"QUAE MEDICAMENTA NON SANANT, FERUM SANAT.
QUAE FERUM NON SANAT, IGNIS SANAT.
QUAE VERO IGNIS NON SANAT, INSANOBILIA REPORTARI OPORTET."
- HYPOCRITES

HYPERTHERMIA FOR ONCOLOGY:

AN EFFECTIVE NEW TREATMENT MODALITY

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ABSTRACT

Hyperthermia is a rapidly developing tumor therapy. The word hyperthermia means increased temperature, referring to the heating of tumors in oncology. An increase in tumor temperature has several favorable physiological effects, such as a decrease in relative blood perfusion of the tumor, cellular membrane changes, acidosis, ATP depletion, altered DNA replication, and an enhanced immune reaction. The clinical results are good and the side effects of the treatment are mild. Nevertheless, an increased number of non-thermal and non-equilibrium effects have been found to alter treatment results. Furthermore, several fundamentally different technical solutions are available today to achieve therapeutic hyperthermia of localized tumors selectively either using hyperthermia alone or in combination with other cancer therapies. The new science and technological advances raise the need for further research and the establishment of new treatment standards.

INTRODUCTION

The use of hyperthermia for cancer therapy was first documented by Hippocrates for the treatment of breast tumor [1]. Hyperthermia was also mentioned throughout the Middle Ages [2], but due to

inadequate heating techniques, the treatment never became a standard medical practice. At the end of the last century, energy delivery by electromagnetic fields became possible, nevertheless, its use for hyperthermia only began about 30 years ago. The mechanisms of oncological hyperthermia have since been debated [3], leading to an increasing number of international hyperthermia conferences, books [4,5,6] and journals [7]. Publications and an increasing number of clinical trials also started to appear in the top medical and scientific journals [8] (Figure 1).

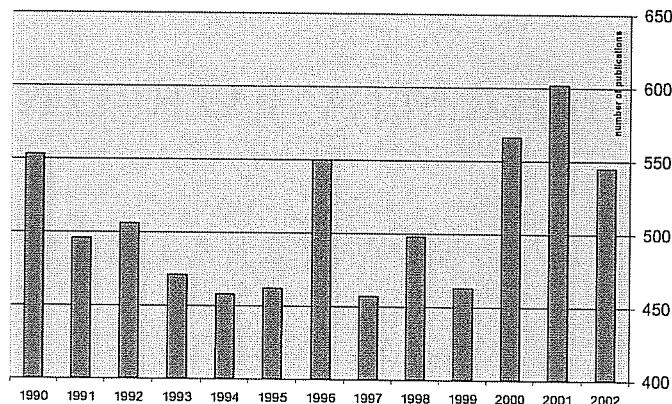

Figure 1. *Yearly number of peer-reviewed publications on oncological hyperthermia* [9].

The state of oncological hyperthermia today is similar to that of radiology at its infancy. When ionising radiation was first discovered, many hypothesized its usefulness in oncology, yet its exact dose, contraindications, limits, and the conditions of optimal treatment were not determined until several decades later. Hyperthermia today, like many early-stage therapies, lacks adequate treatment experience and long-range, comprehensive statistics that could help us optimize its use for all indications. Nevertheless, we will present a wealth of information about the mechanisms and effects of hyperthermia from the scientific literature and our own experience with the hope of proving hyperthermia's worth for further research.

MECHANISMS OF ACTION

In the early days, simple heat diffusion was utilized using hot water or wax baths and heated objects [29]. Today, focused and unfocused energy delivery using electromagnetic fields are used. In this section, we will summarize some well-established and widely accepted mechanism that account for part of the successes and shortcomings of hyperthermia treatments.

1. **Higher baseline temperature** – The rapid growth and higher metabolism of tumors typically yields higher tumor temperatures than the surrounding healthy baseline temperature [30]. One can therefore hypothesize that an elevation in the baseline temperature can selectively destroy the tumor before damaging the surrounding healthy tissue.

2. **Vascular changes** – It has been shown that an increase in temperature can cause vasoconstriction in certain tumors leading to decreased blood perfusion and heat conduction [31,32,33], while causing vasodilation in the healthy tissues, leading to increased blood perfusion and heat conduction in this region [34]. Since blood perfusion and heat conduction are decreased in the tumor, the tumor can essentially trap the heat produced by hyperthermia, causing a selective increase in tumor temperature [35]. Often, however, increased blood flow due to hyperthermia has been observed [36,37]. Yet, blood perfusion of the tumor relative to the surrounding healthy tissue is always lower [38], providing an effective heat trap [39].

3. **Cellular membrane changes** – It has been long known that hyperthermia can cause softening or melting of the lipid bilayer [40,41,42], it can change lipid-protein interactions [43], and it can denature proteins [44]. All of these events can significantly disrupt a tumor cell's capacity to divide.

4. **Altered ionic gradients and membrane potential** – Increased temperatures cause structural alteration in transmembrane proteins causing a change in active membrane transport and membrane capacity [45], leading to substantial changes in potassium, calcium, and sodium ion gradients [46], membrane potential [47], cellular function [48,49], and causing thermal block of electrically excitable cells [47,50].

5. **Acidosis** – Hyperthermia increases biochemical reaction rates [52] and therefore also the metabolic rate. Often, however, there is not enough oxygen to accommodate the increased metabolic rate resulting in hypoxia [53] and anaerobe metabolism producing lactate [54] and cell destruction by acidosis. Acidosis can be prompted by the administration of glucose prior to treatment [55].

6. **ATP depletion** – Increased metabolism can significantly decreases cellular ATP stores leading to increased cell destruction [54].

7. **Altered DNA replication** – Increased temperatures can slow down or even block DNA replication [56,57]. This has been hypothesized to have a sensitizing effect against radiotherapy [58].

8. **Enhanced immune reaction** – Hyperthermia has been shown to stimulate the immune system [56], with observed increases in natural killer cell activity [59]. Moreover, the elevated temperature distributes tumor-specific antigens on the surface of various tumor cells [60] and assists in their secretion into the extracelluiar fluid [61].

9. **Pain reduction** – Certain electric fields (TENS) are used regularly to reduce pain [62]. Hyperthermia, and especially electric field induced hyperthermia, has also shown significant pain-reduction during treatments [63].

COMBINATION THERAPIES

Most current treatments for cancer are difficult to tolerate due to their high toxicity levels. In general, patients are treated with chemo- and radiotherapy to their toxicity limits in order to achieve maximal tumor destruction. However, these treatments are often not enough. Hyperthermia is an ideal combination therapy. It has low toxicity, mild side effects, and has been shown to provide synergies with many of the traditional treatment modalities.

RADIOTHERAPY

The synergy between hyperthermia and classical ionising-radiation is well-known [64]. The primary basis for the synergy is the complementary targets of the two treatments (Table 1). Briefly, ionising radiation is most effective in the M and G_1 phase, in relatively alkaline, well-oxygenated regions. Hyperthermia on the other hand exerts the greatest effects in S phase, in relatively acidic, hypoxic regions. The most active regions of a tumor and regions far from blood supply are usually severely hypoxic, and therefore radiation has little efficacy in these regions. Hyperthermia, however, speeds up the cellular metabolism,

accentuating the hypoxia to apoptotic and necrotic levels. Furthermore, the vascular changes described above aid the synergy by the overall increased blood perfusion creating considerable sensitization to ionizing radiation.

Effect/Method	Ionising radiation	Hyperthermia
Cell cycle specificity	Acts in M+G_1 phase	Acts in S phase
pH-dependence	Acts in relatively alkaline regions	Acts in relatively acidic regions
Oxygen specificity	Acts in well oxygenated tissues	Acts in hypoxic tissue

Table 1. Complementary effects of radiotherapy and hyperthermia.

CHEMOTHERAPY

Chemotherapy drugs are delivered into the tumor through the blood circulation, therefore, it is most effective in the well-oxygenated regions near blood vessel. In this respect, chemotherapy is similar to radiation therapy in that it primarily targets regions of high blood perfusion. As discussed above, this region is complementary to the areas treated effectively by hyperthermia. Moreover, an increase in temperature improves chemotherapy efficacy through faster reaction rates and a thermally activated metabolism. This results in a better therapeutic index increasing target specificity and reducing systemic side effects. Finally, chemotherapy drugs are specific to cells in M and G_2 phase and show little or no efficacy against cells in G_0 phase. Hyperthermia reduces the average time spent in G_0 phase making them susceptible to chemotherapy (Table 2) [65,66].

Effects/Method	Chemo-therapy	Hyperthermia
Place of activity	Near blood vessels	Far from blood vessels
Reaction rate	Normal	Enhanced
Chemo penetration	Low, due to high pressure	Enhanced transport by electroosmosis
Cell division	Acts in M+G_2 phase	Acts in S phase
Activity	No activity in G_0 phase	Decreased time in G_0 phase

Table 2. Complementary effects of chemotherapy and hyperthermia.

SURGERY

Hyperthermia has also been found to have pronounced advantages for surgical interventions. Through hyperthermia induced inhibition of angiogenesis and heat entrapment, the outline of the tumor often becomes pronounced and the size of the tumor often shrinks making previously dangerous operations possible [67]. Postoperative application of hyperthermia has also been thought to prevent relapses and metastatic processes [68]. Intraoperative radiofrequency ablation has also been used to improve surgical outcomes [69].

GENE-THERAPY

The combination of the hyperthermia with the gene-therapy looks very promising, as shown by the successful combination of hyperthermia and HSP-promoter mediated gene therapy in advanced breast cancer patients [70]. Hyperthermia improved the results of the HSP-promoter gene therapy by inducing local HSP production and by enhancing the local rate of release from liposomes [71]. It was shown that this combination therapy was highly selective for mammary carcinoma cells.

DIFFICULTIES WITH HYPERTHERMIA TREATMENTS

Although hyperthermia can have significant benefits, there are several well-known side effects of inappropriate treatments.

1. **Lack of good standards** – Technically it is very difficult to control heat transfer into and within the body, and provide the same reproducible heat dose for each treatment within the target tissue. A "success parameter" taking into account the efficiency of focusing and heat conduction within the body must be established before reliable protocols can be worked out.

2. **HSP production** – Heat can induce heat shock protein (HSP) production. HSP-assisted adaptation mechanisms decrease the efficacy of hypethermia and can aid in the development of resistance to heat, chemo, and radiation therapies. Some tumors have also successfully disabled their apoptotic pathways by upregulating baseline HSP levels. This can significantly impair the efficacy of later hyperthermia treatments. Finally, it has been shown that magnetic fields can induce HSP production [72,73], which is highly undesirable for therapies.

3. **Hot spots** – Inadequate focusing can lead to overheated regions, a.k.a. hot spots, causing necrosis of the healthy tissue.

4. **Inappropriate blood flow** – Inadequate focusing to the surrounding healthy tissue can lead to greatly increased blood flow near and within the tumor. This can induce further tumor growth and can intensify metastases formation.

STANDARDIZATION OF TREATMENT PARAMETERS

As mentioned above, hyperthermia dosing and treatment standardization is still a significant problem. There is considerable discussion over the relevant treatment parameters, controls, and treatment optimization. Discussions are primarily centred on the role of temperature and temperature initialised effects.

Many believe that the single most important factor in hyperthermia is tumor temperature. This view is well supported by the cellular phase transition observed around 42.5°C [74] and the surprisingly accurate fit of the Arrhenius plot to experimental results [75,76]. The observed cellular phase transition, however, was for uniform heating effects without any significant temperature gradients in the system. This and other observations therefore lead to recent doubts about this concept [135].

The application of lower temperatures for longer time periods (same dose) treatments also showed surprisingly good efficacy for whole-body hyperthermia treatments [77]. This finding supports the opinion that the delivered heat dose [78] (absorbed energy) or applied field [79] (electromagnetic influence) are the primary determinants of efficacy.

Both of the above methods assumed uniform temperature distribution within the target tissue. Although the thermal relaxation is quiet rapid, requiring only a few milliseconds across the cell membrane, it is possible to establish a transmembrane temperature gradient by selectively and continuously heating the extracellular matrix. Temperature gradients across the cell membrane can create electro-mechanical pressure (Onsager equations [80]) and electro-thermal currents (Hodgkin-Huxley equations [81]) causing permanent damage.

Recently, numerous scientific theories also started to concentrate on the significance of thermally induced non-thermal effects, such as HSP production [82,83]. The relevance of tumor temperature, heat dose, non-equilibrium, and non-thermal effects are apparent and lead us to conclude that clinical outcome cannot be determined purely on the basis of any of these factors alone.

HSP PRODUCTION

Hyperthermia can affect HSP expression [94] and the immune response [95]. HSPs are highly conserved proteins vital to proper protein folding and hence cell survival [96]. Changes to the cellular dynamic equilibrium (e.g. environmental stresses, various pathogen processes, diseases) activate HSP synthesis as a self-defense mechanism [97]. Since malignant cells divide under abnormal (stressful) conditions, HSPs are typically present in large quantities to aid malignant cell survival [98,99,100]. One of the HSP90 homologues, GRP94 may also act as a mediator of metastasis generation.

HSPs are produced by most treatment-methods devoted to eliminate the malignancy; some examples are classical hyperthermia [101,102], chemotherapy [103], radiotherapy [104], and phototherapy [105]. Other non-thermal effects (e.g. magnetic field stress) can also induce HSP synthesis [106]. Over-expression of HSPs can often provide effective protection against apoptosis and decrease the efficacy of treatments by inducing thermo-tolerance, and resistance to radiotherapy and chemotherapy drugs [107,108]. As a result, HSP profiles in tumor biopsies can also provide good clinical indication for treatment resistance [89].

The role of HSPs is not as clear cut, however. Expression of HSP70 on the cell membrane has been shown to stimulate apoptosis and activate the immune system [109]. Pro-apoptotic effects have been linked to HSP70's role in the activation of p53 [110] and retinoblastoma [111] tumor-suppressers. HSP90-α excretion has also been found to have a stimulatory effect on the growth of lymphoid cells [112]. Finally, several other HSPs are involved in antigen presentation on the cell membrane drawing an immune response [113,114].

In summary, stress-proteins have two apparently opposite actions:

- Intracellular HSP activation builds resistance against apoptosis, immune attacks, hyperthermia, and other treatments, such as radiotherapy and chemotherapy drugs.
- Extracellular display of HSPs can stimulate apoptosis and an immune response.

Ideally, treatments would damage the malignant cells before HSP production is triggered or treatments would harness HSP presentation for the induction of an immune response. We propose that by rapidly, selectively, and continuously heating the ECM by electromagnetic fields, we can destroy the cell-membrane and induce an immune response before the induction of the heat shock response through heat diffusion. Furthermore, we propose that the damage to the cell membrane is only partially due to the absolute temperature, with contributions from the temperature gradient induced transmembrane pressure and ionic currents.

ELECTROMAGNETIC HYPERTHERMIA TECHNIQUES

Numerous heating techniques exist for local and systemic hyperthermia. We will focus our discussions on electromagnetic heat deliveries for the targeted treatment of any malignancy. Three characteristically different electromagnetic heating techniques exist: electric field coupled energy transfer (capacitive coupling), magnetic field coupled energy transfer (inductive coupling) and radiative energy transfer (radiative coupling or antenna array). These methods are summarized in Figure 2 and 3.

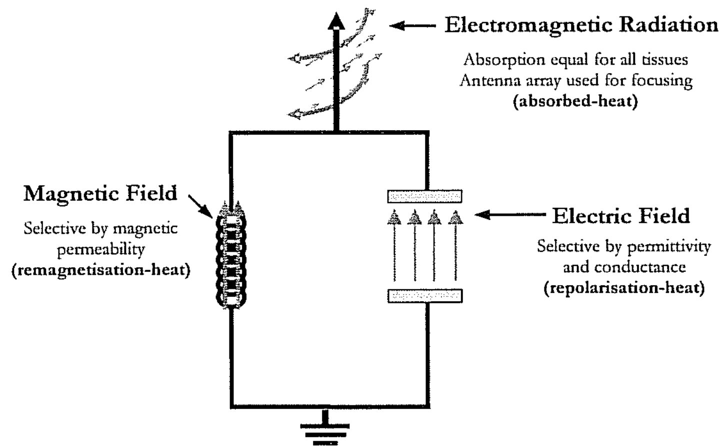

Figure 2. A schematic resonant circuit with magnetic, electric and radiative (Poynting vector) coupling.

Body cross section · RF supply · tumor · Treatment bed · Magnetic coil · Magnetic heating

RF supply · tumor · Capacitive coupling

Body cross section · RF supply · tumor · Antenna array

	Inductive	Capacitive	Antenna
Focus:	By injected magnetic materials	By the dielectric selectivity of the tissues	By intensity, phase and frequency of the antenna radiations
Frequency:	Very low Fixed constant	Low Fixed constant	High Variable
Transmitter:	Air	Water bolus (Water-pillows)	Water bolus (Sigma-eye)

Figure 3. *A comparison of the main parameters, focusing ability, frequency, and transmitter, for electromagnetic hyperthermia.*

Capacitive and inductive coupling are easily quantifiable in the so called "near-field" regime, where the wavelength of the actual field is considerably greater than the source-target distance. For radiatively coupled electromagnetic fields using antenna arrays, a far-field method or a mixed regime calculation is

required for accurate dosing. For microwave applications, the far-field approximation is applicable since the applied wavelength is much smaller than the target distance. For low-frequency microwave or high frequency radiofrequency (100-200 MHz) the wavelength and the source-target distance are comparable, therefore focusing requires numerical approximations with limited accuracy. Some typical frequencies and related parameters are shown in Table 4.

Coupling Method	Typical Frequency	Efficacy	Focusing Method	Electric Field	Magnetic Field	Main area of Heat production
Capacitive	13.56 MHz	22.5%	Self-focused	High	Low	ECM only
Inductive	< 25 MHz	0.24%	Parametrical	Low	High	Entire tissue
Antenna-array	100 MHz	3.45%	Parametrical	Medium	Medium	Entire tissue

Table 3. Comparison of the typical parameters of electromagnetic hyperthermia methods, (ECM = extracellular matrix).

Capacitive coupling in oncological hyperthermia was first used in 1970 [115] and has been widely applied since [116,117,118]. Most hyperthermia devices use capacitive coupling since it requires no extra shielding and the energy deposition is easy to control [79]. Capacitive coupling is applicable for most tumor lesions, including the lung and the brain. Numerous peer-reviewed clinical trials have also shown its efficacy [119,120,121,122,123,124]. One of the disadvantages of capacitive coupling is the large voltage drop, hence large energy deposition, in tissue layers of low dielectric constant and poor conductivity, such as adipose tissue, that can lead to painful burns of these layers. There are proprietary technical solutions to this problem, however. The frequency typically chosen for capacitive coupling is in the 5-30 MHz radiofrequency range chosen to satisfy the Electro-Magnetic Compatibility [EMC] standards.

Inductive coupling is relatively rarely used due to the negligible magnetic permeability of living systems [125]. Inductive heating is typically achieved by low efficiency Eddy-currents. In order to improve the magnetic energy absorption within the target tissue, magnetic materials, such as micro-particles [126] and ferrite rods [127], are usually injected into the targeted area [128]. Ferrite rods (seeds) have also been used for non-oncological ablative therapies [129]. Using the same idea, a new "intracellular hyperthermia" method was developed [130], however, the efficacy of this treatment is still debated [131].

Antenna-array coupling using microwaves or high-frequency radiofrequency (RF) is the third method for electromagnetic energy delivery [132,133]. The antenna arrays surrounding the body deliver a chosen field intensity, phase, and frequency of radiated electromagnetic waves to focus the energy delivery to the targeted location. The higher frequency used in this method is necessary for accurate focusing, however, these frequencies lie outside the European EMC free standards, therefore requiring shielding. Furthermore, the typically applied 80-160 MHz high frequency RF (HFRF) antennas function in a near-field arrangement (the source-target distance is comparable to the wavelength of the applied radiation), thus its accuracy and efficacy are suboptimal and the treatment becomes effectively a capacitively coupled. Nevertheless, multiple controlled clinical trials have shown the efficacy of this method also [134, 135, 136, 137].

Any of these three methods can be used for local and whole-body applications for surface and deep-seated lesions. There is a wide range of frequencies and power settings used from direct current to infrared lasers applications using anywhere from a few watts to a few kW of power. For typical, local, deep-seated target treatments, 8-200 MHz and 100-1000 W are used.

EXTRACELLULAR HYPERTHERMIA

Recently, scientists have started to realize that hyperthermia induced temperature gradients could have significant biological effects. A new branch of hyperthermia know as extracellular hyperthermia [138] or electro-hyperthermia [79] has been developed around this concept. Although this new technique recognizes the benefits of increased tissue temperature and its biological consequences it also argues that non-equilibrium thermal effects are partially responsible for the observed clinical deviations from the purely temperature-based treatment theory.

Electro-hyperthermia is based on a capacitively-coupled energy transfer applied at a frequency that is primarily absorbed in the extracellular matrix due to its inability to penetrate the cell membrane [139]. Although these temperature gradients typically relax within a few milliseconds, a constant energy delivery can maintain this gradient for extended periods of time. An externally applied electric field can maintain temperature gradients of 1 K/μm, creating a permanent heat flow of 1500 $nW/\mu m^2$, which is well above the natural heat-flow (20 $nW/\mu m^2$) across the target cell membranes. This gradient and the resulting heat flow can produce 150 $pA/\mu m^2$ currents through the membrane primarily by Na^+ influx into the cell, which significantly exceed the typical 12 $pA/\mu m^2$ sodium efflux present [138]. This depolarizes and therefore destabilizes the membrane, and stimulates Na^+/K^+ pump activity. This requires ATP resulting in further heat production at the membrane. The membrane permeability of water is much higher than for ions, therefore it is the main transported component in thermo-dynamic coupling. A thermal flux of 0.001 K/nm can therefore build up pressure reaching 1.32 MPa [138]. Since malignant cells typically have relatively rigid membranes due to increased phospholipids concentrations [140], an increase in pressure will selectively destroy malignant cells before it affects healthy ones.

Interestingly, an electric field application without an increase in temperature (using less than 5W power) has also been found effective against cancer [141,142,143,144]. Electric tumor treatment, introduced by B.Nordenstrom, Karolinska Institute, Sweden [145,146], is well accepted in Japan and China [147,148,149] with results reported in several peer-reviewed journals [150,151,152,153,154] and conferences organized on the subject matter [155], yet few studies discuss the biological mechanisms involved in electromagnetic field induced hyperthermia [79, 156].

CLINICAL RESULTS

In this section, we have gathered some results using different hyperthermia techniques and combination therapies to provide the reader with a sense of the potential that hyperthermia provides. Results of several clinical trials and their references are summarized in Table 5.

Localization	Radio-therapy	Chemo-therapy	OR* , [%] conventional alone	OR*, [%] with hyperthermia	Number of patients	Ref:
Head- and neck CA	yes	no	n.a.	92	27	[157]
Head- and neck CA	yes	n.a.	15	20	184	[158]
Head and Neck	yes	no	58	74	65	[159]
Head and Neck (lymph-nodes)	yes	no	41	83	41	[160] [161]
Cervix CA	yes	no	46	66	65	[162]
Cervix CA	yes	no	35	72	66	[163]
Cervical CA	yes	no	52.6	83.3	37	[164]
Cervical cancer	no	yes	n.a.	52	23	[165]
Cervical CA	yes	no	50	80	40	[121]
Cervical CA	yes	n.a.	57.1	82.7	114	[166]
Cervix	yes	no	50	85	40	[167]
Vulva/Vagina	no	yes	19	59	65	[168]
Breast CA (superf.)	n.a.	no	41	61	148	[169]
Breast adenocarcinoma	yes	no	n.a.	100	9	[170]
Breast	yes	no	35	62	306	[171]
Breast (locally advanced, primary)	yes	no	55	91	11	[172]
Breast (recurrent after operation)	yes	no	89	83	6	[172]
Breast (recurrent after radiotherapy)	yes	no	84	92	13	[172]
Breast (recurrent)	yes	yes	n.a.	80	25	[173]
Breast (recurrent)	yes	no	41	69	154	[174]
Breast (advanced)	yes	no	63	83	24	[175]
Malignant non-Hodgkin	n.a.	n.a.	61	64	172	[176]
Gastric Tumors	yes	n.a.	35.5	57.6	293	[177]
Gastric cancer (advanced)	no	yes	n.a.	39	33	[178]
Gastric cancer (advanced)	yes	yes	n.a.	82	21	[179]
Esophageal CA	no	yes	19	41	40	[180]
Esophageal CA	n.a.	n.a.	24.2	50.4	66	[181]
Esophageal CA	yes	no	8	70	53	[182]
Esophageal CA	yes	yes	8	27	53	[183]
Esophageal CA	yes	no	25	63	313	[184]
Esophageal CA	yes	n.a.	59	81.2	66	[185]
Stomach	no	yes	n.a.	39	33	[186]
Pancreas	no	yes	n.a.	36	22	[186]
Hepatocellular CA	no	yes	43	56	48	[187]
Colo-rectal CA	yes	no	10	43	24	[188]
Bladder CA	yes	n.a.	51	73	101	[166]
Bladder CA	no	yes	22	66	52	[189]
Bladder CA	no	yes	22	66	52	[190]
Rectal CA	yes	no	0	11	48	[191]
Rectal CA	yes	no	33	69	117	[192]
Rectal CA	yes	no	55	71	101	[193]
Rectal CA	yes	no	20	100	14	[186]
Rectal CA	yes	no	5	23	122	[194]
Rectal CA	yes	yes	n.a.	60	40	[195]
Rectal CA	yes	n.a.	15.5	20.8	143	[166]
Rectal CA	yes	yes	n.a.	60	37	[196]
Superficial	yes	no	n.a.	100	22	[197]
Superficially located CA	yes	no	62.6	82.8	92	[198]
Various (near-surface)	yes	no	59	83	780	[199]
Subsurface	yes	no	n.a.	96	28	[197]
Superficial tumors	yes	no	25	46	85	[200]
Superficial tumors	yes	no	63	88	16	[201]
Malignant melanoma	yes	n.a.	28	46	70	[202] [203]
Melanoma	yes	no	n.a.	68.7	28	[170]
Melanoma malignum	yes	no	39	72	238	[204]
Lung CA	no	yes	36	68	44	[205]
Lung CA (Non-small cell)	yes	no	20	73	49	[206]
Lung CA (Non-small-cell)	yes	no	n.a.	100	13	[207]
Soft-tissue tumor	yes	no	n.a.	74	31	[208]
Soft-tissue sarcoma	no	yes	n.a.	46	59	[209]
Soft-tissue sarcoma	no	yes	n.a.	87	55	[210]
Sarcoma	no	yes	n.a.	37	38	[211]
Various tumors	yes	no	14	86	14	[212]
Deep-seated	yes	no	n.a.	69	13	[197]
Various tumors	yes	no	7	47	15	[213]
Various (deep-seated)	yes	no	25.2	42.7	862	[199]
Glioblastoma multiforme	yes	no	15	31	112	[214]

*OR – Overall Response-rate: sum of Complete Remission (CR) and Partial Remission (PR)

Table 5. Clinical trials using hyperthermia in combination with radiotherapy and/or chemotherapy.

The trials shown in Table 5 used hyperthermia in combination with radiotherapy or chemotherapy. Due to ethical reasoning, clinical trials testing the efficacy of hyperthermia alone are rare, and applied when the other modalities have falled (resistant tumor, liver/kidney failure, psycho-resistance, etc.) [215, 216, 217, 218, 219].

Although we did not analyze the results of each trial critically here, it can be seen, nevertheless, from the wealth of statistics provided that hyperthermia can significantly improve the clinical outcome of both radiotherapy and chemotherapy. For critical reviews of these and other hyperthermia trials, we direct the reader to recent publications [135, 136, 220, 221, 222].

CONCLUSIONS, PERSPECTIVES

Hyperthermia is an emerging effective treatment method in oncology. It has shown significant improvements in tumor response rates and patient morbidity in combination with other treatment methods, such as surgery, chemotherapy, radiation therapy and gene-therapy or applied as a monotherapy. Nevertheless, hyperthermia is still in its infancy. It lacks standards and a scientific consensus about its effects on malignant and healthy tissues, and the current techniques used to treat patients vary significantly from antenna-array focused electromagnetic energy delivery methods to non-thermal low-power current applications. In order for hyperthermia to gain wide-spread approval and clinical use, the technique requires extensive further research and standardization.

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