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Conference Paper

The History of Hyperthermia Rise and Decline

Sergey Roussakow

Galenic Research Institute, Moscow, Russia

Correspondence should be addressed to Sergey Roussakow; roussakow@gmail.com

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Electromagnetic hyperthermia remains experimental treatment after 40 years of research and application in view of its "temperature concept" based on the belief that temperature is the only parameter of the efficacy. Initial "extreme hyperthermia" concept was based on the wrong premise of much higher thermal susceptibility of malignant cells and broad therapeutic range of hyperthermia, allowing to kill tumor cells by above-threshold (>43°C) temperature without damaging healthy tissues. Indeed, this therapeutic gap is minor or absent which makes the extreme hyperthermia impossible. The next concept of "thermal dose" was based on the ungrounded extrapolation of the biochemical Arrhenius relationship onto the living matter and formed the basis of "moderate hyperthermia" concept, believing that it could enhance tumor oxygenation and radio- and chemosensitivity, ignoring the special features of tumor blood flow. Both concepts have not been confirmed; "thermal dose" is currently proven to be not connected with any clinical outcome. Analysis of randomized trials with respect to biases has not confirmed hyperthermia efficacy. The growing evidence of athermal effects and their broad application has caused development of some athermal cancer treatments. Hyperthermia concept should be cardinally reevaluated now with respect to obvious bankruptcy of the temperature concept and development of the athermal concept.

"Those who cannot remember the past are condemned to repeat it"
George Santayana, *"Life of Reason I"*
"The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact"
Thomas Henry Huxley

1. Introduction

The treatment of any problem begins from the recognition of the problem. "I'm John, I'm alcoholic"—this is the start of a return. There is no any hope for cure without this recognition. Hyperthermia is in crisis already for two decades, but still there is no awareness of the problem. This is the main reason, why hyperthermia in its current state cannot be cured.

First, we have to state unequivocally: "Hyperthermia is in deep crisis." Only a blind does not see it. If we remember how many top class US medical research centers were active in hyperthermia field 20–30 years ago and how many of them show residual activity now, the conclusion is obvious. After 50 years of intensive development, having more clinical trials and publications than any modern popular pharmaceutical, hyperthermia is not accepted in any branch of oncology. One-two occasional inclusion in one-two guidelines as "the last hope therapy" with many controversies is the demonstrative result of this development.

Such a pity situation necessarily should have objective reasons. It is not enough to claim for lack of money, competition with radiology and chemotherapy, and so on. Our recent analysis of hyperthermia randomized trials [1] clearly showed the real reason of the situation: the lack of real clinical

effect. This is the problem and this should be recognized by hyperthermia community first.

Then, the next question arises: we know that hyperthermia has very strong biological and experimental rationale. How could it do not work in practice? Where is the error?

To understand this point, we should overview the theory and history of hyperthermia. We should return back in time to understand, where, when, and why hyperthermia went wrong way, and is there a solution. Because modern hyperthermia is almost exclusively electromagnetic treatment, we should trace the development of both hyperthermia and electromagnetic treatment to understand the current situation.

2. Hyperthermia and Electromagnetic Therapy before 1950: Early Stage, Radiofrequencies, and Establishment of "Thermal Dogma"

2.1. Hyperthermia before 1950: Early Stage. The history of oncological hyperthermia started from some evidences of cancer cure by concomitant febrile diseases described in XVIII-XIX centuries. It seems that the inhibition of tumor growth by high fever caused by malaria was for the first time described by de Kizowitz (France) in 1779. In 1866, Busch [2] (Germany) described the complete remission of histologically confirmed face sarcoma after two erysipelas infections with subsequent 2-year disease-free survival. He then used the intentional contact with erysipelas infection to treat several patients. Apparently, in the second half of XIX century, the practice of infectious febrile therapy was quite common not only in Germany and France but also in Russia [3], and it was used to treat a wide range of diseases including mental diseases. In 1882, Fehleisen discovered Erysipelas agent—Streptococcus pyogenes [4]. He inoculated live bacteria to seven cancer patients and achieved complete remission in 3 cases. Bruns in 1887 reported a case of complete remission in a patient with multiple recurrent melanoma after Erysipelas with temperature over 40°C for several days, with 8-year disease-free survival [5]. He also collected 14 reported cases of erysipelas in proven malignant disease: in most cases there was complete and stable remission. The method was called febrile therapy and hyperthermia per se was only one component of the complex body reaction, and it was not considered as a separate treatment modality.

Systematic school of cancer febrile treatment emerged at the end of XIX century. It was connected to the name of William B. Coley [6], a bone surgeon in New York memorial cancer hospital (now the Memorial Sloan-Kettering). In 1893, Coley described 38 patients with confirmed advanced cancer suffering of erysipelas with high fever; in 12 of them, tumors had disappeared, and 19 had displayed an improvement; in 2 of 10 patients with locally advanced sarcomas treated by Coley, complete remission had occurred [7]. Coley had created a so-called "Coley toxin" or "mixed bacterial vaccine" (MBV), the first specialized bacterial antitumor pyrogen with standardized composition, which subsequently was produced industrially. American Medical Association (AMA) was sharply negative to Coley method: whereas JAMA editorial in 1893 [8] gives a generally positive review of Coley therapy, the editorial in early 1894 [9] explicitly declares ineffectiveness of such therapy. Since that time, it remains the official position of AMA.

Start of Coley toxin practice coincided with scientific and technological revolution in oncology: almost simultaneously X-rays (1895) and radium (1898) were discovered and in a few years oncology was armed with radiotherapy and brachytherapy which displaced all other methods to far periphery of scientific interest. Despite the fact that the first results of radiotherapy in oncology were far not favorable [10], its understandable physical rationale caused the belief that the results must necessarily follow, and the only problem is the improvement of the method. Because of the sharply negative attitude of AMA and the newly formed American Cancer Society (ACS), approximately in 1915 Coley's work was suspended although many oncologists in US and Europe continued to use Coley toxins for many years.

Unlike radiotherapy, study of the mechanisms of action of febrile therapy and thermotherapy at all started only at the 40–50s of XX century, when fundamental papers on thermal damage of Moritz et al. [11–13] were published and, on the other hand, building of the scientific foundation of immunology had started. Coley left a lot of works and enormous amount of materials on the application of his toxins, which had been processed by his daughter Helen Nauts. In 1946, she published a retrospective study of 484 cases of cancers treated with Coley vaccine: in 312 inoperable patients, 5-year survival was 43%, and 61% in 172 resectable ones. [14]. In another example, 25 of 30 patients with advanced cancer showed 10-year disease-free survival [15]. It seems there was a good situation for revival of the method, but the position of AMA and ACS had not changed. Very soon, the development of chemotherapy had pushed the febrile treatment again to the periphery of oncology.

The attitude of medical community to febrile therapy was mainly skeptical. In 1949, famous German surgeon Bauer in his book "Das Krebsproblem" wrote that "these methods strongly impress patients, but not their cancers" [16]. Coley himself has never singled out the temperature as the primary mechanism of the antitumor effect, considering the effects of its vaccine complex. Nevertheless, he repeatedly stated that the higher and the longer the fever, the better the effect of the treatment [17].

The idea of separate use of heating for treatment of cancer had matured almost simultaneously with the idea of Coley bacterial toxins: already in 1898, Swedish gynecologist Westermark [18] published a report on the use of long-term (48 hours) local (by virtue of intravaginal metal coil heated with circulated water to 42–44°C) and regional (hot tubs) heating for treatment of various gynecological diseases. Among others, he described several excellent results in inoperable cervix cancer. He was the first who had shown the ability of the long-term heating to destroy tumors without damaging healthy tissues. Gottschalk [19] in 1899 confirmed the success of heating in cervical cancer and suggested the use of higher temperatures and reduced exposure times. In 1910, Doyen [20] reported on the successful treatment of a number of cancers by heating to high temperatures (55°C) though

in modern terms it was not hyperthermia but high-intensity thermotherapy. Percy [21] in 1916 reported a 3–7-year survival of inoperable cancer of the uterus after local hyperthermia above 45°C; Balfour confirmed these results [22]. In 1918, Rohdenburg [23] summarized the available literature data on spontaneous remissions and found fever, heating, or severe infections in 72 cases out of 166. In 1932, Goetze [24] reported the effectiveness of hot bath in cancer of penis.

Attempts of hyperthermic radiosensitization started shortly after the introduction of radiotherapy. Already in 1913, Muller [25, 26] reported 100 cases of combination of X-ray and diathermy: there were 32 complete remissions and 36 partial remissions. In 1935, Warren [27] study was published on thermoradiotherapy of the hopeless cancer: by combining radiotherapy with different types of long-term induced fever, he achieved considerable effect on 29 of 32 patients. The same time, Doub [28] reported on the effectiveness of thermoradiotherapy in osteogenic sarcoma; Doub [29] and Delario [30] declared a radiosensibilizing effect of the induced febrile therapy. In 1941-42, Shoulders [31, 32] reported on the effectiveness of combination of radiotherapy with febrile therapy in advanced cancer. In 1948, Korb [33] reported result of thermoradiotherapy with internal control: from two basal cell skin carcinomas in one man, one was treated with radiotherapy only without effect, and the second after thermoradiotherapy underwent complete regression.

Experimental study of hyperthermia started immediately after the first clinical results Table 1. In 1903, Loeb has shown that fragments of rat sarcoma treated at 45°C for 30 min did not graft. Jensen received similar results in mouse tumors treated at 47°C for 5 min. It seem he was the first who suggested a higher heat sensitivity of tumor cells compared to normal cells. In 1907, Erlich reported higher heat sensitivity of carcinomas in comparison with sarcomas. In 1908, Haaland reported that 30-minute treatment at 44°C inhibits both sarcomas and carcinomas. In 1911, Vidal reported the increased survival of mice with tumor grafts at higher temperatures. In 1916–1921, Prime and Rohdenburg [34] reported the first systematic study on thermosensitivity of tumors made on 2000 mice inoculated with Crocker murine sarcoma, previously incubated at different temperatures. 100% growth inhibition was observed after treatment at 42°C for 180 min and at 44°C for 90 min. In 1927, Westermark initiated experimental study of hyperthermia on rats [35].

2.2. Electromagnetic Treatment before 1950: Radiofrequency Era and Formation of "Thermal Dogma". History of electromagnetic treatment started from works of Nicola Tesla in USA and Arsen d'Arsonval in France. It was d'Arsonval who is considered the father of electromagnetic therapy [36–38]. d'Arsonval himself considered his treatment conditioned by electromagnetic field effects though it was clear from just a beginning that "undesirable heating" is an inevitable consequence of the electromagnetic impact [39] as Tesla clearly predicted [40]. Because of the field concept, d'arsonvalization used low currents and high voltage to diminish "undesirable heating" and to enhance "field effects" [41]. Near 1905, diathermia was invented by von Zeyneck et al. [42] and then widely promoted and advertized by Nagelschmidt [43]. Diathermia was targeted only for heating and used high currents with low voltages for this purpose. Between 1910 and 1920, diathermia was established in its classical form as a method of deep capacitive heating with a frequency 0.5–2 MHz and a current strength 1–3 A [44, 45]. The use of such diathermia for hyperthermia was limited by overheating of subcutaneous tissues [46–49]. Nevertheless, there were some reports of combination of diathermia and roentgen therapy with promising results [25, 26].

After 1917, works of Julius Wagner von Jauregg on treatment of paresis, syphilis, and some other diseases by malaria had raised again an interest for febrile treatment [50]. It was revealed shortly that febrile treatment is effective for treatment of wide range of somatic diseases. It was also revealed soon that hyperpyrexia caused, for instance, by intramuscular injection of sulfur or oils, is also effective for treatment contemporary with infectious fever. That is, hyperpyrexia was identified as a separate curative factor. From this understanding, only one step remained for the external hyperthermia.

In 1920, magnetron was invented which allowed to receive frequencies up to 150 MHz and started radiofrequency era in electromedicine. In 1928, W. R. Whitney, a vice president of General Electric, had revealed that body temperature of those who are close to short-wave transmitters rises for 2-3 centigrades. This was a discovery of irradiant radiofrequency heating [51], which soon led to the development of Radiotherm in 1931, the first true hyperthermia device. Though still called a febrile therapy, this was a new method of external heating of the body instead of internal heating of the classic febrile therapy. This was the external hyperthermia. Whitney Radiotherm was widespread in USA in the 30s and it was used for treatment of many disorders [52], including cancer [27], with some impressive results. For 1935, more than 100 articles on hyperthermia were published [53], including the first comparative study of different methods of hyperthermia [54]. In 1937, Manhattan hosted the first international conference on hyperthermia [55].

Under this external cover, there was internal struggle between thermal and nonthermal concepts of electromagnetic therapy. d'Arsonval was the first who tried to show nonthermal effect on bacteria and toxins, but the result was inconclusive. Tesla announced the lethal nonthermal effect of high-frequency field on *Mycobacterium tuberculosis* [56]. d'Arsonval had not come to a conclusion on the mechanism of action of high-frequency currents, but he was sure that it is not limited by the heat, suggesting the influence on the chemical reactions [57]. Rise of diathermia as a solely thermal-dependent method after 1910 was connected mainly with the name of Nagelschmidt. It was Nagelschmidt who declared first that heating is the only treatment modality of electromagnetic impact [43]. From that time, the competition of thermal and nonthermal concepts of electromagnetic treatment started.

Since 1920, after the start of radiofrequencies use, nonthermal effects of RF-treatment were many times shown in vitro and in vivo by many researchers. Gosset et al. (France, 1924) exposed different plant cells to 150 MHz RF field and

Table 1: Some results of in vivo experiments on hyperthermia cancer treatment.

	Year	Animal	Tumor	Criterion	Method of heating	6 hr	3 hr	1.5 hr	1 hr
Prime and Rohdenburg [34]	1921	Mice	Crocker sarcoma	Inability of grafting	Water bath in vitro		42°C	44°C	
Westermark [35] Johnson [69]	1927	Rats	Flexner sarcoma Jensen sarcoma	Complete regression	Diathermia in vivo		44°C	45°C	
	1940	Rats	Jensen sarcoma	Inability of grafting	Water bath in vitro		43.5°C		45°C
				Complete regression	Diathermia in vivo	43.5°C			45°C (50%)

displayed cell death after initial growth acceleration; the effect was mainly or entirely not temperature dependent [58]. In 1926, an American surgeon Schereschewsky reported the lethal effect of 8.3–135 MHz RF field (with maximum at 20–80 MHz) on mice without substantial heating [59]. He suggested a specific action of RF fields based on high-frequency vibrations. Having received a position in Harvard Medical School, Schereschewsky continued his research and in 1928 reported the destruction of tumor grafts in mice, once again without substantial heating [60]. At 67 MHz, there was 23% of complete remission in HT group versus 0% in the control group. Exposure to 135 MHz did not show antitumor effect. Schereschewsky concluded that there is a special cell-destructive frequency range 20–80 MHz.

Schereschewsky papers had caused a strong "thermal" opposition. In 1927–1929, some program diathermia papers were published by Christie and Loomis from Rockfeller Foundation defending "thermal purism" [46–49, 61, 62]. Their main thesis was "In fact in our opinion the burden of proof still lies on those who claim any biological effects of high frequency currents other than heat production [*sic*]" [63]. From this time, this statement had become the official position of the Western electromagnetic medicine.

The careful analysis of the Christie and Loomis paper [63] reveals inconsistency of such categorical statements, which were made on insufficient grounds and with disregard of many facts. In particular, they revealed that lethality of 8–50 MHz field exposure was nearly the same, but it was sharply reduced over 50 MHz. This was explained by "any changes of dielectric constant of mouse" which allegedly led to a decrease of "current induced in mice" [64]. Though this statement was not explained, this did not affect the categorization of the final judgment. Now the fallibility of this statement is obvious because an increase of tissues conductivity (and current) with increasing frequency is well known. At the same time, the authors displayed that thermal production in NaCl solution did not diminish but increased over 50 MHz in the same extent as the lethality dropped [65]; this fact had not received any explanation. The study design was unsatisfactory. The authors tried to investigate the impacts of four different factors—frequency, current, time of exposure, and distance between electrodes—simultaneously and in two options: intravital and postmortem. As a result, the groups were too small (2–10 mice, averaged 5 ± 2.6) to receive significant difference. All the data are fragmented due to imbalance of groups. Moreover, the thermometry was extremely imperfect which was recognized by the authors themselves. There was no any statistical processing of the data, except for calculation of averages although the methods of correlation analysis were described in detail by Pearson in the early XX century [66] and were extensively used in the 20s. The authors did not try to reveal any trends though they were easily noticeable. For example in [67, Table 1], the tendency of decrease of lethal temperature with increasing current is traceable, and in [68, graph 7] the same tendency is visible with increasing of the frequency. Only the most rough and approximated tendency of thermal dependence of the lethal effect was noticed by the authors, and it was declared as the only dependence without any sufficient grounds.

It is obvious from just the tone of Christie works than he did not admit the existence of nonthermal effect axiomatically and was initially blinkered. Sure, Schereschewsky work [59] caused a lot of criticism, first of all in terms of thermometry, but it was impossible to deny the existence of nonthermal effects on the base of very controversial and inconsistent trials of Christie and Loomis [63]. However, it happened. In 1933, Schereschewsky, being under a strong "thermal" pressure, abandoned his "unscientific" nonthermal point of view and recognized the thermal essence of his findings [70].

In 1930, US biologist McKinley reported a lethal nonthermal effect of RF field on wasps [71] and later on growth of seedlings and nervous reactions of frogs [72]. It was resumed in the last paper that high frequencies and heat are not synonymous in any way, and though electric field leads to internal heating as a side effect, there is another and still not studied reaction. In the same year, Szymanowsky and Hicks reported a nonthermal inactivation of diphtheria toxin by RF field [73] and then confirmed this result in 1932 [74]. In their last paper they resumed that though nonthermal effect of alternating electromagnetic fields (AEMF) is obvious, its low intensity and hard traceability make it insignificant in clinical research [75].

In 1928, a German physician Schliephake also revealed a lethal effect of RF fields on flies, mice, and rats. Later, suffering from painful nasal furuncle, he received a sharp relief after RF exposure [76]. Soon, Schliephake and his colleague physicist A. Esau had developed a "short-wave therapy." In 1932, the monograph "Short-wave therapy" [77] was published in Germany, marking the born of the first commercial nonthermal technology. Already in 1935 it was republished in English, and generally it was reprinted in Germany six times (until 1960). Wide use of the method and apparatus of

Schliephake in the US led to the intervention of the American Medical Association in 1935 [78]: "huge sales of the new type of high-frequency devices" were discussed in preliminary report of physiotherapeutic council, and it was stated that the extensive use of these machines could lead only to insufficient results and discreditation of diathermia as a useful treatment method. The final report once again confirmed the position of medical community about exclusively thermal effect of AEMF [79].

In the 30s, a confrontation between supporters of the thermal and nonthermal effects had become a political line. The nonthermal concept was supported in Nazi Germany. In 1933, Reiter had reported the nonthermal RF effects on the metabolism of tumors in vitro [80], which caused two responses of Western opinion leaders in Nature [81, 82] in 1936, again confirming the official position of the Western medical community about lack of "specific" and nonthermal effects of RF exposure. In the late 30s, "nonthermal resistance" in Anglo-Saxon world was finally broken, and heat production was considered the only biological effect of high-frequency fields.

Thus, in the late 30s, all the known methods of electromagnetic heating were already known and used; heating was officially recognized as the only biologically significant effect of high-frequency electromagnetic fields; hyperthermia use as a separate treatment modality started; some promising results were received with RF heating; also, the nonthermal effects of RF heating were demonstrated many times, and the first nonthermal RF technology was widely recognized, though being denied by official science.

In about 1937, triode was created and magnetron was refined, and in 1939 Varian brothers developed the first klystron at Stanford. These inventions allowed to receive EM radiation of gigahertz (UHF) range and opened the microwave era. But in 1940, magnetrons and klystrons became not available for medical purposes—the war was approaching, and all the forces were sent to the development of radars. So, the first works on microwave diathermy appeared only in the late 40s, after the World War II.

Thus, the period before 1950 was the early stage of both hyperthermia and electromagnetic treatment. Hyperthermia was mainly still not recognized as a separate treatment method and existed predominantly in the form of febrile therapy, where thermal effect was a part of the complex body reaction. Its use was sporadic and totally enthusiastic. Despite the general success of hyperthermia in the late 30s, its use in oncology remained very limited. Electromagnetic hyperthermia made its first steps into the frameworks of radiofrequency range (0.5–50 MHz) though some promising results had been shown; it was purely empirical and suffered from lack of theory. Despite multiple evidences of nonthermal effects of AEMF, the "thermal dogma" had become the official position of the Western science in 30s: it had declared heating as the only biologically significant effect of high-frequency electromagnetic fields and denied any biological value, and even existence, of the nonthermal effects. With this baggage of knowledge and technologies, hyperthermia entered the second half of XX century.

3. Hyperthermia and Electromagnetic Treatment in 1950–1985

3.1. Hyperthermia in 1950–1965: Concentration. After 1950, the modern period of hyperthermia development as a separate treatment modality had started. Period from 1950 to 1965 could be characterized as a "concentration stage," when the first isolated attempts of hyperthermia use and research were made, and "concentration" of hyperthermia research rose gradually as a necessary prerequisite for the following crystallization.

In 1950, Gessler et al. [89] reported the successful destruction of spontaneous mammary tumors in mice by microwave hyperthermia (2,450 MHz) without significant damage to the animals. In 1957, Gilchrist et al. [90] used radiofrequency inductothermy for destruction of metastases in lymph nodes in vivo in dogs. Development of chemotherapy created new possibilities for hyperthermia. Because of the high toxicity of the first chemotherapeutics, they were administered initially mainly by regional perfusion. This was the ideal design for heating. Already in 1960, Woodhall et al. [91] from Duke University had performed a regional hyperthermic perfusion with alkylating agents in patients with head and neck tumors with 10% of complete response. Then, also in Duke, Shingleton studied effect of local hyperthermia (42°C) by means of capacitive radiofrequency systems (27.12 MHz) during chemoperfusion of intestine and had found a more significant accumulation of alkylating chemotherapies in the heated tissues than in unheated [92]. Rochlin received similar results on the limbs of dogs [93].

Selawry et al. in 1957 had revealed the basic patterns of hyperthermic impact to cell lines heated in water bath: acceleration of cell growth under 39°C with a maximum at 38°C, then interruption of the mitotic cycle at metaphase in the range 39°C-40°C with the subsequent development of irreversible cellular damage over 40°C; lethal range at 42°C–46°C; development of thermotolerance above 39°C and long-term (up to 3 months) thermoresistivity in cells which survived after hyperthermia [94]. These findings had laid in the basement of the modern hyperthermia but unfortunately they are mainly misinterpreted. In particular, common belief in the danger of low-temperature (≤39°C) heating during hyperthermia as it is able to enhance tumor growth, and considering temperatures over 40°C safe in this regard is not grounded because it does not consider the time factor. According to Selawry data, the abovementioned temperature ranges effects are actual for long-time heating only (some days) and not applicable for short-time hour range of hyperthermia procedure. As Selawry showed, the rise of the mitotic index by 12 hours was much higher at 41°C than at 38°C (10.4% versus 4.2%) and dropped to zero at 41°C only in 24 hours. By 6 hours, the mitotic stimulation was nearly equal in the range 38°C–41°C (3.7%–4.1% versus 2.3–2.8% at 36°C), and only temperatures above 42°C stopped entering new cells in the mitotic cycle. Therefore, the entire range of hyperthermia (≤42°C) is potentially tumor growth stimulating at short-time heating, and higher temperatures could be even more dangerous in this regard. Low heating

becomes more dangerous in regard of tumor growth only provided that it lasts more than 24 hours.

Selawry et al. also had reviewed all the existing data about thermoradiotherapy [95].

The true foundation of the modern oncological hyperthermia had been laid by Crile Jr. in his remarkable series of in vivo experiments on mice in the 60s [96–98]. It was Crile who already in 1962 reported all the known patterns of hyperthermia in vivo: ability of tumors to "trap" heat due to decreased perfusion, start of tumor damage at 42°C, half-decrease of lethal exposure time per each centigrade above 42°C, better radiosensitivity and lower thermosensitivity of small tumors and reverse ratio for big tumors, development of thermotolerance after sublethal exposure, enhancement of thermosensitivity by serotonin injections, and additive or synergic effect of combination of heat and irradiation. These results were obtained in tumors implanted in feet of mice and heated in a water bath. Two moments are important to notice in Crile results. First, the serious toxicity of the effective hyperthermia: in fact, enhancement of temperature over 42°C led to damage of both tumor and healthy tissues. Sure, the probability of tumor damage was higher but share of mice which lost their feet after treatment was also significant. Second, though Crile showed that 30 min hyperthermia at 44°C led to the half decrease of irradiation isodose, radiosensitivity of healthy tissues rose in the same extent as of a tumor. Crile, therefore, resumed that thermoradiotherapy has dubious advantage over radiotherapy per se and is indicated only for radioresistant tumors. Thus, just in the beginning of oncologic hyperthermia development as a separate modality, the problem of limiting toxicity was clearly shown.

3.2. Hyperthermia in 1965–1975: Whole-Body Period and Crystallization. The 1965–1975 period was the "crystallization stage" of hyperthermia development, when stable hyperthermic schools and trends began to take shape. It is marked by the name of Manfred von Ardenn, who was a prominent German physicist acting in oncology. Example of von Ardenn is very demonstrative to show the inner patterns of hyperthermic evolution because of some reasons. First, he was a man of extraordinary mind, usually moving step ahead the world hyperthermia, who easily changed concepts and technical solutions if they were ineffective. Second, his physical and technical knowledge were absolutely superior all over the world, and his technical facilities were virtually unlimited. Third, he was the independent researcher in socialistic East Germany; therefore his researches and practice were not affected by commercial biases and were not bound to any technology and its commercialization as it inevitably happened in Western world. Fourth, he was a CEO in his own research institute and therefore was absolutely free in his research. Fifth, it seems that his researches were not limited financially. Sixth and very importantly, he was not limited to hyperthermia in any manner because he looked for cancer treatment at all. Complex impact of these factors created the extraordinary medium for hyperthermia research and development, and it is very interesting to examine which result had been reached in these unique circumstances.

Von Ardenn started his activity in oncology in 1965 when he had developed a two-chamber hyperthermic bath with head cooling. Already in first experiments in vitro made in 1965, he had confirmed the selective thermosensitivity of tumors [99] and soon had presented in Heidelberg University his concept of multistep cancer chemotherapy [100, 101] based on combination of the extreme hyperthermia and tumor acidification by DL glyceraldehyde. In 1966 he had announced "the discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia" [102] which started the worldwide "hyperthermic race".

The general tone of the first von Ardenne works suggests that he initially thought hyperthermia independent, nontoxic, and selective treatment of cancer, and, apparently, he had Napoleonic plans of one-step solution of all cancer treatment problems on the basis of hyperthermia. Meanwhile—it seems, already in 1967—von Ardenne had stumbled upon the phenomenon of noncomparability of results in vitro and in vivo [103] and also had faced the problem of insufficient hyperthermia efficacy, which was reflected in the active search of thermosensibilizers. Many of them were tested between 1967 and 1969, including menadione, effect which was, in turn, strengthen by methylene blue [104]; aterbin [105], progesterone [106], and dimetilstilbestron [107], Tween 80 [108], vitamin A [109], dimethyl sulfoxide [109] and antibodies. Finally, von Ardenne tried to attack cancer by a cocktail of modifiers [108], including radiotherapy [110].

It seems that the idea of tumor acidification by virtue of hyperglycemia had arisen not earlier than in 1968 [111]. It had received the theoretical explanation as hyperglycemic modifications in 1969 [112] although search for other acidifiers still continued in 1970 [113]. At the same time von Ardenne had changed the extreme hyperthermia to moderate one (40°C) [114]. We can only hypothesize that the only possible reason of such change was a toxicity of the extreme hyperthermia. Therefore, von Ardenne had realized "a moderate reload" 25 years earlier than the world hyperthermia did. The other possible reason was that he had revealed soon that hyperglycemia is a stronger factor of tumor killing than hyperthermia and had become to consider hyperthermia as an auxiliary modality. In 1969, he started experiments in vivo on mice based on the combination of hyperthermia, hyperglycemia and soft X-ray [115] and had immediately reported the high effect [116].

In 1972, Ardenne had presented the complete concept of "selective multiphase cancer therapy" (sCMT) [117], in which the "long-term acidification through activation of glycolysis" was the first time mentioned as the primary mechanism of cancer treatment, whereas mild hyperthermia (40°C) was considered only an auxiliary modality. Under the theory of von Ardenne, hyperglycemia induces the activation of anaerobic metabolism in tumor tissue, which leads to the accumulation of lactate and acidification of the tumor; erythrocyte membranes in acidic environment become rigid, which prevents their normal passage through the capillaries and leads to their blockage and fall of the blood flow through a tumor. At the same time, lowering of pH to 6.5 and below leads to destabilization of lysosomal membranes, and

hyperthermia leads to the following release of lysosomal enzymes and autolysis of a tumor. However, the whole-body hyperthermia can also lead to increased metabolism of healthy tissues, in which aerobic nature requires a high oxygen consumption; oxygen is also required for recovery after hyperthermia. As a consequence, in 1973 the concept of von Ardenne had been replenished with the last component—the multistep oxygen therapy [118] considered as multiplier of sCMT [119]. As a result, to the end of 1973 sCMT concept had been completed as a combination of the long-term, high hyperglycemia followed by moderate hyperthermia with concomitant hyperoxygenation [120–122]. Von Ardenne paid much attention to the sequence and the intervals between the different stages, taking into account both synchronization of the cell cycle [123] and thermotolerance as a result of the repeated exposures [124], and even circadian rhythms. Simultaneously, he investigated the mechanisms of cell damage in hyperthermia: peroxidation processes [125], denaturation of proteins [126], and activation of lysosomal enzymes [127]. The sCMT concept of 1974 [128] also included chemotherapy and radiotherapy. Period of 1975-1976 was devoted to the study of combination of sCMT with chemotherapy [129, 130] and, at the same time, to the further search of enhancers of hyperglycemic acidification (particularly, NAD [131, 132], and sodium nitroprusside [133] were used). In 1976, the idea of selective anticancer drugs activated by acidic environment of the tumor [134] was published. The attempts were made to implement it by creating "selectines"—targeted agents released in the tumor tissue due to increased activity of beta glucuronidase [135]. This idea is now being actively developed that is, von Ardenne was once again ahead of his time for 20–30 years.

Meanwhile, the Western world, mainly influenced by the work of von Ardenne, had also entered the hyperthermic race. In 1967, American Cancer Society had issued a separate release on the method of von Ardenne [136], confirming that its clinical application in US started almost before it was applied by von Ardenne himself in GDR, and that information about inventions of von Ardenne called as "top European scientist" [137] appeared in the US synchronously [138]. In 1969–1973, 4–8 years after the first publications of von Ardenne, some fundamental works of Italian [139–142] and British [143] researchers were published, which laid the foundation for a systematic theory of hyperthermia.

Since 1967, Stehlin et al. in the US started a research on regional hyperthermic perfusion based on an extracorporeal heat exchanger [144] (though von Ardenne had developed such exchanger about 1966). Careful analysis of that trial shows that the heating was associated with better local control whereas survival mainly depended on tumor eradication (surgery + amputation). The British pioneers of the whole-body controlled hyperthermia, Pettigrew and Henderson [145, 146] (1971–1974), explicitly referred to the earlier works of von Ardenne, though questioning many of his considerations. It seems it were Pettigrew and Henderson who had first time detected the "toxicity threshold" of WBH—41.8°C. Study of local hyperthermia was continued: Cerino et al. [147] in 1966 investigated the local effects of ultrasound in bone cancer in vivo and concluded that the effect was mediated by heating. K. Overgaard and J. Overgaard (1972) [148] used short-wave diathermy for local heating.

Thus, from 1965 to 1975 hyperthermia had experienced a considerable progress. Whole-body hyperthermia and regional hyperthermic perfusion technologies were developed, and study of local hyperthermia continued. Solid scientific base of hyperthermia was established, and the concept of extreme hyperthermia based on the use of temperatures above 42.5°C was clearly formulated. Some hyperthermia schools had arisen, namely, von Ardenne school, Italian, British, US schools, and Soviet school inspired by von Ardenne.

At the same time, the negative results had been accumulated. The initial enthusiasm of "virtually unlimited selectivity" of hyperthermia quickly gave way to the understanding of the inefficiency of hyperthermia as a separate method, as it is clearly seen from von Ardenne research progress. By 1975, the limitations of whole-body hyperthermia had become increasingly accepted in view of inability to increase system temperature above 42°C without high toxicity, high complexity, and labor intensity [145, 146]. Nevertheless, the nature and feasibility of the hyperthermia seemed to be obvious, and the general opinion was that only correct technical solutions are required. The attraction of the attention of world oncology by hyperthermia was the main result of that early period.

From the technological point of view, no one special cancer hyperthermia machine was designed in that time. All the researchers used a regular physiotherapy units and generators. The first known whole-body "Tronado" machine developed near 1974 by W. Guettner from West Germany consisting of 12 serial "Erbotherm 69" 434 MHz 200W microwave generators (later from 4 1-2 kW generators) [149]. It seems that Dr. Holt from Australia was the only known user of this machine.

3.3. Hyperthermia in 1975–1985: Local Period and Structuring. The next decade from 1975 to 1985 was the stage of structuring of modern hyperthermia. During this period, world hyperthermia had obtained its internal organizational structure represented by a number of hyperthermic societies and the international hyperthermia journal. Hyperthermia trials had become usual, and network of the institutions engaged in hyperthermia research had enlarged significantly. Modern scientific base of hyperthermia had been mainly completed. Thermal chemo- and radiomodification and the role of tumor microcirculation in pathogenesis of tumor damage were the scientific mainstream. All the main hyperthermia technologies were developed at that time, and the main manufacturers of hyperthermia equipment were established. The refusal of whole-body and full refusal of convection-heating hyperthermia, which were the main modes of hyperthermia in the previous period, in favor of electromagnetic localized applications, were the main technological trend of the decade.

Though Western "scientific machine" with its distributed structure quickly stepped forward with US as the world leader, von Ardenne Institute had maintained the leadership in many aspects. His sCMT concept with moderate

hyperthermia was safe but suffered from insufficient efficacy. The next von Ardenne's solution was the extreme local heating against the background of moderate whole-body heating. His first paper on combination of local and whole-body hyperthermia was published in 1977 [150], and the same year the new Selectotherm concept was introduced: a combination of local heating by virtue of radiofrequency (27.12 MHz) scanning irradiator with concomitant long-term (4 hours) systemic exposure of near infrared range (IR-A) irradiation [151, 152]. In 1978, after the appearance of von Ardenn Selectotherm concept, a similar Pomp-Siemens WBH + LH machine had been introduced. Instead of the infrared heating, it used microwave heating by dipole antennas operating at 433 and 2450 MHz [153]. The concept had appeared ineffective and soon Siemens had left hyperthermia race forever. The similar idea of microwave WBH was tried to realize by Gelvich in Russia in the early 70s and it also failed. Instead of it, the Yakhta-5 concept was developed in Russia near 1985 by combination of RF (13.56 MHz) WBH and RF (40.56 MHz) local heating.

Contrary to all his contemporaries which considered hyperthermia a stand-alone factor, von Ardenne considered hyperthermia only an amplifier of tumor acidification [154] in Selectotherm concept. The phenomenon of complete blockade of tumor blood flow at pH 6.1 and 41°C was discovered soon [155]. About 10 papers were published by von Ardenne on the selective inhibition of microcirculation in tumor tissue. In particular, he examined the role of pH-modified red blood cells [156] and change of their size in hyperglycemic environment [157], role of clogging of blood vessels by red cells [158], increased perfusion pressure [159], microvascular permeability [160], low blood pressure [161], platelet aggregation [162], and also the mechanisms of involvement of the vascular wall in the disorders of microcirculation [163]. In 1985, the impact on microcirculation had been acknowledged by von Ardenne as a central mechanism of sCMT [164]. It should be noted that von Ardenne microcirculation studies were much more practical than contemporary studies of western teams [165], first of all because he studied microcirculation at real HT temperatures range <43.5°C while others operated with temperatures more than 43.5°C which they erroneously considered possible to achieve.

Thus, the technology of whole-body infrared hyperthermia had been technically realized by von Ardenne already in 1977, whereas the similar development was initiated by the US National Cancer Institute only in 1978 [166], and working prototype was built in 1983 only [167], but in local hyperthermia von Ardenne already was not the leader. In 1976, LeVeen et al. [168] in US reported some interesting clinical results on local hyperthermia of some deep tumors, including lung tumors, made by virtue of his own prototype of capacitive radiofrequency device (13.56 MHz). Nevertheless, conceptually von Ardenn was still ahead his contemporaries for two decades: while they dreamed about more than 43°C fantastic heating with local "dream machines," he was already aware of the impossibility of such local heating. He considered a combination of local and systemic heating as the only possibility to achieve a homogenous local heating.

Since the use of microwaves for the superficial heating was simple and clear from just the beginning (2450 MHz, 915 MHz, and 433 MHz were used [89, 148, 169]), heating of the deep-seated tumors was the challenge. Delivery of hyperthermia range heat into the deep tissues is a serious technical problem till now. Capacitive, inductive, and irradiating heating could be used for this purpose.

Between 1976 and 1978, the development of all the major technologies for deep heating had started. Capacitive and inductive technologies as the most simple methods, which had already been proven in diathermic applications, were historically used for deep heating the first [92]. The inductive technologies (Magnetrode [170] and other solutions) had shown their heating inefficacy (<20% of successful heating) already at the early stage and were mainly disregarded though there were an attempts to reanimate the method from time to time [171, 172].

In 1976, LeVeen et al. reported the eradication of tumors in animals and substantial regression in 21 patients using 13.56 MHz capacitive machine [168]. This was a capacitive coupling 13.56 MHz machine with three pairs of "cross-firing" electrodes located around the "zone of interest." Power was targeted to each pair of electrodes in series by short bursts (0.1 s). As a result, center zone between electrodes was permanently heated with the "cross-fire" whereas superficial fat was heated 0.1 s only during each 0.3 s cycle. It is very interesting to note that already in 1979 Sugaar and LeVeen [173] had reported some effects which developed with this machine only but not with other frequencies and heating modalities and seemed to be not heat dependent. In particular, alongside with the expected heat degeneration of tumor cells, significant changes in the tumor stroma happened as well, resembling lesions in acutely rejecting organ allografts. In 1977, Marmor et al. also reported some promising experimental results with this technology which could not be explained by temperature only [174]. Unfortunately, later some "fantastic" results were reported by Storm et al. [175] with this machine: 75% of human sarcomas were heated at ≥45°C and 50% at ≥50°C without damage of healthy tissues with huge 8–10°C temperature difference between tumor and healthy tissues [176]. From the modern point of view, these results are absolutely impossible. LeVeen machine remained a prototype.

In 1976–1978, radiofrequency 8 MHz capacitive technology (Yamamoto Vinita Co. Ltd., Japan) was elaborated and marketed under Thermotron trademark. Since 1980, Thermotron RF8 unit with power 1200 W had become commercially available. From the heating point of view, ease of use and manufacturing are nearly the only advantages of capacitive technology while there is a number of disadvantages: high subcutaneous fat heating, instability of low-frequency RF field, and its dependence on electrodes size, location, and distance and tissues parameters, with easy hot-spot formation. Thermotron had used high-intensive surface cooling (up to −5°C) to compensate subcutaneous fat heating. Field disturbances were minimized by exact fixation of the electrodes on gentry to always ensure their parallel and symmetrical position. Though not being perfect, Thermotron was the first stable hyperthermia machine designed with

clear understanding of advantages and disadvantages of the capacitive technology.

Majority of European and US specialists had initially rejected capacitive concept considering its known disadvantages. Instead of it, surrounding irradiative solutions with interference heating had been introduced in the 80s. The idea was to achieve a steerable heating focus in the deep tissues due to interference of irradiation from some surrounding sources without substantial surface heating. Base calculations had been done by Guy [177, 178] in the early 70s. It was clear that such systems are highly frequency dependent because the lower frequencies (less than 40 MHz) with long wavelength flatten a peak of SAR in deep tissues, and the higher frequencies (more than 150 MHz) with shorter wavelength dissolve the peak because of insufficient penetration depth. Looking ahead, this problem had not been solved.

Some irradiative technologies were developed nearly simultaneously at 1978–1980: the "annular phased-array" (APA) 50–110 MHz technology of BSD Corp., coaxial 10–80 MHz TEM technology of Lagendijk [179], and 4-waveguide "matched phased array" (MPA). The first technology was marketed since the 80s as BSD-1000 system; the two latter ones had remained prototypes though Lund (Sweden) was about to market MPA technology as a Variophase system. At phantom testing, all the techniques showed nearly the equal ability to create deep heating focus [180]. Unfortunately, in clinical practice the selective heating of deep focus was never achieved. Moreover, TEM and MPA technologies had shown the insufficient heating efficacy (<50% of heat-successful treatments).

BSD1000 system included 16 coupled (8 couples) horn applicators arranged on two octagons fed synchronously with 50–110 MHz amplifier. Early reports were very optimistic reporting more than 70% of heat-successful treatments (≥42°C). Later trials on larger groups were much less promising: only 30–50% of heat-successful treatments.

The hyperthermic community had been structured. In 1975, Washington hosted the first International Symposium on Cancer Therapy by Hyperthermia and Radiation, followed by the second one in 1977, third in 1980, and fourth in 1984 [181, 182]. Near 1981, US National Cancer Institute (NCI) had offered a Hyperthermia Equipment Evaluation Contract for evaluation and comparison of different types of existing hyperthermia equipment. At least three universities were contracted (Stanford, Utah, and Arizona) and more than 20 types of the equipment were tested. In 1981, the North American Hyperthermia Society (NAHS) had been founded, and in 1985 International Hyperthermia Journal had been founded. In 1978, Hyperthermia Study Group had been founded in Japan followed by establishment of Japanese Society of Hyperthermic Oncology (JSHO) in 1984. Hyperthermia treatment in Japan has been covered by insurance since 1985. Together with abundant grants of Japanese government for hyperthermia research, this caused the fast development of hyperthermia in Japan.

The main "moving centers" of the world hyperthermia had been identified: North American (almost all big universities including Universities of Texas, Wisconsin, Pennsylvania, North Carolina, Southern California, Utah, Stanford and Duke), Japanese, and European (von Ardenne institute and Dutch cluster).

In 1985, hyperthermia was considered a promising method in oncology. It was many times called the potential fourth basic method of treatment in oncology, after surgery, chemotherapy, and radiotherapy.

4. Electromagnetic Treatment after 1950: Microwave Era

4.1. Electromagnetic Treatment in 1950–1960: Early Microwave Period. As it was mentioned above, the first work on microwave diathermy of Mayo Clinic had appeared only in 1947, just after the II World War. Raytheon Microtherm was the first commercial microwave device with 1,2–2,5 GHz frequency and a power of 125 W. From 1948 to 1953, some works on microwave diathermia were published, followed by the long silence caused by detection and recognition of the adverse effects of microwaves.

Actually, these effects—cataracts in dogs and rabbits and testicular degeneration in rats—had been discovered already by 1948, just after the start of microwave research, but it took time to accept them and to realize the potential danger of the new devices. At the same time, evidence of danger of microwave radiation had been received from military and industry. As a result, from 1953 to 1960, the research activity in the field of microwaves had completely shifted from medical use to the development of security standards. In 1957–1960, the so-called Tri-Service program was implemented in US under the auspices of the U.S. Department of Defense to develop safety standards of microwave exposure.

4.2. Electromagnetic Treatment in 1960–1985: Maturing of Microwave Technology and Rise of Nonthermal Effects. The major contributor to the development of the theory of biological effects of electromagnetic fields was Herman Schwan, a German physicist contracted by US Defense Department. Near 1953, Schwan had begun the systematic study of the mechanisms of absorption of microwave radiation and had found that it is uneven and depends on the frequency properties of tissues and their components [183]. Schwan had shown that microwave exposure should be based on rigorous biophysical calculations that the "efficiency of existing microwave devices is unpredictable from a practical point of view," and experimental methods are extremely dubious [184, 185]. Electromagnetic medicine required adequate biophysical basis which had not yet been established [186]. As it is evident from the materials of the symposium on biological effects of microwaves which took place in June 1970 in Richmond (USA), there was only initial presentation of the merits, which was a subject to refinement in practically all areas [187]. Susskind figuratively compared microwave devices of that time to "gun shooting in the dark room" [188]. Establishment of the scientific basis of microwave therapy was mostly completed around 1985 when the theoretical basis of interaction of high-frequency AEMF with biological tissues had been completed and dielectric properties of various tissues and organs had been determined [189, 190].

The period between 1950 and 1960, as it was mentioned before, was poor enough for medical findings in electromagnetic treatment, but this had significant consequences. 10 years of research on the dangers of EMF in the 50s had cooled the medical community to the use of microwaves, which, in turn, had changed the approach from applied research (heating) to the fundamental ones, and data about nonthermal effects of EMF had begun to accumulate more intensively. In 1959, researchers from the Mayo Clinic had found the effect of "pearl-chain formation" [191]: fatty drops in diluted milk were aligned into chains at high-frequency irradiation. The effect was inexplicable in terms of heating. Indeed, the effect was not new: it was described in 1927 by Muth [192] and later in 1939 by Liebesny [193] in blood emulsion. Also in 1959, a similar effect had been observed by Teixeira-Pinto et al. [194]: a weak constant electromagnetic field caused the alignment of single-cell microorganisms in the line. Moreover, depending on the frequency organisms could line up alongside or across the field lines. In an earlier experiment, Heller and Teixeira-Pinto [195] had shown that 5-minute nonthermal effect of EMF on embryos of garlic in distilled water led to chromosomal abnormalities after 24 hours, similar to exposure to ionizing radiation and antimitotic agents. They had assumed that the reason was the orientational effect of EMF. Also in 1959, a study of Humphrey and Seal [196] had been published on the use of DC to treat cancer, initiating the development of electrotherapy of cancer, though the papers on galvanization of 1875 [197] and 1886 [198] had already shown the mature understanding of the technology. At that time galvanization was used mainly for treatment of superficial lesions like hemangiomas [199] and had lost its significance after invention of cauterization to reborn in XX century as a cancer treatment modality. Already in 1951, Pohl [200] had found that dielectric particles in AEMF are not only aligned but also move alongside the gradient of the AEMF, and this phenomenon had been called dielectrophoresis (DEF). In 1966, he had used DEF for separation of alive and dead cells [201]. In the 70s the method had been developed in detail [202, 203]. In 1970, the lethal effect of the weak (10–200 mA) AC (50 Hz) for *Escherichia coli* had been detected by Pareilleux and Sicard [204]. Then, this effect had been rediscovered in 1992 by Canadian researchers [205] and had been called "bioelectric effect" (BEE). In 1972, the increase in membrane permeability had been detected by Neumann and Rosenheck [206] after a pulse of direct current, which had led to the development of technology known as electroporation (EP). It had been theoretically grounded in 1973-1974 by Crowley [207] and Zimmermann et al. [208], and it had firmly entered the arsenal of cell biology from the mid 70s. It is remarkable that, even in 1977, the discussion of the electrical breakdown began with grounding of the non thermal nature of the effect. Later in 1989, Chang [209] had applied alternating radio frequency current for electroporation and had obtained the more efficient transfection at the substantially smaller percentage of irreversible cell damage [210]. In 1978, Nordenström [211, 212] had reported the first clinical trials of galvanization called by him "electrocancer therapy" on lung cancer.

In 1982, Schwan [213] had summarized all the data on the nonthermal effects available at the time and had highlighted the following described phenomena: (1) the formation of "pearl chains," (2) the spatial orientation of nonspherical particles and cells, (3) dielectrophoresis, (4) deformation of cells, (5) destruction of cells, (6) cell fusion, and (7) rotation of cells.

It is important to notice that all the main technologies of electromagnetic hyperthermia had been developed between 1975 and 1985, that is, at the time when biophysical basis of electromagnetic treatment had not been entirely completed. This had determined the inevitable technological bugs which will be analyzed in detail below, as well as the fact that modern hyperthermia technologically operates mainly by representations of the 70s or, the better case, of the early 80s.

5. Hyperthermia and Electromagnetic Treatment after 1985

5.1. Hyperthermia in 1985–1995: Unsuccessful Local Attack and WBH Return. Meanwile, the understanding of hyperthermia problems rose. In 1987 Hiraoka et al. [214, 215] had reported their results on Thermotron use. Whereas the maximum temperature ≥43°C had been reached at 38% of the tumors and 42°C-43°C in 23% of the tumors (totally 61% ≥42°C), the intratumoral temperature differences exceeded 2°C and the minimum temperature ≥42°C had been reached only in 11% of the tumors. These were far not favorable results for the extreme hyperthermia concept. In 1988, the institutional reports on NCI Hyperthermia Equipment Evaluation Contract were published by Stanford [216] (21 devices compared), Utah [217] (10 devices compared), and Arizona [218] universities. Stanford had reported only 14% of treatments with minimum temperature ≥41°C while 56% of all treatments were associated with acute toxicity. The most interesting fact is that the maximum temperature (<42.5°C) was limited by toxicity, and 14% of treatments were necessitated to diminish temperature in view of toxicity. Average temperature 39.6–42.1°C in deep tumors had been obtained only with three devices. In 1989, a report on BSD-1000 use [219] had been published. Average temperature was 41°C and toxicity, both systemic and local, had been directly named as the reason of the insufficient heating. In the same year, very large phase I study on BSD-1000 APA technology had appeared [220]. From 1980 to 1986, 353 patients had been treated with 1412 HT treatments in 14 US medical centers. The clinical effect was less than average with 10% of CR and 17% of PR, and thermal dose was not a significant parameter, while RT effect was significant ($P = 0.001$). It seems that acute treatment-limiting toxicity was 42%.

Thus, though hyperthermia had remained a mainstream and "hot topic" in scientific journals, practical oncologists and radiologists and even many researchers in US had cooled to the method. Already in 1987, Hornback [221] wrote "Clinical hyperthermia today is a time-consuming procedure, done with relatively crude tools, and is an inexact treatment method that has many inherent technical problems. Certainly, excellent research work can be accomplished by private radiation oncologists working in the community.

If the individual is willing to commit the time and effort required to participate in clinical studies in this interesting, challenging, exasperating, not-too scientific field; then he or she should be encouraged to do so. The field is not without its risks and disappointments, but many cancer patients with recurrent or advanced cancers that are refractory to standard methods of medical care can unquestionably be helped by hyperthermia. It is not, as some have suggested, the fourth major method of treating cancer after surgery, radiation and chemotherapy. It may be innovative, but it still is an experimental form of therapy about which we have much to learn".

This was the evidence of the divergence of the "scientific" hyperthermia and clinical practice. This hidden disappointment of clinicians with scientists had been prepared by the fact that clinical practice did not confirm the scientific concepts: hyperthermia had appeared not so efficient but toxic and extremely time and labor consumptive. Practical fail of the whole-body hyperthermia was already evident. Scientists believed that these were temporary problems and development of technologies will solve them. Clinicians felt that hyperthermia problems are deeper than just a technology. Hyperthermia gains in leading practical oncology centers, that is in Kettering-Sloan Memorial, were modest.

Scientific evidences contrary to hyperthermia concept had also been accumulating. Already in the early 70s, Burger et al. [222, 223] had shown that damage of healthy tissues starts from 40.5°C; that is, the thermotolerance of the healthy tissues does not differ from that of malignancies. This was a serious challenge to just a basis of hyperthermia concept based on the axiom of the much higher thermosensitivity of malignant tissues contemporary to the healthy ones. The cautious attempt of Upjohn company to assess hyperthermia prospects had ended with paper of Bhuyan [224]: despite the possibility of greater sensitivity of neoplastic cells to hyperthermia compared to normal cells was called "very promising," it was clearly indicated that early results on cell lines were dubious because of the possible mistakes. These weak signals had been disregarded.

Understanding the limitations of local hyperthermia, especially the impossibility to heat tumors homogenously, had forced investigators to return to the whole-body concept with its homogenous heating. In 1983, US company Enthermics Medical Systems in collaboration with Wisconsin University had developed a system for extreme infrared hyperthermia [225] which later had become the Aquatherm system [226]. Almost simultaneously, Texas University had started the own whole-body program. Later in 1995, International Systemic Hyperthermia Oncological Working Group (SHOWG) had been established [227] under the leadership of HI Robins from University of Wisconsin.

In 1985/1987, von Ardenne had rejected Selectotherm WBH + LH concept and had replaced it with IRATHERM concept based on whole-body infrared hyperthermia only. Multistep oxygen therapy received a new rationale: it had been considered immunostimulator [228, 229]. In 1991, von Ardenne Clinic for Systemic Cancer Multistep Therapy (sCMT) had been launched based on von Ardenne Institute of Applied Medical Research in Dresden, allowing systematic clinical trials. In 1992, a new system for extreme whole-body hyperthermia IRATHERM 2000 had been launched, and in 1993 the final version of sCMT had been completed [230]: extreme whole-body hyperthermia + selective hyperglycemia thermopotentiation + supportive hyperoxemia.

Meanwhile, hyperthermia was ready for the battle for recognition.

In 1988, the small trial of Valdagni et al. [231] had been published comparing thermoradiotherapy (TRT) with RT alone on 44 N3 metastatic squamous cell cervical lymph-nodes though only 36 nodes were included in the assessment. Hyperthermia was delivered by 280–300 MHz applicator MA-150 (BSD Corp.) Later in 1994, the report on long-term followup [232] had been introduced. Excellent short-term and long-term results had been reported both for local control (83% versus 41%) and 5-year survival (53% versus 0%) though thermal analysis had failed to show a significant correlation between heating parameters and endpoints. The RT dose was high and nearly equal in both groups (67.5 Gy versus 68 Gy). Some points limit the acceptability of these results. First of all, this is a small size of the trial and the fact that it was the initial enrollment only because the entire trial had been terminated "by ethical reasons." Second, the immediate result looks brilliant if to compare CR only but comparison of the total effect (CR + PR) gives dubious result: 89% versus 81% in RT control. In this regard, survival effect looks absolutely decisional but there is a significant remark: such unbelievable effect has never been reproduced before and after. In all the later randomized trials [233–239], there was no significant effect on survival. Moreover, it tended to be worse in TRT arm in some trials [237, 239]. The extremely low survival in the RT control of Valdagni trial, provided that highly effective RT was used, is also questionable. Therefore, Valdagni et al. effect to survival has not been confirmed in later trials and looks dubious enough. At the same time, it should be noted that this trial had reported the highest tumor temperature among all the other superficial trials: mean maximum temperature was 43.3°C and minimum was 40.4°C. It could in some extent explain the clinical results but the absence of correlation of the endpoints with the thermal parameters makes this explanation weak. The highest temperature reached 48°C–52°C. Very surprisingly, in such high temperatures, "only one burn" had been reported, and both acute and late toxicities in TRT arm were equal to that in RT control. This is an alarming result because later Perez et al. [234] had shown 30% of burns, in TRT arm versus 0% in RT only arm, Engin et al. [236] had reported 40% of burns, and Jones at al. [239] 46% of burns versus 5.7% only in RT only arm, and all these trials showed less heating. It is also surprising that after such excellent results and preliminary termination of the trial, the Valdagni group had not initialized the next trial. Resuming, there are too many reasons to not trust in Valdagni et al. results.

Since 1984, five big randomized clinical trials on TRT with superficial [233–236] and deep HT [240] had been launched in the leading US research institutions. The common belief in the success of the trials was so strong that only two of them [234, 240] compared TRT with RT alone whereas other three ones compared different protocols of TRT as

if its efficacy is already proven. The result had appeared absolutely disappointing: any trial did not show the effect of hyperthermia.

It was a good time for reassessment of hyperthermia rationale. There were enough facts to question the hyperthermia concept. Unfortunately, it was not done. All the researchers had refused to review the hyperthermia rationale. Insufficient heating in view of inadequate technique had been considered the only reason of the trials fail and it was a false conclusion. Toxicity was the reason of the insufficient heating as it was directly stated earlier in Stanford [216] and Shimm et al. [219] reports. This was not a technical problem and not a problem of thermometry: this was the inherent problem of hyperthermia itself and its real name is the narrow therapeutic range.

Hyperthermia community now tends to consider the negative trials of the early 90s not significant because of insufficient heating and imperfect technique. This is incorrect. All the modern hyperthermia technologies as it clearly stated above had been introduced before the 90s. All the randomized trials of the early 90s were executed in leading US universities with the best available equipment. Moreover, when later RTOG had tried to repeat the deep-heating trial with the better "second generation" equipment, the result was also negative [241]. Also, the deep heating with the "second generation devices," namely, BSD2000 with its SIGMA applicator, was lower than that with old BSD1000 APA system [242]. Therefore, the technique of heating in these trials was adequate from the modern look. It is confirmed by high temperatures reached in these trials. For instance, in Kapp et al. trial [233] the minimum temperature in superficial tumors was 40.2°C, average 42.5°C, and maximum 44.8°C. Modern guideline of Erasmus University [169] for superficial tumors recommends to reach minimum temperature 40°C and maximum 43°C-44°C. In the modern trials on deep-seated tumors, average temperature never reaches 42°C while it was reached usually in the trials before 1995 [214, 216].

It should be considered that in terms of heating and technique the negative trials of early 90s were absolutely adequate. They were inadequate to anticipations of the early 80s based on the incorrect concepts: it was anticipated that tumors could be homogenously heated to more than 43°C with high selectivity (5–10°C of difference between tumor and surrounding tissues was reported by Storm et al. in 1979 [176]) without significant damage of healthy tissues due to "almost endless selectivity between cancer cells and healthy cells" though inadequacy of these "heating anticipations" was shown already before 1990.

The trials had shown that it is impossible to heat tumors homogenously more than 42°C. Less than 50% of entire tumors had been heated up more than 42°C in average with more than 2°C difference of temperatures within a tumor, but the reason was not technical. There was no any obstacle even to evaporate tissues with the existing techniques. Toxicity was the limiting factor. In fact, these clinical trials had just displayed the critical problem of hyperthermia: the absence of therapeutic range. Damage of healthy tissues went alongside the damage of tumors and limited the extent of heating. Ineffective thermal control was not a reason. Effective thermal control would only additionally restrict the heating.

The possibility of correction of hyperthermia rationale had been lost. Since that time, hyperthermia was derived from the reality, as earlier it was derived from the practice. It moved to a dead end.

Technology. In general, near 30 different hyperthermia prototypes were tested by 1985 [216–218] though only few of them were marketed later. There was no substantial progress in hyperthermia technologies after 1985 despite significant activities. Contrary, in some cases the technical improvements had even worsen the clinical results. Though some new hyperthermia machines had been introduced at that time (Synchrotherm-RF (Italy) local machine, Aquatherm (USA), and von Ardenne IRATHERM and Heckel HT3000 (Germany) whole-body systems), such strong and versatile players like Bruker (Oncocare) and ODAM (Jasmin) had left the market.

Near 1985, two 13.56 MHz capacitive hyperthermia systems had been introduced: Oncocare of Bruker and Jasmin 3.1000 of ODAM (France). Both systems had very short history and in fact had remained prototypes. Jasmin deserves a special attention because of more complex design: it was a powerful system with one upper and two capacitively coupled lower applicators with appropriate fixation, each having separate 600 W RF generator (totally up to 1,800 W). The system was able to move a deep heating focus by changing output energy of each applicator [243]. Though good heat distribution had been shown on phantoms, and 41-42°C had been reached in deep tumors in clinical trials with enough safety [244], the clinical effect had been more than modest [245]. Oncocare was a classical design 13.56 MHz/600 W capacitive system with two symmetrical electrodes and had shown the similar clinical results [246]. Both systems had been withdrawn soon after publication of the first clinical results in 1989–1996, and both Bruker and ODAM had left the hyperthermia field.

Thermotron had changed a little since its development. Total power of the system was enhanced from 1200 W to 1500 W. It seems that it had not enhanced its efficacy.

BSD-2000 concept with the entirely new SIGMA-60 applicator was introduced in the late 80s instead of BSD1000 [247, 248]. Horn irradiators had been replaced by 8 coupled dipole antennas with a little different frequencies range (70–100 MHz instead of 50–110 MHz in BSD-1000) and improved PC-guided electronic phase and amplitude steering. Despite the better technical parameters of the new BSD2000 system [249], the deep-heating capacity of BSD1000 was nearly the same [250] or even better [242]. Toxicity had remained nearly the same: acute toxicity was treatment limiting in 50% of treatments and systemic stress was treatment limiting in 30% of the treatments [250]; it looks that a little had changed to mid-2000s [251]. Returning to the beginning, it seems that initial heating calculations of Turner et al. [252, 253] from BSD Corp. were done with too favorable parameters, and Guy [177] calculations showing less central heating and much more superficial heating were more practical [179].

IRATHERM WBH concept had been developed by von Ardenne and dermatology department of Charite Clinic near 1985. The concept was based on the use of near infrared irradiation (IR-A, 760–1400 nm). IR-A ability to penetrate to subcutaneous vascular network and to heat it up had been displayed already in 1931. Contrarily, IR-B (1.4–3 mcm) and IR-C (3 mcm–1 mm) irradiation is mainly absorbed in the upper skin layer [254]. IR-A is separated by water filters [255] since the 1920s. IRATHERM 2000 system uses 5 groups of irradiators: 2 ventral and 3 dorsal. Active resistance of the body to heating is the main problem of the IR-A concept. The power of perspiration cooling could reach 1400 W, leading to long heating period (up to 2 hrs before reaching 42°C) and significant loss of fluid (up to 2 liters) and subsequent development of dehydratation and electrolytic disorders. This causes the necessity of effective monitoring of electrolytic balance and vital functions [256].

Aquatherm concept developed at Wisconsin University by Robins et al. [225] near 1985 and introduced as Aquatherm system near 1995 [226] was the entirely different WBH concept based on IR-C heating. It had been initially developed with respect to perspiration factor and seemed superior to IR-A concept from some points of view. Patient (except of the head) is placed in hollow metal cylinder whose surface is heated up to 65°C (55–70°C) and therefore becomes the infrared irradiator (mainly IR-C). The temperature of the air at skin surface reaches 45–55°C. Because of high humidity (>90%) in the cylinder, the perspiration is blocked and residual loss of heat with breathing and convection is insignificant. As a result, heating is soon (<80 min) and could be achieved with low power (500–1000 W) and without significant fluid loss.

Heckel HT3000 IR-A WBH system had been introduced in the 90s [257]. This was in fact a simplified analogue of von Ardenne IR-A concept with only 4 IR-A irradiators located from the ventral side only. This narrows the "gate" for irradiation and theoretically should enhance heating time and skin toxicity though the HT3000 system uses a conventional functional bed with convenient mattress instead of the rigid IRATHERM couch which often causes decubitus (8% of grade III-IV) [258]. As far as we know, there is still no evidence-based confirmation of the efficacy and safety of HT3000 machine.

The series of hyperthermia machines under trademark Yakhta were produced in Fryazino (Russia) since 1985. There were some superficial machines: 2.450 MHz Yakhta-2, 915 MHz Yakhta-3 and 533 MHz Yakhta-4. Yakhta-5 WBH + LH concept had mainly repeated the earlier von Ardenne Selectotherm concept, though using 13.56 MHz irradiative solution instead of IR-A for systemic heating and 40.68 MHz capacitive unit for local heating instead of 27.12 MHz in Selectotherm. Though a number of these devices have been produced in USSR and then in Russia since 1985, only few of them are in use now. Two 40.68 MHz capacitive prototypes named Supertherm and Extratherm (with scanning electrodes) were developed in Obninsk, Russia, near 1995. Though less superficial fat heating is reported, there are no enough data about their efficacy and safety.

Generally, a lot of solutions had been designed at that time. Breakthrough Medical, Genemed (Japan), Labthermex, Lund Scientific (Sweden), SMA (Italy), Getis (Germany), and HPLR 27 [259] (France) presented their concepts, sometimes looking very promising, but all of them had remained prototypes.

5.2. Hyperthermia in 1995–2005: Reaction. Reaction of hyperthermia community and industry after fail of HT trials of the 90s followed soon.

Just after the fail of the first RTOG deep-heating study (84-01 [240]), the attempt was made (RTOG 89-08 [241]) to compensate the damage based on the use of "second generation" equipment (BSD2000). Though it was a phase I/II trial which usually shows much better results (like it was in phase I/II trial of 84-01 study [260]), this time the result was modest: CR + PR rate was 34% with less than 2 HT sessions per week and 16% only with 2 HT sessions. Response did not correlate with maximum tumor temperature but a strong association with radiation dose had been revealed: 54% CR with ≥45 Gy versus 7% with <45 Gy ($P < 0.0001$). The toxicity of the treatment was less than earlier (18% of acute toxicity versus 68% in the previous trial) but it could be associated with caution of researchers which that time did not run for temperature. As a result, the temperature distribution was even worse than in that the previous trial, especially for minimum temperature (38.5°C only). There was no III phase trial initiated with such weak results, and RTOG had discontinued its hyperthermia activity, once again without any final decision concerning these 15 years of in vain activity. Nevertheless, the remarkable in all respects monograph of Seegenschmiedt et al. [261, 262] had been issued in 1995-1996 without any respect to negative results. It looked like hyperthermia is still a promising and highly effective modality ready for acceptance.

In 1996, Matsuda had proudly reported hyperthermia status in Japan. At that time, Japan was the world leader in clinical hyperthermia with 215 units of equipment installed, established national market leader Thermotron RF8 (more than 120 units) for deep-heating, extensive membership in JSHO, grant-in-aid by the Japanese government, and coverage by insurance for hyperthermia treatments. Deep-seated tumors share had constituted 60% of all treatments, while this percentage was negligible in Europe and USA.

In 1989–1991, before the fail of the trials of the early 90s, five more randomized trials on superficial TRT had been launched under the umbrella of International Collaboration Hyperthermia Group (ICHG). After the first fails of the abovementioned trials, they had been merged together. The common results were published in 1996 [237]. Although the three of five arms had displayed the negative results, and survival in hyperthermia group was worse and dissemination was more severe, these results had been hidden. Overall statistics was favorable for HT group due to the excellent local control in the two remaining groups though this success had been bought for the sake of 2-fold growth of dissemination and 2.5 growth of mortality [1]. Also, after publication of van der Zee et al. paper in 2010 [169], it could be assumed that these good results had been received due to preselection

of patients and incorrect randomization [1]. Nevertheless, the trial was announced successful and had become the cornerstone of hyperthermia evidences.

The next publication of Overgaard et al. trial on TRT of skin melanoma [238] in 1996 had introduced the method to display the effect of hyperthermia based on the use of inadequate comparator—low dose radiotherapy. Total dose 24 and 27 Gy with hypofractionation (8/9 Gy × 3 sessions) had been used for treatment of malignant skin melanoma. This was near 50% of standard 50 Gy dose usually used for treatment of superficial tumors and 35% of 68 Gy dose in Valdagni et al. [231] study, and it was absolutely clinically ineffective dose taking into account the well-known radioresistance of melanoma. Naturally, the trial was a clinical radiobiological study without any clinical significance. The local control in TRT group was less than average and survival data were hidden. This trial had been once again considered successful.

In 1998, Sneed et al. [263] trial on brachytherapy (BT) with versus without interstitial HT in multiform glioblastoma had been published. The trial was excellent in all respects with only one but decisive bias: while the arms were excellently equalized in all aspects, 69% of patients (25) had been reoperated in HT arm versus 58% only (19) in BT control, and the influence of the reoperation rates (Δ11%, 6 patients) had not been assessed. Reoperations had started from 13 to 14 weeks with median time of reoperation 32–45 weeks. As it is clearly seen from time-to-progression (TTP) graph, initially the two arms were equal, and divergence had started nearly at 25 weeks and had reached its maximum nearly at 40–45 weeks. Coincidentally, 45 weeks were a median time of reoperation for HT arm. Then, convergence of the arms had started and nearly had reached the equality at 65–70 weeks. Then, divergence had started again but it seems that effect of the later peak of reoperations in HT arm should last longer. The final difference between two arms was near 10%, that is, 3-4 patients (taking into account 33 and 36 patients in the groups) which is much less than the difference in quantity of reoperated patients (6 patients). Also, 2-year survival probability was 31% in HT group versus 15% in the control group, and this 15% difference once again constitutes 4-5 persons which is less than "reoperation impact." It is obvious that, with respect to "reoperation bias," the result could become insignificant; that is, this bias could have the decisive impact on the result of the trial. Therefore, the results of the trial could not be accepted without the appropriate recalculation.

Next to Overgaard et al. trial, the series of randomized trials with inadequate comparator had been launched. In 2000, Dutch Deep Hyperthermia Group trial (van der Zee at el. [264]) had been published. Total dose 67 Gy (≤60 Gy to tumor mass) was used for treatment of IIIB stage bulky cervix cancers though it had been known that such low doses significantly decrease treatment effect [265], and doses less than 70 Gy to tumor mass are inadequate in cervix cancer, and 75–90 Gy to tumor mass was a standard treatment. The study had shown a good gain in TRT group both for local control and disease-free and overall survival [266], but these results were significantly worse than those received with standard high-dose radiotherapy, which makes them clinically insignificant. Also, the study was designed in the manner which does not allow to separate the effective mode of application among the number of treatment schedules and equipment types used (APAS, TEN, and MPA systems were used) [1]. The trial is considered successful.

In 2001, Harima et al. [267] trial on TRT of cervix cancer had been published having the improved design. The inadequate dose to tumor mass (60.6 Gy) in this trial was masked by high enough total dose (82.2 Gy) because 21.6 Gy was targeted to parametria with central shielding. This had allowed to show effect of hyperthermia by local control versus low-dose RT from the one side, and at the same time to improve the survival which was the weak point of all the previous hyperthermia studies. This trial also included one more innovation—preselection of the aged patients. It is well-known that local control after hyperthermia is better in older patients. In Harima trial, the sample of not-pretreated patients in TRT group was 10 years older (64.9 years) than the anticipated age of the first diagnosis of cervix cancer in Japan (55 years) and 14 years older than DDHG trial group (51 years). The reported results of the trial were extremely successful.

In 2005, Jones et al. trial on TRT of superficial tumors had been published [239]. Though good enough gain of local control had been displayed (66% versus 42% in RT control), some serious biases do not allow to consider this trial positive. Incorrect randomization is revealed which led to 10% more RT dose in TRT group. This dose difference alone could explain the received clinical effect. Other biases were the high percentage of pretreated patients and preselection of "heatable" patients. Survival in TRT arm was worse during all time of the trial. As it is usual after 1996, this trial had been announced successful.

In 2003, the results of II phase SHOWG trial on thermochemotherapy (TChT) of malignant pleural mesothelioma by virtue of Aquatherm machine were published [268]. Despite the mild effect (20% of partial remission only), it was decided to initiate the III phase trial. In 2004, disappointing preliminary results of the trial had been reported on ASCO meeting [269]. Despite less-severe sample (0–II stage instead of I–III stage in the II phase study), the effect on TChT group was twice worse than on ChT control (15% versus 30% of partial remission) but with higher toxicity. After 2004, International SHOWG had discontinued and its leader Robins had finally left hyperthermia field. Instead of it, German Interdisciplinary Working Group on Hyperthermia [270] had been created with its base in Charité (Berlin). IWGH was mainly targeted to von Ardenne sCMT research, whereas von Ardenne Institute and Clinic had stopped nearly the same time. Though it was announced that this is because the institute had reached its goals, the absence of randomized results makes this reason inconclusive. Fail of SHOWG trial together with the termination of von Ardenne Institute could be considered as the fall of whole-body hyperthermia.

It should be especially noted that von Ardenne "Systemic Cancer Multistep Therapy" (sCMT) is not a real WBH indeed. In fact, sCMT is a combination of two different

modalities, hyperthermia and hyperglycemia, where hyperglycemia is the more potent factor because it could entirely block tumor perfusion per se [271] whereas hyperthermia per se never blocks tumor perfusion entirely at temperatures ≤43.5°C. Hyperthermia following hyperglycemia causes higher tumor temperature and significant decrease of pH whereas without hyperglycemia this pH decrease is insignificant [272]. Therefore, the above conclusions about fall of WBH refer to WBH per se, not to sCMT whose potential still has not been evaluated evidently.

Therefore, despite a number of "positive" trials and some meta-analyses on hyperthermia, medical community soundly did not consider these results evident. Hyperthermia had not been approved as a standard method of treatment in oncology. Without any error analysis and bereft of any correction of its rationale, hyperthermia stubbornly tried to break through the wall of evidence-based medicine, becoming more and more divorced from the reality.

The consensus of the International Kadota Forum on hyperthermia held in 2004 [273] in Japan is very demonstrative. After usual reference to excellent laboratory results, the authors refer to 28 randomized trials on hyperthermia though only 18 "positive" trials are displayed in the corresponding table, and only 14 of them were really randomized. Concerning the rest of the trials, there is the only phrase: "Nine randomized studies failed to show a significant benefit from addition of hyperthermia." There is no even an attempt to explain the negative results though these were the most extensive and reputable studies. There is no any analysis of so-called "positive" studies which in fact were almost uniformly biased. Therefore, the advocacy of hyperthermia is based on a dubious data while the reputable and evidence-based but negative trials are just disregarded. At the same time, the problem with hyperthermia acceptance is claimed because of "limited availability of equipment, the lack of awareness concerning clinical results, and the lack of financial resources." This was a beginning of "hyperthermia low acceptance in view of low attention and money" myth. It seems that medical community was very well acquainted with the results of hyperthermia but trusted to the most reputable trials which were uniformly negative. The lack of financial resources was absolutely natural after the huge funds and forces were just wasted in the 80s–90s without any reimbursement. Limited availability of equipment was in high extent caused by the reluctance of doctors to use it.

Technology. Flexible capacitive applicators were introduced near 1995 by Synchrotherm-RF 13.56 MHz capacitive system. The similar applicators were used earlier in Russian Yachta hyperthermia machines, though at 533 MHz and higher frequencies. Taking into account a well-known instability of low-frequency RF field, Synchrotherm flexible solution seems controversial because field inhomogeneity (and hot-spots formation) increases significantly in any deviation of electrodes from the pure flatness. Idea of "field concentration/focusing" by virtue of the flexible electrodes which is actual for far field in microwave range does not work in the near field at 13.56 MHz: contrarily, the dominating electrostatic interactions cause high tangential and side currents, thus decreasing the heating in the field of interest and creating multiple hot spots. Probably, this was a reason of later Synchrotherm decay.

The new applicator SIGMA-Eye for 3D steering was introduced for BSD-2000 system [274] in the 2000s in view of the insufficient focusing of the previous 2D SIGMA-60 applicator. Alongside triple quantity of antennas (24 totally in 3 groups), the frequency was enhanced to 100 MHz to reach a smaller central peak. Though the better steering was reported [275], the heating efficacy had appeared near 2–2.5 times lower than that of the previous SIGMA-60 applicator [276]. Practical results show that BSD-2000 still do not allow to heat up the desired volume selectively because hot spot before the target region is virtually inevitable [277], localization of other hot spots is almost unpredictable [278], and in general the heating looks rather like a homogenous heating of the entire volume than like a selective heating of target volume [1, 279].

It seems that BSD-2000 concept experiences problems. The high toxicity of the technology still demonstrated in clinical trials [251] looks like its inherent feature because the interference of fields in the near field region is not completely controllable and is inevitably connected with multiple floating hot spots formation (which, by the way, was obvious initially). Real-time thermometry is the only possibility to control the process but there is no satisfactory technical solution. In fact, MR thermometry is just the only possibility but it is still relatively applicable only for extremities and small pelvis with many limitations [276]. Sure, due to hyperthermia research, MR thermometry develops soon but it does not develop hyperthermia itself which in fact is "sitting and waiting" while MR thermometry matures. And it looks rather like fleeing from the problem because even if MR thermometry is satisfactory, it does not solve the problem. The same situation already happened in the 80s–90s: without effective thermometry, the heating was high enough, and there were some clinical results though with high toxicity; with more effective thermometry, the heating and toxicity became lower but clinical effect disappeared. There is no any premise for another end in this case. Taking into account the final results [1] of the STS trial [251] where HT was ineffective even in the best heated and thermocontrolled case of extremities, thermometry far not looks the main problem of the technology. At last, in-built MR thermometry finally makes BSD-2000 the "research only" technology. It is impossible to imagine in clinical practice a modifier which is more expensive and labor intensive than a modifying modality itself.

Near 2000, an innovative Oncotherm EHY2000 unit had been introduced, based on the new modulated electro-hyperthermia (oncothermia) technology. The main idea of the technology was the rejection of the central role of the temperature. Instead of it, the not-temperature-dependent effects based on the power absorption, extracellular heating and modulation, were the core of the technology. The classic capacitive design had been cardinally reevaluated. Instead of the high-power/intensive cooling concept, the low-power approach with mild physiological-range cooling had been

offered. Concept of "skin sensor" had abandoned the most problematic point of all hyperthermia machines—necessity of thermometry. Functionally asymmetric electrodes with grounded lower one had provided the necessary field stability and enhancement of heating in the "zone of interest." Special fractal modulation of the carrying frequency had markedly enhanced the selectivity of power deposition in tumor tissue. Thus, looking from outside like a regular 13.56 MHz capacitive solution, EHY2000 was a principally new electrohyperthermia machine and technology. Detailed description of oncothermia technology, science, and trials [280] is beyond the range of this essay devoted to classical oncological hyperthermia only.

5.3. Hyperthermia Since 2005: Crisis, Resetting, Dead End and Decay. In 2005, Vasanthan et al.'s [281] randomized multicenter (5 centers in 4 countries) trial on TRT of cervix cancer had been published. Contrarily to previous trials sponsored by hyperthermia societies and industry, this trial was independently sponsored by International Agency of Atomic Energy (IAAE). In this trial, HT was studied versus adequate RT dose to tumor mass (72 Gy, TD 84 Gy). The result had appeared disappointing: TRT did not differ from RT only by local control but had shown the worse survival. In IIb stage group, the worsening of survival was statistically significant. The subsequent trial of Mitsumori et al. [282] on TRT of non-small cell lung cancer (also sponsored by IAAE) also had not shown the effect of hyperthermia.

There was one more unpleasant surprise of Vasanthan trial: it was the "most hyperthermic" study among all deep heating studies held before. The average tumor temperature reached 41.6°C (40.6°C and 40°C in Harima and DDHG trials correspondingly). The pure hyperthermic approach had appeared ineffective though it was clear already after the early 90s negative trials.

There was no possibility to wait with reassessment of hyperthermia rationale any more. In 2005, the program paper on resetting of hyperthermia rationale had been published [283]. Unfortunately, it was not a real reassessment. The paper once again speculated on "successful" trials in the frame of the old concept of "thermal dose" which is in fact the "dose of temperatures." Hyperthermia fails were not assessed accordingly and central place of temperature was even not discussed. It had been just recognized at last that the extreme hyperthermia concept is impossible. Instead of it, moderate hyperthermia concept (40–42°C) had been offered based on the effect of hyperthermia to bloodflow and tumor oxygenation, studied by Song team [284] to the moment. In fact, it was just an attempt to give another justification for temperature concept, a face lift instead of the capital reconstruction.

In 2007, a paper of Jones et al. [285] had been published advocating the use of hyperthermia as a radiotherapy sensitizer for treatment of chest wall recurrences based on the mentioned "positive" trials. In the same year, National Comprehensive Cancer Network (NCCN) had included consideration of the addition of hyperthermia for women with recurrent locoregional advanced breast cancers after first-line surgery or radiation failed, after substantial discussion and controversy among the NCCN panel members and as a category 3 recommendation (the recommendation is based upon any level of evidence but reflects major disagreement). In particular, McCormick from Department of Radiation Oncology of Memorial Sloan-Kettering Cancer Center was a counterpart [286]. This small success was too insignificant to compensate the harm from sound fail of IAAE trials in 2005 [281] and 2007 [282]. Crisis of hyperthermia was obvious.

"The last hope" of hyperthermia community was associated with Issels et al.'s trial [251] on TChT of soft tissues sarcomas. This was the largest and the most complex trial for all the history of hyperthermia, the real "crusade." The prospective, randomized, controlled, multicenter III phase trial was sponsored by European Society for Hyperthermic Oncology (ESHO), European Organization for Research and Treatment of Cancer (EORTC), US National Institute of Health (NIH), German Cancer Society, Helmholtz Association, and private sponsors. 341 patients with localized high-risk soft tissue sarcomas (STS) had been enrolled at nine centers in Europe and North America for 9.5 years (1997–2006). The trial was designed to study HT efficacy in the complex treatment of STS by the most effective protocol: neoadjuvant chemotherapy (with and without HT) → definitive surgery → adjuvant RT → adjuvant chemotherapy (with and without HT). Regional HT was applied by virtue of state-of-the-art BSD-2000 hyperthermia units. In 2010, the following results had been reported: there was no effect on overall survival, but short-term local response rate (CLR + PLR) was twice higher in HT arm (34% versus 16%), and Local Progression Free Survival was significantly enhanced in HT arm (32 months versus 18 months; 76% versus 61% after 2 years and 66% versus 55% after 4 years).

Unfortunately, this result was totally based on the systematic bias: all the possible points of distortion (tumor size, grade of disease, volume of surgery, RT, and chemotherapy) were distorted to various extent but unidirectionally in favor of HT arm. Total distortion rate exceeded 90% while the relative efficacy gain did not exceed 1.25. The only difference in the extent of chemotherapy (median 8 cycles on HT arm versus 5 cycles in the control arm, 60%) more than explains the gain of the effect in HT group. In comparison with the earlier results of Sarcoma Meta-Analysis Collaboration (SMAC), the best results in HT arm of Issels et al.'s trial were substantially worse than results in control arm of SMAC [1]. With respect to the distortions and SMAC comparison, the another question arises: whether hyperthermia worsens the results of conventional treatment? Nevertheless, the result had been as usual announced positive, and the authors had advocated that "regional hyperthermia combined with preoperative or postoperative chemotherapy should be considered as an additional standard treatment option for the multidisciplinary treatment of locally advanced high-grade STS" [287].

Meanwhile, the new basement of the "reset" hyperthermia had been collapsing. "When hyperthermia is applied in vitro, no fundamental differences can be seen between the response to normal and tumor cells." This phrase of Kelleher and Vaupel [288] explicitly reflects the modern look

on the problem and confirms the old "open secret" of the absence of difference in thermal resistance between healthy and malignant cells, and this is the final judgement to the extreme hyperthermia concept. Extreme outer hyperthermia, both local and systemic, is impossible without significant difference in thermal sensitivity between normal and tissue cells because otherwise the heat damage of the healthy tissue is inevitable. At equilibrium steady-state phase at hyperthermia, the temperature difference between healthy and tumor tissues does not exceed 1°C even for relatively selective capacitive solutions. It seems that, for interference irradiative solutions, a tumor is virtually always heated less than the surrounding tissues [279].

Kelleher and Vaupel had also revealed that the gain in tumor oxygenation due to hyperthermia is modest and transient and cannot be used for enhancement of radiotherapy effect [289]. This confirms the data of immunohistochemistry study of Sun et al. [290] from Memorial Sloan-Kettering Cancer Center with hypoxia markers showing that real effect of the moderate hyperthermia on microcirculation is bidirectional and inconclusive. Because the "reset" concept of the moderate hyperthermia is entirely based on the idea of better oxygenation of tumors, this could be the final judgement to the mild/moderate hyperthermia concept. Though still there are some rapturous opinions [291] concerning promises of mild hyperthermia based on Song and team works [284] and they are still reporting these results [292], the new data make these results questionable which would be discussed below.

As the last shot, in 2011 de Bruijne et al. [293] from Erasmus Hyperthermia Center had demonstrated in retrospective study that, after correction to tumor size, CEM 43°C T90 thermal dose is not associated with any clinical endpoint (CLR, LDFS, OS). This looks like the final judgement to temperature concept of hyperthermia at all. As a result, after more than 100 years of development, hyperthermia is based on the dubious fundament and bereft of a rationale.

Technology. There were a few new machines developed in Western counties after 2005.

Near 2006 Oncotherm had developed the new "multilocal" machine EHY3010ML. Using the newest technology of textile electrodes with virtually unlimited size, the innovative concept of simultaneous local treatment of multiple tumors and metastases without heating of healthy tissues was realized [280].

Celsius TCS hyperthermia system had been introduced in 2006 in Germany. Despite being declared as "innovative," this was just a replica of traditional 13.56 MHz/600 W capacitive scheme with two rigid symmetrical electrodes and intensive cooling similar to Oncocare and Synchrotherm-RF. The most impressive and really innovative feature of the system was just the absence of any innovation. This was a typical "me too" approach, similar to a rising trend in the modern pharmacy, the attempt to present the old solutions in the "new skin." It seems that this machine is far from perfection. First of all, because it is hard to await that a regular 13.56 MHz concept would be successful after fail of many much more perfect predecessors like LeVeen machine, Oncocare, Jasmin, Synchrotherm (discontinued in 2011) and many other solutions. Second, the use of not properly fixed electrodes seems to be a serious defect of a capacitive machine. Instability of low-frequency RF field and hot-spots formation together with high superficial fat heating form the "Procrustean bed" of the capacitive technology. The main possibility to relatively stabilize the field between symmetric capacitive electrodes is their rigid fixing to keep them always parallel and symmetrical like in Thermotron. It seems that any capacitive solution which uses not exactly fixed symmetric electrodes is not safe enough. For example, in Celsius TCS preclinical report [294] an intensive hot spot had been displayed in 1 of 4 clinical examples: at prostate cancer treatment and at low power 80–120 W, the temperature in rectum where thermometer was placed (i.e., out of interest zone) suddenly had risen to 45-46°C and had been remaining at the level for 20 minutes. This is a typical hot spot of tissue-damaging exposure. It seems that it should be the typical defect for any low-frequency capacitive system with not properly fixed symmetric electrodes.

Unexpectedly, hyperthermia had become a "hot topic" in China. Since 1995, many new hyperthermia machines were presented there by the companies HY SenMo, ZD, ZRL, NRL, MoreSteps and others. Majority of them are just replicas of Thermotron though acting at 13.56 MHz open ISM frequency with an attempt to enhance the classical design. Because two problems of capacitive technology are high superficial fat heating and low deep heating, high "superposition" field strength on the crossing of the paired electrodes fields could allow to reach enough deep heating while the surface heating is low. This is in fact a low-frequency capacitively coupled version of the earlier APAS-TEM idea [179] and repeat of the LeVeen design [173]. It was then implemented by Synchrotherm-Pulsar system having 2 pairs of electrodes and double power 1200 W. There is no data about its efficacy and safety. The majority of Chinese manufacturers develop a similar idea of "double Thermotron." It is hard to say, could any of these solutions be more effective than the existing classic Thermotron capacitive solution.

Looking from outside it is clearly seen that this Chinese "hyperthermic enthusiasm" is based on the uncritical acceptance of the abovementioned "just heat it" appeal of hyperthermic community. Because Chinese have not received "hyperthermia vaccination," like Western world did, and therefore have not the appropriate historical memory, this simple and attractive appeal will necessarily find acceptance.

5.4. Hyperthermia at the 2010s: Decay Goes to Renaissance? World hyperthermia lies in ruins. It's especially obvious if to compare the current state with the 80s and 90s. United States which was a worldwide leader in hyperthermia research and development, where almost every big university was involved in these researches, now is virtually "free of hyperthermia" zone. Dr. Beecher institute, Duke University, and some activity in Texas University, these are pathetic remnants of the former boiling activity. "Hyperthermia vaccination" was so strong in US that BSD2000 machine still cannot receive FDA approval since 1990. It seems that there is no any FDA approved machine for deep hyperthermia. Only superficial

hyperthermia is accepted but it had been accepted before 1990.

Japanese cluster based mainly on Thermotron RF8 is silent after the sound fail of IAAE trials in 2005–2007. There is no any development, and research activity has decreased markedly. After that fail, Thermotron RF8 is not already an engine of Japanese hyperthermia and this place remains vacant.

Residual hyperthermic activity remains in Europe. German IHWG still studies sCMT von Ardenne concept and tries to elaborate the concept of "critical" whole-body hyperthermia (more than 42.5°C) offered by Russian doctor Suvernev [295]. It seems that this direction is problematic enough. ESHO powered by BSD Corp. is still active, at least at a conference level. DGH is mainly powered by the German private market based on insurance payments for hyperthermia treatment. Danish cluster seems to be inactive. The last review of van der Zee et al. [169] had shown that the oldest and the most reputable in Europe Dutch cluster has stopped its development. English school of hyperthermia had decayed already after Pettigrew and Henderson at 70–80s and had finally evaporated after "successful" ICHG study [237] in mid-90s. Italian cluster, one of the oldest in Europe, shows some potential for development but in frame of the old hyperthermia concept, therefore without any future.

42 of 46 existing manuals and monographs on hyperthermia had been published before 1996 and 33 of them—before 1990. The excellent Seegenschmiedt et al. monograph [261, 262] had completed this "before 1996" period without any mention of any negative result. In fact, hyperthermia is still based on the old-fashioned ideas and concepts of the 80s.

At the same time, we see the second wave of interest to hyperthermia worldwide. Quantity of publications is a good indicator. In 1991, just before the crisis of the 90s, near 350 papers on hyperthermia were published (Pubmed). At the 2000s, this quantity dropped to 200 papers per year, and had returned to precrisis level 300 papers in 2009. Some new monographs have been published. We see three main reasons of this renaissance. First, "the throne is never vacant." There is a strong request for universal modifier of conventional treatments whose efficacy is obviously insufficient. There is still no any candidate to this position except for hyperthermia. Second, the new generation of scientists and physicians came into oncology which is free of "hyperthermic disappointment," has not experience of hyperthermia usage and does not remember hyperthermia fails, but studied hyperthermia from the textbooks based on very simple and attractive concepts of the 80s.

Third, there was no any cardinal solutions made concerning hyperthermia, and hyperthermic community together with the industry made everything possible to "smooth the blows" and kept it safe. They produced some myths about hyperthermia: hyperthermia is of course effective, the negative studies are not valid, the reason of hyperthermia unacceptability is the evidence-base medicine barrier and competition of Big Pharma, and the main problem of hyperthermia is the lack of attention and money and some technical points like thermometry [273]. An article in Polish Journal of Environmental Studies [296] is an excellent sample of such mythology. All these myths are wrong. Evidence of hyperthermia effect is based on the dubious data, the negative trials were adequate, and extremely much funds and forces were invested in hyperthermia research and development. More than 12,000 publications and >700 clinical trials with near 30 randomized trials among them are much more than necessary for the acceptance of any drug or treatment method. When 10 randomized trials on hyperthermia started in 1984–1991, the evidence-based barrier was absent because the concept of EBM had been offered in 1991 only, and even this barrier had not object to fulfill the tremendous Issels et al.'s trial at 1996–2006. All the necessary technical solutions had appeared many years ago. Thermometry is not a point at all because of the fail of temperature concept.

As it is clearly seen from the mentioned papers [273, 296], the most impressive feature of hyperthermia community is a great interpretational bias in the form of complete disregard of any negative results: only positive results are considered valid while the negative ones are just not mentioned. We see this disregard, for instance, in Kadota consensus [273] and in the remarkable Seegenschmiedt monograph: for example, [261, Figure 10.13 on page 213], presents effect of TRT versus RT only. Among many phase II nonrandomized "estimation" trials whose results should be considered with the great caution [297], the only randomized trial of Perez et al. [234] is displayed. This trial was negative for hyperthermia arm (32% of CR versus 30% with less toxicity in RT only group) and only small tumors (<3 cm) showed a TRT gain. Only these <3 cm subgroup positive results are displayed in the figure to confirm TRT effect and the negative arm is disregarded. As a result, there is an impression of uniform success of TRT though it is absolutely not correct: much more negative results of randomized trials [233, 235, 236] had been received to the moment (references up to 1995 are present in the monograph) but they are also not mentioned. This interpretational bias is characteristic for all the hyperthermia publications after 1991.

Therefore, the only reason of hyperthermia unacceptability is the "temperature-based" hyperthermia itself, namely its low efficacy, high toxicity, and labor intensity. This open conclusion should be done at last otherwise; we will see the second wave of hyperthermia with the same result as the first one, just a prolongation of the agony with more expenses. This already happens. "Temperature race" lasts though it should be stopped more than 10 years ago—it is just moving from the "vaccinated" Western countries to neophytes—China is becoming the main hyperthermia market. But term of the "vaccination" expires even in the Western countries with change of generations, and those who cannot remember the past are condemned to repeat it.

Technology. In 2011, Due.R srl, the manufacturer of Synchrotherm RF system, had dissolved after some years of collapsing (−10% of market every year) though recently one more "me too" Synchrotherm-like Androtherm system has come into the market. The problems of "me too" machines are discussed above.

6. Electromagnetic Treatment Since 1985: Stagnation of Diathermia, Nonthermal Renaissance, and Problems of Nonthermal Research and Application

Diathermia had been "thermally-frozen" since the 30s. FDA Inspection Technical Guide on Diathermia of 1973 states "It is the opinion of FDA and the consensus of experts that pulsing the output of r.f. diathermy (as opposed to continuous wave) produces no extra beneficial therapeutic effects. Any physiological responses produced by pulsed r.f. diathermy are attributable to heat produced by the average power output" [298]. Therefore, the nonthermal development of diathermia had being blocked by the institutionalized thermal dogma just at the intention level. Only recently this opinion had been soundly questioned: the nonthermal nature of the different pulsed patterns was displayed [299].

Nonthermal effects have been gradually becoming the mainstream of electromagnetic research since 1985. Currently, the nonthermal effects of AEMF could be classified as follows: (1) ponderomotoric effects due to polarization of dielectrics: (a) dielectrophoresis; (b) rotation of cell and nucleus; (c) orientational effect ("pearl-chain" formation), (2) membranotropic effects: (a) electropermeabilization and electroporation; (b) cell fusion; (c) changes of transmembrane transport; (d) changes of membrane structure; (e) membrane destruction, (3) molecular effects caused by direct impact of AEMF on macromolecules: (a) genotropic effects on DNA; (b) proteinotropic effects. Summation of these microeffects led to development of nonthermal macroeffects: (1) effect on cell proliferation; (2) cell death: (a) necrosis; (b) apoptosis; (c) "mitotic catastrophe"; (3) disturbance of microcirculation.

To the end of XX century, the number of nonthermal publications had reached the critical mass (more than 20,000 Pubmed publications) which had made the transition to practical application inevitable. Currently, there are a number of directions and technologies based on the nonthermal effects: (1) dielectrophoresis; (2) electroporation; (3) bioelectric effect; (4) galvanotherapy; (5) electrotherapy; (6) electric field therapy; (7) magnetotherapy; (8) electrohyperthermia. Some nonthermal technologies have been commercialized or close to commercialization (see Table 2).

Though ponderomotoric effects of EMF are clear and proved, the delicate subcellular mechanisms of ELP-AEMF are not clear still. Effect on DNA is suggested [300]. DNA could be a fractal antenna possessing electronic conductivity and autosymmetry. It could interfere with AEMF at low-frequency and radiofrequency range [301]. It had been shown that exposure of DNA to ELP-AEMF leads to the expression of heat-shock proteins (HSP70) [302]. Astumian had displayed that proteins could act as molecular machines transferring energy from one form to another by virtue of cyclic conformational transitions [303], and these molecules could absorb AEMF energy. This especially refers to enzymes whose action is based on cyclic conformational transitions; AEMF acts as an external energy source allowing to shift the reaction from the equilibrium [304]. Tsong team had shown that AEMF affects Na^+/K^+-ATPase: ionic transport in their experiment depended rather on AEMF frequency and amplitude and then on ATP concentration [305]. The peak effect on K^+ transport was near 1 kHz and near 1 MHz for Na^+ transport. It is reported that non thermal effect of ELP-AEMF (53 GHz, 0.06 mW/cm^2) inhibits the growth of *E. coli* and affects transmembrane Na^+/K^+-transport [306]; antibiotics enhance the effect and it is considered membranotropic. Effect on redox status is suggested [307].

AEMF affects cell proliferation, and this effect is frequency dependent resembling a resonance. In 2009, Barbault et al. paper had been published [308]. 1524 tumor-suppressing frequencies had been revealed in the range from 0.1 Hz to 114 kHz. Most frequencies (57–92%) were specific for a single tumor type. The newly developed and FDA-approved tumor-therapy fields (TTF) technology is also efficient in suppressing tumor growth [309, 310]. There are some possible explanations of this effect. The authors of TTF technology explain it on the basis of intracellular orientational effect of AEMF: AEMF-induced dielectroforetic forces inhibit an assembly of mitotic spindle [311]. another explanation had been offered by Vodovnik et al. [312]: external AEMF leads to hyperpolarization of membrane on the one side with simultaneous hypopolarization on the other side of a cell; the membrane potential of dividing cells is diminished compared to resting cells; following fast complex and nonlinear processes of hyperpolarization and depolarization and resulting changes of ion currents, membrane potential of dividing cells rises which inhibits proliferation.

Nevertheless, it should be mentioned that the use of the non thermal effects is still questionable for many reasons, and many problems could happen in this way. First, the great "systematic error" is still present in the non thermal research with its roots coming from the "thermal dogma." As it follows, for example, from the Kaiser paper [313], non thermal effects are positioned only in the "non thermal range," when there is no macroscopic temperature elevation, that is, in extremely low power (ELP) range. This is incorrect and fruitless approach. Thermal and non thermal effects develop simultaneously, and it is impossible to reach strong enough non thermal effects with those field strengths which do not cause substantial heating. This old sentence of Schwan should be a slogan of any "non thermal" research and application. Adair [314] clearly showed in 2003, using biophysical criteria, that continuous RF and microwave radiation with intensity less than 10 mW/cm^2 are unlikely to affect physiology significantly through athermal mechanisms because biological systems are fundamentally noisy both on molecular scale and macroscopically; therefore, the direct physiologically significant effect of EMF must be greater than that from the ubiquitous endogenous noise. The "nonthermal" applications of the 30s [77] failed for this reason—trying to remain "pure athermal,"—and this is also a danger for the new nonthermal applications. It seems that oncothermia technology is the only one which realizes this problem in principle and can reasonably divide thermal and nonthermal investments into general effect at hyperthermic-range temperatures [315]

Table 2: Commercialized nonthermal AEMF technologies in clinical oncology.

Technology	Trademark	System	Inventor	Implementation	Company	Since
Electrohyperthermia	Oncothermia (modulated electrohypethermia)	EHY2000 EHY3000	A Szasz (Hungary)	Approved in EU (CE), Russia, China	OncoTherm Group (Germany-Hungary)	1988
Electroporation	electrochemo therapy (ECT)	Cliniporator	LM Mir (France)	Approved in EU (CE)	IGEA Srl (Italy)	~1980
		EndoVe	D Soden (Ireland)	I/II phase [83]	Mercy University Hospital (Ireland)	
	electro gene therapy (EGT)	MedPulsar	GA Hofmann DP Rabussay Z Zhang (USA) [84]	Approved in EU (CE)	Genetronics Biomedical Corp. (USA)	~1997
		TriGrid	RM Bernard	FDA approved for clinical trials	Ichor Medical Systems Inc. (USA)	1994
Electric field therapy	tumor treatment field (TTF)	NovoTTF-100A	Y Palty (Israel)	Approved by FDA [85] after III phase trial [86]	NovoCure Ltd. (Israel)	2000
Magnetotherapy	therapeutic electromagnetic field (TEMF)	—	Wascher RR Williams D Bouldin FE (USA) [87]	I-II?	EMF Therapeutics Inc. (USA)	~2000
Galvanotherapy	electro cancer therapy (ECT)	ECTplus	Н/Д	Approved in EU (CE)	CUTH Meditech GmbH (Germany)	2006
		NEUFLO	Schroeppel EA, Kroll MW (USA) [88]	Approved by FDA for research	Ionix Medical Inc. (USA)	~2000

though we see emerging understanding of this problem even in diathermia [299].

The maximum activity in EMF study after 1985 was concentrated in two areas: safety of extremely low-frequency AEMF (ELF, <300 Hz) produced by electric lines and equipment and safety of extremely low power (ELP) high-frequency AEMF connected with the use of mobile phones. The essence of the both directions is that old thermal-based safety limits experience a strong pressure of the evidences of harmful non thermal effects of EMF and should be reevaluated with respect to the non thermal effects [316]. This battle has still not completed. For now, both ELF and ELP AEMF are recognized as potentially dangerous [317, 318] but safety limits have still withstood. Because both ELF and ELP AEMF do not cause any heating, their effects are non thermal, and the recognition of the danger of their effects is a tacit recognition of the existence of non thermal effects.

Since the 90s, research of extremely low-frequency AEMF (ELF, <300 Hz) produced by electric lines and equipment had started. Some of them displayed the possibility of oncogenic effect of ELF-AEMF: it had been shown in vivo that medium-term effect facilitates tumor growth, especially at the breast cancer, and long-term effect could provoke a spontaneous cancer development [319, 320]; resistance of breast cancer to tamoxifen had risen under the influence of 50/60 HZ, 1.2 mcT AEMF [321, 322]. The rising quantity of such studies had forced WHO to convene an international workshop in 1997 [317]. Experts had resumed that high-intensive ELF-AEMF could be dangerous though low-intensity influence (<2T) characteristic for everyday exposure is not dangerous though claiming for insufficient knowledge and necessity of further studies. Other studies had displayed also the antiproliferative effect of ELF-AEMF [323, 324]. Despite a number of publications on ELF-AEMF effects, their effect on human being remains controversial.

Since 1995, tremendous and rising quantity of trials was devoted to the exposure of high-frequency AEMF of extremely low power (ELP) connected with the use of mobile phones [325]. ELP-AEMF had reported to be connected to children leukemia, brain tumors, breast cancer, gene toxic effects, neurological disorders and neurodegenerative diseases, allergic diseases, miscarriage, and some cardiology disorders [326]. Therefore, the thermal-dependent safety standards elaborated in the 50s are considered not enough and should be replaced by the new standards based on the non thermal effects [316]. In 2011, the Working Group on Carcinogenicity of radiofrequency electromagnetic fields had classified RF-EMF as "possibly carcinogenic to humans" (Group 2B) due to limited evidences [318]. Therefore, in general it is considered safe but the final conclusion is not possible still.

As it is clear from the abovementioned, actually both these mainstream nonthermal directions are fruitless from the medical effect point of view. The frequency range of ELF EMF (<300 Hz) is obviously out of the range of resonance frequencies of cells, subcellular, and molecular structures which lies in kHz–MHz range. ELP EMF power level is below physiological limit of 10 mW/cm^2 [314]. Therefore,

these trials could be useful for safety reasons but they are of little significance for treatment purposes, especially taking into account the well-understandable controversy in the direction of their effects: prooncogenic and antiproliferative properties are often reported by different researchers for the same EMF applications. For example, Girgert et al. [322] have revealed prooncogenic effect of ELF-AEMF (50 Hz, 1.2 mT) at breast cancer. This effect was multigene, complex, and unidirectional [327–329]. Novikov et al. [330] have revealed Erlich tumor eradication in mice after exposure to weak ELF magnetic field (42 mT); characteristic patterns 1 Hz/300 nT, 4.4 Hz/100 nT, and 16.5 Hz/150–300 nT were revealed. Berg et al. [331] have revealed that ELF magnetic field (50 Hz, 15–20 mT) selectively affects cancer cells: induction of apoptosis, depression of angiogenesis, necrosis, and synergy with hyperthermia and chemotherapy are reported. Wen et al. [332] have revealed the synergy of ELPF magnetic field (100 Hz, 0.7 mT) and radiotherapy.

Another dimension of the "systematic error problem" is a maniac desire to see thermal effects everywhere. There is something sacral in this "thermal belief": thermal effects go deeper and deeper, to molecular level and beyond the measurable limits, but they are still considered "thermal" in their nature—"week thermal" or "quazy-thermal." The ideas of "molecular thermometers" which register those temperature changes which are not registered with thermometers [333] or of the "resonant heating in micro hot-spots" [334] are examples of this type of thinking, and it turns the problem of relationship of "thermal" and "nonthermal" into a scholastic problem of the same nature as the ancient problem of "a hen and an egg." It is obvious that any process is accompanied with thermodynamic changes but it does not mean that it is "thermal" by its nature. Any mechanical process could be scholastically reduced to thermodynamics, but could thermodynamics explain a mechanical process? Could it be described correctly in terms of temperature, enthalpy, and entropy instead of mass, force, velocity, and acceleration? Of course not, but this is what radiofrequency physics in its "thermal dogmatic" form has been trying to do for more than 70 years.

The problem is aggravated by the fact that ELP field researches are conducted at the sensitivity limit of the modern techniques which inevitably causes a number of errors. In 2006, Leszczynski and Meltz [335] discussed the problem of low reproducibility and high variability of the new screening techniques of transcriptomics, proteomics, and metabolomics in the search for biological and health effects of electromagnetic fields, with prone to produce false positive results.

These thermal-athermal games at the sensitivity limit are well illustrated by the following example. In 2000, de Pomerai et al. [336] reported a nonthermal ELP microwave (750 MHz, 0.5 W,) induction of HSP synthesis in the soil nematode Caenorhabditis elegans. Later in 2006, this group had revealed the error of the temperature measurements and reported that the revealed mild heating (near 0.2°C) could explain the effect [337] and had retracted the primary paper [338]. Also, Qutob et al. [339] had reported the lack of gene expression after 4 hours of pulsed microwave (1.9 GHz, 0.1–10 W/kg) exposure in human glioblastoma cells, Whitehead et al. [340] also had not revealed any changes of gene expression on cultured C3H 10T1/2 cells after continuous 24 hours 835/847 MHz exposure, and Hirose et al. [341] had not revealed an effect of 24–48 hr 2.145 GHz ELP (80–800 mW/kg) exposure on p-53 protein phosphorylation and expression in vitro. In 2009, de Pomerai group had confirmed the conclusion about the absence of nonthermal ELP microwave HSP induction in the soil nematode Caenorhabditis elegans [342]. In contrast, in 2007, Zhao et al. [343] had reported that even relatively short-term exposure to cell phone radiofrequency emissions (1.9 GHz) can upregulate elements of apoptotic pathways in cells derived from the brain and that neurons appear to be more sensitive to this effect than astrocytes. In the same year, Zhao et al. [344] had confirmed that ELP microwave exposure (1.8 GHz, 2 W/kg) changes the gene expression of rat neurons (24 up regulated genes and 10 downregulated genes among 1200 candidate genes were revealed). The only conclusion of these studies is "no conclusion".

The above problems of nonthermal studies are mainly objective. There are also many subjective problems mainly caused by both theoretical and practical errors of researchers. First, the vast diversity of nonthermal effects creates a fallacious impression that almost any electromagnetic exposure could treat cancer. With this trend, even "toaster cancer treatment" is not excluded. Indeed, it seems that there is a limited number of combinations of field parameters and technologies of their application which are suitable for nonthermal cancer treatment. Second, there is a trend to uncritical extrapolation of different known effects of EMF despite the power level and field type. For instance, Tello et al. (2001) [345] explain the effects of constant EMF by the effects of AEMF which is incorrect. Indeed, there is no any electromagnetic modality which applies all the known EMF mechanisms. Effects of EMF are dispersed at the entire frequency and power spectrum, and each effect has its frequency and power optimum. Other wide-spread mistake is the use of ponderomotoric effects which demand high enough field strength for the explanation of ELP-AEMF effects, which looks at least controversial. Demodulation, molecular, atomic and subatomic effects of ELP-AEMF are becoming a hot topic in research [346], but the real significance of such an "informational" effects is still questionable. Next, problem of EBM barrier is becoming more and more critical for development of the new medical technologies. Now, it is expensive enough to receive even preclinical evidences. In case of electromagnetic treatments with great versatility of frequency-power-modulation combinations, it could be the insoluble problem. At last, the quality of nonthermal trials is still low. The main reason is that high-quality evidence-based trials are too expensive for nonmainstream modalities.

The case of Dr. Holt is a good example of impact of these subjective reasons for hyperthermia fate. Dr. John Holt had been practicing hyperthermia since 1968 in Western Australia, starting from WBH wax bath according to Pettigrew and Henderson [347], and in 1974 turned to microwave HT. Initially he did it in combination with radiotherapy but since 1991 he left his hospital in favor of his private practice where

he treated cancer patients by combination of MW HT and special type of chemotherapy called by him "glucose blocking therapy." He used the whole-body "Tronado" machine of W. Guettner from West Germany consisting of 12 Erbotherm 69 434 MHz 200 W microwave generators (later from 4 1-2 kW generators).

From just the beginning, Dr. Holt's attitude to HT looked like pure belief. Already in 1974 he wrote "The implications of this discovery (*meaning MW treatment*) are tremendous: (1) No patient will ever become a chronic cancer nursing problem again if treated correctly with microwave radiation. (2) Inpatient accommodation for microwave radiation patients will be much less than required for all other types of therapy. (3) Cytotoxic therapy is "dead" in its present form. Perhaps it may occasionally survive in association with other methods for some rare cancers. (4) X-ray therapy is of value for pituitary adenomata, artificial menopause, intracranial arterio-venous malformations, syringemyelia, rheumatic diseases, pterygia and warts, and so forth. (5) Cancer surgery will be revolutionised. It will be needed to make diagnosis and perform such operations as are essential to prevent complications which will arise from tumour necrosis. Radical cancer surgery is therefore unnecessary. Surgery need only remove the primary and microwave therapy will be able to kill the metastases".

"All current cancer research in the world becomes pointless, except that relating to experiments relating to human cancer and microwave therapy".

"There is therefore no need to wait five or ten years to predict that this type of microwave radiation therapy can cure cancer. The author can predict without fear or favour that this will be found to be correct in due course" [348].

Such rapturous and uncritical position looks unscientific. It seems that Dr. Holt had not got enough rationale for such revolutionary conclusions. Also in 1974, Dr. Holt discovered the new phenomenon. He was sure that cancer cells absorb irradiation of 425–440 MHz range (but not at higher or lower frequencies) and "re-irradiates it at a lower frequency but a higher intensity" [349] (like fluorescence). This was detected by some "wave analyzer" though he said that "adequately sensitive equipment to test this theory has not been available" [349]. This fluorescence discovery was not confirmed like the other exclusive properties of 425–440 MHz range. The new discoveries were not long in coming: near 1980 a theory of cell Central Executive Officer (CEO) controlling development and function of cell was offered [350], and theory of cancer as defect of glucose metabolism was developed [351] (both not confirmed).

Initially, Dr. Holt considered HT as a radiotherapy modifier and many times wrote that it does not cure cancer if used alone and that use of HT as a monotherapy is not ethical [149, 352]. Already in 1977, he stated that effect of MW HT is partly nonthermal [353]. This was concluded from the fact that effect of 434 MHz treatment was much stronger than effect of similar heating [354]. It was concluded that 434 MHz MW exposure has nonspecific thermal effect and specific nonthermal effect. The thermometry had been performing up to 1977. After that, Dr. Holt did not use thermometry any more [349]. In 1985 it was stated that "Microwaves are not Hyperthermia" [349] though there was no any reasonable explanation of nonthermal effects except reirradiation which is not a mechanism in fact. Since 1991, he had been treating cancer by MW HT in combination with "glucose blocking agents" (low-dose cyclophosphamide, cystine disulphide, or penicillamine disulphide) developed by him [355] and without radiotherapy.

The construction of ungrounded but breakthrough theories based on dubious facts was typical for Dr. Holt. His prone to sweeping generalities based on insufficient data was obvious. The most problematic point: he did not need proofs. His theories were all sufficient and he always "predicted without fear or favour" that they should be with necessity "be found to be correct in due course." It is amazingly but as it follows from his paper "Enigma of cancer" [347], that all theories and practice of Dr. Holt were entirely built on single observations, isolated cases, and the sweeping generalities without any scientifically correct experiment or measurement. The first evidence-based trial had broken these theories.

In 1996, the big enough RCT on RT + MW HT at rectal cancer was published by Trotter et al. [356]. There was no difference between RT and RT + HT groups. Dr. Holt was involved in this trial as a principal investigator. In their letter to editor in response to the Trotter et al., Drs. Holt and Nelson claimed that this study should not have been published without the "correct historical perspective" meaning the earlier nonrandomized results of the 70s. They also stated that the rectal cancer for this study was agreed to under duress as it was not their cancer of choice for the trial, and this is "why we have refrained from having one or both of our names on the paper." In his reply, Dr. Trotter points out that it was Dr. Holt who recommended the doses of MW therapy and radiation for the combined treatment arm, and he endorsed the choice of rectal cancer drawing attention to a survival advantage observed in rectal cancer in an earlier retrospective comparison.

In 2001, Dr. Holt's concept reached the universal value [357]. He believed that all Alzheimer's disease, Creutzfeld-Jakob disease, multiple sclerosis, scleroderma, herpes zoster, hepatitis, amyotrophic lateral sclerosis, ankylosing spondylitis, and systemic lupus erythematosus patients have benefited and most have had their disease eliminated by treatment with 434 MHz therapy.

In 2005, the fundamental 280 pages report on the microwave cancer treatment (UHF) was issued by Australian National Health and Medical Research Council [358] based on the study of the long-time practice of Dr. Holt in Western Australia. Very detailed retrospective study comparing efficacy and safety of RT alone, RT + UHF and UHF alone did not reveal advantages of UHF alone and RT + UHF versus RT alone. Vice versa, UFH treatment was associated with lower efficacy and higher toxicity. Systematic review did not reveal any advantage of hyperthermia at all. This was not only the sound end of Dr. Holt practice but also the strong blow to Australian hyperthermia at all. It also led to discreditation of the idea of nonthermal cancer treatment.

Now it is obvious that Dr. Holt claim on "nonthermal" effects was not grounded and was built on the wrong

premises. All his nonthermal effects were hypothetic. Since the 1920s till now, nonthermal effects were found in RF range (<300 MHz) with peak frequency near 10 MHz whereas effect of microwaves is considered purely thermal. 434 MHz has not any special feature which makes it special. This was a "nonthermal belief" rejecting "ugly facts" which is no wit better than "thermal belief" described above.

Despite all the problems, nonthermal cancer applications develop. About 2010, some momentous events had happened. In 2009, it had been first time objectively displayed in oncothermia in vivo study [315] that, under the mask of hyperthermia range 42°C heating, the temperature was responsible only for 25% of general cell-destructive effect while 75% of cell deaths were caused by nonthermal (not temperature-dependent) effects. In 2011, the nonthermal TTF technology had received FDA approval for treatment of brain tumors in combination with chemotherapy [85]. Thus, the nonthermal device for less than two years had received the approval for deep-seated tumors treatment of which the leading US hyperthermia manufacturers cannot receive since 2000. In 2012, the oncothermia device had been installed for clinical trials in Prince of Wales Hospital, Australia. Australia is a "free of hyperthermia zone" since the case of Dr. Holt. It is very symbolic that it is oncothermia, the technology based on nonthermal effects, which run the blockade.

These are nonthermal effects which are the front line of development of physical factors application in cancer treatment now, whereas thermal concept had exhausted far ago and has been stagnating since the early 90s. Despite the fact that thermal concept remains the only officially recognized [298], and it is still early to resume the triumph of the nonthermal approach, since the 2000s hyperthermia had finally gone from the front line of research in oncology, and in fact it has lost its positions in practical application.

Sure, it is still early to say about the nonthermal breakthrough in cancer treatment. Though TTF technology is already FDA approved, its III phase clinical results are far not so favorable as it was awaited. Although oncothermia is currently the hyperthermia world leader with more than 250 devices installed, it is impossible to resume its final success prior to obtaining III phase trials results because there was the same "success" with other hyperthermia technologies before III phase trials. Anyway, we will receive the answers in the nearest future.

7. The True History of Hyperthermia

The initial hyperthermia concept of 60s was simple and straightforward. It was totally based on the known imperfection of tumor bloodflow: hypovascularization makes tumor a "heat trap" and allows to overheat it more than surrounding tissues in view of their cooling with thermoenhanced bloodflow; heating over 43-44°C causes tumor death though its exact mechanism is unknown [96–98]. Toxicity of this heating approach was well realized, and Crile directly wrote that hyperthermia could be used only in case of radioresistant tumors.

Everything had changed in the mid-60s after Manfred von Ardenne had come into the topic. He had loudly announced "the discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia" and had run the global "hyperthermic race." This was the main error of the initial hyperthermia concept: the huge overestimation of heat-resistance of healthy tissues and contemporary underestimation of the heatresistance of malignant tissues. This error came from laboratory and was entirely based on results of early experiments with cell cultures which were fallacious because of the bad understanding of very different properties and behavior of cell cultures and real tissues. The loss of malignancy of cultured malignant cells and, vice versa, the malignant-like behavior of cultured healthy cells and the loss of viability are only small part of these problems [224]. Though von Ardenne itself had changed his mind very soon, which was reflected in the feverish search of hyperthermia enhancers, this change of mind was not announced and the initial slogan was not cancelled. It had been already accepted as the basement of the new "hyperthermia belief".

Hyperthermia was more belief than a science from just the beginning. Von Ardenne acted as a messiah, a mysterious "top European scientist" for USA and Japan, not less mysterious "Soviet scientist" for Western Europe, and even more mysterious "secret German nuclear physicist" for USSR, and his words were the revelation. There was a real impression that hyperthermia is that thread, pulling which the cancer knot could be unleashed, and the magic wunderkind and great physicist had specified the true path at last. Any reasonable skepticism was rejected, any supportive data were accepted with delight and without any criticism. Even now, when this belief is already bereft of any ground, it has not changed in principle.

Sure, it was not von Ardenne who started hyperthermia. Hyperthermia had started long before his coming and had been developing gradually and very cautiously. Von Ardenne also was not a believer. He was a real scientist who trust only facts, but he was in a great extent a "scientific showman," who produced new ideas and technical solutions with lightning speed, absolutized raw results, and easily changed his mind without any excuse. He was a genius physicist in the inert medicine, another consciousness, another "phase state." When the facts had changed soon, von Ardenne just followed them, and in fact he had left the hyperthermia field almost just after he had entered it because his systemic cancer multistep therapy (sCMT) is not a hyperthermia. But "hyperthermic belief" already did not need him: it had become all sufficient.

Von Ardenne was just a strong catalyser who had almost turned a modest marginal direction in the scientific mainstream. Why "almost"? Because hyperthermia was initially based on wrong premises, and a short enough time was given from the first excitation to understanding and cooling: 30 years from 1966 to 1996.

Science was opposite to "hyperthermic madness" from just a beginning. Many scientists initially concerned the higher thermal resistance of healthy cells in vitro [359–361]; the wave of belief had just swallowed these single opinions. In Seegenschmiedt et al. monograph [261] of 1996, these "marginal" opinions were referred to as an unfortunate necessity and curiosity. Already in 1967, Burger et al. had

shown that healthy tissues in vivo are damaged already over 41°C [222, 223]; this quiet voice from the far-away South Africa had been disregarded. Currently dominant position is simple and unequivocal: there is virtually no difference in thermosensitivity of healthy and malignant cells in vitro [288]. This gets an understanding of the question of the therapeutic range of hyperthermia: does it exist at all? There are some theoretical considerations supposing that it could be even negative.

It is well known that the direct cell-damaging effect of hyperthermia is connected with protein denaturation. Slight functional and reversible denaturation of proteins mainly connected with change of the tertiary structure of proteins starts already above 41°C, which is a physiological limit of body temperature; it becomes significant over 43–45°C [362, 363]. It is also well known that the main mechanism of the restore of damaged tertiary structure of proteins is intracellular chaperons, namely, heat-shock proteins (HSP) [364], and that malignant cells express much higher levels of HSPs than normal ones [365]. Therefore, the malignant cells are better protected from the moderate heat-stress then normal cells, and single papers report that normal cells are less resistant to moderate heating than malignant cells. Moreover, 2-3-day and more intervals between HT sessions allow to restore the initial level of thermal sensitivity of normal tissues because their thermal induced resistance reverses in 72 hours. It should be mentioned also that tumor cells thermoresistance and vascular thermoresistance of tumor tissues lasts an order of magnitude longer than that of normal cells. This fact good enough explains many results when HT courses with more sessions were less effective than shorter ones. Over 43°C, tumor bloodflow cut off becomes the main factor of the tumor damage, but at the same time the direct thermal damage of healthy tissues grows. The acute toxicity of whole-body hyperthermia over 42°C clearly shows what happens when the temperature of healthy tissues exceeds 42°C. It is also well-known now that selectivity of tumor heating usually does not exceed 1°C [214]. Therefore, there is a small range between 42°C and 43°C, where malignant cells theoretically could be damaged in more extent than the surrounding healthy tissues. This is a very narrow and critically instable therapeutic region which works correctly only provided that tumor is heated homogenously. Unfortunately, tumors are mainly heated up very unequally: the reported difference of temperatures within a tumor exceeds 2°C [214]. The situation is compounded with the fact that those "low-heat" areas are those well-perfused and effectively enough cooled by bloodflow regions of tumor where active and proliferating malignant cells are located, which therefore could survive. At last, taking into account that real effect of extreme hyperthermia starts from 43°C, at which the temperature of the surrounding tissues reaches critical level of 42°C; the therapeutic range disappears at all.

The simple conclusion follows: extreme hyperthermia could be either effective but toxic or not toxic but ineffective. Though being suggested already since mid-80s, the definite conclusion on negative therapeutic range of the extreme hyperthermia was made for the first time only in 1991: it was displayed that thermoenhancement rates (TERs) of toxicity of some chemotherapies at WBH outweight the TER of their efficacy [366]. It took one more 14 years before this had led to the change in hyperthermia rationale [283] though the fact itself has still not accepted by hyperthermic community.

In the 70s, the new "basement error" of hyperthermia had been developed: the illusion of "virtually endless selectivity of extreme heating" had been created predominantly by Storm et al. [367] works. Unbelievable 8–10°C difference between normal and tumor tissues had been reported. It is hard to say now, was it a thermometry mistake or something else, it does not' matter. It is important that, together with dogma of "endless selectivity of thermal resistance," this already looked like nearly a "final solution" in cancer treatment.

Now the real hyperthermia race had started. At the turn of 70s and 80s, new hyperthermia machines were springing up like mushrooms overnight. Almost every big US university medical center had its hyperthermia group and many of them offered their own technical solutions. Those who had not a machine, heated with any suitable warmer [368, 369]. Near 1980, US National Cancer Institute (NCI) had launched a contract for evaluation of hyperthermia equipment trying to control this boiling activity and supporting hyperthermia development at the same time. Simultaneously, multiple clinical trials had started.

The first wake-up calls had sounded in late-80s when institutional reports on NCI contract had been reported. Heating is not enough, toxicity is limiting, 43°C in unreachable in view of toxicity—this was a resume of Stanford report [216]. Impossibility of extreme temperatures questioned the entire concept of the extreme hyperthermia. "Thermal dose" concept [370] had been offered in advance. Thermal dose, designed to replace the rapidly losing its value temperature, which is in fact just a "dose of temperatures," was an artificial construction based on an extrapolation of in vitro Arrhenius relationship of heat damage onto living tissues. To that date it looked grounded because difference in gain rate over and under 42°C was known since 60s. To the moment, futility of this parameter is obvious [293].

Though hyperthermia problems had been already obvious to the most advanced users and scientists [221], it still looked very strong before 1990. The extreme hyperthermia concept had been finally furnished after explanation of tumor bloodflow [284]: heating over 42.5°C causes "cut-off" of tumor bloodflow with subsequent hypoxia, acidosis and following necrosis of tumor tissue. Hyperthermic activity had reached its maximum: the record number of 8 monographs and 350 papers had been published in 1990. Ten big randomized III phase "trials for recognition" sponsored by RTOG and leading US universities had been launched. Hyperthermia triumph was almost in hands, but it had not happened.

Instead of the triumph, the huge disappointment awaited the hyperthermic community: all the trials [233–236, 240] had failed to show hyperthermia benefit. Nothing had been confirmed: thermal parameters mainly did not correlate with the endpoints, heating was not enough in frame of the extreme HT concept, toxicity was too high, and a number of sessions did not influence the effect. The result of the 25-year boiling activity was nothing. Hyperthermia has not ever

recovered from this blow. This was a beginning of the dawn of hyperthermia.

Though, the dawn promised to be long becuse the great inertia continued to push hyperthermia ahead. A number of international and national hyperthermic societies with thousands of members, some big research world clusters with hundreds of hyperthermic opinion leaders, the specialized international hyperthermia journal and the industry behind this structure could not fall in a day. And—maybe the most significant factor—hyperthermia had been already included in advance in the base manuals on radiotherapy. As the time has shown, maybe this was the strongest factor of its survival.

First of all, conclusions on the negative trials were unexpectedly mild. Despite all the trials were equivocally negative, there was no cardinal resume. Whereas the earlier Stanford institutional report conclusion was simple and clear, these conclusions had left hyperthermia alive. Though it was already obvious that the core problem is the narrow (absent) therapeutic range and this is a problem of the method per se, all the conclusions referred only to the technical problems of heating and heating control, remaining for the industry a possibility to recover them. Then, RTOG had attempted to recover the situation and had launched the new deep hyperthermia trial [241] with "second generation" equipment before the first negative trial [240] had been published. These phase I/II trial results were negative again, and RTOG had left the topic forever.

This was the turnover point. After independent sponsors—RTOG and big universities—had finally left hyperthermia trials in 1996, and hyperthermic societies had taken the trials in their hands, the trend had momentarily turned out. Since that moment, all the trials had been becoming positive. Conspirology of this turnover is not the topic of this essay but the basic moments should be called. Due to EBM, it is well known now that industry-sponsored clinical trials are often biased and have 5–20 times more probability of positive result. Interrelations of the hyperthermic societies with hyperthermic equipment manufacturers are "open secret"; it is enough just to visit ESHO website. Even without respect to these interrelations, both industry and hyperthermic societies at that time were united with the common aim—survival—though they had had common interests. Our earlier critical analysis displays that all the hyperthermia-sponsored trials since 1996 were heavily biased [1], and their results were either dubious or clinically insignificant.

First, International Collaboration Hyperthermia Group (ICHG) had merged the resting five just-launched randomized trials, at least 3 of those obviously moved to the negative result. Surprisingly, in 1996 a "very positive" trial had been published from this merge [237]. Though 3 of 5 arms remained negative [1], this fact even had not got the abstract. Simultaneously published "positive" Overgaard et al. trial [238] was clinically insignificant [1] in view of inadequate control. Surprisingly, the fundamental Seegemschmiedt et al. monograph [261] was published in 1996 "like nothing happened."

Understatement of the negative results is a common problem, which forms the "positive bias" of the entire modern medicine: because nobody is interested in negative results, they are poorly published and quoted. Often, negative trials are even not published. The published negative papers are usually brief and of lower quality. They are never reprinted and very rarely commented. Contrarily, the positive trials are usually often quoted and referred to, they are reprinted and commented and discussed in letters and editorials. As a result, looking from the pages of medical journals, the medicine per se looks much more successful than it is really. Concerning hyperthermia, this "conspiracy of silence" is elevated to the rule: if problem is not mentioned, it is absent.

1996 was the turnover year in one more meaning: this was the last year of scientific hyperthermia. As it is clear from the above, before the 90s, the hyperthermia was a scientific hypothesis, albeit with a touch of belief, though it is quite usual for a nice and promising hypothesis. In the 90s, the usual "great tragedy of Science" happened: the slaying of a beautiful hypothesis by an ugly fact. In the frame of scientific paradigm, there were two further options only: either to explain the facts and change the hypothesis accordingly for the new testing or to withdraw it. In 1996, hyperthermia had chosen the third way: ugly facts were just declared inadequate, disregarded, and understated. Nothing had changed in the hypothesis per se; the methods of obtaining proofs had been changed instead of it. Among many biases described by EBM, almost all were used in these hyperthermia-sponsored trials: inadequate comparator, defects of randomization, preselection of patients, selective data reporting, incorrect analysis, selective data publication, systematic bias, and so forth [1]. This already was not a scientific approach. Without continuous correction to distortions (ugly facts), any hypothesis becomes a subject for unguided process of errors accumulation, and finally turns into pseudoscience. Ignorance or distortion of facts, which are known to the authors but contradict to their concepts; refusal of attempt to compare theoretical concepts with real results when it is possible; use, in the basement of theory, of incorrect data, not proved statements or erroneous data—all these signatures of pseudoscience were more and more obvious in hyperthermia since 1996.

The next ten years from 1996 to 2005 were a decade of the gradual and cautious hyperthermia revanche. Only 3 randomized clinical trials on external electromagnetic hyperthermia had been held during this decade [239, 264, 267]. All of them were sponsored by hyperthermic societies and all were considered positive. In fact, all the results once again were dubious and/or clinically insignificant [1]. Anyway, accumulation of such "positive" results allowed meta-analyses [273, 285, 371], the first step to evidence, but these meta-analyses had inevitable and obvious weak place: there were a number of negative trials without any explanation. It is not enough just to say "Nine randomized studies failed to show a significant benefit from addition of hyperthermia" [273]—this should be explained. Anyway, even such weak evidence had allowed hyperthermia to reach some acceptance: it was once mentioned in NCCN guidelines in US and had been agreed upon for advanced cervix cancer treatment in Dutch.

On the other side of Pacific Ocean everything went well. Thermotron had obtained an acceptance in Japan without III phase trials. Government supported it with grants, and the treatments were covered with insurance. After US hyperthermia had failed in 1996, Japan became a real world leader with more than 200 hyperthermia units installed. As a result, world Kadota consensus meeting in 2004 was held in Japan. This was the highest point of hyperthermia rise after the catastrophe of the 90s. Though the consensus [273] claimed for low acceptance, lack of money and equipment, and low acquaintance of physicians with "possibilities of hyperthermia," the future once again looked promising: fails of the 90s had been nearly forgotten and new trials were accepted; Japan looked as a bright example.

As usual, a fly in the ointment did not hesitate to appear. In 2004, the grand failure of the first and the only randomized trial on whole-body hyperthermia had happened: the result in hyperthermia arm was twice worse than in chemotherapy control [269]. It could be a burst but everything had been done to blow off steam without explosion. These preliminary results had been reported only once orally at ASCO meeting. It was promised to continue the trial, but though it was sponsored by International Systemic Hyperthermic Oncological Workgroup, the result was so strikingly negative that there was no any possibility to correct it. The trial had been terminated. Noone paper was published on the result, and this result was never commented or referred to. ISHOW had dissolved silently. The result should be erased by understatement.

Nobody had expected that it is Japan where the next powerful blow will come from soon. New ugly facts had come in 2005 from the old trouble-maker—independent trials. In the late 90s, two big randomized clinical international multicenter trials [281, 282] had been launched under the sponsorship of International Agency of Atomic Energy (IAAE). Both had appeared negative. The longest day has an end.

Fail of Vasanthan et al. cervix cancer trial [273] published in 2005 was the most painful. First, the highest temperature was reached in this trial, but results in HT group were worse than those in RT control, and it was impossible to explain it. Second, the design of the trial was close to two previous "positive" trials [264, 267] which had been already included in the "golden database" of HT evidence. Therefore, these evidences were becoming questionable. It is not surprising therefore, that hyperthermic opinion leaders had rushed to explain why their trials were successful whereas Vasanthan trial failed, but it was inconclusive [372]. Third, all the old "sins" of hyperthermia had been remembered.

This ugly fact was impossible to ignore any more. The situation demanded urgent actions, and in 2005 hyperthermic opinion leaders had announced the "resetting of hyperthermia rationale" [283] at last: extreme hyperthermia is impossible—moderate (mild) hyperthermia (MHT) based on the thermal dose calculation had been announced the actual concept.

The name of the event is demonstrative itself. Not "reassessment", not "correction"—it was a remarkable attempt of exactly the "resetting": to cancel everything happened before with one action and start from zero without any burden of the former sins. And this is principal, without necessity to change anything: the same equipment and the same procedures, just the lower temperature. Taking into account that "hyperthermic temperatures" were in fact moderate already for more than decade (and in some meaning from just the beginning [373]), this was just a legitimization of the de facto state of the art with simultaneous trial to disown all the old fails and sins. It was a genius action in all respects. History shows that a new technology has got at least 20–30 years from the hypothesis to disappointment or acceptance. With this reset, hyperthermia whose time was up was soundly considered for one more 20–30 years of existence in its "mild" version. The desperate attempts of hyperthermic establishment to keep hyperthermia safe would deserve respect if these are scientific actions. Unfortunately, it looked rather like an attempt to save hyperthermia by any means.

Anyway, the maneuver was successful. Revival of hyperthermia was visible, sometimes rapturous [291]. New rationale looked obvious and visible. The number of publications had been rising. Publication of the second negative IAAE trial [282] in 2007 already did not hurt hyperthermia too much—it looked like "greetings from the past."

Unfortunately, this once again was only a temporary relief. The reset was fallacious and ineffective. First of all, though hyperthermia had refused old extreme concept as ineffective, its "golden database" included only "positive" data received in the frame of the old and ineffective extreme concept [296]. New evidence were slow to emerge. It was an obvious contradiction. Second, it had been shown many times that thermal parameters are not connected with endpoints in any way and thermal dose is of lowest significance. Next, nothing had changed in the hyperthermia practice. In Erasmus Medical center nothing had been changing since 1985, and hyperthermia remained extreme [169]—they just had not noticed any "resetting" of the rationale. Manufacturers still recommend to heat tumors from 40°C to 45°C [374]. Was it a "tactical" reset without real changes, a real "maneuver"?

But the main problem of the "resetting" was that the new hyperthermia concept was built on dubious premises and once again seemed to be fallacious. It was totally based on Song team works [284, 292, 375, 376] which reported "abundant evidence" that MHT (39–42°C) leads to significant enhancement of tumor bloodflow and long-lasting (1-2 days), sustained enhancement of tumor oxygenation [375]. According to Song team, this rise of oxygenation at MHT was stronger than at extreme HT (16 mmHg versus 12 mmHg [284]), and MHT was the more potent radiosensitizer than carbogen breathing and nicotinamide [375], and this effect is a stable platform for using MHT as general-purpose radio- and chemosensitizer [376]. This was a discovery of one more magic "almost endless" effect of hyperthermia and once more it seemed to be fallacious.

First, the effect of the significant, sustained, and long-lasting improvement of tumor oxygenation by MHT had been revealed only by Song laboratory and was not supported by other groups, which have not revealed a sustained increase

of both tumor bloodflow and oxygenation after MHT [289, 377]. According to Vaupel and Kelleher, the real effect of MHT on tumor bloodflow and oxygenation is limited and transient and cannot be used for radiosensitization. These are contrary points of view. Second, Song's effect is very controversial because in fact the "better oxygenation without better perfusion" concept was declared without any satisfactory explanation of the effect. The offered explanation [376] is extremely weak and is entirely built on wrong premises and unwarranted suggestions. Understanding of tumor physiology could help in explaining these controversies.

Special features of the tumor vasculature are well known. Tumor vessels are partly a normal host vessels included in the tumor structure and partly the newly developed tumor vessels. The normal vessels dominate in the smallest tumors and became rare as tumor grows; they have a normal structure with dense endothelium, basal membrane, and muscular layer. In the dominating newly developed vessels, there is an endothelium-like lining without dense contacts and with gaps between cells, and there is no basal membrane (at least constant one) and a muscular layer. As a result, the newly developed vessels are highly permeable, and there is 5–10% of plasma loss during every passage of blood through a tumor [378]. Sometimes, the vascular wall is absent and blood lacunas are formed adjacent to the vessels. In general, the tumor bloodflow is described as "unclosed." As a result, the enhanced interstitial pressure [379], which rises as tumor grows [380], is the obvious feature of a tumor. Alongside with the enhanced vascular permeability, the lack of adequate drainage, tumor growth, and hypoxic swelling of cells are the reasons of the tumor interstitial pressure growth. Because normal lymphatic vessels located at tumor borders are the main collectors of tumor interstitial fluid, this fluid is delivered from inner areas of tumor by convective flow. In view of inhomogeneity of tumor interstitial matrix formed by alternation of "liquid" and "gelatinous" areas, this flow exists in the form of sustained "currents." Phenomenon of different calibers of tumor vessels is wide spread: newly developed thing vessel often precedes a much larger "normal" vessel, thus limiting its bloodflow. Tumor capillaries are twisted, atonic, and enlarged in diameter and highly permeable. In tumor, virtually there is no reserve capillaries: all of them are always open and perfused. There is a number of shunting vessels (which are not metarterioles in a usual meaning) responsible for shunting of the major part of tumor bloodflow bypassing capillaries [381]. The tumor shunting capacity could be so great that causes refractory hypoxemia at lung tumors in view of great intrapulmonary shunting [382, 383]. Finally, the absence of the muscular layer makes impossible the usual regulation of bloodflow by vasoconstriction and vasodilatation. Bypass shunting is the main type of regulation of the tumor bloodflow. The major part of tumor vessels and capillaries is always dilated and atonic [382].

Let us hypothesize what happens in a tumor during mild hyperthermia. Tumor has not its own inflow and outflow vessels and is fed by the bloodflow of the surrounding tissues. Taking into account the smallest ability of tumors for muscular regulation (see above), the changes of tumor perfusion are just a reflection of the changes of surrounding tissues perfusion, which grows exponentially as the temperature rises. But vasodilatation of tumor vessels is negligible; therefore, the main mechanism of perfusion enhancement is the rise of blood velocity. First, this speed up is limited by development of vascular turbulence and the subsequent rise of resistance, from the one side, and by different calibers of tumor vessels with number of bottlenecks in the network, from another side. The turbulence could block microvessels both functionally and physically (sludge). As a result, the major part of the enhanced bloodflow is just shunted through the tumor shunting vessels. Second, the speedup of capillary bloodflow deteriorates the capillary gas exchange. In normal capillaries, erythrocytes are in close contact with a capillary wall for some time. This contact is necessary for an effective gas exchange. In the enlarged tumor capillaries, there is no close contact of erythrocytes with capillary walls which leads to significant decrease of gas exchange efficiency and is the major reason of tumor hypoxia. Slower tumor capillary bloodflow and prolonged time of the passage are a relative compensation of the defect. The speedup of capillary bloodflow significantly worsens the situation: due to the limited time of passage, the gas exchange is limited, and functional shunting [384] develops alongside with the abovementioned anatomic shunting, looking like "arterialization" of tumor blood-flow. Turbulent sludge of blood cells could block capillaries at all. As a result, bidirectional changes of tumor microcirculation at MHT could both improve tissue oxygenation or have no changes or deteriorate hypoxia. Also, it could be supposed that perfusion and oxygenation at MHT significantly rise in the initially well-vasculated regions and clusters, whereas, in the previously hypoxic and hypoperfused badly vasculated regions and clusters, the bloodflow does not rise or even decrease. At the same time, oxygen mass transfer will always and significantly rise, and this is registered by "macro photo" with the existed oxygen tension measurement methods. The size of polarographic microcell of usual oxygen-measuring electrode is 300 micrometers, and it averages oxygen tension in adjacent area near $1\,mm^3$. This is a too big scale to register real microcirculation changes, but it is enough to measure oxygen mass transfer. Additionally, the rise of tumor perfusion at MHT will inevitably lead to enhancement of intratumoral pressure, strengthening of interstitial currents and rise of probability of lymphogenous dissemination.

Fortunately, there is an excellent paper for Sun et al. [290] from Memorial Sloan-Kettering Cancer Center clarifying the problem. Immunohistochemistry staining with hypoxia markers allowed to receive a "micro photo" of tissue hypoxia status and has confirmed all the above suggestions. It is obvious that changes of tumor microcirculation are multidirectional from just the beginning of heating: some microvessels functions and hypoxia decreases, some of them functions with no changes in hypoxia status, and some are blocked with deterioration of hypoxia. The average result looks like some improvement of hypoxia status during moderate heating, but this improvement mainly ceased in 1 hr after treatment. The most interesting is that it seems that 24 hrs after treatment the tissue hypoxia becomes heavier than it was before the treatment.

This could be the only rationale of Song et al. phenomenon of "long-term better oxygenation after MHT." If microcirculation status of tumor becomes worse after MHT; that is, if many capillaries and vessels are blocked and shunting proportion rises, then oxygen mass transfer rises in view of diminishment of tumor oxygen uptake. With a "macro photo," it will be detected like "better tumor oxygenation," and the better this "oxygenation" looks, the worse the real hypoxia status of the tumor. It seems therefore that "long-term better oxygenation after MHT" reported by Song et al. actually could be "a long-term worsening of tumor hypoxia after MHT," that is, the absolutely contrary effect.

This makes the suggested oxygen-dependent radiosensitization effect of MHT dubious. Better oxygenation of previously well-oxygenized areas does not lead to the enhancement of radiosensitivity, whereas aggravation of hypoxia significantly reduces it. Shunting oxygen is useless for radiosensitization. This also refers to chemopotentiation effect: if microcirculation is worsen by MHT, delivery of drug will be less effective though total drug clearance through the tumor will rise for the account of bypassing, making an impression of the better treatment [381].

Therefore, it seems that the moderate hyperthermia concept of Song and his followers is incorrect. The hyperthermia state-of-the-art could be formulated as follows: hyperthermia always causes enhancement of perfusion during the session (1 phase) and worsening of microcirculation afterwards (2 phase); the amplitudes of the both phases effects are proportional to the heating temperature, at least up to 44°C [289]. In this meaning, extreme HT is always more effective than MHT. Radiosensitizing effect of MHT, if exists, is caused rather by the usual hyperthermic destroy of the tumor microcirculation than by the effect of tumor reoxygenation.

For seven years since the resetting, there is no any evidence of MHT efficacy. Surprisingly, in the later work [292] Song et al. once again operate with the extreme 42.5°C heating though calling it a "mild hyperthermia." This is the logical end of the resetting: just change of the name and replacement of the explanation without any change in practice and procedure. What is the most impressive in this resetting: the self-consistent and well-grounded rationale of the extreme hyperthermia was replaced with inconsistent and controversial MHT rationale. This is the essence of mid-2000s "resetting maneuver": impossibility of extreme HT and the lack of results caused an attempt to "face lift" by virtue of the artificial MHT concept; bankruptcy of the face lift caused hidden return to the initial extreme concept under the mask of MHT; the result is an impression of hyperthermia renovation without any real changes.

"The second coming" of the extreme hyperthermia does not inspire any optimism. This is the one more consequence of the former inconclusive decisions concerning hyperthermia. Because until now the extreme hyperthermia (>42.5°C) was never reached, it could be still hypothesized that if it would be possible to reach technically, it would be effective. This was an implied conclusion of the negative trials of the 90s.

The results of experiments on combination of whole-body and local heating (WBH + LH) deny this opinion. It was obviously shown in the 90s that this combination really provided much better heating up to 42.9°C versus 41.3–41.7°C at WBH and 39.9°C at LH ($P = 0.0012$), and WBH + LH heating was much more uniform [385]. Thermal dose of CEM 43° T_{90} in combination group was 12 times higher than in local HT group (49 min versus 4 min) [386]. Unexpectedly, this near to ideal heating led to much-worse experimental results at dog sarcomas than LH only: time of local control did not differ ($P = 0.59$) but metastases developed sooner ($P = 0.02$), and probability of metastases development was 2.4 times higher in the WBH + LH group at higher toxicity [386]. These data contradict thermal dose concept and thermal concept of HT at all and suggest that the extreme hyperthermia could be a miracle even if it is technically possible. Some other results support this point of view: particularly, Hiraoka et al. reported that clinical effect at <43°C heating is better than that at >43°C [215], von Ardenne had soon refused his Selectotherm WBH + LH concept, and similar Pomp-Siemens machine was clinically insuccessful. The most likely reason is that, at temperatures over 42°C, toxicity of HT significantly outweighs its benefits.

As it was discussed in detail above, Issels et al.'s tremendous STS trial [251] had led to fiasco [1]. Despite the official "positive" result of the trial, the huge systematic bias in view of the doubled treatment power in HT-arm versus control arm and poor clinical results cause the question: whether hyperthermia worsened the clinical results?

Resuming, currently we see hyperthermia bereft of acceptance, rationale, and evidences. It is the time to terminate this prolonged experiment.

At the same time, the history of electromagnetic therapy in oncology is only at its beginning. Recognition of inconsistency of thermal dogma would release significant forces and funds which are now being spent for support of agonizing hyperthermia and would remove the intentional block created by this dogma. New methods of electromagnetic treatment, some of which already exist and some are in development, will replace hyperthermia, and, probably, we will see the "fourth basic method of cancer treatment" at last. Possibly, it will be associated with hyperthermia-range heating, but let it do not deceive you: the "temperature hyperthermia" is over.

Conflict of Interests

The author is General Consultant of OncoTherm Group in Russia and CIS countries and Director of National Medical Corporation Inc. which sells oncothermia equipment and, therefore, has a direct financial relation with OncoTherm Group.

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