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Thermoradiotheraphy of cancer: an effective approach

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REVIEW

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Abstract

Hyperthermia (HT) means using controlled temperatures of 40-45$^{\circ C}$ for cancer treatment. HT is applied with different methods *e.g.* superficial-HT, locoregional deep-HT, interstitial-HT, intracavity-HT, and whole body-HT. HT can apply in different tumor sites such as breast cancer, melanoma, head and neck, cervix cancer, and glioblastoma. Literatures show that addition of HT to radiotherapy, chemotherapy, or both, will result better tumor response rate, local control, and survival rate; without increasing toxicity. HT can also improve palliative effects in patient. In recent years, due to substantial technical improvements made in achieving selected increase of temperatures in superficial and deep-seated tumors, thermometry, and treatment planning; HT is becoming more clinically accepted in Europe and the USA. HT, as an adjunct cancer treatment modality, is certainly a promising approach; however, it is not well known yet worldwide. Therefore, it seems there is need to know more about that. The purpose of this review is to provide an overview on the application of HT combined with conventional cancer treatment modalities, mainly radiotherapy. The article also introduces mechanism of HT, heating delivery modes, thermometry, and it summarizes results of randomized trials form Western research groups.

Introduction

Nowadays, to eradicate tumor cells and achieve better clinical results, combined treatment regimens are being used [*e.g.* surgery + radiotherapy (RT), surgery + Chemotherapy (ChT), RT + ChT, RT + gene therapy, RT + immunotherapy] [1, 2, 3, 4]. The reason for combination therapy is to increase survival rates and ensure that all tumor cells are eradicated. Respecting to RT, one of the most important problems is hypoxic cells in the centre of tumors which may not be eliminated by using RT alone. Due to insufficient blood perfusion; these cells are more resistant to RT [5]. The Oxygen Enhancement Ratio (OER) for χ and γ Rays is 2-3. Thus, to reach the same cell damages in hypoxic conditions, one needs to increase radiation dose 2-3 times; that certainly will increase the absorbed dose in normal tissues [5]. During recent decades, the following treatment procedures have been tested to overcome hypoxic cells:

- Radiotherapy using a high LET (Linear Energy Transfer) ray, *e.g.* neutron, with high penetration and low OER [5].
- Hyperbaric oxygen, there are certain methods of increased oxygen delivery by the blood such as normobaric oxygen/ carbogen breathing, nicotinamide, blood transfusion, erythropoietin [6, 7].
- Using drugs that specifically increase sensitivity of hypoxic cells (see below: section Chemotherapy plus hyperthermia) [8, 9, 10].
- Hyperthermia (HT), studies show that the controlled increased of the tumor temperature by 3-8$^{\circ C}$, above normal body temperature, for 60-90min, remarkably, increases radio- and chemo sensitivity of the hypoxic cells [11, 12].

The purpose of this review is to introduce HT as an adjunct cancer treatment modality with conventional cancer treatment modalities. However, the focus is mainly on the issues that are related to using HT in combination with RT. The article also introduces HT mechanism, various HT delivery modes, thermal dosimetry, and briefly shows results of randomized trials performed by Western research groups during last two decades.

The history of hyperthermia

The word HT comes from the Greek HYPER, *i.e.* "over, beyond" and THERME, *i.e.* "heat". For millennia, mankind has recognized the therapeutic benefit of using thermal baths as a mean of treating malignant and infectious diseases. As far back as 5000 B.C., ancient Greeks and Egyptian doctors recognized the value of heat in some medical treatments [13].

For many years, scientists have recognized that cancer cells are more sensitive to heat than normal cells, and that at high temperatures cancer cells break down [14]. In the late 19th Century, physicians and scientists began studying the curative effects of hot mineral waters and concluded that its physiologic effects on the body were responsible for the cures witnessed [13]. A worldwide interest in HT was initiated by the 1st international congress on hyperthermic oncology in Washington DC in 1975, when it was shown that HT combined with other treatment modalities yielded markedly improved results. In the last two decades HT has been used in conjunction with RT and/or ChT for cancer treatment.

Hyperthermia mechanism in treatment

In normal tissues, blood vessels dilate when heat is applied, dissipating the heat and cooling down the cell environment. Unlike healthy cells, a tumor is a tightly packed group of cells, and blood circulation is restricted and sluggish [15,16]. At sites with insufficient perfusion, areas with hypoxia and a low pH will develop [17]. Tumor masses tend to have hypoxic cells within the inner part of the tumor. Cells in chronic hypoxic areas are relatively radioresistant, but very sensitive to heat [18,1920]. In summary, prolonged hypoxia generally leads to metabolic changes, such as acidity, and it is these changes that are responsible for the increased sensitization to hyperthermia [21,22,23,24].

HT is especially effective in treating cells under conditions of hypoxia and low pH. HT damages the membranes, cytoskeleton, and nucleus functions of malignant cells. It causes irreversible damage to cellular perspiration of these cells. Heat above 40°C also pushes cancer cells toward acidosis (decreased cellular pH), which decreases the cells' viability and transplantability. Furthermore, heat preferentially kills cells in the S phase of the cell cycle, which are known to be resistant to RT. It is also thought that HT induced accumulation of proteins inhibits the malignant cells from repairing the damage sustained. Tumor blood flow is increased by HT despite the fact that tumor-formed vessels do not expand in response to heat [25]. This makes HT an ideal complementary treatment to RT.

The effect of hyperthermia on tumor cells

Under well-defined nutrient conditions, acute hypoxia alone does not have any significant influence on the cellular response to hyperthermia [26,27,28]. However, a selective tumor cell killing effect is achieved at temperatures between 40 and 45°C *in vivo*, that is related to tumor physiology. The architecture of the vasculature in solid tumors is chaotic, resulting in regions with hypoxia and low pH [29,30,31], which is not found in normal tissues in undisturbed conditions. These environmental factors make cells more sensitive to HT. The effect of HT depends on the temperature and exposure time [32]. Generally, normal tissues tolerate a hyperthermic treatment of 1 hour up to 45°C without relevant clinical damage [33]. Only nervous tissues appear more sensitive. For the central nervous tissue, irreversible damage was found after treatment at 42-42.5°C for longer than 60 min [34]. Treatment of peripheral nervous tissue for more than 30min at 44°C, or an equivalent 'dose', results in temporary functional loss, which recovers within 4 weeks [35]. The main mechanism for cell death is probably protein denaturation, observed at temperatures between 40-45°C, which leads to alterations in multimolecular structures like cytoskeleton and membranes, and changes in enzyme complexes for DNA synthesis and repair [36]. HT also interferes with the cellular repair of radiation-induced DNA damages, probably by an effect on cellular proteins [37].

Radiotherapy plus hyperthermia

The HT mechanisms and its effect on tumor cells justify using additive complementary of heat and RT. Why HT is an ideal companion to RT? It is because that radiation kills the oxygenated outer cells, while heat acts on the inner low-oxygen cells. HT oxygenates the hypoxic cells and so making them more susceptible to radiation damage. Two issues should be considered in the use of combined RT and HT:

- The Thermal Enhancement Ratio (TER): TER is 1.5-2 in temperatures of 40-45°C. For radiation-induced cell kill TER is greater under hypoxic conditions, increases with higher temperatures and longer exposure times, and decreases with longer time-intervals between the two modalities. Maximum TER is obtained when RT and HT are applied simultaneously. *In vivo* studies have demonstrated that the effect of RT can be enhanced by HT up to 1.2-5 [38,39]. Nevertheless, using RT and HT spontaneously is not possible for all patients and tumor sites. Maximum therapeutic gain will be obtained when HT is used within 6 hrs after RT [40,41,42,43,44,].
- Thermotolerance: most of the tumor cells are killed when temperature ≥ 43°C is applied for 40-60min, but a few of them remain alive. The remaining cells got resistance to heat, which is called thermotolerance and returns to ground state in a few days. The higher the initial temperature induces a higher thermotolerance. The kinetics and degree of thermotolerance that develops is dependent not only on the heating temperature, but also on the cell type, the time of heating, and the interval between successive heat treatments [45]. However, applying a standard RT dose, *i.e.* 2 Gy/fraction, will not affect a thermal resistance [46, 47].

A number of randomized controlled trials comparing RT plus HT to RT alone have demonstrated that the average complete response for RT alone can be increased significantly by the addition of HT [48, 49, 50, 51, 52]. Overall, HT is probably the most potent radiosensitizer known to date [53].

Chemotherapy plus hyperthermia

For the combination of ChT and HT, the following process can explain the additive effects. Drug concentration will be less in the insufficiently perfused tumor regions. In addition, many drugs are potentiated by heat. Furthermore, it has been shown for mitomycin C, nitrosureas, cisplatin, doxorubicin, melphalan, cyclophosphamide, anthracyclins, mitoxantrone, and bleomycin that the addition of HT to ChT can counteract drug resistance [54,55,56,57,58]. Generally, interaction is only seen when the two treatments are given in close sequence. The most important mechanisms for an interactive effect are increasing intracellular drug uptake, enhanced DNA damage and higher intratumor drug concentrations, resulting from an increase in blood flow.

The drug enhancement ratio depends on temperature and exposure time. The effect of these drugs can be enhanced by a factor of 1.2-10, and an extremely high TER of 23 was even observed for *in vitro* application of melphalan to drug-resistant cells at temperature of 44°C [54]. With antimetabolites vinblastine, vincristine and etoposide, most experiments did not show an interactive effect. In the case of etoposide, cytotoxicity was even

reduced, which was explained by instability of the drug at an increased temperature. Whether the clinical combination of HT and ChT leads to therapeutic gain depends on the temperature increase in the organs for which the used drug is toxic and the heating method [59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71].

Trimodality treatment

There is an increasing interest in the clinical application of trimodality treatment, in which RT, ChT and HT are combined. Earlier trimodality treatment trials in Japan demonstrated the value of adding HT in patients with oesophageal cancer [72, 73, 74,]. More recent studies on preoperative treatment in rectal cancer, head and neck tumors and recurrent breast cancer have revealed that trimodality treatment is feasible and appears effective [75, 76, 77, 78, 79, 80].

Methods to increase tumor temperatures

To reach temperatures 3-8°C above normal body temperature in a defined target volume is a technical challenge and still under development [81]. HT, in most of the cases, is applied using electromagnetic waves. Electromagnetic energy is transferred to the material by polarization and rotation of dipolar molecules, and drift of electrons and ions. The amount of energy transferred by the electric field to a material can be derived from *Poynting's theorem*, where the average power (P) deposition to the material is given by:

(1) $$P = \frac{1}{2}\sigma \cdot |E|^2$$

where σ is electric conductivity (Sm^{-1}) and E is the complex electric field vector. For HT the energy absorption in a material is often normalized to its mass density [ρ (kgm^{-3})] and is then called specific absorption rate (SAR), measured in Wkg^{-1} [82]:

(2) $$SAR = \frac{1}{2\rho}\sigma \cdot |E|^2$$

Human basal metabolic rate is above 1 Wkg^{-1}. Perfusion counteracts the temperature rise. Perfusion rates in human tumors are around 5-15 ml/100g per min, but they vary widely. To reach therapeutic temperatures of 40-45°C necessitates power density of 20-40 Wkg^{-1} at the target region [81]. At present, the optimum temperature distribution for clinical purposes is unknown. Temperature distributions achieved to date have limited absolute values and homogeneity, mainly because of physical and physiological characteristics such as electrical tissue boundaries, local perfusion variations, and perfusion regulations. Approximately 50% of deeply located tumors reach at least 42°C at one particular measurement point.

Studies have shown that uncritical adoption of preclinical results into clinical guidelines for tumor temperatures is not justified. Nevertheless, many phase II clinical studies have shown associations between tumor response and characteristics of temperature distribution (minimum temperature or minimum thermal dose in the tumor area). Even though the tumor temperatures that have to be reached for clinical efficacy are still unclear, one should achieve temperature distributions as high, in the range of 40-45°C, and homogeneous as possible [81].

Local hyperthermia

"Superficial tumors can be heated by means of antennas or applicators emitting mostly microwaves or radiowaves placed on their surfaces with a contacting medium. Several types of applicators have been used clinically, *i.e.* waveguide applicators, horn, spiral, current sheet, and compact applicators" [81]. The electromagnetic coupling of the applicator to the tissue is ensured by a water bolus. Commercially available electromagnetic applicators have a typical emitting diameter of 15cm at a frequency of 150-430MHz with therapeutic depths not more than 3cm [81].

Interstitial and endocavitary hyperthermia

For interstitial HT, antennas or applicators are implanted within the tumor, and in most cases a heat treatment is administered in combination with brachytherapy. "This technique is suitable for tumors that are less than 5cm in diameter, but mainly in any location feasible for implantation (*i.e.* head and neck, prostate)" [81]. "Various antenna types are available, including microwave antennas, radiofrequency (RF) electrodes, ultrasound transducers, heat sources (ferromagnetic seeds, hot water tubes), and laser fibers. To ensure therapeutic temperatures at all points of the target volume requires a distance between adjacent applicators of not more than 1·5cm. But such close positioning is very invasive. Furthermore, positioning and orientation of microwave antennas can be critical because of their sensitivity to interference. The restricted axial length results in further limitations in the SAR distribution. The development of segmented RF electrodes leads to an interstitial HT system capable of three-dimensional (3D) control, ensuring improved temperature control in the target volume. These systems are undergoing clinical evaluation. Endocavitary antennas are inserted in natural openings of hollow organs such as the urethra, rectum, vagina, cervix, and oesophagus. They are based on the same physical principles as interstitial antennas, with dimensions in the range of centimeters (and therefore, larger clinical penetration depth)" [81].

Regional hyperthermia and part-body hyperthermia

The cylindrical Sigma family applicators, with arrays of antennas are used for deep-seated tumors, *i.e.* of the pelvis or abdomen. Patient is positioned within the applicator and the space between applicator and skin is filled with a water bolus. For children and lower extremities the Sigma-30 (diameter: 30cm) or Sigma-40 (diameter: 40cm) is used. The Sigma-60 (diameter: 60cm) is a widely spread applicator, which consists of four dipole antenna pairs arranged in a ring around the patient. Even though each antenna pair can be controlled in phase and amplitude, there are restrictions in terms of the generated SAR distribution. "Model calculations show significant improvements in control of power distribution by increasing the antenna number with the assumption of optimum adjustment of phases and amplitudes. The frequency of 100-150MHz may be an additional variable" [81]. The 3D anatomy decisively influences the power distribution. The theoretical studies led to use of applicator, *i.e.* Sigma-Eye (38×58cm) with 12 channels,

which allow 3D SAR control. The disadvantage of the Sigma-Eye is that it can not use for all patient sizes. A new generation of the applicators, *i.e.* Sigma-60-Ellipse (37×58cm), which is elliptical in shape, is under investigation [83]. Recently, we found that the Sigma-60 and the Sigma-Eye can be replaced by the Sigma-60-Ellipse applicator [84].

Whole-body hyperthermia

There are different systems for application of whole-body-HT. Here we described two most important systems.

- "The Aquatherm system is an isolated moisture-saturated chamber equipped with water-streamed tubes (50-60°C) on the inner sides, in which the patient is positioned. Long-wavelength infrared (IR) waves are emitted. A substantial increase in the skin blood circulation is induced, and energy absorbed superficially is transported into the systemic circulation. Since energy release through perspiration is blocked, the heating time is quite short (60-90min)" [81].
- "The Iratherm-2000 system uses special water-filtered IR radiators, resulting in an IR spectrum with a maximum near to visible light. The penetration depth in this frequency range is about 2 mm" [81].

In carcinomas with distant metastases, a steady state of maximum temperatures of 42°C can be maintained for 1 hr with acceptable adverse effects [33, 34]. Every system for whole-body-HT can cause superficial overheating, resulting in thermal lesions. Thus, careful continuous control of skin temperatures combined with controlled power input is required to ensure that the procedure is safe. With experience, systemic temperatures of up to 41·5-42·0°C can be achieved with acceptable side-effects with both systems. Systemic toxicity can include cardiac disorders, changes in the coagulation system (thrombocytopenia and disseminated intravascular coagulation), and permeability of the capillary endothelial [34]. Because there is a large fall in peripheral resistance and consequent hypovolaemia, fluid substitution is necessary. Overcompensation can lead to pulmonary oedema in connection with the capillary leak syndrome. "Whole-body-HT is clinically feasible, with systemic temperatures of 41·8-42°C achieved. However, the efforts needed (including intensive medical care) are much greater than for locoregional methods" [81].

Thermal dosimetry

"The basic premise underlying the need for thermal dosimetry is the ability to write a verifiable prescription for HT" [85]. "As in any form of therapy, a sound dosimetric basis leads to unambiguous treatment, data acquisition, data reporting, quality assurance, and comparison of treatments" [86, 87]. During HT treatments, the measurement of the actual temperature distribution in the tumor or immediately adjacent tissue is crucially important to the clinical evaluation of the HT quality [88]. For superficial tumors, thermometers lie on the skin or introduce percutaneously. When deep-seated tumors are under treatment, HT departments apply intratumor and/or intraluminal thermometry. Some researchers believe that intratumor thermometry is an absolute necessity to determine the temperature distributions achieved [89, 90, 91, 92]. Whereas, others suggest that if intraluminal thermometry is available, intratumor thermometry is neither an important requirement for prevention of toxicity, nor supportive for SAR-steering [93, 94, 95, 96, 97].

In intratumor thermometry, thermal catheters must be implanted within the tumor either under CT guidance percutaneously or intraoperatively. In intraluminal methods, thermal probes are placed through the lumen in contact with the tumor [98]. Since, intratumor thermometry has some disadvantages (*i.e.* time consuming, painful for patient, side effects such as infection and tumor seeding) most of the HT-centers have abandoned this costly method.

In order to obtain as much information as possible about the temperature distribution, a step-by-step movement of thermal probes (*i.e.* thermocouples, fiber-optic probes) within the catheter tracks allows the acquisition of data, which map a temperature profile through the treatment region. From all the temperature measurements acquired as temperature *vs.* time and temperature *vs.* depth plots, time-averaged temperatures can be calculated at each monitored site. In addition, the time-averaged temperatures above 10, 20, 50 and 90% of the monitored points (reported in terms of T_{10}, T_{20}, T_{50}, and T_{90}) and also T_{min}, T_{mean}, and T_{max} allow comparison of different HT treatments in regard to the quality of heating [99, 100, 101]. More recently, the clinical application of the thermal isoeffect dose concept has been applied in retrospective analyses of clinical data. The purpose of such studies was to guide future clinical studies in which different treating protocols for different times at different temperatures are converted into equivalent minutes at 43°C [102].

3D non-invasive thermometry might be provided by magnetic resonance tomography (MRT), which can characterize temperature as well as perfusion [103]. Integration of a HT system in a tunnel-like MRT is technically demanding. This problem has been solved at the Duke University Medical Center, North Carolina, USA, with a smaller applicator for the thigh region [104]. A commercially available hybrid system, a 1·5 T tunnel magnet (MR Tomograph Symphony, Siemens) has installed at the Charité Medical Center in Berlin, Germany [105].

At present clinical HT has to rely on intratumor or intraluminal thermometry in most practical situations [92, 95]. This invasive or minimally invasive thermometry is, besides the problems with the extremely limited information about highly inhomogeneous thermal dose distributions, a major clinical problem in the acceptance of HT [93, 106].

Under clinical circumstances the quality of the measured temperature distributions is critically dependent on the accuracy of the thermometry system and the distribution of the temperature measuring points over the target volume. Parameters with impact on the quality of measurement are the number of probes, their spacing,

and their location. Hence, mandatory to allow the technical and clinical quality analysis of the HT treatment delivered is that the quality of the collected temperature data is without dispute [107].

Reference	Tumor	Endpoint	N[@]	RT	RT + HT
[113]	Various superficial*	Complete response rate			
	All tumors		109	42%	66%
	Previously irradiated		39	24%	68%
[114]	All pelvic tumors*	3 years overall survival	358	24%	30%
	Bladder		143	22%	28%
	Rectum		101	22%	13%
	Cervix		114	27%	51%
[50]	Breast cancer*	Complete response rate	308	41%	59%
[51]	Glioblastoma multiforme*	2 years survival	112	15%	31%
[115]	Various	2 years survival	184	34%	35%
[116]	Melanoma*	2 years local NED®	134	28%	48%
[117, 118]	Head & neck*	Complete response rate	44	41%	83%
		5 years survival		0%	53%
[119, 120]	Various	Complete response rate overall	236	30%	32%
		In small tumors (diam.<3 cm)	55	39%	52%
		In large tumors (diam.>3 cm)	181	27%	25%

[@]N= number of patients; *Statistical significant difference;
®NED= no evidence of disease.

Table 1: Comparison of the results of radiotherapy (RT) *vs.* radiotherapy plus hyperthermia (RT + HT) in randomized trials from Western research groups until October 2009.

Clinical results

"The synergistic interaction between heat and radiation dose has been validated in certain clinical studies" [108]. In a review study van der Zee reported on all randomization trials performed until 2002. She reported 19 positive trials and 8 trials with no significant difference following a combination of RT and ChT or RT plus ChT and HT compared with the same treatment without HT [108]. Since then, two more positive phase III trials of ChT + HT [109, 110], and one non-decisive trial of RT + HT [111] are published. Table 1 shows the results of all phase III trials, reported during 1991-2009, comparing RT alone *vs.* RT + HT, conducted by Western research groups. Earlier Falk and Issels reported on state of the art of HT and described beside phase III trials, also 17 selected phase I or II trials investigation, the effect of HT combined with RT, ChT, or both in total of more than 2200 patients [112]. All studies, except two, show a statistically significant higher (up to a doubling) tumor control and/or cure rate for the combined treatment modality. Additionally, all studies report comparable acute and late toxicity in both treatment arms. The positive results of the most recent trials explain the renewed enthusiasm in HT, which is reflected in the growing number of institutes interested in the application of HT [53].

Hyperthermia-induced toxicity

Normal tissue toxicity will result directly from HT when the tolerance limits are exceeded. "Experimental studies have shown that most normal tissues are not damaged when the temperature over 1 h of treatment does not exceed 44 °C" [33]. During local-HT, it is not always possible to avoid higher temperatures due to the heterogeneity of the temperature distribution and the limited thermometry. The patient is not always able to feel painful hot spots, *e.g.* when the target area has been subjected to surgery in the past and sensitivity is disturbed. The toxicity from superficial-HT is usually a skin burn (in 25% of the patients with recurrent breast cancer [113, 114], healing with conservative treatment). During HT for deep-seated tumors the skin is extensively cooled, through which the hot spots will develop in deeper tissues. A temperature that is too high in subcutaneous fat or muscle tissue results in a feeling of pressure, which is not always recognized by the patient. As a result, patients may be reluctant to mention unpleasant sensations. Subcutaneous fat or muscle tissue burns do not usually cause much discomfort: the patient feels a subcutaneous lump, which is tender for a few days to a maximum of a few weeks and then disappears spontaneously. Subcutaneous fat burns were seen in 3-12% of the patients treated with deep-HT. The risk of developing skin burns appears to be higher following treatment with a RF capacitive heating technique (5-16%) than with a radiative heating technique (0-3%) [115, 116, 117]. The randomized studies did not show an increase in acute or late toxicity of RT. Whether the toxicity of ChT is enhanced depends on the temperature in the drug-sensitive tissues. Toxicity from whole-body-HT depends on the patient's general and the physiological conditions during the treatment [81]. Serious toxicity from regional HT perfusion with modern technology and proper choice of perfusate composition, flow rate and pressure, blood gas values, drug doses, temperature dose and scheduling, is limited [118, 119].

Discussion and conclusion

The technical application of HT is feasible and effective if combined with RT and/or ChT. Clinical studies on regional HT combined with RT, ChT or both have shown impressive results at clinical relevant temperatures in local advanced tumors of different entities in terms of objective response rate, local tumor control and survival rate. Especially in well defined clinical situations in breast cancer, melanoma, head and neck tumors, cervix cancer and glioblastoma, the addition of HT to RT significantly improves tumor response and survival rate; thus, should be considered as a presently proven therapy to improve patients' outcome.

The clinical results give new insight into the mechanisms of HT in multimodal oncological treatments. HT is thought to affect tumor sensitivity to other treatments mainly through micro-environmental factors such as pH. The hypothesis is that hypoxic and therefore resistant tumor regions are preferentially eliminated under HT conditions because associated hypo-vascularisation results in higher temperatures and higher sensitivity due to hypoxia. This assumption has been questioned, since chronic hypoxia also leads to an adaptation (development of tolerance), and the real temperature distribution on a cellular tissue level (hypoxic *vs.* well vascularised areas) is uncertain [81].

The results from experimental studies show that HT is both the ideal complementary treatment to, and a strong sensitizer of, RT and many drugs used in ChT. However, in spite of the remarkable therapeutic gain that has demonstrated in patients; HT still is not widely recognized as a useful treatment. There are several reasons for this lack of acceptance. Firstly, results from the 1st randomized trial in the USA failed to show a benefit for adding HT to RT, which mainly was due to inadequate equipment and quality assurance procedures. Luckily, the next trials were mostly positive [108]. Secondly, most of the early positive randomized trials have been relatively small and/or were performed in Asia and Russia and therefore, have received less attention than the negative trial in the USA. The third reason is a weak advertising on HT and lacks public awareness. HT added to RT and/or ChT results in up to a doubling of complete response rate and survival [114]. If a drug were to achieve similar successes, its corporate sponsor would have announced it as a new breakthrough in cancer treatment and it would have received extensive attention from the media. HT equipment is manufactured by a few relatively small organizations with lack of the financial support for mass media promotion [120].

Nowadays, HT has been regarded as a beneficial adjuvant treatment, specifically recommended for locally recurrent tumors, and for primary cancers. HT is probably the most potent radio- and chemo- sensitizer known to date [53]. However, it is not yet a fully developed modality for all tumor sites, there are still problems with the routine clinical application of HT, and there is still room for further technological improvements. Nevertheless, new finding from combination of HT and gene therapy, immunotherapy, bone marrow purging, *etc.* made more interest to apply this method as an adjunctive treatment modality. Certainly, in the near future more patients will have benefit from the combined treatments including HT.

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CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare