

A Brief Overview of Hyperthermia in Cancer Treatment

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Abstract

Despite the large economic and intellectual efforts, cancer is still not easily treatable disease by conventional therapies. This led ultimately to reconsider hyperthermia, like one of interesting treatment methods connected to immunity and tumor metabolism. Hyperthermia has also the ability to play an additional role when used together with the conventional methods of treatment: surgery, radiotherapy, chemotherapy and immunotherapy. Recent trials in Holland and Germany have demonstrated that hyperthermia can prolong life and decrease disease re-appraisal when used in combination with radiotherapy and chemotherapy. Some tumors seem more responsive than others. In this brief summary we will attempt to give a vision of hyperthermia from a physical stand point, but more importantly we will give clinical and biological aspects. The results obtained in these trials on certain types of cancers such as cervix cancer, recurrent breast cancer and head neck cancer, melanoma, sarcomas, liver, glioblastoma and pancreatic cancer support the use of this technique, although some clinical and technical problems persist and have not been completely resolved.

Keywords: Heat treatment; Hyperthermia; Oncology; Heating techniques; Clinical results

Introduction and Some Historical Notes

Hyperthermia (HT) is the delivery of heat to tumor mass. However this cancer therapy has long been neglected by mainstream medicine. The principal factors that have hampered the clinical use of HT are: the reproducibility of heat deposition into the tumor mass and the not easily measurement of the temperature of the tumor mass and its surrounding tissues [1,2]. The main problem is the missing appropriate dosimetry for clinical protocols [3] Nevertheless, we can say that the application of heat or rather the rise in body temperature (fever) have begun the modern oncology [4]. Re-reading their stories, we could also say that the introduction of drugs and the abandonment of Coley's bacterial toxins coincided with a mistaken view of cancer [5]. The tumor was considered more as a foreign object that grows and which is no longer part of the organism of origin. Fortunately the nature after the many failures of high-dose chemotherapy and radiation therapy has brought us to reconsider the patient and not the tumor mass. Recognizing the complexity of the human body the combinations of the therapies and integrative approaches started to rise. The failures of radiotherapy on advanced disease, pushed Warren in 1935 to use a combination of ionizing radiation with an artificial systemic heating [6]. The data reported were interesting and 29 patients on 32 with advanced cancer experienced an immediate improvement of the general conditions and an increase in survival of 6 months All patients however experienced remission [6,7]. This interesting method of treatment (heat plus radiotherapy) was forgotten, until 1967, when Cavaliere and his group, in Rome successfully treated patients with hyperthermic limb perfusion [8] affected by metastatic melanoma and sarcoma. These researchers were the first to demonstrate some important aspects: 1st tumor cells in

vitro are more sensitive than normal cells to heat; 2nd the amount of cells killed is proportional both to the length of exposure and to the degree of temperatures to which they are exposed [7].

Hyperthermia heating equipment and techniques

Hyperthermia can be defined as a therapy able to raise the temperature in the tumor mass between 41 and 45°C by external physical means. The applied temperature in the complex tumor-mass cannot be kept homogeneous; the methods try to concentrate on the tumor-cells by completing the heat with complementary applications. The energy to be deposited into the tumor mass is obtained using external devices. The raising of temperatures can be loco regional or systemic heating interesting the whole body depending on the aim of the treatment.

Loco regional hyperthermia may be external, interstitial or endocavitary [9]. Single or confined tumor mass is mostly be heated by Radiofrequency (RF), microwave or ultrasound. The easiest and most effective solution was the capacitive coupling of the energy. The original device has been ameliorated peculiarly on the electrode application and on matching EM wave between the two electrodes by Siemens Germany named Thermo flux (1910) where the two electrodes were hold by the therapist. This device was renewed, (Radiotherm, 1947) [7], when the electrode holders were applied. The method was unpopular, and forgotten. One of the pioneering works trying to develop a simple and clinically applicable device was made by Harry LeVeen [10]. LeVeen et al. treated the tumor mass with a capacitive method, using the 13.56 MHz medically free frequency in international standards [11]. The method has been applied since and is widely applied still [12,13]. This capacitive method (or diathermy) is based on the application of two external electrodes at opposite poles of the tumor mass. Between the two poles an Electromagnetic wave (EM)

with a frequency of 13.56 MHz is applied. This wave changes its polarity every 74 nanoseconds, producing standard Joule-heat by the RF-current, connected to the conductivity of the tissues, as well as “exciting” the molecules with high permittivity inside the tumor mass, producing a friction-like heating, the so-called dielectric loss, depending on the electric permittivity of the tissues. The method was further developed and commercialized by Synchrotherm Italy (1985) (Figure 1). The fact that the tumor mass has a greater volume of water and cannot dissipate the heat due to the defected microvasculature which down-regulates the blood-flow over a threshold compared to normal tissue [14], while causing vasodilatation in the healthy tissues leading to increased relative blood perfusion and heat conduction in this region [15,16]. This blood-flow difference allows an increase of heat in a selective way in the tumor mass [17-19].



Another capacitive method similar to that of LeVein is the Japanese Thermotron-RF8 device that works with lower frequency (8 MHz) [20,21]. As reported by Hager and Cheung, tissue penetration by EM is function of frequency, lowering the frequency increases the penetration [9,22]. The two devices have a good penetration on the order of 2-15 cm, but due to their principle of action their action is seriously limited by the fat tissue presence [9,22], which could be dangerously overheated.

BSD another radiofrequency device approved by American FDA, works at frequency range between 75-120 MHz. Its peculiarity is the delivering apparatus that consists in an array of antennae surrounding the body of cancer patient and appropriately focused to concentrate the energy in three dimension (3D) at the tumor mass. For technical notes on this device see the booklet published by Daryoush Fatehi published on line.

Microwave and ultrasound applicators are two other modalities. The wave frequency for microwave is of the order of 1 GHz. As outlined by Robert et al. the heat generation results mainly from dielectric relaxation and the energy deposition are obtained by wave guided applicators [23]. For a complete review on microwave applicators see Cheung IAY, Al-Atrash J [24].

Other approach is the heating by mechanical waves. The ultrasound (US) uses frequencies between 0.5-10 MHz and the heat production happens as the result of the absorption of this ultrasound vibration in the tissue [22]. The focused energy-deposit could be used for targeting the tumor-mass, which is applied by the recent High-Intensity Focused Ultrasound (HIFU) methodology. This methodology is also called thermal surgery due to the development of temperatures over 50 °C in few seconds and has been used for prostate, localized liver tumors, breast and pancreatic tumors [25-28]. Prostatic HIFU application is not without side effects, in fact as outlined by Elterman et al. urosepsis, indwelling catheterization and bladder problems occurred frequently [25]. HIFU as outlined by Zhou [27] has certain limitations, some technical are linked to the source of energy (the ultrasound), others to the length of the treatment session and to the imaging. A reliable thermometry is a limitation but this is common to many commercial devices.

Actually interstitial hyperthermia, a loco regional way of tumor treatment, is gaining a lot of consensus. Interstitial HT delivers heat to the tumor mass directly and this is accomplished using high frequency needle (375 kHz), laser fiber optic conductors or ferromagnetic rods. Typically, this type of therapy is applied in image guided way, usually ultrasound-guided. This therapy offers many advantages compared to other invasive procedures such as reduction of morbidity and mortality. Furthermore, the technique is applied in an out-hospital way reducing the hospital costs. One kind of interstitial treatments is the definitive ablation technique [29]. The ablation methods work on a typical burn-necrosis basis, and the energy is typically provided by impedance-heating with minimally invasive electrode insertion; no heat-flow exists through the skin. Some typical applications are for liver [30], lung [31,32], breast [33]. The modern laser ablative techniques work with ultrafast pulses with ultra large energy-density flow. Depending on the pulse-duration it can be a few 100 W/cm² and in ns intervals can go to 107-108 W/cm² [34], but the provided energy altogether reaches its maximum a few tenths of watts. Their application for liver [35,36], is common. This emerging technology is more-and-more shifted to become the tool of surgery intraoperative or applied by interventional radiology, isolated a little bit from the general hyperthermia practices.

Special emerging hyperthermia in oncology is based on nano-particle applications [37]. In this method, the nanoparticles which are usually administered in a suspension [38] are small heat-absorbers. They are selectively heated up by outside magnetic field, which acts exclusively only on these nanoparticles. The trick there is the accurate targeting of the heat-absorption. The overheated nanoparticles soon give their heat-energy to their neighborhood and heat-up the complete lesion in their vicinity. Huge energy is pumped into these nanoparticles being able to heat-up the complete mass, containing a huge amount of electrolytes. However, most of the electrolytes are uselessly heated up because the heat has to be concentrated on the tumor-cells and exclusively on their membranes to damage them decisional. This request needs a higher preciosity, addressing the nanoparticles selectively on the surface of the tumor-cells, which can be made by antibody-nanoparticle conjugates [39]. It releases of therapeutic

targets at the connected malignant cells while minimizing off-target side effects. The nanoparticle absorption however could block the apoptotic processes induced by complementary therapies, [40,41]. When the delivering nanoparticle which is especially bonded to the membrane of the malignant cell is heated up by outside field, it could make double effect: damage the membrane by heat and/or release the drug which was delivered to the target [42].

A new kind of capacitive coupling was developed by oncothermia (1991, Germany). This method cuts itself adrift from the classical capacitive concepts, and instead of the plane-wave, the RF arrangement more emphasizes the impedance coupling together with multiple specialties [43,44]. The device is similar in its structure to capacitive hyperthermia but concentrates its heat effects on membranes of tumor cells and on the extracellular matrix in its immediate vicinity. A typical device of Oncothermia used in our institutions is illustrated (Figure 2).

It is in fact a nano-heating technology [45], (it is also called nanothermia), and in this meaning it is similar to the nanoparticle heating. The main differences from the conventional capacitive heating is summarized in Table 1.

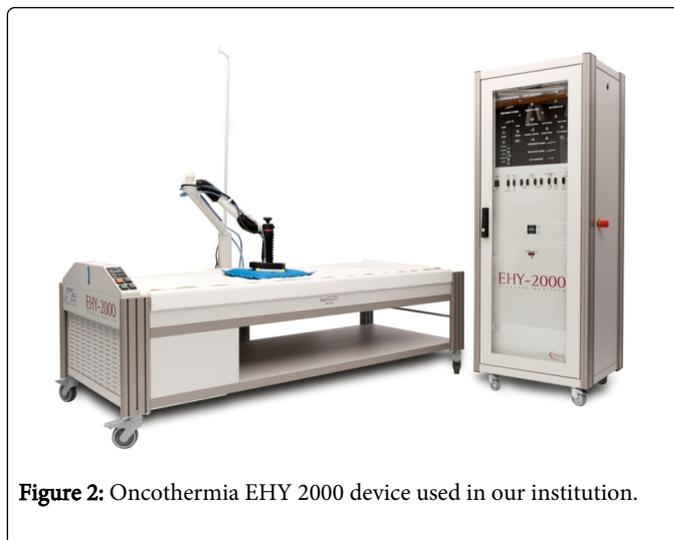


Figure 2: Oncothermia EHY 2000 device used in our institution.

	Parameters		Traditional Capacitive HT	Oncothermia
1	Heating	methods	Macro-heating (selected by macroscopic impedance differences)	Microheating (nano-selected by microscopic impedance differences)
		object	Entire tumor volume	Cell membrane of malignant cells
		Output power	Over 1W/cm ² (generally > 500 W) the goal is to heat up the tumor-mass as high temperature	Less than 0.5 1W/cm ² (generally < 250 W) moderate overall heating high selective (nano) heating enough producing
		focusing	Smearred by patient movement and by heat spreading by time	Remains focused on nano-parts (current follows the movements), low heat-spreading due to mild mass-effect
2	Penetration depth (same frequency)		Determined by the plane waves	Longer
3	Physiologic Effect	Effect on transports	Vasodilatation first, and vasoconstriction over a threshold temperature, not controlled	Mild overall heating, only slight vasodilatation, below the vasoconstriction threshold
		Effects on homeostatic feedbacks	Feedback trying to reestablish the homeostatic equilibrium, works against the heating	Weak homeostatic counter-actions, hyperthermia acts alone
		Immune activation	Immune cells are active over 40°C, it is uncontrolled	Perfect condition for immune activation
		Surface cooling	Strong cooling with extra bolus solution, vasoconstriction in the subcutaneous tissue, higher risk of electric burn by isolation layer	Homeostatic cooling, no extra (secondary)bolus cooling, keeping the homeostatic equilibrium
4	Adverse effects	Support of tumor growth	Strong vasodilation and starts to deliver more glucose, competing with the cell- distortion potential of heat	Mild vasodilatation and the reestablished adherent connections limit the extra glucose delivery
		Risk of metastases	High vasodilatation increases the risk of malignant invasion and the heated healthy volume risks the dissemination	Effect of adherent connections and cytoskeleton of malignant cells blocks the invasion and dissemination
		Safety	Frequent burn toxicity	Rare burning toxicity

5	Selectivity by object and characteristics	Tumor Conductivity	Theoretically works, but RF voltage centered coupling the electrodes and the macro heating cancel the effect	Effectively works with tight impedance coupling by micro heating /overheating cancels the selectivity and the effect)
		Cell permittivity		
		Membrane β Dispersion		
6	Selectivity by pathologic pattern	Fractal modulation	Does not exist	Built -in
7	Complementary Application	Chemotherapy (CT)	Forced over threshold ($> 40^{\circ}\text{C}$) makes vasoconstriction limiting drug delivery to tumor	Complete synergy with the drug delivery extending the chemotaxis with electrostatic
		Radiotherapy (RT)	Forced over threshold ($> 40^{\circ}\text{C}$) creates hypoxia decreasing the efficacy of RT	No hypoxia present –radio sensitization is complete
8	Heating results on cell death		Necrosis is dominant, minor apoptosis by internal apoptotic pathways (in mitochondria)	Dominantly apoptosis via external membranes pathways (Surface cell membrane)
9	Electrode System		Symmetric electrode, Voltage dominating, plane wave coupling	Double asymmetric electrode, current centered impedance coupling
10	DoseFacility		Only temperature ($^{\circ}\text{C}$) [CEM 43 CT x (min)]	Energy like of ionizing radiation
11	Immune activity		Uncontrolled immune effects, necrosis [CEM 43 CT x (min)]	Massive production of apoptotic bodies with production of Danger Signals
12	Abscopal effect		Rare abscopal conditions	Abscopal conditions, immunogenic cell death

Table 1: Comparison of Classical Capacitive HT with Oncothermia on various physical, physiological and biologic parameters

Oncothermia solves this problem without artificial nano-particle delivery. Oncothermia selectively targets the membrane rafts of the malignant cells (~5nm range) and delivers energy for their heating up clearly performing the classical hyperthermia process in nano-range [45]. Oncothermia is a capacitive impedance coupled energy-absorption, it heats the sensitive parts of the malignant cells selectively and effectively. The details of these effects were discussed in numerous papers and chapters of books [43,46-53].

Oncothermia is hyperthermia, only it heats up not the complete tumor mass, but the membranes rafts selectively. It determines a well-absorbed energy on the targeted volume, initializing special effects by their extreme thermal potential, orienting the massive cellular distortion in malignant cells [54]. This method is devoted to keep all positive effects of conventional hyperthermia together with improvement of the imperfections and answer on the challenges. The clue is the microscopic (nanorange) energy-liberation instead of the overall heating of the mass of target [55]. Their selection is based on the high glucose metabolism of the malignant cells (Warburg effect [56], special electromagnetic environment of the malignant cells (Szentgyorgyi effect) [57], with Schwan’s beta/delta-dispersion [58-60], and the pattern of malignancy [61-64] which deviates from their healthy neighborhood, and breaks the “social” signals which are commonly regulating and controlling the healthy cells [65]. Detailed explanation of oncothermia as method was made elsewhere [42,66], and its technical realization was published too [67].

Oncothermia is a highly sophisticated method trying to answer on some of the challenges of hyperthermia [68], and is intended to reintroduce hyperthermia by new standards [69]. It is based on a strong synergy between the temperature and the electric field [70]. The Radiofrequency (RF) current is chosen with a proper amplitude

modulated radiofrequency [71], which is absorbed by the nanoscopic range of the malignant cells (45). The physiological differences of the malignant cells from their healthy counterparts [68] distinguishes the malignancy which is self-selected by additional time-fractal modulation [72], and on such way it is also highly personalized [73].

Biological effects of hyperthermia

The biological response of the tumor to heat depends on both the intrinsic characteristics of the tumor cell itself and on the surrounding environment. Indeed modifications of the tumor microenvironment may increase or decrease the response to heat [74].

Between the range of 40 and 43°C, the majority of cancer cells tend to die, while the majority of healthy cells tend to survive [75]. When cancer cells are subjected to high temperatures (40-43° C) they suffer irreversible damage, in a time and dose dependent way. Heat cell killing occurs exponentially as function of time and dose and its shape is not dissimilar from those obtained by X-rays [76]

The biochemical processes affected by heat are several, as outlined by Pietrangeli and Mondovi [75], and are here summarized:

- DNA, RNA synthesis, DNA repair mechanism and cell respiration are inhibited
- Tumor cell membranes in presence of heat become more permeable and fluid. This may partially explain the increased uptake of drugs.
- DNA polymerases- β key enzymes in multistep repair system and are strongly inhibited.
- Mitochondria suffer different alterations in their cristae

- Enhanced production of heat shock proteins (hsp) is common and this affects thermo-tolerance and tumor immunogenicity.
- Heat increases the influx of reactive oxygen radicals mediating in part the cytotoxicity
- Hyperthermia in combination with drugs promoting apoptosis, has synergistic effect [76]

The greater sensitivity of tumor cells to heat depends from these biochemical effects but also by the microenvironment in which the tumor cells are embedded [73,74].

Tumor cannot grow over a mass > of 1-2 mm³ (10⁶ cells) without organizing a nutritive support through a new vasculature. The neo-vasculature is however insufficient and in the majority of case is disorganized and lacking an ordered hierarchy. The net result even if there is a new vascularization is an imperfect oxygenation and a presence of areas of hypoxia and necrosis. These areas are not distributed evenly in the tumor mass. The result at the cellular level is a combination of low pH, low presence of oxygen, shortage of sugars and other nutrients. The cancer cell that grows at a distance from the capillaries > of 100-200 μm is unable to obtain sufficient oxygen and nutrients and becomes a suffering cell. These suffering cells to ameliorate their state trigger a defense system called Hypoxia Inducible Factor (HIF). HIF is sensitive to oxygen and to resolve this undernourished and hypoxic state induce the production of Vascular Endothelial Factor (VEGF) by tumor cells and its stroma. The principal action of VEGF is the production of neo angiogenesis but triggers also inflammatory reaction. HIF, furthermore, determines the metabolic conversion in tumours to anaerobic glycolysis, the so-called Warburg effect. Following Warburg effect a lot of lactic acid is produced and the extracellular pH becomes acidic producing many biological effects that are out of this discussion [56,76,77]. The acidic and hypoxic environment has negative effects on chemotherapy and radiotherapy, but seems to benefit hyperthermia (Table 2). This hostile environment does not interfere on the action of hyperthermia as demonstrated in glioblastomas by Koutcher and Gerweck [79,80], indeed it seems that hyperthermia could benefit especially for the cells in a state of acute hypoxia compared to those subjected to chronic hypoxia [78-80]. Hahn et al. have shown that metabolic state and energy deprivation increase the heat sensitivity [81]. This aspect, suggests the use of HT with Trans Arterial Chemoembolization (TACE) Another important aspect is related to the change in the composition of the membranes as shown by the groups of Tanaka H and Kokura suggested by one of our group already in 1995 [82-84].

Tumor Structure Cells Affected	Chemotherapy	Radiotherapy	HT	Immunotherapy
Oxygenated Cells	++	+++	+++	+++
Hypoxic Cells	+ -	---	+++	++
Vascular Structure	+	++	+++	+-
Stroma	+	+	++	++
Microcirculation	-	+	++	+

Table 2: Comparison of the effects of HT, Radiotherapy, Chemotherapy and immunotherapy on several cells and tumor structure

Before discussing the positive association between radiotherapy chemotherapy and hyperthermia is useful to discuss the effects of hyperthermia on tumor apoptosis. As reported by Wong [85] apoptosis is an ordered, balanced and programmed cell death process normally present in all cells but lacking in tumor. The tumor tends to have a reduced apoptosis due to a disrupted balance of pro-apoptotic and anti-apoptotic proteins such as Bcl-2 family proteins, p53 expression, and reduced caspase activity, abnormalities of death receptor signaling, or increased endogenous Inhibitors of Apoptosis Proteins (IAPs) [85]. Hyperthermia as evidenced by Ahmed and Zaidi enhances apoptosis [86]. HT leads to increased apoptosis through several biologic processes as increased tumor membranes permeability, increased production of oxygen free radicals, inhibition of DNA repair and alteration of cellular cytoskeleton [86,87]. Other authors have demonstrated that the enhanced apoptotic effect of hyperthermia happens by changing the expression of apoptosis genes, such as p53, Bcl-2 and Bax [88]. Other authors have experimentally shown, at least in melanoma, that the apoptotic effect of HT is obtained by activating not caspases 8 or 9 but activating a non-conventional apoptotic pathway caspases 3/7 [89].

Another important biologic effect of HT is the capacity to enhance the antigenic presentation to effector cells, and the production of heat shock proteins (hsp) [90-93]. Furthermore, HT recruits into the tumor area neutrophils, macrophages, natural killer cells, myeloid suppressor cells and regulatory T cells [92-94]. The recruitment of these cells into the tumor area is normally induced by the hypoxia and coincides with a state of immune suppression [93,95-98]. Hyperthermia as outlined by Repasky group has the ability to increase the perfusion and the oxygenation (see paragraph hyperthermia radiotherapy) of the tumor area reducing so the immune suppressive state and increasing the effectiveness of immunotherapy [93,96]. The association of radiotherapy and hyperthermia, does not only increase the action of radiotherapy but as outlined by Muthana et al. can also affect the behavior of the regulatory T cells and the macrophage activity [94]. In fact, the association of the two therapies decrease the recruitment of the regulatory T cells, compared to hyperthermia alone, and macrophages seems to be affected by this association, decreasing the expression of M2 types [94]. Furthermore, reprogramming in the tumour microenvironment macrophages, hyperthermia in vivo modulates many aspects of innate and adaptive immunity, such as Natural Killers or heat shock proteins [94,97,98] aiding in tumour eradication hallmark of cancer, with its auto sustaining abilities regarding inflammation [90]. The increase of induced by hyperthermia [97], particularly HSP 70, has been found to act as a recognition structure for Natural Killer (NK) cells, increasing their activity [97-100].

Another important anti-tumor effect of HT is the capacity to inhibit angiogenesis. In the late 1988 Fajardo et al. demonstrated that capillary endothelial cells were thermo sensitive. The extent of inhibition was inversely proportional to temperature [101]. Recently Roca et al. have shown that Hyperthermia inhibit angiogenesis in vitro and in vivo by controlling extracellular matrix degradation through the induction of Plasminogen activator inhibitor-1 (PAI-1) [102].

Previous information shows that hyperthermia thanks to its various biological and physiological effects can be used positively with radiation therapy and chemotherapy. A recent review by Horsman has clearly demonstrated that hyperthermia is a potent enhancer of radiotherapy [103]. This effect is evident in vitro and in vivo and from clinical trials emerge that the association improves both local control

and survival, without increasing the side effects [103]. According to Horsman [103] and Schildkopf [104] the reasons for the radio sensitization are several and involve tumor vasculature and oxygenation, inhibition of DNA repair mechanism and the increased formation of toxic DNA double strand breaks. Song et al. since 1985 outlined the importance of hyperthermia in improving perfusion and oxygenation [14,16,17]. These authors noted that this effect was present at mild hyperthermia (40-42°C) and that an enhanced response to radiotherapy and chemotherapy was present [105]. Despite the increased response by combining radiation and hyperthermia as demonstrated by several clinical trials (see the following paragraph), several authors have shown that the improvement in perfusion and oxygenation is not unique and shows a great variability [106,107]. This variability is related in part to the heterogeneity in the organization of tumor neo vasculature and in part to non-uniform distribution of regional regulatory mechanisms inside it [106,108].

Chemotherapy is regarded as the only rational approach to cancer therapy, but it is full of side effects and a number of failures [109]. For chemotherapy we do not just mean the use of cytostatic drugs but also the use of monoclonal antibodies. The reduction of the side effects of chemotherapy and an increase in its effectiveness is certainly a desired result. Preliminary studies of Engelhardt [110], Dahl [111], Hahn [112] Urano [113] and Issels [114] have revealed that hyperthermia showed a synergism with chemotherapy as well as with radiotherapy. We have summarized the synergism and activity of drugs and HT in various micro-environmental conditions, in Table 3. Nevertheless oncologists have shown a deep distrust and ignorance about the use of this association.

Chemotherapy	HT	Oxygenated Cells	Hypoxic Cells	pH ≤ 7
Adriamycin	↑↑	↑↑	ND	ND
Cyclophosphamide	↑↑	↑↑	ND	ND
Bleomycin	↑↑↑	↑↑	↑↑↑	↑↑↑
Mitomycin –C	↑↑	↑↑↑	↑↑↑	↑↑↑
BCNU/TMZ	↑↑	↑	↑↑	↑↑
Carboplatin	↑↑	↑	↑↑↑	↑
Vincristine	↑	↑	ND	ND
Methotrexate	↑	↑	ND	ND
5FU	↑	↑	ND	ND

ND: not determined; †: association strength, BCNU/TMZ: Carmustine (bischloroethylnitrosourea) **Temozolomide**

Table 3: Possible association of chemotherapy with HT and possible potentiation of drugs by HT on oxygenated, hypoxic and pH

The activity of drugs in presence of hyperthermia is in the majority of cases additive and increase with the increase of the temperature [112,115]. A right combination, as illustrated in Table 3, can treat all the cell populations present in the tumor environment (oxygenated, hypoxic, cells in acidic microenvironment). When we use drugs and HT, the drugs behavior can be according to Hahn [112] and Dietzel [115] of three types. The first recognized type is drugs increase their activity slightly with temperature. Example of these kind of drugs are,

Thio-TEPA, Carmustine, lomustine and methyl-CCNU. The second type of behavior, is drugs exhibit increased effectiveness above 42°C. Example of this kind of drugs is Bleomycin. The third type of response regards drugs not active at physiological temperatures but becoming active at temperature of 42°C, see Amphotericin B [115].

Another important aspect to take into consideration is the sequence of administration of heat drugs and Radiotherapy. Regarding the association hyperthermia and radiotherapy Overgaard [116] has clearly demonstrated that the maximum effect is obtained when the two treatment modalities are used synchronously, but as observed by the author this is clinically impractical and therefore should be used in sequence. The clinical data show that the synergism between hyperthermia and radiotherapy can be observed applying HT before or after RT for a period of 4-8 hours. Other authors consider that the additive effect practically disappears if the two therapies are performed at a distance of more than two hours before or after [117].

Chemotherapy may be used synchronously, and generally as noted in the previous section, its activity is additive. The only drug that should be used with caution with hyperthermia and usually after 24 hours is the gemcitabine [117]. The possible interaction of drugs with hyperthermia and with the various physiological parameters present in the tumor microenvironment is illustrated in Table 3. As it is possible to see the synergism between HT and drugs is more useful for hypoxic cells. Another important synergism is between Radiotherapy, chemotherapy and HT (trimodality therapy). In this case the result in the local control of the tumor depends from the sequence of the treatment as demonstrated by Teicher et al for bleomycin, HT and radiotherapy [118]. The authors have demonstrated that Bleomycin is more toxic towards hypoxic cells in presence of HT and that the most successful sequence for obtaining a greater killing effect is bleomycin followed by HT and then by radiotherapy [119]. A right sequence does not have only a better local control of tumor and a decrease in side effects but may control the immune response too. In fact as described by Lee [93] and Muthana [94] and summarized in Table 4, a right sequence between chemotherapy, radiotherapy and HT could control many suppressive cells (Myeloid derived suppressor cells, Regulatory T cells) reducing the suppressive arm of immunity. In the future, studies covering the interaction between chemotherapy, radiotherapy and drugs able to modulate myeloid cells or regulatory T cells (i.e. programmed death-1 [PD-1] and T lymphocyte antigen-4 [CTLA] inhibitors) are desirable [95,120].

Chemotherapy	MDSCs	Tregs	HT
Gemcitabine	Direct toxicity		↑↑
TRA	Elimination of transformation		NA
5FU	Cell death	reduction	↑
Cyclophosphamide		reduction	↑↑
Sunitib	reduction		NA
COX2 Inhibitors	reduction	reduction	↑

MDSCs: Myeloid derived suppressor cells; Tregs: T regulatory cells; TRA: trans retinoic acid; Na: not acquired; †: increase

Table 4: Possible effects of chemotherapy/radiotherapy + HT on Myeloid derived cells and on T regulatory cells (Tregs)

Clinical Benefits of Hyperthermia

In medicine, the results from clinical trials with appropriate statistical means, give us safety in the therapeutic methods useful for treating a specific disease. Several studies have been performed with the appropriate statistical means on hyperthermia and are summarized in Table 5 for RF and MW methods and in Table 6 for oncothermia. The data are not exhaustive and are a collection of those published by several authors [9,121-123]. Analyzing these results it is evident that hyperthermia is really additive methods of treatment, alone is less efficacious and even some success has been obtained, this remains a simple isolated case or a lucky case.

	Tumor Histology	Number of patients	CR%	OR %
RT	Melanoma [124]	19	21	32
RT	Head & Neck [125]	106	34	
RT	Breast Advanced primary – recurrent [126]	307	59	
RT	Cervical cancer [127]	114	83	
RT	Rectal cancer [127]	143	21	
RT	Bladder Cancer [127]	101	73	
RT	Glioblastoma [128]	79	31	
CT	Oesophageal carcinoma [129]	40		41
*	Rectum [130]	36		↑
*	Liver [131]	80		↑
*	Gastric Cancer [132]	33		39↑

CR%: complete response compared to RT or chemotherapy (CT) alone; OR: overall response; ↑ increase in survival; * Trimodality therapy

Table 5: Results of Hyperthermia used with Radiotherapy (RT) and chemotherapy (C) and with trimodality therapy * (modified by 9, 122, 123)

Tumor Histology	Number of patients	Median of Survival (months)
Advanced, relapsed brain gliomas, Phase II, retrospective [133]	12	10
Glioblastoma [134]	92	16
Gastric Cancer [135]	RT 16	81
"	"	"
"	* 4	25
Liver metastases colon rectal origin [136]	22	28
Colon Cancer Phase II prospective [137]	154	
	CTM 53	75
	Only Oncothermia 50	81

	CT 51	91
Ref: references; CTM: Chinese traditional medicine, CT: chemotherapy		

Table 6: Summary of the studies made by oncothermia treatment

Conclusions

Using the words of Dewhirst [138] (who reported Eric Hall) we can say that “the biology is with us, but the physics is against us”. The situation has not changed since 1994, and hyperthermia at least in the United States followed by the majority of countries has abandoned this treatment technique. Only Germany and the Netherlands have continued to study this methodology. The reasons for this neglect are many and as expressed by Dewhirst very much related to the fact that until a few decades ago there were no effective means to store energy in the tissues and ability to clinically determine the temperature reached. Currently some companies are developing other methods to overcome these obstacles. What is sure is that the response to the heat of the tumor is in favor of the patient. This resulted in at least some countries to use the technique privately and out of hospitals, losing in some cases seriousness. Only the method of interstitial hyperthermia techniques has had a strong development, but we have not described simply because we are not skilled in this application.

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