Review Article

Thermal and Nonthermal Effects of Radiofrequency on Living State and Applications as an Adjuvant with Radiation Therapy

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Abstract

One of the most frequently applied bioelectromagnetic effects is the deep heating of living species with electromotive force energy. Despite its long history, hyperthermia is a rarely applied oncotherapy because of controversial results and complicated control. The challenge in clinical studies of oncological hyperthermia is the disharmony of the local response and local control with overall survival. Both whole-body (complete isothermia for the body) and local (isothermia for the chosen target) heating show excellent local effects; however, this is not followed with the expected elongation of survival time. A possible solution could be nonisothermal heating to the heterogeneity of the malignancy itself. The distinguishing parameters to select the target are the electromagnetic properties of the malignant tissue together with the physiological differences between malignant cells and their healthy counterparts. Selection could allow for cellular targeting, generating natural reactions, such as programmed cell death (apoptosis) followed by immunogenic cell death involving extended immune reactions. This complex method is a new kind of hyperthermia, named modulated electrohyperthermia (tradename oncothermia). The selective, nonequilibrium energy absorption is well synergized with modern radiation therapies, presenting a solution of an active and controllable tumor-specific immune reaction and subsequent abscopal effects.

Keywords: *Abscopal effect, apoptosis, electromagnetic effects, immunogenic cell death, ionizing, modulated electrohyperthermia, oncothermia, radiofrequency current, radiotherapy*

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Introduction

Hyperthermia is an ancient treatment. Fire and the Sun, as the overall energy source of the Earth, had symbolic significance in ancient human cultures. As a consequence, heat delivery was naturally a medical possibility. Application of heat for tumors was used in ancient medicine, and the first description of this particular treatment was made by Hippocrates.

The original idea of hyperthermia was based on a simple principle: the heated tumor exhibits an accelerated metabolism without extra supply and the "starving" tumor destroys itself by acidosis. This approach is supported by the impoverishment of Adenosine triphosphate and enrichment of lactate in treated tumors,[1] and furthermore, due to the change in energy consumption, the tumors are more sensitive to heating than their healthy counterparts.

Various heat deliveries were applied in the middle ages for tumors mainly for ablative intention. The birth of electromagnetic heating techniques at the end of the 19th century renewed medical heating methodology. Methods to heat up the whole body or specific regions were developed rapidly.

Two concepts of electromagnetic energy absorption as oncological treatment were developed in parallel by Carl D.W. Busch (1826–1881) in Germany and the French physician Arsene d'Arsonval (1851–1940), who worked out the temperature-based and electromagnetic field effects, respectively. In the first half of the 20th century, the market competition between the two methods was decided when Siemens, the largest producer of medical devices, launched heating devices with emphasis on temperature growth.

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At the same time, oncological hyperthermia turned to electromagnetic direction, the birth of ionizing radiation by the discovery of X-rays by Wilhelm Conrad Rontgen (1845–1923) occurred at the end of the 19th century. The first textbook on radiotherapy (RT) was published in 1903,[2] and publications continued afterward, building RT as one of the three "gold-standard columns" of monotherapies.

Oncological hyperthermia could not reach the status of the widely accepted "gold standard." Despite the long history of the method, its medical applications are relatively rare; its recognition is similar to that of therapies at their infancy. Despite the statistical evidence in research and clinical applications, hyperthermia could not break through the limitations of the last alternative in late palliative care. Effects of oncological hyperthermia are mostly acknowledged, but the clinical evidence has many challenging problems.[3]

The main success of hyperthermia lies in its complementary applications and mostly in combination with RT. Sensitizing classical ionizing radiation by hyperthermia is unambiguous,[4-7] and the synergy between methods is well known[8,9] and has been successfully applied.[10-12] The success of complementary treatments with RT has a broad spectrum of evidence[13-17] and is well summarised by various review articles.[18-21] To characterize the gain, the thermal enhancement ratio was introduced.[22]

The complementary effects exhibit three aspects that act in parallel:

1. Radiation is most effective in M and G_1 phases of the cell cycle in relatively alkaline, well-oxygenated regions, while hyperthermia predominantly acts in S phase[23] in moderately acidic, hypoxic regions, which complements the cell cycle arrest
2. Various other molecular parameters increase to sensitizing effect,[24] e.g., heat-induced decrease of DNA-dependent protein kinase[25]
3. Hyperthermia physiologically increases the blood flow by vasodilatation to regulate thermal homeostasis, compensating for the increased temperature by cooling blood flow, which delivers extended oxygen supply for radio effects.[26,27]

The last point of synergy is contradictory. It naturally opposes the original "starvation" concept, because the higher metabolic rate of the proliferating mass compensates for the missing supply by nonlinearly increasing blood flow.[28-30] The effects of higher radiosensitivity begin to compete with the number of nutrients by vasodilation and better perfusion through the vessel walls. On the other hand, in massive tumors the neo-angiogenic arteries do not vasodilate, as they lack musculature in their vessel wall.[31] In this way, the healthy and malignant tissues differ in their reaction to heat.[32] It has been shown that an increase in temperature can cause vasoconstriction in certain tumors, leading to decreased blood perfusion and heat conduction,[28,29,33] while causing vasodilatation in healthy tissues leading to increased relative blood perfusion and heat conduction in this region.[34,35] Blood perfusion of the tumor relative to the surrounding healthy tissue is always lower[35] and thus could provide an effective heat trap.[36] The bloodstream compensates for the overheating by regulating the flow capacity of the vessels, and as a result of this physiological feedback, effective vascular response to heating is observed. The bloodstream has a central role in maintaining overall homeostasis, not only by temperature regulation but also by other parameters (e.g., acid-alkaline equilibrium, glucose delivery, and immune actions). The vascular response to heating differs in malignant tissues compared with healthy tissues over a tumor-specific threshold. Over the threshold, vasocontraction occurs instead of the vasodilatation, which downregulates the oxygenation and lowers the efficacy of RT.[27] Furthermore, over the threshold downregulating natural killer cell cytotoxicity[37] and other immune actions[38] appears too. The tumor blood flow also exhibits tumor-specific changes from approximately 38°C.[32] Substantial cellular damage has been observed at temperatures above 41°C–42°C.[39] There is a limit with the cellular phase transition at approximately 42.5°C,[40] which surprisingly fits the results of the Arrhenius plot.[41,42]

Reduced survival, despite local success, was observed in clinical studies at high-level evidence of oncological hyperthermia. One of the first phase III trials investigating thermo-RT compared with RT alone by extensive international cooperation for breast cancer showed clear and significant local remission, although the overall survival was unchanged.[43] Another study observed that the local progression-free survival of breast cancer was improved by thermo-RT, although the survival time was better with RT alone.[44] Additional development of distant metastases was shown when hyperthermia was combined with RT compared with earlier data.[45] Interestingly, when local control was not successful, the survival rate was better by RT alone than in addition of thermal treatment.[43] A similar study found evidence of toxicity.[20]

Pelvic localizations were studied in one of the flagship trials of oncological hyperthermia.[10] Local control for cervix tumors showed strongly significant results. Nevertheless, the local effects on bladder and rectum

tumors were not significant, but were positive for thermal treatments. However, the change in survival time was significant only in the cervix cohort and was not favorable in rectum and bladder tumors. Later, the cervix results were questioned by a controlled study,[46] which showed improvement of the local control but worsening of the survival time by hyperthermia in addition to RT.

Further study of uterine cervix carcinomas showed a benefit in terms of survival,[47] but newer critics have questioned this result.[48,49] Other high-level evidence, a phase III trial of cervical carcinomas with complementary hyperthermia and brachytherapy, registered the same controversies between survival time and local control involving 224 patients.[50] A recent study of cervical carcinomas[51] was also inconclusive in the comparison of RT-based differences of complementary chemotherapy (CT) or hyperthermia, and thus, the study was terminated. The interim results showed, however, that the event-free survival was slightly worse in the thermo-RT group than in the chemo-RT group, but the difference was not statistically significant.

It is not only the cervical carcinoma studies that suffer from controversy between survival time and local control. A study on locally advanced nonsmall cell lung cancer (NSCLC) also showed significant improvement of the overall response rate in local measures, although there was no change in overall survival.[52] Later, a multicenter phase III trial for NSCLC showed no improvements in overall survival in the hyperthermia cohort.[53] The cause was directly shown: the appearance of distant metastases was five-times higher (10/2; $P = 0.07$) in the thermo-RT group compared with RT alone.[53]

Other recent findings in heatable surface tumors show the same contradiction between the local control and survival rate.[54] A recent study found that the local control was better when less energy was administered than prescribed.[55]

The dissemination of malignant cells most likely causes the poor results of the survival rate, forming micro- and later macro-metastases. These controversial data are questioning the successful applicability of heat therapy in oncology and the hope of a promising approach[56] could be lost.

However, the data showing highly significant improvement of local control obtained with hyperthermia and RT represent facts that we must consider as the basis for further development of oncological hyperthermia and to correct the problems with overall survival. To overcome the issues, we must concentrate on blocking invasion and reducing dissemination. The task is to prevent formation of metastases caused by heating. Furthermore, we may eliminate the metastases formed earlier, before thermal treatment with local hyperthermia of the primary tumor.

To overcome this problem, we have modified the isothermal concept of oncological hyperthermia to heterogenic, selective heating by bioelectromagnetic selection and excitation of apoptotic pathways of malignant cells by the absorbed energy. The method is a new kind of hyperthermia, introduced as modulated electrohyperthermia (mEHT; tradename, oncothermia).[57]

Methods

The applied hyperthermia technique was the mEHT method, which uses capacitively coupled energy-transfer [Figure 1].[58] Capacitive coupling technique (CCT) is a relatively old technical solution. The first CCT device was marketed under the name "Universal Thermoflux" by Siemens. It was later further developed and launched to market by the name of Radiotherm in the early 1930s. The first modern medically oriented CCT was published in 1976 by H.H. LeVeen[59] and has been widely applied since.[60-64]

The capacitor in CCT is formed by the approximately plane-parallel electrodes and ensures a homogeneous temperature in the deep-seated target by regulating the applied size ratios of the electrodes. However, living structures form very heterogeneous impedances and well-controlled heat-sinks by physiological regulatory signals. Due to these conditions, the CCT technique has drawbacks when the task request is localized isothermal heating in depth.

The concept of heating by mEHT differs from conventional heat therapies. Technically, it uses CCT but in a redesigned form, taking a well-compensated resonant circuit to maximize the RF current and at the same time minimize the voltage on the electrodes at a given output power. The patient is an electric part of the preciously tuned system, representing active electrical impedance, so it is not simply an "energy absorbent." Approaching the proper impedance matching the solution has negligible reflected power (order of 1 W), mimicking the galvanic contact with the skin as much as possible.

While the goal of conventional hyperthermia treatment is to heat the tumor mass homogeneously, mEHT is genuinely breaking the isothermal approach. Instead of homogenous heating of the target, mEHT uses excellent selection to force absorption of energy on the malignant cells, heating them locally to the hyperthermia temperature to induce cellular changes in the targeted cells [Figure 2].

The biophysical differences of the malignant cells compared with their healthy counterparts allow proper

selection of targeted cells. The biophysical alterations of malignant cells are connected to their intensive proliferative behavior with lack of apoptotic activity. The energy source building new structure is accelerated glycolysis, which is measurable by positron-emission tomography (PET). The consequence of the metabolic differences allows for the development of a high ionic concentration in the tumor mass; thus, cells can be distinguished by the flow of the current.[65]

The other distinguishable characteristic of malignant cells is their autonomy. These cells are individual, breaking intercellular bonds[66] and junctions,[67] and "fighting" with all other cells for metabolic energy. This autonomy is recognized by differences in the increased dielectric constant of the extracellular electrolyte in the near vicinity of malignant cells (Szent-Gyorgyi effect).[68] The high dielectric constants around the malignant cells channelizes the RF current.[69]

The RF current exhibits a characteristic dispersion in the MHz frequency range (β/δ dispersion[70] and the Schwan effect[71]), which concentrates the action on lipid–protein interactions, and selects water-bound states[72] at the membrane, using it effectively for appropriate targeting.[73] The concentration of lipid rafts on the membranes of malignant cells is significantly higher than on the membrane of nonmalignant cells.[74] Consequently, the dense lipid rafts of the selected malignant cells by the above biophysical differences become an easy target of the energy absorption. Due to the electric properties of the clusters of transmembrane proteins,[75] their selection for absorption is automatic.

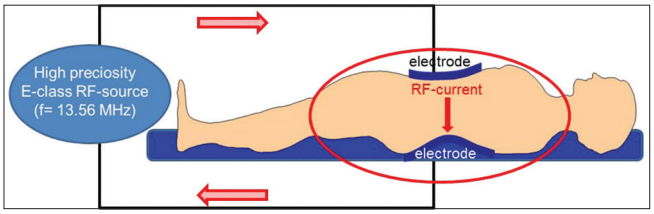

Figure 1: The capacitive system is matched very precisely

Results

The synergy of the electric field with temperature-induced changes on malignant cells is tracked from the laboratory to the patient's bed.[76] This complex interaction is more effective than conventional hyperthermia.[77] The temperature gradient changes membrane processes and promotes signaling pathways for natural apoptosis[78] instead of thermal necrosis.

The absolute differences between mEHT and conventional isothermal hyperthermia with the same temperature have been studied *in vitro*[79] and *in vivo*.[80] The temperature of the malignant cells acts as if they are at least 3°C higher than the environmental average.[81] The selective targeting of mEHT appears as mild conventional hyperthermia in the tumor mass, averaging the overheated rafts. Consequently, the blood flow remains in the optimal fever-range level,[82-84] avoiding additional adverse processes such as increased glucose delivery, increased invasion, and high risk of dissemination. The proliferation marker Ki67 has been shown to be significantly suppressed by mEHT compared with its untreated counterpart.[85] The formation of new E-cadherin-β-catenin complexes to bond the cells intercellularly helps block invasion, "gluing" the cells to the location.[76]

Experimental studies have clearly shown the excellent synergy of mEHT with RT. The advantage of the application of oncothermia is significant.[86] Interestingly, comparison with water-bath isothermal heating shows an optimum ratio at an average medium temperature of 42°C [Figure 3].

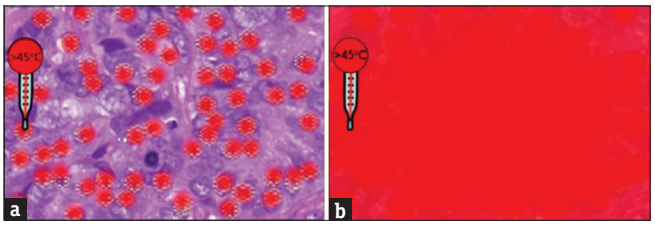

Figure 2: mEHT uses the heterogeneous selective heating (a), instead of the homogeneous, isothermal one (b)

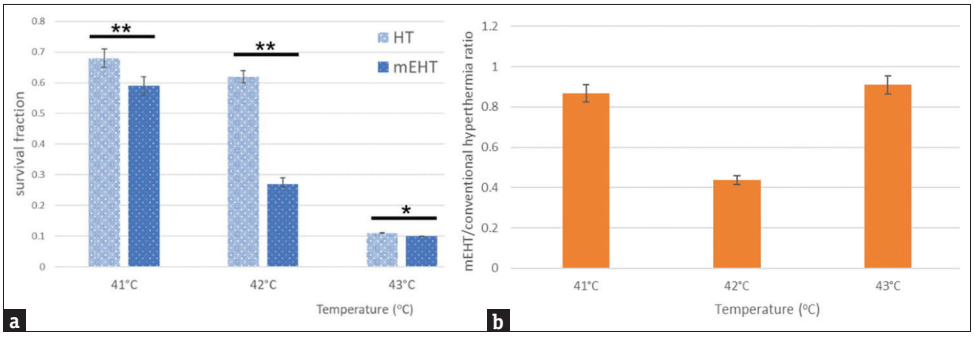

Figure 3: (a) Surviving fraction after 60 min heat treatment by conventional hyperthermia (HT; water-bath) and mEHT, for SCCVII (SCC7), a mouse head and neck carcinoma cell line *in vitro*. (b) Ratio of mEHT/HT survival

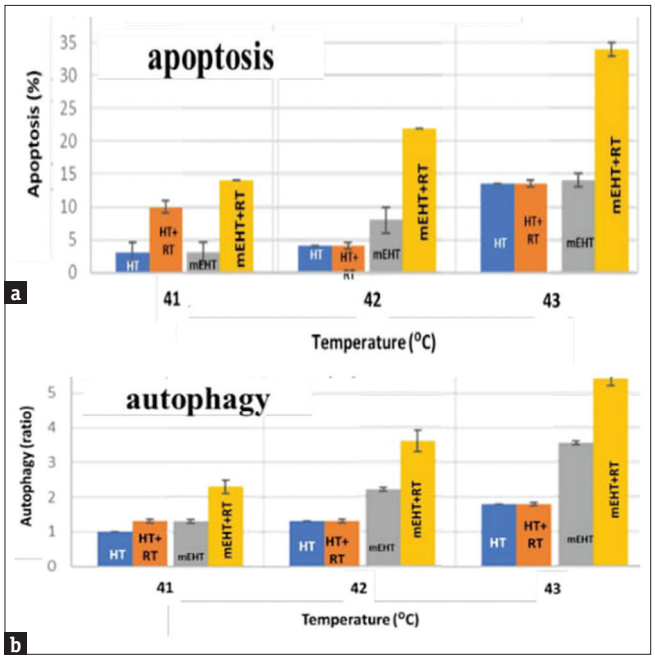

Figure 4: (a) Apoptosis and (b) autophagy induced by HT and mEHT in combination with RT for SCCVII (SCC7), a mouse head and neck carcinoma cell *in vitro*. Apoptosis is expressed as a percentage, while autophagy is expressed as folding rate

The same study[87] showed significant improvement of the apoptotic ratio by mEHT in combination with RT compared with the water-bath combined with RT. There was also a large increase in autophagy with the mEHT combinations [Figure 4]. The fingerprint of the extrinsic apoptotic pathway, caspase-8, was significantly higher in the RT + mEHT combination, as has been shown previously.[79,87] Cell cycle arrest of malignant cells has also been clearly demonstrated.[88] Another radiation study was performed *in vivo*[89] and showed significantly less hypoxia in FSall tumors 3 days after treatment with 15 Gy combined with mEHT at 41°C for 30 min. A significant decrease in vascular endothelial growth factor has also been shown when mEHT is applied alone or in combination with RT.

Clinical studies of mEHT are consistent with the experimental data. Enhancement of oxygen in the target for sensitizing RT has been shown in a blood flow trial,[90] and increased permeability of blood vessels has been shown by a pharmacokinetic trial.[91] Sensitive organs, such as the brain, can also be treated safely, as shown by a dose escalation study.[92]

This method has been applied successfully in various cancer types, mostly complimentary with various chemotherapies. Remarkable results were achieved with gliomas,[93-96] colorectal cancers,[97,98] lung cancers,[99,100] uterine cervix carcinomas,[101] malignant ascites,[102] sarcomas,[103,104] pancreas carcinomas,[105,106] and prostate cancer.[107,108]

A successful case of definitive RT with concurrent mEHT for stage IIIB NSCLC[109] projects the feasibility of mEHT combined with RT. Another case, the treatment of advanced cervical cancer with complex trimodal (mEHT + CT + RT), supports the possibility of combined therapy.[110] A large number of case reports were published with complementary RT + mEHT, which may be followed in the open-access Oncothermia Journal.[111]

Two examples of representative case reports for mEHT + RT combined with CT (mEHT + RT + CT) for inoperable advanced metastatic esophagus cancer are shown in Figures 5 and 6.[112]

Together with the extended number of studies in a combination of mEHT with CT, only some pilot studies were performed with a combination of RT. Some exciting results have been shown in pilot studies. In a small study [Figure 7],[113] the superiority of RT + mEHT was observed, but the small number of patients does not allow for conclusive results.

Quality of life (QoL) of the patient is the integrative goal of mEHT combined with elongation of overall survival. Bone metastases frequently reduce QoL by intense pain. The mEHT method is helpful in these cases as well [Figure 8].[113]

Preoperative application of mEHT for liver metastases was performed by Prof. H. Renner[114] [Klinikum Nord, Nürnberg, Germany; Figure 9]. The primary tumors were inoperable (R2) rectal carcinomas (n = 7). Trimodal therapy was applied: RT, 45 + 5 Gy (fractional); CT, 5-FU/Mitomicine-C (×2); oncothermia, 60 min, diameter 30 cm (8–×10). Following oncothermia, all patients were eligible for operation. The results of the operations were excellent: 71% of patients exhibited complete resection (R0) while one was partially resected (R1) and one was not successfully operated (remained R2).

The successful application of mEHT in combination with CT[101] has demonstrated the feasibility of mEHT in uterus cervix carcinomas. A phase III randomized clinical trial using trimodal (mEHT + CT + RT) therapy is currently ongoing[115-117] for this localization. Interim results of 160 patients after the PET control before and after therapy shows promising results after 6 months of local disease control [Figure 10]. The trimodal protocol was as follows: radiation, 25 × 2 Gy external and 3 × 8 Gy brachytherapy; CT, 3 × 80 mg/m^2 cisplatin, and mEHT 2 × 55 min/week (4 weeks).

Both therapies, RT and mEHT, are local treatments that target the tumor. Circulating tumor cells (CTCs) are present even in early stages of cancer, which can

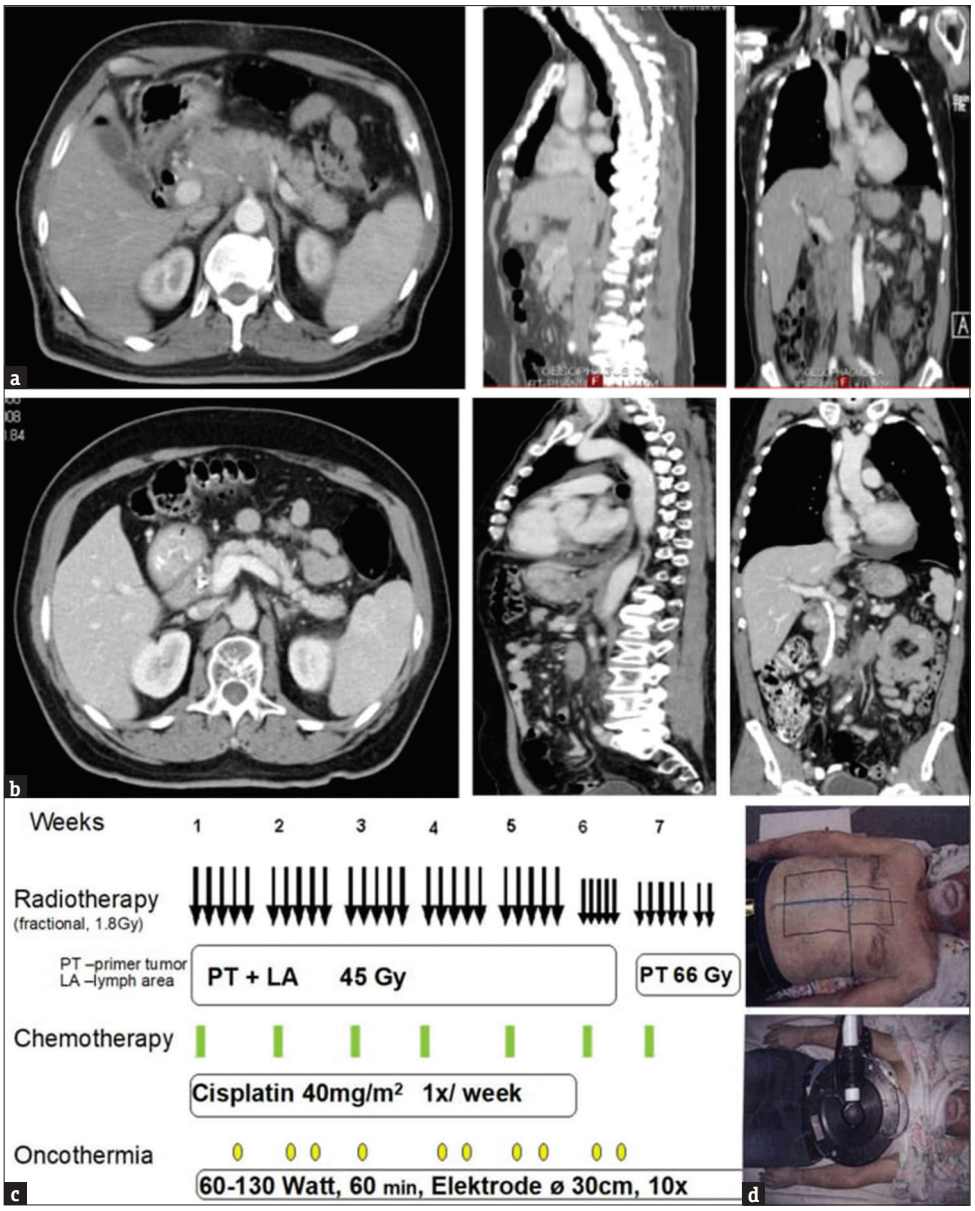

Figure 5: Treatment of relapsed, inoperable esophagus cancer (a) before mEHT therapy, (b) after mEHT therapy, (c) trimodal protocol, (d) placement of electrodes

form micro- and macro-metastases by extravasation in sensitive organs, reducing the possibility of patient survival. Intercellular signal transduction and molecular transport between cells allow RT to act on neighboring cells, resulting in a bystander effect. Systemic effect of local RT was first observed by R.H. Mole, who named it the "abscopal effect."[118] Bystander mechanisms using other messengers extends its effective influence and could be abscopal,[119,120] active on distant metastases or on CTCs.[121] Discovering its controversies[122] and hunting for bystander and abscopal effects is a hot topic in cancer therapies.[123,124] The abscopal effect was first observed in hyperthermia applications 40 years after it was demonstrated in RT.[125]

Although mEHT is a local treatment, it could also act systemically via the abscopal effect, which was shown *in vivo*,[126-128] and a possible mechanism is discussed below. This vaccination-like mechanism, which has been proven in experimental studies, has been observed in human case reports.[129-132] The abscopal effect induced by mEHT is a new strategy.

The abscopal effect observed in a patient with multiple metastatic stage IIIB NSCLC is an excellent example[133] [Figure 11]. Despite the advanced stage, the patient refused CT and requested other possible treatment options. RT in combination with mEHT and additional immune-stimulating granulocyte-monocyte colony stimulation factor (GM-CSF) was performed

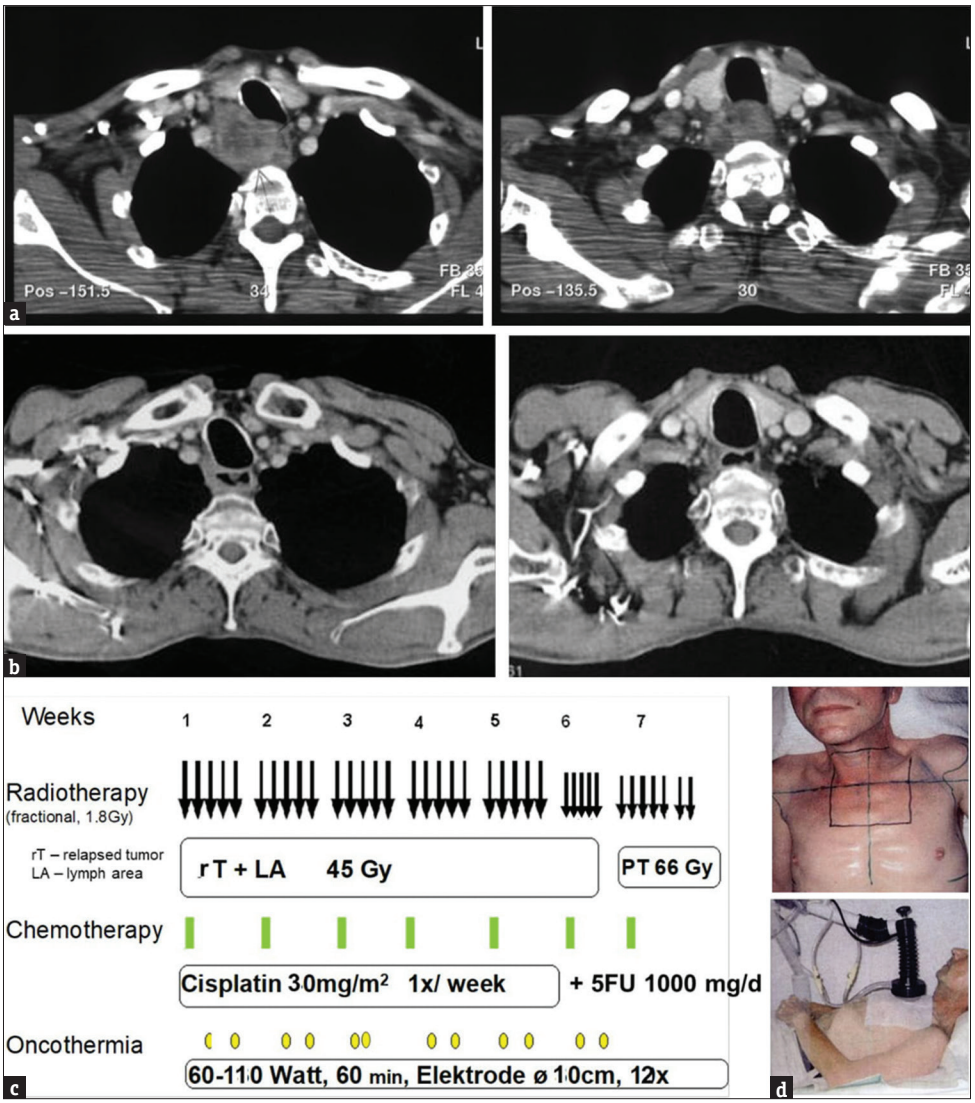

Figure 6: Treatment of relapsed, inoperable esophagus cancer (a) before mEHT therapy; (b) after mEHT therapy, (c) trimodal protocol, (d) placement of electrodes

to induce the abscopal effect. Local field RT directed at the lung mass was delivered at a dose of 1.7 cGy in 28 daily fractions, 5–6 times per week. This was followed by oncothermia after radiation three times per week. After 2 weeks of treatment, GM-CSF (250 μg, Leukine®, USA) was administered subcutaneously daily for 10 days. A complete abscopal effect was observed on distant metastases with partial response of the primary tumor.

The abscopal effect has also been investigated in an ongoing trimodal phase III clinical study.[134] One patient in the study had neck and thorax nodes, bone, and lung metastases on pretreatment scan. This patient was HIV negative, stage IIIB, and aged 34 years. Following complex trimodal therapy including two rounds of CT, a complete abscopal effect was measured without further evidence of disease. Overall, 24.1% of the patients (13 of 54 patients) showed a complete abscopal effect; the therapy eliminated the active cancer in the cervix, and metastases in pelvic and extra-pelvic areas disappeared, as observed by PET [Figure 12].

Discussion

Synergy of RT and mEHT is the common goal, to restore apoptosis in malignant cells as much as possible. The common root of these methods is energy absorption by micro/nano parts of the malignant cells selected by precise focusing and biophysical differences in RT and mEHT, respectively. DNA nano-targeting in RT harmonizes well with the nano-targeting of mEHT.[135] The premise of both treatments is similar. The expected effects of ionizing radiation, where the target is DNA, and energy, which

Therapy / week-days	Mon.	Tue.	Wed.	Thu.	Fri.	Number of patients	Overall response (%)
Radiotherapy + Oncothermia (mEHT)	RT	RT mEHT	RT	RT mEHT	RT	16	81 %
Chemotherapy + Oncothermia (mEHT)		mEHT	CHT	mEHT		8	38 %
Oncothermia monotherapy		mEHT		mEHT		4	25 % a

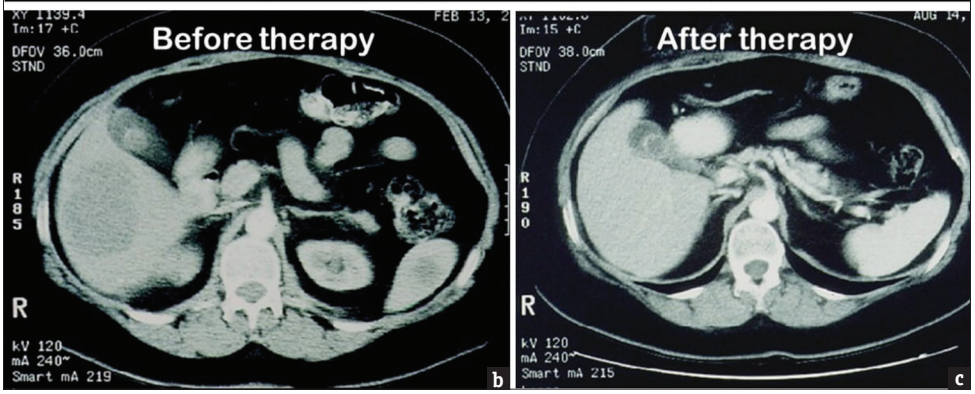

Figure 7: Advanced liver metastases of various types of primary tumors. Investigator: Prof. H. Aydin; Institute: Clinic and Institute of radio-oncology, zentralkrankenhus reinkenheide, Bremerhaven, Germany; oncothermia: ×2/week; concomitant chemotherapy; vinorelbine (20 mg/m^2/week); concomitant radiotherapy: 10 MV, 1.5–1.8 Gy fractional radiation × 5/week, overall dose; 21–24 GY. (a) Protocols and response rates; (b) Successful case before RT + mHET combined therapy; and (c) after therapy

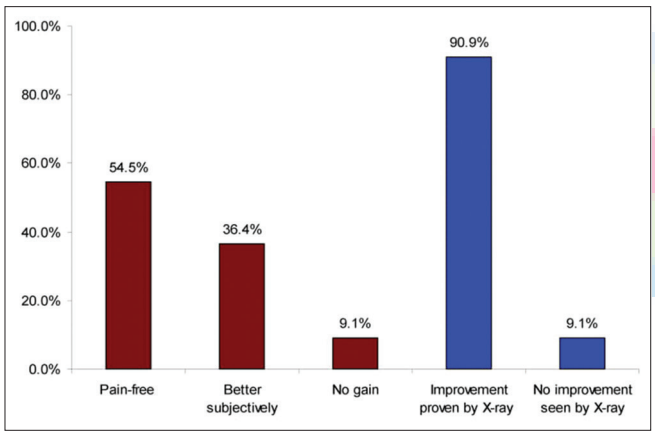

Figure 8: Bone metastasis treatment by 18–20 Gy, fractionally 1.8–2 Gy/day, 5x/week, plus mEHT every second day

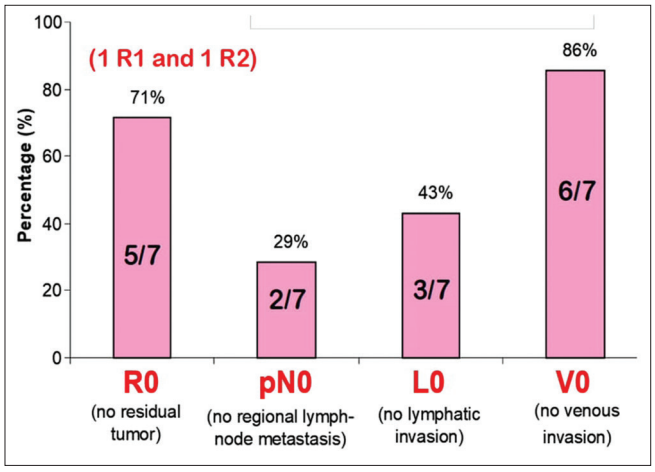

Figure 9: Results of the operations performed postoncothermia on previously inoperable patients

heats up its environment is useless, and can result in adverse effects. RT is an exemplary method for selective targeting of chemical bonds to arrest the cell cycle in malignant cells and induce apoptosis instead of proliferation. The goal of mEHT is to selectively kill malignant cells in a natural way, by inducing apoptotic cell death.[136] The goals of mEHT and RT are not identical only in the local action, but expected to be nonlocal by the various mechanisms of bystander and abscopal effects, which extend the local therapy systemic and allowing for successful action against systemic malignancy.

RT and mEHT differ in the targets of energy-absorption and the selection of treatable cells. The relatively easy focusing of high energetic ionizing radiation by the beam size and shielding windows differs from the biophysical targeting mechanism of mEHT, which could be automatic with a well-chosen modulated RF current through the target. The major mechanisms of cell death induced by RT[137] include apoptosis, senescence, autophagy, and necrosis, which could be promoted by mEHT as well.[79,86,138,139] The well-known DNA fragmentation-driven process in RT is also common with mEHT.[140] A portion of the RT effect occurs via the extrinsic apoptotic pathway of death-receptor ligands in the FADD complex, producing Caspase-8/10 and culminating with apoptosis by cleaved Caspase-3.[137] This mechanism is strongly activated by mEHT as well.[87]

To improve the apoptotic signal, mEHT repairs intercellular connections.[85] New connections also make the missing signal transmissions possible. The

restored intercellular bonds of E-cadherin[76] bridge cells, forming a β-catenin complex and allowing for signal transduction. Intercellular connections do not only transmit signals; they can also block the invasion of cells by bonding malignant cells to their neighbors.

Targeting of lipid rafts is similar to nano-particle heating, but no artificial nanoparticles are involved; all are naturally present on the membrane of malignant cells.[141] The active energy absorption on the rafts combined with the various selection mechanisms ensures that the lipid rafts are induced to trigger apoptosis.[142] The general principles of cellular distortion are similar in mEHT and RT. Both target a part of the malignant cell (rafts in mEHT and DNA in RT) to induce chemical reactions, which lead to apoptosis [Figure 13]. Naturally, both processes have additional effects (e.g., mEHT acts on the membrane potential of mitochondria, while RT can induce membrane damage), but the major reactions are localized.

The conceptual difference in mEHT and RT is the temperature. The energy absorption produces heat and causes thermal effects. Certain thermal effects are conditional for mEHT. However, the thermal effect is not identical to the temperature increase. Thermal effects are often mixed with temperature development and sometimes equalize the thermal reactions with temperature changes. This is an incorrect approach, because thermal effects of phase changes of the materials or molecular excitations by absorbed heat energy are usually independent of the change in temperature. The temperature in these cases is a conditional factor, but its change is not necessary. An obvious example is boiling water, which absorbs a lot of heat (thermal effect) until the water evaporates without changing temperature. The thermal effect is not equal to the temperature change; however, the

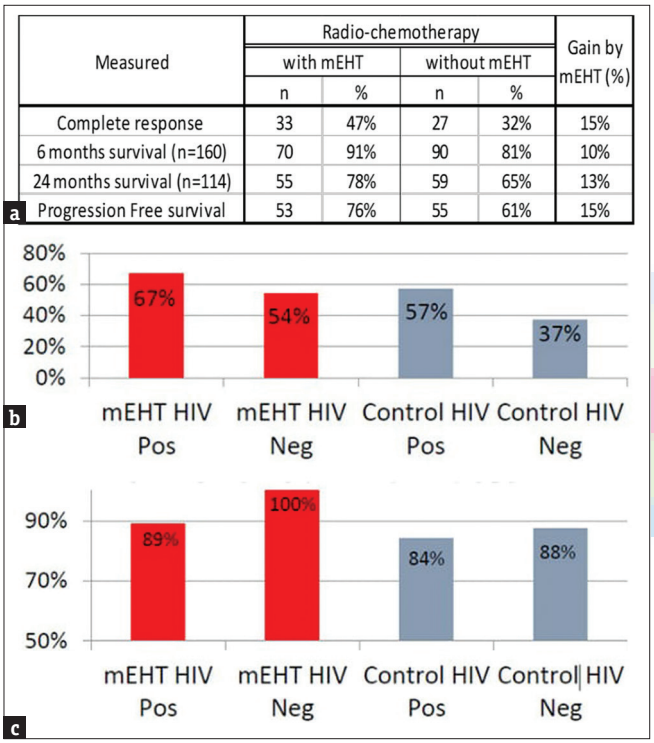

Figure 10: Interim of Phase III trial of participants with FIGO stage IIB (initial distal parametrium involvement) to IIIB cervical cancer. (a) Response rates. (b) Overall survival rates 6 months after the trimodal combined theraby. (c) Overall survival by HIV infections

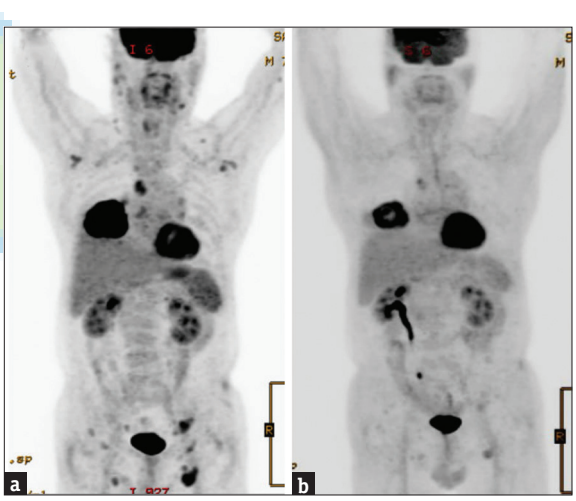

Figure 11: Metastatic non-small cell lung cancer; (cT2 cN2 Mx stage IIIB); (a) Before therapy. (b) After therapy. The distant metastases disappeared while the primary tumor showed a partial response

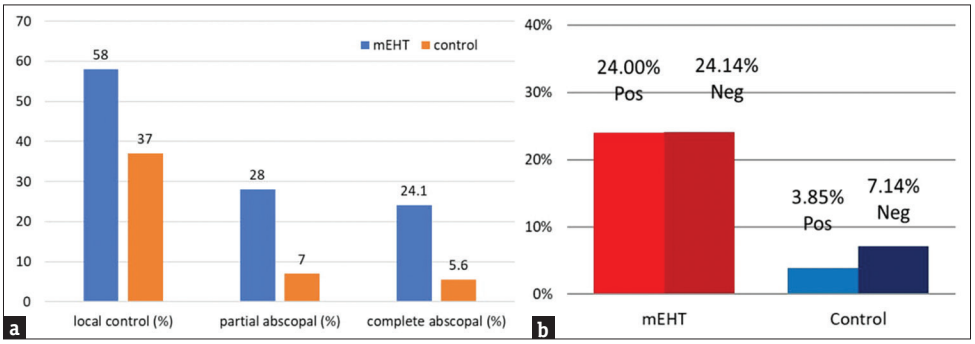

Figure 12: (a) Observed local and abscopal effects by PET scan. (b) Participants with abscopal effect by HIV status. Applied protocol: radiation, 25 × 2 Gy external and 3 × 8 Gy brachytherapy; chemotherapy: 3 × 80 mg/m^2 cisplatin; mHET (oncothmia): 2 × 55 min/week (4 weeks) (n = 54)

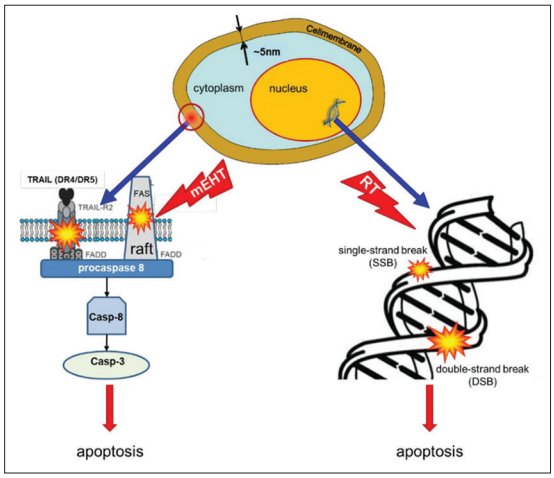

Figure 13: The principles of mEHT and RT are similar: a nano-range excitation initiates apoptosis

consequence of heat absorption usually changes the temperature. Distinguishing heat absorption from the temperature change is mandatory in the case of oncological hyperthermia when our task is to change the chemical reactions and the chemical bonds involved in the cellular signals to eliminate malignant cells from the system. The desired effects are the molecular changes where the temperature is only a condition, and its change is not requested.

The thermal effect is limited to nanoscopic local "points," which are most sensitive to any lethal attack on malignant cells. For this, a broad spectrum of biophysical and technical achievements are used. The first is the well-chosen radiofrequency current,[143] which constructs a thermal gradient between extra-and intracellular

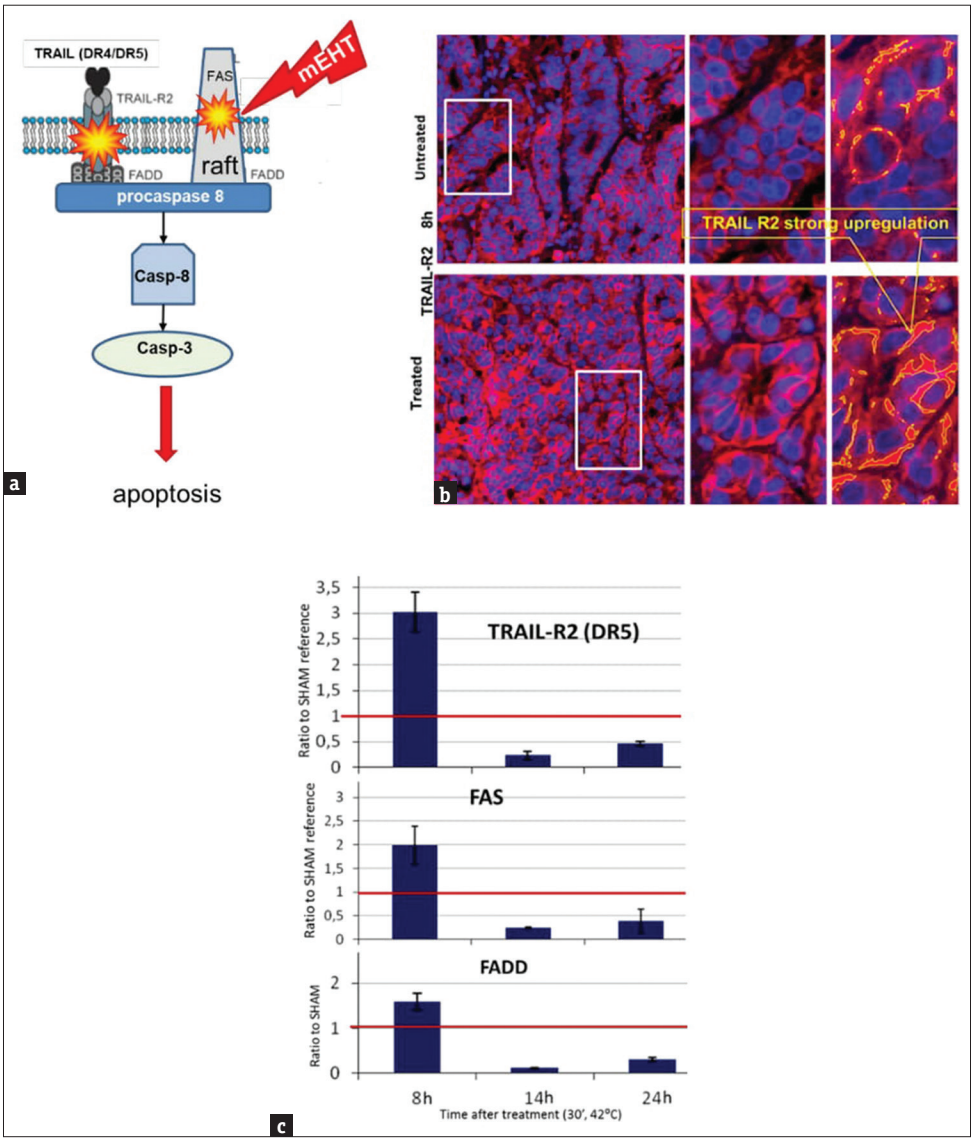

Figure 14: (a) Extrinsic excitation of trail death receptor and other molecules in lipid rafts. (b) immunohistochemistry detection of TRAIL R2 in the treated sample (HT29 × enograft) following 8 h of mEHT treatment. (c) Membrane expression of TRAIL-R2, FAS, and FADD following mEHT

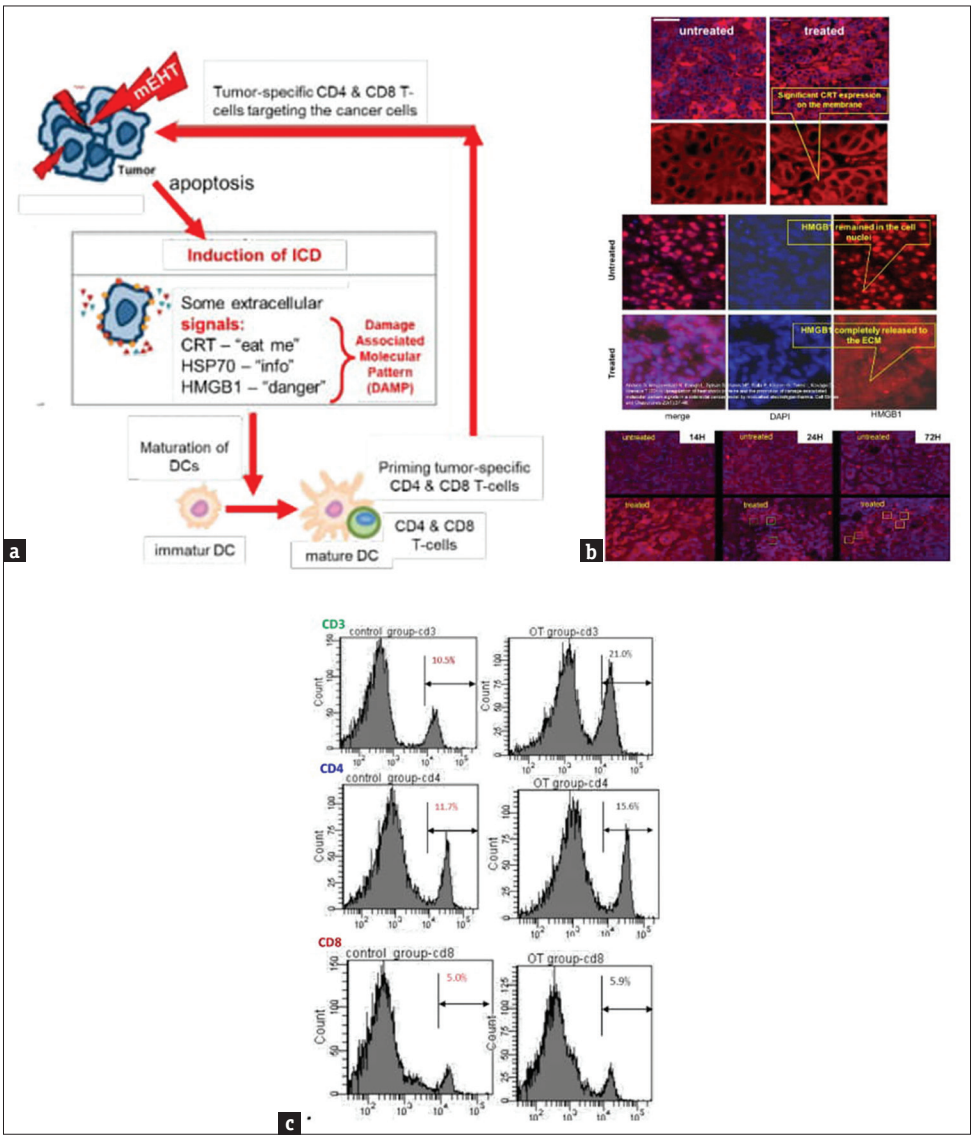

Figure 15: (a) Mechanism of immunogenic cell death induction (CRT calreticulin) (adapted from). (b) Immunohistochemistry registration of CRT, HMGB1, and HSP70 as factors of DAMP (HT29 × enograft experiment). (c) T-cell characteristics by CDs following concomitant application of DC + mEHT

electrolytes. The RF carrier frequency was chosen according to the medical standards of 13.56 MHz with appropriate time-fractal modulated current,[144] which is essential to have the proper effect (a technical description can be found elsewhere[145,146]). The temperature gradient is one of the driving forces of the signal propagation that starts at the outer membrane of the cell as extrinsic excitation. The excitation requires energy absorption and changes the molecular structure, and thus these are thermal, but not temperature dependent.[147,148] The action is like a first-order phase transition with latent energy exchange at constant (transition) temperature.

The dose of the thermal effect is not the temperature. The temperature is not a dose! (It does not change by the volume/mass.) This can lead to controversial results, as has been demonstrated with the clinical study described earlier.[10,46] This challenge requests a reference point.[148,149] This challenge could be solved by mEHT, which uses the well-known gold standards, with an energy-dose concept in the protocol. The energy is controlled to apply the largest tolerable energy-dose (J/kg).[147,150-152] The efficacy is measured by the absorbed energy (J/kg), and the safe limit is determined by energy transfer through the skin (J/m^2). The control of this last point makes safe and complication-free mEHT possible.

The new strategy of tumor treatment with local therapies is tightly connected to the abscopal mechanism,[153] which allows cellular distortion to extend to bystander cells and distant malignant lesions. One of the

mechanisms is considerably investigated by mEHT and the starting point of the mechanism is likely apoptosis. mEHT induces an extrinsic signal for apoptosis [Figure 14][154,155] and produces damage-associated molecular pattern (DAMP)[156] and immunogenic cell death (ICD).[126]

This type of apoptosis induces ICD with DAMP [Figure 15] and is a novel type of "cancer vaccination"[157] that has been patented in the US[158] and EU[159] with the application of mEHT.

Conclusions

Oncological hyperthermia is recently at a crossroads, facing a challenge by immune oncology: how to target the sensitive bonds by energy-absorption producing apoptosis and its immunological consequences. A recognized specialist of hyperthermia formulated a long time ago[160]: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment."

mEHT offers a new paradigm with nanoscopic heating, providing an adequate answer to the present challenges. mEHT breaks the long-term dominance of the isothermal heating approach. It uses nano-heating technology to select and heat the membrane of malignant cells effectively. The heating is concentrated mostly on the cell membrane, thus nano-range energy liberation can be precisely controlled without considerable wasted energy and without disadvantages that result from heating the tumor environment. The results and general benefits of mEHT open a new kind of local heating and destroy primary and metastatic tumor lesions by apoptosis-inducing ICD by DAMP. The selective, nonequilibrium energy absorption is well synergized with modern RT, presenting an effective and controllable tumor-specific immune reaction and in consequence abscopal effects. Due to the highly precise and effective energy delivery, the actual dose of mEHT is the same as the dose of RT: The Gy (J/kg).

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Conflicts of interest

The author is Chief Scientific Officer of Oncotherm GmbH.

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