is well observed in the combination therapy compared to single Oncothermia. [67]. When chemotherapy was combined with oncothermia, it gives a better response that it is used as a single treatment. [62]

The same results were reported concerning carcinoma of pancreas, reports presented at ASCO [63] and other conferences [64, 65, 66] indicated that oncothermia improved the results when combined with conventional treatments. The statistical significance was clearly shown by comparing the results of six different clinics in two countries studying the same cancer having the same cohort with the same protocol. Their definite agreement and deviation from the general databases offer statistical evidence. In spite of that the lung is a complicated organ and has a cooling effect due tyo ventilation of breathing, but oncothermia was proved to be effective as a treatment for lung cancer, that is due to non-equilibrium features of the treatment [60, 66].

Presently oncothermia has installations in 30 countries on five continents providing at least 200.000 treatments in a single year in numerous small medical offices and in large university clinics, too. Oncothermia has altogether 62 clinical up-to-date studies, involving 3790 patients from five countries (Germany, Hungary, Italy, S. Korea, and China). Further clinical trials are in progress for advanced ovarian, breast, pancreas, liver, colorectal and esophagus cancers, in many countries like Germany, Italy, China, S. Korea, S. Africa, and Japan. Multiple clinical and preclinical studies are in progress in various university research centers, too.

Conclusion

The war against cancer [67] had not been finished yet. There are multiple excellent clinical results of the local control of the solid tumors, but the survival time is far not well impressive. Many patients fail to respond to the conventional “gold standard” therapies, and have advanced cases, many times forming terminal stage after multiple treatments. No curative treatment exists for these cases, only palliation helps for a short time; the first goal is to provide acceptable quality of life which is an important factor for oncothermia, too. Oncothermia is devoted to offer curative treatment for patients as the facility of the “no other is possible”, for patients in “hopeless cases” providing over 3rd line treatment approach. However, oncothermia has curative value even in these advanced situations, and makes curative therapy in 3rd-line or over. The professional literature clearly shows the rare facility of the evidence-based clinical trials for these high-line treatments. Other evidences have to be shown when randomized controlled trials are not possible [68]. The challenges of evaluation appear forcefully in case of patients with advanced stages, having inoperable (or partly resected) tumors, having relapsed malignancies, patients who are resistant to the gold-standard treatments, etc. Oncothermia is facing to this challenge as well. Efficacy of oncothermia is shown by multiple curative cases with detailed case reports. Oncothermia is a new, nano-heating hyperthermia method in oncology. It has good clinical achievements in the far-advanced clinical cases, studies, making stable basis of the clinical applications in various advanced primary and metastatic malignancies.

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Table 1. Comparison of median SEER and Oncothermia of overall survival-times

		Patient No		Overall Survival	
#	Tumor location	SEER	Oncothermia	SEER Median	Oncothermia Median
1	Brain glioma	2897	157	11.49	22.4
2	Colo-rectal	242920	295	45.60	27.6
3	Esophagus	18302	17	9.07	29.37
4	Ovary	39383	27	31.78	37.83
5	Corpus Uteri	68271	9	1264	61.5
6	Kidney	38270	52	51.92	36.1
7	Liver	12696	39	7.33	19.8
8	Lung	268106	275	965	16.2
9	Pancreas	47368	124	7.25	12.4
10	Soft-tissue	11256	26	88.88	35.1
11	Stomach	42813	81	10.24	14.7
12	Prostate	243451	18	83.09	38.78

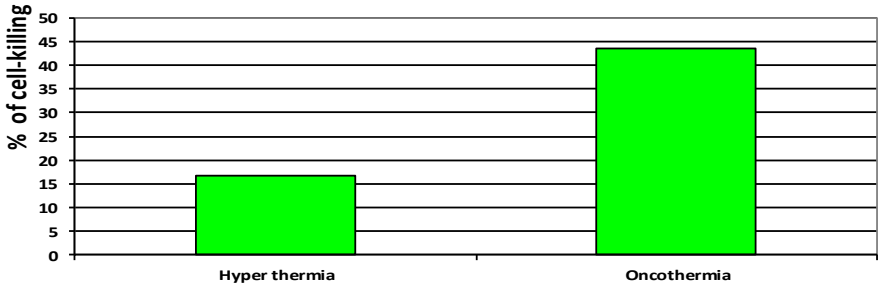
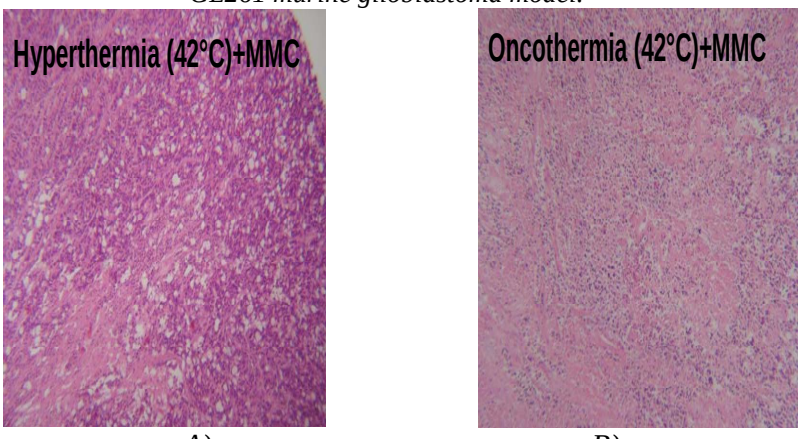


Fig. 1. The macro-evaluation of the efficacy of oncothermia in comparison to the hyperthermia in HT29 tumor xenograft. Change of the areas of dead and vivid parts in percentage of the untreated control on the same experimental animal (data average of 3 animals each). Similar experiments were carried out with the same results for A431 human epidermoid carcinoma xenograft model and GL261 murine glioblastoma model.



A) *B)*

Fig. 2: Investigating the difference of the effects of i.p. administered Mitomycin-C. A). The cell-killing Ais relative to the control tumor on the same animal. (Two-two animals were measured with double tumors on each for control.) B) Hematoxilin-eosin stained microscopic images of tumor samples.

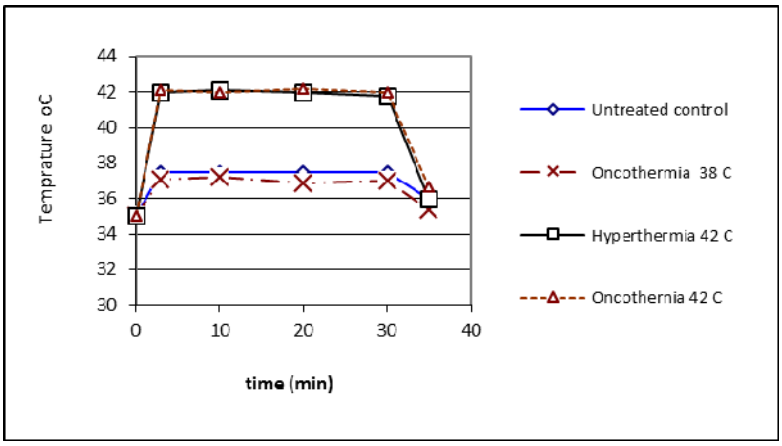


Fig. 3. A sample of the temperature pattern of hyperthermia and oncothermia (at diff. temperature)

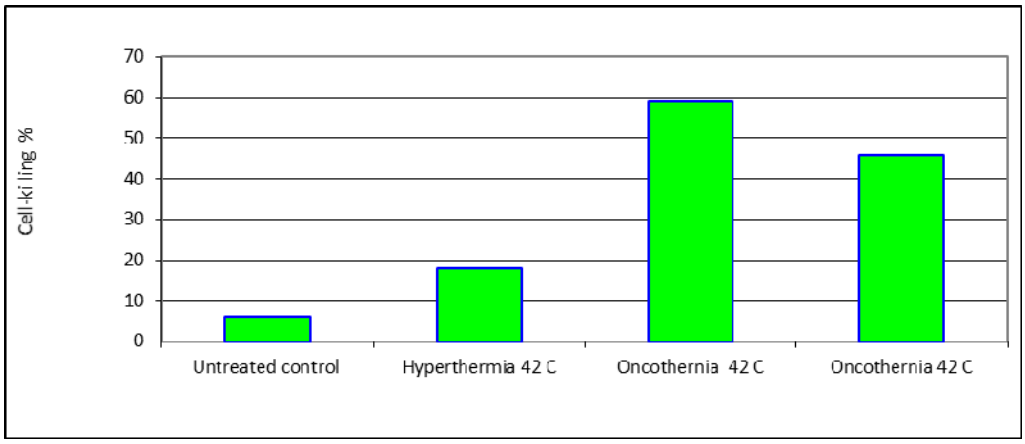


Fig. 4. Comparison of percentage of cell-killing of hyperthermia and oncothermia at different temperatures.

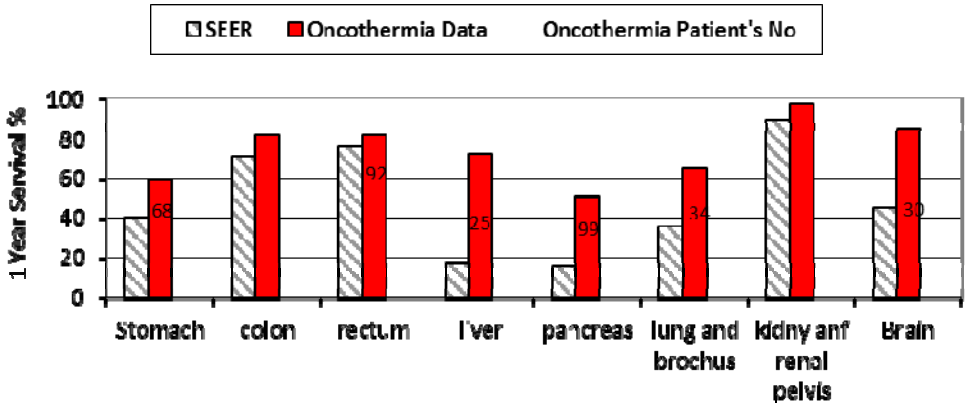


Fig. 5. Comparison of the first-year survival rates of various cancers with the large databases. Improvement of the first-year survival percentages of oncothermia (advanced patients) compared to SEER and Eurocare data weighted average. No of patients of various cancer group are written on each column.