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Where, when and why hyperthermia went wrong way?

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'Those who cannot remember the past are condemned to repeat it'.

Geroge Santayana, 'Life of Reason I'

'The great tragedy of Science – the slaying of a beautiful hypothesis by an ugly fact.'

Thomas Henry Huxley

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Abstract

'Hyperthermia is generally regarded as an experimental treatment with no realistic future in clinical cancer therapy' – Horsman and Overgaard said in 2007, though, trying to combat this statement. It's difficult to find another method in medicine which remains experimental after 40 years of research and application. Hyperthermic community usually claims to technical problems of heating and heating control to justify this failure. To our mind, the problem is the 'temperature concept' of hyperthermia. Electromagnetic hyperthermia was finally derived from electromagnetic therapy near 1935, after 30-year fight between thermal and non-thermal concepts of electromagnetic fields application. It was based on a belief that only thermal effect has value, and temperature is the only parameter of efficacy (thermal/temperature dogma). Non-thermal (temperature independent) effects were denied. Initial concept of extreme hyperthermia of 1970th was based on the wrong premise of higher thermal susceptibility of malignant cells. Therefore, it was believed that hyperthermia has a broad therapeutic range which allows to kill tumor cells by above-threshold (>43°C) temperature without damage of healthy tissues. Proofs of inadequacy of this concept were received already in 1980th when it become obvious that really this therapeutic gap is minor or absent, which makes the extreme hyperthermia impossible. To correct it, the concept of 'thermal dose' was introduced. This was based on ungrounded extrapolation of biochemical Arrhenius equation onto living matter. Series of randomized clinical trials of early 90s showed inefficacy of the extreme hyperthermia and called into question the thermal dose concept, but the latter was ignored. Instead of the extreme hyperthermia, the concept of moderate hyperthermia based on the same thermal dose concept was introduced in 2000s: it was believed that moderate hyperthermia could enhance tumor perfusion and subsequently enhances radio- and chemo-efficacy. Though it's declared that this approach was fruitful and its effect was confirmed in randomized clinical trials, it's not correct. The careful analysis of these trials has shown multiple biases. After correction to the distortions, the efficacy of the moderate hyperthermia is not confirmed. Ignorance of the special features of tumor bloodflow was the reason of this failure. Therefore, there are some points when and where hyperthermia had gone the wrong way: 1) 1930s when temperature was equated to thermal energy and non-thermal (temperatureindependent) effects were denied; 2) 1960s when greater thermal sensitivity of tumor cells was incorrectly postulated; 3) 1980s when incorrect 'thermal dose' concept was introduced; 4) 1990th when obvious proofs of inconsistency of temperature concept were ignored; 5) 2000s when moderate hyperthermia concept was introduced. As a result, during the last 20 years, the 'temperature' hyperthermia is in stalemate. Since 1970s, growing evidence of non-thermal effects and their broad application in different fields (dielectrophoresis, bioelectric effect, electroporation, galvanotherapy, etc.) caused a development of some non-thermal field cancer treatment techniques. Hyperthermia concept should be cardinally re-evaluated now with respect to obvious bankruptcy of the temperature concept and development of non-thermal concept.

Introduction

The treatment of an alcoholic begins from the recognition of the problem. 'I'm John, I'm alcoholic' – this is a start of 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 can't 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 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 a 'the last hope therapy' with many controversies is a demonstrative result of this development.

Such a pity situation necessarily should have objective reasons. It's not enough to claim for lack of money, competition with radiology and chemotherapy and so on. Our recent analysis of hyperthermia randomized trials1 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 the 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 an 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 an almost exclusively electromagnetic treatment, we should trace the development of both hyperthermia and electromagnetic treatment to understand the state-of-the-art.

Hyperthermia and electromagnetic therapy before 1950: early stage, radiofrequences and formation of 'thermal dogma'

Hyperthermia before 1950: early stage

History of oncological hyperthermia is originated from some evidences of cancer cure by concomitant febrile diseases described in XVIII-XIX centuries. It seems that 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 with a subsequent 2-year disease-free survival. He then used intentional contact with erysipelas infection to treat several patients. Apparently, in the second half of XIX century practice of infectious febrile therapy was quite common, and not only in Germany and France, but even 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 began to emerge at the end of the XIX century, and associated with 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 who have had erysipelas with high fever; in 12 of them, tumors had disappeared, and 19 displayed an improvement; in 2 of 10 patients with locally advanced sarcomas treated by Coley, complete remission 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, at the end of the XIX century, 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 mechanism caused the belief that the results must necessarily follow, and the only problem is an improvement of the method. Because of 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 mechanisms of action of febrile therapy and thermotherapy at all started only at 40-50th of XX century, when fundamental papers on thermal damage of Moritz et al.[11,12,13] were published and, on the other hand, building of the scientific foundation of immunology 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 in 172 resectable - 61%[14]. In another example, 25 of 30 patients with advanced cancer showed 10- year disease-free survival[15]. It would seem, there was a good situation for revival of the method, but the position of AMA and ACS had not changed. Very soon, 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 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 F Westermark[18] published a report on use of long-term (48 hours) local (by virtue of intravaginal metal coil heated with circulated water to 42-44°C) and regional hyperthermia (hot tubs) for treatment of various gynecological diseases.
He described several excellent results in inoperable cancer of the cervix. He was the first who had shown the ability of long-term heating to destroy tumors without damaging of healthy tissues.
Gottschalk[19] in 1899 confirmed the success of hyperthermia in cervical cancer and suggested the use of higher temperatures and reduced exposure time. In 1910, Doyen[20] reported on the successful treatment of a number of cancers by heating to high temperatures (55°C). Percy[21] in 1916 reported a 3-7-year survival in 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 remission and found fever, heating or severe infections in 72 cases out of 166. In 1932, Goetze[24] reported about the effectiveness of a 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 in hopeless cancer: by combining radiotherapy with different types of long-term induced fever, he had achieved considerable effect in 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 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. In 1903, Loeb has shown that fragments of rat sarcoma treated at 45°C for 30 min didn't grafted. Jensen received similar results in mouse tumors treated at 47°C for 5 min. It seems, 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 about 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 N Westermark initiated experimental study of hyperthermia on rats.[35]

	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]	1927	Rats	Flexner sarcoma Jensen sarcoma	Complete regression	Diathermia in vivo		44°C	45°C	
Johnson	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%)

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

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 a father of electromagnetic therapy[36,37,38] d'Arsonval itself 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[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 of 0.5-2 MHz and a current strength of 1-3 A[44,45]. Use of such diathermia for hyperthermia was limited by overheating of subcutaneous tissues. 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[46]. 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 to 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, vice-president of General Electric, 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[47], which soon led to 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 an external hyperthermia. Whitney Radiotherm was widespread in USA in 30th and it was used for treatment of many disorders[48], including cancer[49], with some impressive results. For 1935, more than 100 articles on hyperthermia were published[50], including the first comparative study of different methods of hyperthermia[51]. In 1937, Manhattan hosted the first international conference on hyperthermia[52].

Under this external cover, there was internal struggle between thermal and non-thermal concepts of electromagnetic therapy. d'Arsonval was the first who tried to show non-thermal effect on the bacteria and toxins, but the result was inconclusive. Tesla announced the lethal non-thermal effect of high-frequency field on Mycobacterium tuberculosis[53] d'Arsonval did not come to a conclusion on the mechanism of action of high frequency currents, but he was sure that it is not limited by heat, suggesting the influence on the chemical reactions[54]. Rise of diathermia as a pure 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 non-thermal concepts of electromagnetic treatment started.

Since 1920, after the start of radiofrequencies use, non-thermal effects of RF-heating were many times shown in vitro and in vivo by many researchers. Gosset et al. (France, 1924) exposed different plant cells with to 150 MHz RF-field and displayed cell death after initial growth acceleration; the effect was mainly or entirely non thermal dependent[55]. In 1926, an American surgeon Schereschewsky reported about lethal effect of 8.3-135 MHz RF-field (with maximum at 20-80 MHz) on mice without substantial heating[56]. He suggested a specific action of RF fields based of high-frequency vibrations. Having received a position in Harvard Medical School, Schereschewsky continued his research, and in 1928 reported on destruction of tumor grafts in mice, once again without substantial heating[57]. At 67 MHz, there was 23% of complete remission in HT group vs. 0% in the control group. Exposure to 135 MHz didn't show antitumor effect. Schereschewsky concluded that there is a special cell-destructive frequency range 20-80 MHz.

Schereschewsky papers caused a strong 'thermal' opposition. In 1927-1929, some program diathermia papers were published by Christie and Loomis from Rockfeller Foundation defending 'thermal purism'[58,59,60,61,62,63]. The main thesis was 'All those who claim to any other biological effects of high frequency currents, except of heat production, must prove it'64. From this time, this statement has become the official position of the western electromagnetic medicine.

A careful analysis of the Christie и Loomis paper[64] 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'[65]. 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 with increasing frequency is well-known. At the same time, the authors displayed that thermal production in NaCl solution didn't diminish but increased over 50 MHz in the same extent as the lethality dropped[66]; this fact hadn't 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 differences. 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 of calculation of averages, although the methods of correlation analysis were described in detail by Pearson in the early XX century[67] and were extensively used in 20th. The authors didn't try to reveal any trends though they were easily noticeable. E.g., in table I[68] the tendency of decreasing of lethal temperature with increasing current is traceable, and in graph 7[69] 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's obvious from just the tone of Christie works than he didn't admit the existence of nonthermal effect axiomatically, and was initially blinkered. Sure, Schereschewsky work[56] causes a lot of critisizm, first of all in terms of thermometry, but it was impossible to deny the existence of non-thermal effects on the base of very controversial and inconsistent trials of Christie and Loomis64. However, it happened. In 1933, Schereschewsky, being under a strong 'thermal' pressure, abandoned his 'unscientific' non-thermal point of view and recognized the thermal essence of his findings[70].

In 1930, US biologist McKinley reported a lethal non-thermal effect of RF-field on wasps71, and later – on growth of seedlings and nervous reactions of frogs72. 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. The same year, Szymanowsky and Hicks reported a non-thermal inactivation of diphtheria toxin by RF-field73 and then confirmed this result in 193274. In their last paper they resumed that though non-thermal effect of AEMF is obvious, its low intensity and hard traceability makes it insignificant in clinical research75.

In 1928, German physician Erwin 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 an RFexposure[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 non-thermal technology. Already in 1935 it was re-published 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' was discussed in preliminary report of physiotherapeutic council and it was stated that 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 30th, a confrontation between supporters of the thermal and non-thermal effects had become a political line. Non-thermal concept was supported in Nazi Germany. In 1933, Reiter who later became one of the most famous Nazi criminal physicians, reported the non-thermal 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 non-thermal effects of RF exposure. In the late 30th, 'non-thermal 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 30th, 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 was recognized as separate treatment modality, and some promising results were received with RF-heating; also, non-thermal effects of RF-heating was demonstrated many times, and first non-thermal 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 late 40th, after the war.
Thus, the period before 1950 was the early stage of both hyperthermia and electromagnetic treatment. Hyperthermia was mainly still not recognized as a separate method and existed predominantly in the form of febrile therapy, where thermal effect was a part of a complex body reaction. Its use was sporadic and totally enthusiastic. Despite of a general success of hyperthermia in late 30th, 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 showed; it was purely empirical and suffered from lack of theory. Despite of multiple evidences of non-thermal effects of alternating electric fields, 'thermal dogma' became the official position of the western science: it stated that heating is the only biologically significant effect of high-frequency electromagnetic field and denied any biological value, and even existence, of non-thermal effects. With this baggage of knowledge and technologies, hyperthermia entered the second half of XX century.

Hyperthermia and electromagnetic treatment in 1950-1985

Hyperthermia in 1950-1965: concentration

After 1950, the modern period of hyperthermia development as a separate treatment modality started. Period since 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. [83] 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. 84 used radiofrequency inductothermy for destruction of metastases in lymph nodes in vivo in dogs.

Development of chemotherapy creates new possibilities for hyperthermia. Because of high toxicity of first chemotherapeutics, they were administered initially mainly by regional perfusion. This was ideal design for heating use. Already in 1960 Woodhall et al85 from Duke University performed 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) during chemoperfusion of intestine by means of capacitive radio frequency systems (27.12 MHz), and found a much more significant accumulation of alkylating chemotherapies in the heated tissues than in unheated[86]. Rochlin received similar results on the limbs of dogs[87].

Selawry et al. in 1957 revealed the basic patterns of hyperthermic impact to cell lines heated with water bath in vitro: acceleration of cell growth under 39°C with a maximum at 38°C, then interruption of the mitotic cycle at metaphase in the range of 39-40°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 that survived after hyperthermia[88]. These findings laid in the basement of 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 able to enhance tumor growth, and considering temperatures over 40°C as safe in this regard, is not grounded because it doesn't consider the time factor. According to Selawry data, the above mentioned temperature ranges are actual for long-time heating only (some days) and not applicable for short-time minute-range of hyperthermia procedure. As Selawry showed, the rise of mitotic index in 12 hours was much higher at 41°C than at 38°C (10.4% vs. 4.2%) and dropped to zero at 41°C only in 24 hours. In 6 hours, mitotic stimulation was nearly equal in the range 38-41°C (3.7-4.1% vs. 2.3-2.8% at 36°C), and only temperatures above 42°C stopped entering a new cells in the mitotic cycle. Therefore, the entire range of hyperthermia (≤42°C) is potentially tumor grows stimulating 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 also reviewed all the existing data about thermoradiotherapy.[89]

The true foundation of modern oncological hyperthermia was laid by Crile in his remarkable series of in vivo experiments on mice in 60th [90,91,92]. It was Crile who already in 1962 reported all 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, 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 on Crile results. First, serious toxicity of the effective hyperthermia: in fact, rise of temperature over 42°C led to damage both of 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 44°C 30 min hyperthermia led to 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.

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 take shape. It marked by name of Manfred von Ardenn, who was a prominent German physicist acting in oncology. Von Ardenn example 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 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 happens in western world. Fourth, he was a CEO in his own research institute, and therefore had absolute freedom in 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's very interesting to examine which result was reached in these circumstances.

Von Ardenn started his activity in oncology in 1965 when he developed two-chamber hyperthermic bath with head cooling. Already in first experiments in vitro made in 1965 he confirmed selective thermosensitivity of tumors[93], and soon presented in Heidelberg university his concept of multistep cancer chemotherapy [94,95] based on combination of extreme hyperthermia and tumor acidification by DL-glyceraldehyde. It was 'the discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia' in 1966, [96] which started worldwide 'hyperthermic race'.

The general tone of the first von Ardenne works suggests that he initially thought hyperthermia independent, non-toxic and selective treatment of cancer, and, apparently, had Napoleonic plans of one-step solution of cancer treatment problems on the basis of hyperthermia. Meanwhile, it seems, already in 1967, von Ardenne stumbled upon the phenomenon of non-comparability of results in vitro and in vivo[97], and also faced a problem of lack of effect of hyperthermia, which was reflected in an active search of termosensibilizers. Many of them were tested between 1967 and 1969, including menadione, which effect was, in turn, strengthen by methylene blue[98]; aterbin[99], progesterone[100] and dimetilstilbestron[101], Tween 80[102], vitamin A103, dimethyl sulfoxide[103] and antibodies. Finally, von Ardenne tried to attack cancer by a cocktail of modifiers[102], including radiotherapy[104].

It seems that the idea of tumor acidification by virtue of hyperglycemia had arisen not earlier than in 1968[105]. It received full theoretical explanation as hyperglycemic modifications in 1969[106], although search for other acidifiers still continued in 1970[107]. At the same time von Ardenne has moved from extreme to moderate hyperthermia (40°C)[108]. We can only hypothesize that the only possible reason of such change is toxicity of extreme hyperthermia. Therefore, von Ardenne realized 'a moderate reload' 25 years earlier then the world hyperthermia did. The other possible reason was that he soon revealed that hyperglycemia is a stronger factor of tumor killing than hyperthermia, and became 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[109], and immediately reported the high effect[110].

In 1972, von Ardenne presented a complete concept of 'selective multiphase cancer therapy' (sCMT)[111], in which '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 as an auxiliary modality. Under the theory of von Ardenne, hyperglycemia induces 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 lead to their blockage and fall in blood flow through the tumor. At the same time, lowering pH to 6.5 and below leads to the destabilization of lysosomal membranes, and hyperthermia leads to the following release of lysosomal enzymes and autolysis of the tumor. However, the whole-body hyperthermia can also lead to increased metabolism of healthy tissue, 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 was replenished with the last component – the multi-step oxygen therapy[112] considered as multiplier of sCMT[113]. As a result, to the end of 1973 sCMT concept was completed as the combination of long-term, high hyperglycemia followed by moderate hyperthermia with concomitant hyperoxygenation[114,115,116]. Von Ardenne paid much attention to the sequence and the intervals between the different stages, taking into account both synchronization of the cell cycle[117] and thermotolerance as a result of repeated exposures[118], and even circadian rhythms. Simultaneously, he investigated the mechanisms of cell damage in hyperthermia: peroxidation processes[119], denaturation of proteins[120], activation of lysosomal enzymes[121]. The sCMTconcept of 1974[122] also included chemotherapy and radiotherapy. Period of 1975-1976 was devoted to study of combination of sCMT with chemotherapy[123,124] and, at the same time, to the search of enhancers of hyperglycemic acidification (particularly, NAD[125,126] and sodium nitroprusside1[27] were used). In 1976, the idea of selective anticancer drugs activated by acidic environment of the tumor128 was published. An attempts were made to implement it by creating 'selectines' – a targeted agents released in the tumor tissue due to increased activity of beta-glucuronidase129. 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, also entered the hyperthermic race. In 1967, American Cancer Society issued a separate release on the method of von Ardenne130, confirming that its clinical application in the 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'131 appeared in the US synchronously132. In 1969-1973, 4-8 years after the first publications of von Ardenne, some fundamental works of Italian[133,134,135,136] and British[137] 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 extracorporeal heat exchanger[138] (though von Ardenne developed such exchanger about 1966). Careful analysis of that trial shows that heating was associated with local control whereas survival mainly depended on tumor eradication (surgery + amputation). The British pioneers of the whole-body controlled hyperthermia Pettegrew and Henderson[139,140] (1971-1974) explicitly refer to the earlier works of von Ardenne, though questioning many of his considerations. It seems, it were Pettegrew and Henderson who first time detected the 'toxicity threshold' of WBH – 41.8°C. Study of local hyperthermia was continued: Cerino et al. 141 in 1966 investigated the local effects of ultrasound in bone cancer in vivo and concluded that the effect was mediated by heating. J Overgaard and K Overgaard (1972)[142] used short-wave diathermy for local heating.

Thus, from 1965 to 1975 hyperthermia has experienced 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 and US schools and Russian school inspired by von Ardenne.

At the same time, negative results had been accumulated. The initial enthusiasm of 'virtually unlimited selectivity' of hyperthermia quickly gave way to the understanding of 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[139,140]. Nevertheless, the nature and feasibility of the hyperthermia seemed to be obvious, and the general opinion was that only the

correct technical solutions are required. The attraction of an attention of world oncology by hyperthermia was the main result of that early period.

Hyperthermia in 1975-1985: local period and structuring

The next decade since 1975 to 1985 was a stage of structuring of modern hyperthermia. During this period, world hyperthermia obtained its internal organizational structure represented by different hyperthermic societies and the journal. Hyperthermia trials became usual, and network of institutions engaged in hyperthermia research enlarged significantly. Modern scientific base of hyperthermia was mainly completed. Thermal chemo- and radiomodification and the role of tumor microcirculation in pathogenesis of tumor damage were a scientific mainstream. All the main hyperthermia technologies were developed that time, and main manufacturers of hyperthermia equipment were established. Refusal of whole-body and convection-heating hyperthermia at all, which was the main mode of hyperthermia in previous period, in favor of electromagnetic localized applications, was the main technological trend of the decade.

Though western 'scientific machine' with its distributed structure quickly stepped forward with US as a world leader, von Ardenne Institute maintained leadership in many aspects. His sCMT concept with moderate hyperthermia was safe but suffered from insufficient efficacy. The next von Ardenne's solution was an extreme local heating against the background of moderate whole-body heating. His first paper on local hyperthermia was published in 1977[143], and the same year a 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[144,145]. In 1978, just after von Ardenn Selectotherm concept, a similar Pomp-Siemens machine was introduced combining whole-body and local heating. Instead of infrared heating, it used microwave heating by dipole antennas operating at 433 and 2450 MHz[146]. The concept appeared ineffective and soon Siemens left hyperthermia race forever. The similar idea of microwave WBH was tried to realize by Gelvich in Russia in early 80th and it also failed. Instead of it, concept Yakhta-5 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 local hyperthermia only an amplifier of tumor acidification[147] in Selectotherm concept. The phenomenon of complete blockade of tumor blood flow at pH 6.1 and 41°C was discovered soon[148]. 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[149] and change of their size in hyperglycemic environment[150], role of clogging of blood vessels by red cells[151], increased perfusion pressure[152], microvascular permeability[153], low blood pressure[154], platelet aggregation[155], also the mechanisms of involvement of the vascular wall in the disorders of microcirculation[156]. In 1985, the impact on microcirculation was acknowledged by von Ardenne as a central mechanism of sCMT[157]. It should be noted that von Ardenne microcirculation studies were much more practical than contemporary studies of western teams[158], first of all because of he studied microcirculation at real HT temperatures range <42°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 was technically realized by von Ardenne already in 1977, whereas similar development was initiated by the US National Cancer Institute only in 1978[159], and working prototype was built in 1983 only[160], but in local hyperthermia von Ardenne already was not a leader. In 1976, LeVeen et al.161 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 far 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 use of microwaves for superficial heating was simple and clear from just the beginning (2450 MHz, 915 MHz and 433 MHz were used[83,142,251]), heating of deep-seated tumors was a 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, development of all the major technologies for deep heating started. Capacitive and inductive technologies as the most simple methods which was already proven at diathermic applications,

were historically used for deep heating the first[86]. Inductive technologies (Magnetrode[162] and other solutions) showed their heating inefficacy (<20% of successful heating) already at the early stage and were mainly disregarded, though there are an attempts to reanimate the method from time to time[163,164].

In 1976, LeVeen et al. reported the eradication of tumors in animals and substantial regression in 21 patients using 13.56 MHz capacitive machine161. This was 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 this 'cross-fire' whereas superficial fat was heated 0.1 s only during each 0.3 s cycle. It's very interesting to note that already in 1979 Sugaar and LeVeen[165] reported some effects which developed with this machine only but not with other frequencies and heating modalities and seems to be not heat-dependent. In particular, alongside with the expected heat degeneration of tumor cells, significant changes in the tumor's stroma happened as well resembling lesions in acutely rejecting organ allografts. In 1977, Marmor and Hahns also reported some promising experimental results with this technology which couldn't be explained by temperature only166. Unfortunately, later some 'fantastic' results were reported by Storm et al.[167] with this machine: 75% of human sarcomas were heated ≥45°C and 50% ≥50°C without damage of healthy tissues with huge 8-10°C temperature difference between tumor and healthy tissues[227]. 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 1200W became commercially available. From the heating point of view, easy to use and manufacture 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 from electrodes size, position and distance and tissues parameters, with easy hot-spot formation. Thermotron used high-intensive surface cooling (up to -5°C) to compensate subcutaneous fat heating.

Field disturbances were minimized by exact fixation of 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 capacitive technology.

Majority of European and US specialists initially rejected capacitive concept considering its known disadvantages. Instead of it, surrounding irradiative solutions with interference heating were introduced in 80th. 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 were done by Guy[239,168] in early 70th. It was clear that such system is highly frequencydependent because lower frequencies (less that 40 MHz) with long wavelength flatten a peak of SAR in deep tissues, and 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 in full.

Some irradiative technologies were developed nearly simultaneously at 1978-1980: 'annular phased-array' (APA) 50-110 MHz technology of BSD Corp., coaxial 10-80 MHz TEM technology of Lagendijk et al.[286] and 4-waveguide 'matched phased array' (MPA). The first technology was marketed as BSD-1000 system, the two latter ones remained prototypes though Lund (Sweden) was about to market TMP technology as Variophase system. At phantom testing, all the techniques showed nearly the equal ability to create deep heating focus169. Unfortunately, in clinical practice the selective heating of deep focus never was achieved. Moreover, TEM and MPA technologies showed insufficient heating efficacy (<50% of heat-successful treatments).

BSD1000 system included 16 coupled (8 couples) horn applicators arranged on two octagons fed synchronously by 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 patients received heat-successful treatments.

The hyperthermic community had been structuring. 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[170,171]. Near 1981, US National Cancer Institute (NCI) 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 equipment were tested. In 1981, the North American Hyperthermia Society (NAHS) was founded, and in 1985 International Hyperthermia Journal was founded. In 1978, Hyperthermia Study Group was founded in Japan followed by establishment of Japanese Society of Hyperthermic Oncology (JSHO) in 1984. Since 1985, hyperthermia treatment in Japan is covered by insurance. Together with abundant grants of Japanese government for hyperthermia research, this caused the fast development of hyperthermia in Japan.

Electromagnetic treatment after 1950: microwave era

Electromagnetic treatment in 1950-1960: early microwave period

As it was mentioned above, first work on microwave diathermy of Mayo Clinic appeared only in 1947, just after the war. Raytheon Microtherm was the first commercial microwave device with 1,2-2,5 GHz frequency and a power of 125W. Since 1948 to 1953, some works on microwave diathermia were published, followed by a 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 – were discovered already in 1948, just after the start of microwave research, but it took time to accept them and realize the potential danger of the new devices. At the same time, evidence of danger of microwave radiation was received from military and industry. As a result, since 1953 to 1960, research activity in the field of microwaves completely shifted from medical use to 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.

Electromagnetic treatment in 1960-1985: maturing of microwave technology and rise of non-thermal effects

Major contributor to the development of the theory of biological effects of electromagnetic fields was Herman Schwan, a German physicist contracted by U.S. Defense Department. Near 1953, Schwan began a systematic study of the mechanisms of absorption of microwave radiation and found that it is uneven and depends on the frequency properties of tissues and their components[172]. Schwan has 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[173,174]. Electromagnetic medicine required adequate biophysical basis which has not yet been established[175]. As it's evident from the materials of the symposium on biological effects of microwaves, which took place in June 1970 in Richmond (USA), that time there were only initial presentation of the merits, which were subject to refinement in practically all areas[176]. Susskind[177] figuratively compared microwave devices of that time to 'gun shooting in the dark room'. 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 was completed and dielectric properties of various tissues and organs were determined[178,179].

Period between 1950 and 1960 as it 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 50th cooled the medical community to the use of microwaves, which, in turn, changed the approach from applied research (heating) to the fundamental ones, and data about non-thermal effects of EMF began to accumulate more intensively. It allowed to move from their demonstration to their study. In 1959, researchers from the Mayo Clinic found the effect of 'pearl-chain formation'[180]: 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[181], and later in 1939 by Lebesny[182] in blood emulsion. Also in 1959, a similar effect was observed by Heller et al.183: weak constant electromagnetic field caused the alignment of single-cell micro-organisms in the line. Moreover, depending on the frequency organisms could line-up alongside or across the field lines. In an earlier experiment, Heller et al.[184] has shown that 5-minute non-thermal effect of EMF on embryos of garlic in distilled water led to chromosomal abnormalities after 24 hours, similar to exposure to ionizing radiation and anti-mitotic agents. He assumed that the reason was the orientation effect of EMF. Also in 1959, a study of Humphrey and Seal[185] was published about use of DC to treat cancer, initiating the development of electrotherapy of

cancer, though a papers on galvanization of 1875[186] and 1886[187] had already shown the mature understanding of the technology. That time galvanization was used mainly for treatment of superficial lesions like hemangiomas[188] and lost its significance after invention of cauterization to reborn in XX century as cancer treatment modality. Already in 1951 Pohl[189] found that dielectric particles in AEMF are not only aligned, but also move alongside the gradient of the AEMF, and this phenomenon was called dielectrophoresis (DEF). In 1966, he used DEF for separation of alive and dead cells[190]. In 70th the method was developed in details[191,192]. In 1970, a lethal effect of the weak (10- 200 mA) AC (50Hz) for Escherichia coli was detected by Pareilleux and Sicard[193]. Then, this effect was rediscovered in 1992 by Canadian researchers[194] and called 'bioelectric effect' (BEE). In 1972, the increase in membrane permeability was detected by Neumann и Rosenheck[195] after a pulse of direct current, which led to the development of technology known as electroporation (EP). It was theoretically grounded in 1973-1974 by Crowley[196] and Zimmermann[197], and it firmly entered the arsenal of cell biology from the mid 70th. It is remarkable that even in 1977, a discussion of electrical breakdown begins with grounding of non-thermal nature of the effect. Later in 1989, Chang[198] has applied alternating radio frequency current for electroporation and obtained more efficient transfection at a substantially smaller percentage of irreversible cell damage[199]. Since 1978, Nordenström[200,201] reported the first clinical trials of galvanization called by him 'electrocancer therapy' on lung cancer.

In 1982, Schwan[202] summarized all the data on non-thermal effects available at the time, and 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, 7) rotation of cells.

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

Hyperthermia and electromagnetic treatment after 1985

Hyperthermia in 1985-1995: unsuccessful local attack and WH return

Meanwhile, the understanding of hyperthermia problems rose. In 1987 Hiraoka et al.[203,204] reported their results on Thermotron use. Whereas a maximum temperature ≥43°C was reached at 38% of tumors and 42-43°C in 23% of tumors (totally 61% ≥42°C), the intratumoral temperature differences exceeded 2°C and minimum temperature more than 42°C was reached only in 11% of tumors. These was far not the favorable results for extreme hyperthermia concept. In 1988, institutional reports on NCI Hyperthermia Equipment Evaluation Contract were published by Stanford[205] (21 devices compared), Utah[206] (10 devices compared) and Arizona[207] universities. Stanford reported only 14% of treatments with minimum temperature ≥41°C while 56% of all treatments were associated with acute toxicity. The most interesting fact: 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 was obtained only with three devices. In 1989, a report on BSD-1000 use[208] was published. Average temperature was 41°C and toxicity, both systemic and local, was directly named as the reason of the insufficient heating. The same year, very large phase I study on BSD-1000 APA technology appeared[209]. Since 1980 to 1986, 353 patients were 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 treatmentlimiting toxicity was 42%.

Thus, though hyperthermia remained a mainstream and 'hot topic' in scientific journals, practical oncologists and radiologicts and even many researchers in US had cooled to the method. Already in 1987, Hornback[210] 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 divergence of 'scientific' hyperthermia and clinical practice. This hidden disappointment of clinicians with scientists was prepared by the fact that clinical practice didn't confirm the scientific concept: hyperthermia appeared not so efficient but toxic and extremely time and labor consumptive. Practical fail of 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, i.e in Kettering-Sloan Memorial, were modest.

Scientific evidences contrary to hyperthermia concept also accumulated. Already in early 70th, Burger[211,212] showed that damage of healthy tissues starts from 40.5°C, that is the thermotolerance of the healthy tissues doesn't differ from that of malignancies. This was a serious challenge to just a basis of hyperthermia concept based on the axiom of much higher thermosensitivity of malignant tissues contemporary to the healthy ones. Cautious attempt of Upjohn company to assess hyperthermia prospects ended with paper of Bhuyan[213]: despite of possibility of greater sensitivity of neoplastic cells to hyperthermia as compared to normal cells was called 'very promising', it was clearly indicated that early results on cell lines were very dubious because of the possible mistakes. These weak signals were ignored.

Understanding of limitations of local hyperthermia, especially of the impossibility to heat tumors homogenously, forced investigators to return to whole-body concept with its homogenous heating. In 1983, US company Enthermics Medical Systems in collaboration with Wisconsin University developed system for extreme infrared hyperthermia[214] which later became Aquatherm system[215]. Almost simultaneously, Texas University started whole-body program. Later in 1995, International Systemic Hyperthermia Oncological Working Group (SHOWG) was established[216] under leadership of HI Robins from University of Wisconsin.

At 1985/87 von Ardenne rejected Selectotherm WBH+LH concept and replaced it with IRATHERM concept based on whole-body infrared hyperthermia only. Multistep oxygen therapy received a new rationale: it was considered as immunostimulator[217,218]. In 1991 von Ardenne Clinic for Systemic Multistep Cancer Therapy (sCMT) was launched based on von Ardenne Institute of Applied Medical Research in Dresden, allowing systematic clinical trials. In 1992, new system for extreme wholebody hyperthermia IRATHERM 2000 was launched, and in 1993 the final version of sCMT was completed[219] extreme whole-body hyperthermia + selective thermopotentiation + supportive hyperoxemia.

Meanwhile, hyperthermia was ready for battle for recognition.
In 1988, the small trial of Valdagni et al[220] was 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 follow-up[221] was introduced. Excellent short-term and long-term results were reported both for local control (83% vs. 41%) and 5-year survival (53% vs. 0%), though thermal analysis 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 vs. 68 Gy). Some points limit the acceptability of these results. First of all, this is small size of the trial and the fact that it was initial enrollment only because the trial was terminated 'by ethical reasons'. Second, immediate results looks brilliant if to compare CR only but comparison of total effect (CR+PR) gives dubious results: 89% vs. 81% in RTcontrol. In this regard, survival effect looks absolutely decisional but there is a significant remark: such unbelievable effect was never reproduced not before not after. In all later randomized trials[222,223,224,225,250,252,258], there was no significant effect to survival. Moreover, it tended to be worse in TRT arm in some trials[250,258]. The extremely low survival in the RT-control 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 reported the highest tumor temperature among all the others superficial trials: mean maximum temperature was 43.3°C and minimum 40.4°C. It could in some extent explain the clinical results but absence of correlation of the endpoints with thermal parameters makes

this explanation weak. The highest temperature reached 48-52°C. Very surprisingly, in such a high temperatures, 'only one burn' was reported and both acute and late toxicity in TRT arm were equal to that in RT-control. This is an extremely alarming result because later Perez et al.[223] showed 30% of burns in TRT arm vs. 0% in RT only arm, Engin et al.[225] reported 40% of burns and Jones at al.[258] – 46% of burns vs. 5.7% only in RT only arm, and all these trials used less heating. It's also surprising that after such an excellent results and many reasons do not trust in Valdagni et al results.

Since 1984, five big randomized clinical trials on TRT with superficial[222,223,224,225] and deep HT[226] were launched in the leading US research institutions. The common belief in the success of the trials was so strong that only two of them[223,226] compared TRT with RT alone whereas other three ones compared different protocols of TRT as if its efficacy is already proven. The result was absolutely disappointing: any trial didn't 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 refused to review the hyperthermia rationale. Insufficient heating in view of inadequate technique was 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[205] and Shimm et al.[208] reports. This was not a technical problem and not a problem of thermometry: this is 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 early 90th as not significant because of insufficient heating and imperfect technique. This is absolutely incorrect. All the modern hyperthermia technologies as it clearly stated above were introduced before 90th. All the randomized trials of early 90th were executed in leading US universities with the best available equipment. Therefore, the technique of heating in these trials was adequate from the modern look. It's confirmed by high temperature reached in these trials. For instance, in Kapp et al. trial[222] the minimum temperature in superficial tumors was 40.2°C, average 42.5°C and maximum 44.8°C. Modern guideline of Erasmus university[251] for superficial tumors recommends to reach minimum temperature 40°C and maximum 43-44°C. In the modern trials on deep-seated tumors, average temperature never reaches 42°C while it was reached usually in trials before 1995[203,205]. Also, the deep heating with 'second generation devices', namely BSD2000 with its SIGMA applicator, was lower that with old BSD1000 APA system.

It should be considered that in terms of heating and technique the negative trials of early 90th were absolutely adequate. They were inadequate to anticipation of early 80th based on 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[227]) 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 showed that it's impossible to heat tumors homogenously more than 42°C. Less than 50% of entire tumors were 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 existing techniques. Toxicity was the limiting factor. In fact, these clinical trials had just displayed the critical problem of hyperthermia: absence of therapeutic range. Damage of healthy tissues went alongside with damage of tumors and limited 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 was 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[205,206,207], though only few of them were marketed later. There was no substantial progress in hyperthermia technologies after 1985 despite of significant activities. Contrary, in some cases technical improvements even worsen the results. Though some new hyperthermia machines were introduced that time (Synchrotherm-RF (Italy) local machine,

Aquatherm (USA) and Heckel HT3000 (Germany) whole-body systems), such strong and versatile players like Bruker (Oncocare) and ODAM (Jasmin) left the market.

Near 1985, two 13.56 MHz capacitive hyperthermia systems were introduced: Oncocare of Bruker and Jasmin 3.1000 of ODAM (France). Both systems had very short history and in fact 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 600W RF-generator (totally up to 1,800W). The system was able to move a deep heating focus by changing output energy of each applicator[228]. Though good heat distribution was shown on phantoms, and 41-42°C was reached in deep tumors in clinical trials with enough safety[229], the clinical effect was more than modest[230]. Oncocare was a classical design 13.56MHz/600W capacitive system with two symmetrical electrodes, and showed the similar clinical results[231]. Both systems were withdrawn soon after publication of the first clinical results in 1989-1996, and both Bruker and ODAM had left the hyperthermia field.

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

BSD-2000 concept with an entirely new SIGMA-60 applicator was introduced in late 80th instead of BSD1000[232,233]. Horn irradiators were replaced to 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 of the better technical parameters of the new BSD2000 system[234], the deep-heating capacity of BSD1000 was nearly the same[235] or even better236. Toxicity had remained the same: acute toxicity was treatment-limiting in 50% of treatments and systemic stress was treatment-limiting in 30% of the treatments[235]; it looks that a little changed to mid-2000th[277]. Returning to the beginning, it seems that initial heating calculations of Turner et al.[237,238] from BSD Corp. were done with too favorable parameters, and Guy[239] calculations showing less central heating and much more superficial heating were more practical[286].

IRATHERM WBH concept had been developed by von Ardenne and dermatology department of Charite Clinic near 1985. The concept was based on use of near infrared irradiation (IR-A, 760-1400 nm). IR-A ability to penetrate to subcutaneous vascular network and heat it up was displayed already in 1931. Contrary, IR-B (1.4-3 mcm) and IR-C (3 mcm - 1 mm) are mainly absorbed in the upper skin layer.240 IR-A is separated by water filters[241]. IRATHERM 2000 system uses 5 groups of irradiators: 2 ventral and 3 dorsal. Active resistance of body to heating is the main problem of the IRATHERM concept. The power of perspirational cooling could reach 1400W, leading to long heating period (up to 2 hrs before reaching 42°C) and significant loss of fluid (up to 2 liters), dehydratation and electrolytic disorders. This causes the necessity of effective monitoring of electrolytic balance and vital functions[242].

Aquatherm concept developed in Wiskonsin university by Robins et al.214 near 1985 and introduced as Aquatherm system near 1995[215] was the entirely new 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 which 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, perspiration is blocked and 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 was introduced in 90th[243]. This is in fact a simplified analogue of von Ardenne IRATHERM system 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 rigid IRATHERM couch which often causes decubitus (8% of grade III-IV)[244]. There is 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 concept mainly repeated earlier von Ardenne Selectotherm concept with combination

of WBH and local heating, though using 13.56 MHz radiative solution instead of IR 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 had 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, there were a lot of solutions designed that time. Breakthrough Medical, Genemed (Japan), Labthermex, Lund Scientific (Sweden), SMA (Italy), Getis (Germany), HPLR 27[245] (France) presented their concepts, sometimes looking very promising, but all of them remained prototypes.

Hyperthermia in 1995-2005: reaction

Reaction of hyperthermia community and industry followed soon.
Just after the fail of the first RTOG deep-heating study (84-01[226]), the attempt was made (RTOG 89-08[246]) to compensate the damage based on use of 'second generation' equipment (BSD2000). Though it was a phase I/II trial which usually show much better results (like it was in phase I/II trial of 84-01 study[247]), this time the results was modest. CR+PR rate was 34% with less than 2 HT sessions per week and 16% only with 2 HT sessions. Response was not correlated with maximum tumor temperature but a strong association with radiation dose was revealed: 54% CR with ≥45 Gy versus 7% with <45 Gy ($p < 0.0001$). The toxicity of treatment was less than earlier (18% of acute toxicity vs. 68% in the previous trial) but it could be associated with caution of researchers which that time didn't run for temperature. As a result, the temperature distribution was even worse than in the previous trial, especially for minimum temperature (38.5°C only). There was no III phase trial initiated with such weak results, and RTOG discontinued its hyperthermia activity but once again without any final decision concerning this 15 years of in vain activity. Nevertheless, remarkable in all respects monograph of Seegenschmiedt et al.[248,249] was issued in 1995-1996 without any respect to negative results. It looked like hyperthermia is still a promising and highly effective modality ready to acceptance.

In 1996, Matsuda had proudly reported about hyperthermia status in Japan. At the 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. Deep-seated tumors share was 60% of treatments, while this percentage was negligible in Europe and USA.

In 1989-1991, before the fail of the trials of early 90th, five more randomized trials on superficial TRT were launched under the umbrella of International Collaboration Hyperthermia Group (ICHG). After the first fails of above mentioned trials, they were merged together. The common results were published in 1996[250]. Despite of the three of five arms displayed negative results, survival in hyperthermia group was worse and dissemination was more severe, these results were hidden. Overall statistics was favorable for HT group due to the excellent local control in the two remaining groups, though this success was bought for the sake of 2-fold growth of dissemination and 2.5 growth of mortality. Also, after publication of van der Zee et al. paper in 2010[251] it could be assumed that these good results were received due to pre-selection of patients and incorrect randomization. Nevertheless, the trial was announced as successful and became the cornerstone of hyperthermia evidences.

The next publication of Overgaard et al. trial on TRT of skin melanoma[252] in 1996 introduced a method to display the effect of hyperthermia based on use of inadequate comparator – low dose radiotherapy. Total dose 24 and 27 Gy with hypofractionation (8/9 Gy x 3 sessions) was 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 Valgany et al.[220] study, and it was absolutely clinically ineffective dose taking into account well-known radioresistance of melanoma. Naturally, the trial was a clinical radiobological study without clinical significance. The local control in TRT group was less than average and survival data were hidden. This trial was once again considered as successful.

In 1998, Sneed et al.[253] trial was published on brachytherapy (BT) with vs. without interstitial HT in multiform glioblastoma. 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 were re-operated in HT arm vs. 58% only in

BT control, and the influence of reoperation rates (Δ11%) was not assessed. Reoperations started from 13-14 weeks with median time of reoperation 32-45 weeks. As it is clearly seen from time-toprogression (TTP) graph, initially the two arms were equal, and divergence started nearly at 25 weeks and reached its maximum nearly 40-45 weeks. Coincidentally, 45 weeks was a median time of reoperation for HT arm. Then, convergence of the arms started and nearly reached the equality at 65-70 weeks. Then, divergence 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 less than difference in quantity of reoperated patients (6 patients). Also, 2-year survival probability was 31% vs. 15% in the control group, and this 15% difference once more constitutes 4-5 persons which is less than 'reoperation impact'. It's obvious that with respect to 'reoperation bias', the result could become insignificant, that is this bias could have decisive impact for the result of the trial. Therefore, the results of the trial couldn't be accepted without appropriate recalculation.

Next to Overgaard et al. trial, the series of randomized trials with inadequate comparator were launched. In 2000, Dutch Deep Hyperthermia Group trial (van der Zee at el.[254]) was published. Total dose 67 Gy (≤60 Gy to tumor mass) was used for treatment of IIIB stage bulky cervix cancers, though itwas known that such low doses significantly decrease treatment effect[255], 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 showed good gain in TRT group both for local control, disease-free and overall survival[256] 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 doesn't 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). The trial is considered successful.

In 2001, Harima et al.[257] trial on TRT of cervix cancer was published having the improved design. Inadequate dose to tumor mass (60.6 Gy) in this trial was masked with by high enough total dose (82.2 Gy) because 21.6 Gy was targeted to parametria with central shielding. This allowed to show effect of hyperthermia by local control vs. 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 – pre-selection of aged patients. It's well-known that local control after hyperthermia is better in older patients. In Harima trial, sample of not-pre-treated patients in TRT group was 10 years older (64.9 years) than anticipated age of the first diagnosis of cervix cancer in Japan (55 years) and 14 years older than in DDHG trial (51 years). In the final reported results (with all the biases), the trial was extremely successful.

In 2005, Jones et al. trial on TRT of superficial tumors was published[258]. Though good enough gain of local control was displayed (66% vs 42% in RT control), some serious biases don't 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 high percentage of pre-treated patients and pre-selection of 'heatable' patients. Survival in TRT arm was worse during all time of the trial. As usual, this trial was announced as successful.

In 2003, the results of II phase SHOWG trial on thermochemotherapy (TChT) of malignant pleural mesothelioma by virtue of Aquatherm machine were published[259]. Despite of very mild effect (20% of partial remission only), it was decided to initiate III phase trial. In 2004, disappointing preliminary results of the trial were reported on ASCO meeting[260]. Despite of less severe sample (0-II stage instead of I-III stage in II phase study), the effect in TChT group was twice worse than in ChT control (15% vs. 30% of partial remission) but with much higher toxicity. After 2003, International SHOWG discontinued and its leader Robins finally left hyperthermia field. Instead of it, German Interdisciplinary Working Group on Hyperthermia[261] was created with its base in Charité (Berlin). IWGH was mainly targeted to von Ardennes CMT 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, absence of randomized results makes this reason inconclusive. Fail of SHOWG trial together with termination of von Ardenne Institute could be considered as the fall of whole-body hyperthermia.

It should be specially noted that von Ardenne 'Systemic Cancer Multistep Therapy' (sCMT) is not a real WBH. In fact, sCMT is a combination of two different modalities, hyperthermia and hyperglycemia, where hyperglycemia is the more potent factor because it per se could entirely block tumor perfusion[262] 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 while without hyperglycemia this pH decrease is insignificant[263].

Therefore, above conclusions about fall of WBH refers to WBH per se, not to sCMT which potential still have not been evaluated evidently. Therefore, despite of a number of 'positive' trials and some meta-analyses on hyperthermia, medical community soundly didn't consider these results evident. Hyperthermia was not 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 reality.

Resume of the International Kadota Forum on hyperthermia held in 2004[264] in Japan is very demonstrative. After usual reference to excellent laboratory results, the authors referred to 28 randomized trials on hyperthermia though only 18 'positive' trials were displayed in the corresponding table, and only 14 of them were really randomized. Concerning the rest of the trials, there was the only phrase: 'Nine randomized studies failed to show a significant benefit from addition of hyperthermia'. There was no even an attempt to explain the negative results, though these were the most extensive and reputable studies. There was no any analysis of so-called 'positive' studies which in fact were almost uniformly biased. Therefore, the advocacy of hyperthermia was based on dubious data while reputable and evidence-based but negative data were just disregarded. At the same time, the problem with hyperthermia acceptance was claimed because of 'limited availability of equipment, the lack of awareness concerning clinical results, and the lack of financial resources'. This was s beginning of 'hyperthermia low acceptance in view of low attention and money' myth. It seems that medical community was very well acquainted with results of hyperthermia but trusted to the most reputable trials which were uniformly negative. Lack of financial resources was absolutely natural after a huge funds and forces were just wasted in 80th-90th 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 lowfrequency RF-field, Synchrotherm flexible solution seems controversial because field inhomogeneity (and hot-spots formation) increases significantly in any deviation of electrodes from pure flatness. Idea of 'field concentration/focusing' by virtue of flexible electrodes which is actual for far-field in microwave range doesn't work in the near-field at 13.56MHz: contrary, 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[265] in 2000th in view of insufficient focusing of the previous 2D SIGMA-60 applicator. Alongside with triple quantity of antennas (24 totally in 3 groups), the frequency was enhanced to 100 MHz to reach a smaller central peak. Though better steering was reported[266], the heating efficacy had appeared near 2-2.5 times lower than that of the previous SIGMA-60 applicator[267]. Practical results show that BSD-2000 still don't allow to heat-up the desired volume selectively because hot-spot before the target region is virtually inevitable[268], localization of other hot-spots is almost unpredictable[269], and in general the heating looks rather like a homogenous heating of the entire volume than as a selective heating of target volume[270].

It seems that BSD-2000 concept experiences problems. The toxicity of the technology still demonstrated in clinical trials[277] 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 hotspots formation (which, by the way, was obvious initially). Real-time thermometry is the only possibility to control the process but there is no a 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[267]. Sure, due to hyperthermia research, MR thermometry develops soon but it doesn't develop hyperthermia itself which in fact is 'sitting and waiting' while MR-thermometry matures. And it looks rather like flee from the problem because even MR thermometry is satisfactory, it doesn't solve the problem. The same situation already happened in 80th-90th: 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 results1 of the STS trial[277] 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's 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 was 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, not-temperature-dependent effects based on the extracellular heating and modulation were the core of the technology. The classic capacitive design was cardinally re-evaluated. Instead of high-power/intensive cooling concept, low-power approach with mild physiological-range cooling was offered. Concept of 'skin sensor' abandoned the most problematic point of all hyperthermia machines – necessity of thermometry. Functionally asymmetric electrodes with grounded lower one provided necessary field stability and enhancement of heating in the 'zone of interest'. Special fractal modulation of the carrying frequency markedly enhanced selectivity of power deposition in tumor tissue. Thus, looking from outside like a regular 13.56 MHz capacitive solution, EHY2000 was a principally new electro-hyperthermia machine and technology. Detailed description of oncothermia technology, science and trials is beyond the range of this essay devoted to classical oncological hyperthermia only.

Hyperthermia since 2005: crisis, reload, dead-end and decay

In 2005, Vasanthan et al.[271] randomized multicenter (5 centers in 4 countries) trial on TRT of cervix cancer was published. Contrary 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 vs. adequate RT dose to tumor mass (72 Gy, TD 84 Gy). The result was disappointing: TRT didn't differ from RT only by local control but showed worst survival. In IIb stage group, the worsening of survival was statistically significant. The subsequent trial of Mitsumori et al.[272] on TRT of non-small cell lung cancer (also sponsored by IAAE) also didn't show 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 was ineffective, though it was clear already after early 90th negative trials. There was no possibility to wait with reassessment of hyperthermia rationale any more. In 2005 the program paper on re-setting of hyperthermia rationale was published[273]. 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 was just recognized at last that extreme hyperthermia concept is impossible. Instead of it, moderate hyperthermia concept (40-42°C) was offered based on effect of hyperthermia to bloodflow and tumor oxygenation, studied by Song et al.[274] 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, paper of Jones et al.[275] was published advocating the use of hyperthermia as a radiotherapy sensitizer for treatment of chest wall recurrences based on the same 'positive' trials. The same year, National Comprehensive Cancer Network (NCCN) 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[276]. This small success was too insignificant to compensate the harm from sound fail of IAAE trials in 2005[271] and 2007[272]. Crisis of hyperthermia was obvious.

'The last hope' of hyperthermia community was associated with Issels et al. trial[277]. 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) were enrolled at nine centers in Europe and North America for 9.5 years (1997-2006). The trial was designed to study HT efficacy in 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 were reported: there was no effect to overall survival but short-term local response rate (CLR + PLR) was twice higher in HT arm (34% vs. 16%), and Local Progression Free Survival was significantly enhanced in HT arm (32 months vs. 18 months; 76% vs. 61% after 2 years and 66% vs. 55% after 4 years). Unfortunately, this result was totally based on 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 efficacy gain didn't exceeded 25%. The only difference in volume of chemotherapy (8 cycles in HT arm versus 5 cycles in the control arm, +60%) more than explains the gain of effect in HT group. In comparison with earlier results of Sarcoma Meta-Analysis Collaboration (SMAC), the best results in HT arm of Issels et al. trial were substantially worse than results in control arm of SMAC. With respect to the distortions and SMAC comparison, the another question arises: whether hyperthermia worsen the results of conventional treatment? Nevertheless, the result was as usual announced as positive, and the authors 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'[278].

Meanwhile, the new basement of '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[279] explicitly reflects the modern look on the problem and confirms the old 'open secret' of absence of difference in thermal resistance between healthy and malignant cells. But may be the authors didn't aware that this phrase is a final judgement to 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 heat-damage of healthy tissue is inevitable. At equilibrium steady-state phase, difference between healthy and tumor tissues doesn't exceed 1°C for capacitive solutions. It seems that for interference irradiative solutions, a tumor is virtually always heated less than the surrounding tissues[270].

Kelleher and Vaupel also revealed that gain in tumor oxygenation due to hyperthermia is modest and transient and can't be used for enhancement of radiotherapy effect[280]. This confirms the data of immunohistochemistry study of Sun et al.[281] from Memorial Sloan-Kettering Cancer Center with hypoxia markers showing that real effect of moderate hyperthermia on microcirculation is bidirectional and inconclusive. Because the 'reset' concept of moderate hyperthermia is entirely based on the idea of better oxygenation of tumors, this could be a final judgement to mild/moderate hyperthermia concept. Though we still see some rapturous opinions[282] concerning promises of mild hyperthermia based on Song and team works[274], and they are still reporting these results[283], the new data makes these results questionable which would be discussed below.

As the last shot, in 2011 de Bruijne et al.[284] 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. Celsius TCS hyperthermia system was introduced in 2006 in Germany. Despite of being declared as 'innovative', this was just a replica of traditional 13.56 MHz/600W capacitive scheme with two rigid symmetrical electrodes and intensive cooling similar to Oncocare and Synchrotherm-RF. The most impressive feature of the system was just an 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 solution if far from perfection. First of all, because it's 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. The second, use of not properly fixed electrodes seems to be a serious defect of a capacitive machine. Instability of lowfrequency RF-field and

hot-spot 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, which is the Thermotron solution. It seems that any capacitive solution which uses not exactly fixed electrodes is not safe enough. For example, in Celsius TCS pre-clinical report[285] an intensive hot-spot was displayed in 1 of 4 clinical examples: at prostate cancer treatment and at low power 80- 120W, the temperature in rectum where thermometer was placed (that is, out of interest zone) suddenly raised to 45-46°C and remained at the level for 20 minutes. This is a typical hot-spot of tissuedamaging level. It seems that it should be the typical defect for any low-frequency capacitive system with not properly fixed electrodes.

Unexpectedly, hyperthermia become a 'hot topic' in China. Since 1995 many new hyperthermia machines were presented there by companies HY SenMo, ZD, ZRL, NRL, MoreStep 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 lower deep heating, high 'superposition' field strength on the crossing of paired electrodes fields could allow to reach enough heating while surface heating is low. This is in fact a low-frequency capacitively coupled version of the earlier APAS-TEM idea[286] and repeat of LeVeen design[165]. It was then implemented by Synchrotherm-Pulsar system having 2 pairs of electrodes and double power 1200W. There is no data about its efficacy and safety. The majority of Chinese manufacturers develop a similar idea of 'double Thermotron'. It's hard to say, could any of these solutions be more effective than existing classic Thermotron capacitive solution.

Looking from outside it's clearly seen that this 'hyperthermic enthusiasm' is based on the uncritical acceptance of the above mentioned 'just heat it' appeal of hyperthermic community. Because Chinese haven't received 'hyperthermia vaccination', like Western world did, and haven't appropriate historical memory, this simple and attractive appeal will necessarily find acceptance.

Hyperthermia at 2010th: decay goes to renaissance?

World hyperthermia lies in ruins. It's especially obvious if to compare the current state with 80th and 90th. United States which was a worldwide leader in hyperthermia research and development, and where almost every big university was involved in these researches, now is virtually a 'free of hyperthermia' zone. Dr. Beecher institute, Duke University and some activity in Texas University – these are a pathetic remnant of the former boiling activity. 'Hyperthermia vaccination' was so strong in US that BSD2000 machine still can't 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 was accepted before 1990.

Japanese cluster based mainly on Thermotron is silent after sound fail of IAAE trials in 2005- 2007. There is no any development and research activity 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 studies sCMT von Ardenne concept and tries to elaborate a concept of 'critical' whole-body hyperthermia (more than 42.5°C) offered by Russian doctor Souverniov. It seems that this direction is problematic enough. ESHO powered by BSD Corp. is still active, at least on a conference level. DGH is mainly powered by 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.[251] shows that the oldest and the most reputable in Europe Dutch cluster stopped its development. English school of hyperthermia decayed already after Pettigrew and Henderson at 70-80th and finally evaporated after 'successful' ICHG study[250] in mid-90th. 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 were published before 1996 and 33 – before 1990. Excellent Seegenschmiedt et al. monograph[248,249] completed this 'before 1996' period without any mention of any negative results. In fact, hyperthermia is still based on the old-fashioned ideas and concepts of 80th.

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 90th, near 350 papers on hyperthermia were published (Pubmed). At 2000th, this quantity dropped to 200 papers per year, and have returned to pre-crisis level 300 papers in 2009th. Some new monographs have been published. We see three main reasons of this renaissance. The first, 'the throne is never vacant'. There is a strong request for universal modifier of conventional treatments which efficacy is obviously insufficient. There is still no any candidate to this position except of hyperthermia. Second, the new generation of scientists and physicians came into oncology which is free of 'hyperthermic disappointment', haven't an experience of hyperthermia usage and don't remember hyperthermia fails, but studied about hyperthermia from the textbooks based on very simple and attractive concepts of 80th.

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 keep 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 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[264]. An article in Polish Journal of Environmental Studies287 is an excellent sample of such mythology. All these myths are wrong. Evidence of hyperthermia effect is based on 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 acceptance of any drug or treatment method. When 10 randomized trials on hyperthermia started in 1984-1991, evidencebased barrier was absent because the concept of EBM was offered in 1991 only, and even this barrier didn't object to launch a tremendous Issels et al. trial at 1996-2006. All the necessary technical solutions appeared many years ago. Thermometry is not a point at all because of fail of temperature concept.

As it clearly seen from the mentioned papers[287,264] 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 negative ones are just not mentioned. We see the same disregard, for instance, also in the remarkable Seegenschmiedt monograph: for example, Fig. 10.13 on page 213[248] presents effect of TRT vs. RT only. Among many phase II non-randomized 'estimation' trials which results should be considered with great caution[288], the only randomized trial of Perez et al.[223] is displayed. This trial was negative for hyperthermia arm (32% of CR vs. 30% with less toxicity in RT only group) and only small tumors (<3 cm) showed a TRT-gain. Only <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's absolutely not correct: much more negative results of randomized trials[222,224,225] were received to the moment (reference 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 'temperature-based' hyperthermia itself, namely its low efficacy, high toxicity and labor-intensity. This open conclusion should be done at last, otherwise we'll 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's just moving from 'vaccinated' Western countries to neophytes – China is becoming the main hyperthermia market. But term of the 'vaccination' expires even in 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, dissolved after some years of collapsing (-10% of market every year), though recently one more 'me too' Synchrotherm-like Androtherm system came into the market. The problems of 'me too' machines are discussed above.

Electromagnetic treatment since 1985: stagnation of diathermia, non-thermal renaissance and problems of non-thermal research and applications

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'[289]. Therefore, non-thermal development of diathermia was blocked by institutionalized thermal dogma just at the intention level. Only recently this opinion was soundly questioned: non-thermal nature of different pulsed patterns at diathermia was displayed[290].

Non-thermal effects are the mainstream of electromagnetic research since 1985. Since 90th, research of extremely low-frequency AEMF (ELF, <300 Гц) produced by electric lines and equipment started. Some of them displayed the possibility of oncogenic effect of ELF-AEMF: it was shown in vivo that medium-term effect facilitates tumor growth, especially of breast cancer, and long-term effect could provoke a spontaneous cancer development[291,292]; resistance of breast cancer to tamoxifen rises under the influence of 50/60 HZ, 1.2 mcT AEMF[293,294]. The rising quantity of such studies forced WHO to convene an international workshop in 1997[295]. Experts 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. Further studies displayed also anti-proliferative effect of ELF-AEMF[296,297]. Despite of number of publications on ELF-AEMF effects, their effect on human being remains controversial.

Since 1995, tremendous and rising quantity of trials is devoted to exposure of high-frequency AEMF of extremely low power (ELP) connected with use of mobile phones[298]. In general, it's considered safe but final conclusion is not possible. ELP-AEMF 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[299].Therefore, thermal-dependent safety standards elaborated in 50th are considered not enough and should be replaces by the new standards based on non-thermal effects.[300]

AEMF affects cell proliferation, and this effect is frequency-dependent resembling resonance. In 2009, Barbault et al. paper was published301. 1524 tumor-suppressing frequencies were 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[302,303]. There are some possible explanations of this effect. Authors of TTF technology explain it on the basis of intracellular orientational effect of AEMF: AEMF-induced ponderomotoric forces inhibit an assembly of mitotic spindle[304]. Another explanation was offered by Vodovnik et al.[305]: external AEMF leads to hyperpolarization of membrane on the one side with simultaneous hypopolarization on the another side of a cell; membrane potential of dividing cells is diminished comparing to resting cells; following to fast complex and non-linear processes of hyperpolarization and depolarization and resulting changes of ion currents, membrane potential of dividing cells rises which inhibits proliferation.

Currently, non-thermal effects of AEMF of high enough power 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) genotropic effects caused by direct impact of AEMF for DNA. Summation of these micro-effects led to development of non-thermal macroeffects: 1) effect on cell proliferation; 2) cell death: a) necrosis; b) apoptosis; c) 'mitotic catastrophe'; 3) disturbance of microcirculation.

Delicate sub-cellular mechanisms of ELP-AEMF are not clear still. Effect to DNA is suggested[306]. DNA could be a fractal antenna possessing electronic conductivity and autosymmetry. It could interfere with AEMF at low-frequency and radiofrequency range[307]. It was shown that exposure of DNA to ELPAEMF leads to expression of heat-shock proteins (HSP70)[308]. Astumian et al. displayed that proteins could act as molecular machines transferring energy from one form to another by virtue of cyclic conformational transitions[309] and these molecules could absorb AEMF energy. This especially refers to enzymes which action is based on cyclic conformational transitions; AEMF acts as an external energy source allowing to shift the reaction from equilibrium[310]. Tsong team showed that AEMF affects Na+/K+- ATPase: ionic transport in their experiment depended rather of AEMF frequency and amplitude then of ATP concentration[311]. The peak effect on K+ transport was near 1 kHz and near 1 MHz for Na+ transport. It's reported that non-thermic effect of ELP-AEMF (53 GHz, 0.06 mW/cm^2) inhibits growth of E.coli and

affects transmembrane Na+/K+-transport[312]. Antibiotics enhance the effect. The effect is considered membranotropic. Effect on redox status is suggested[313].

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

Technology	Trademark	System	Inventor	Implementation	Company	Since
Electro-hyperthermia	Oncothermia (Modulated Electro-Hypethermia)	EHY2000 EHY3000	A Szasz (Hungary)	Approved in EU (CE), Russia, China	OncoTherm Group (Germany-Hungary)	1988
Electroporation	ECT (Electro Chemo Therapy)	Cliniporator	LM Mir (France)	Approved in EU (CE)	IGEA Srl (Italy)	~1980
		EndoVe	D Soden (Ireland)	I/II phase[314]	Mercy University Hospital (Ireland)	
	EGT (Electro Gene Therapy)	MedPulsar	GA Hofmann DP Rabussay Z Zhang (USA)[315]	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	TTF (Tumor Treatment Field)	NovoTTF-100A	Y Palty (Israel)	Approved by FDA[316] after III phase trial[317]	NovoCure Ltd (Israel)	2000
Magnetotherapy	TEMF (Therapeutic Electro-Magnetic Field)	-	Wascher RR Williams D Bouldin FE (USA)[318]	I-II?	EMF Therapeutics Inc (USA)	~2000
Galvanotherapy	ECT (Electro Cancer Therapy)	ECTplus	Н/Д	Approved in EU (CE)	CUTH Meditech GmbH (Germany)	2006
		NEUFLO	Schroeppel EA, Kroll MW	Approved by FDA for research	Ionix Medical Inc (USA)	~2000
			(USA)[319]			

Table 2. Commercialized non-thermal AEMF-technologies in clinical oncology

About 2010, some momentous events had happened. In 2009, it had been first time displayed in oncothermia study[320] that under the mask of 42°C hyperthermic heating, temperature was responsible only for 25% of general cell-destructive effect while 75% of cell deaths were caused by non-thermal (not temperature dependent) effects. In 2011, non-thermal TTF technology received FDA approval for treatment of brain tumors in combination with chemotherapy[316]. A non-thermal device for less than two years received approval for deep-seated tumors treatment, which the leading US hyperthermia manufacturers can't receive since 2000. In 2012, oncothermia device was installed in Prince of Wales Hospital, Australia. Australia is a 'zone free of hypertermia' since the case of Dr. Holt. It's very symbolic that it was oncothermia, the technology based on non-thermal effects, which run the blockade.

It seems that interest to non-thermal effects is rising more and more in XXI century. Girgert et al.[294] revealed pro-oncogenic effect of ELF-AEMF (50 Hz, 1.2 mT) at breast cancer. This effect was multigene, complex and unidirectional[321,322,323]. Novikov et al.[324] 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, 16.5 Hz/150-300 nT were revealed. Berg et al.[325] 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.[326] revealed synergy of ELPF magnetic field (100 Hz, 0.7 mT) and radiotherapy.

It should be mentioned that the use of non-thermal effects is still questionable for many reasons, and many problems could happen on this way. First, there is a controversy in non-thermal effects direction. Pro-oncogenic and anti-proliferative properties are often reported by different researchers for the same EMF applications. Second, the vast diversity of non-thermal effects creates a fallacious impression that almost any electromagnetic exposure could have cancer treatment effect. With this trend, even 'toaster cancer treatment' appearance 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 cancer treatment. Third, there is

a trend to uncritical extrapolation of different known effects of EMF despite of power level and field type. For instance, Tello et al. (2001)[327] explain effects of constant EMF by 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 entire frequency spectrum and each effect has its frequency optimum. Other wide-spread mistake is the use of ponderomotoric effects which demand high enough field strength for 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[328] 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 a new medical technologies. Now, it's expensive enough to receive even pre-clinical evidences. In case of electromagnetic treatments with great versatility of frequency-power-modulation combinations, it could be the insoluble problem.

At last, a great 'systematic error' still present in the non-thermal research with its roots coming from the 'thermal dogma'. As it follows, e.g., from the Kaiser paper[329], non-thermal effects are positioned only in the 'non-thermal range', when there is no macroscopic temperature elevation, that is in ELP range. This is the incorrect and fruitless approach. Thermal and non-thermal effects develop simultaneously, and 'it's impossible to reach enough non-thermal effects with those field strengths which don't cause substantial heating'. This old sentence of Schwan should be a slogan of any 'nonthermal' research and application. The 'non-thermal' applications of 30th[77] failed for this reason – trying to remain 'pure non-thermal', – and this is also a danger for the new non-thermal applications. It seems that oncothermia technology is the only one which realizes this problem in principle and can reasonably divide thermal and non-thermal investments into general effect at hyperthermic-range temperatures[320], though we see emerging understanding of this problem even in diathermia[290].

Another dimension of this 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 of 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[330] or of 'resonant heating in micro hot-spots'[331] are examples of this type of thinking, and it turns the problem of relationship of 'thermal' and 'non-thermal' into a scholastic problem of the same nature as the ancient problem of 'a hen and an egg'. It's obvious that any process is accompanied with thermodynamic changes but it doesn't mean that it's 'thermal' in 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 tries to do for more than 70 years.

These are non-thermal effects which are the front line of development of physical factors application in medicine now, whereas thermal concept has exhausted for a long time, and stagnate since the early 90th. Despite the fact that thermal concept remains the only officially recognized[289], and it's still early to resume the triumph of non-thermal approach, since 2000th hyperthermia finally went from the front line of research in oncology, and in fact lost its positions in practical application.

Sure, it is still early to say about success of non-thermal technologies. Though TTF technology is already FDA-approved, its III phase clinical results are far not so favorable as it was awaited. Despite of oncothermia is currently the world leader with more than 250 devices installed, it's impossible to resume its final success prior to obtaining of III phase trials results, because there was the same 'success' with other hyperthermia technologies before III phase trials. Anyway, the answer will be received in the nearest future.

The true history of hyperthermia

The initial hyperthermia concept of 60th 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 thermo-enhanced bloodflow; heating over 43-44°C causes tumor death, though its exact mechanism was unknown [90,91,92]. Toxicity of this heating approach also was well-realized, and Crile directly wrote that hyperthermia could be used only in case of radioresistant tumors.

Everything had changed in mid-60th after Manfred von Ardenne came into the topic. He loudly announced 'the discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia' and run the global 'hyperthermic race'. This was the main error of the initial hyperthermia concept: huge overestimation of heat-resistance of healthy tissues and contemporary underestimation of heat-resistance 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 bad understanding of very different properties and behavior of cell cultures and real tissues. Loss of malignancy of cultured malignant cells and, vice versa, malignant-like behavior of cultured healthy cells and loss of viability are only small part of these problems[213]. Though von Ardenne itself very soon had changed his mind 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 a basement of a 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 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 hasn't changed in principle.

Sure, it was not von Ardenne who started hyperthermia. Hyperthermia started long before he came and developed 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 left the hyperthermia field almost just after he entered it because his systemic cancer multistep therapy (sCMT) is not a hyperthermia. But 'hyperthermic belief' already didn't need him: it became 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 since 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[332,333,334] – the wave of belief had just swallowed these single opinions. In Seegenschmiedt et al. monograph248 of 1996, these 'marginal' opinions were referred as an unfortunate necessity and curiosity. Burger already in 1967 showed that healthy tissues in vivo are damaged already over 41°C[211,212] – this quiet voice from the far-away South Africa was disregarded. Even in 1998, it was believed that brain tissues could tolerate up to 44°C[253]. Currently dominant position is simple and unequivocal: there is virtually no difference in thermosensitivity of healthy and malignant cells in vitro[279]. This gets an understanding of the question of the therapeutic range of hyperthermia: does it exist at all? There are some theoretical considerations which suppose that it could be even negative.

It's 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 tertiary structure of proteins starts already above 41°C, which is a physiological limit of body temperature; it becomes significant over 43-45°C [335,336]. It's also well-known that the main mechanism of restore of damaged tertiary structure of proteins is intracellular chaperons, namely heat-shock proteins (HSP)[337], and that malignant cells express much higher levels of HSPs than normal ones[338]. Therefore, 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 HTcourses with more sessions were less effective than shorter ones. Over 43°C, tumor bloodflow cut-off becomes the main factor of 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's also well-known now that selectivity of tumor heating usually doesn't exceed 1°C[203]. 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[203]. 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 in surrounding tissues reaches critical level 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-80th, the definite conclusion on negative therapeutic range of the extreme hyperthermia was made for the first time only in 1991: it was displayed that thermo-enhancement rates (TER) of toxicity of some chemotherapies at WBH outweight the TER of their efficacy[339]. It took one more 14 years before this had led to a change in hyperthermia rationale[273], though the fact itself has still not accepted by hyperthermic community.

But initially nothing seemed foretold troubles. In 70th, the new 'basement error' of hyperthermia was developed: the illusion of 'virtually endless selectivity of extreme heating' was created predominantly by Storm et al.[340] works. Unbelievable 8-10°C difference between normal and tumor tissues was reported. It's hard to say now, was it a thermometry mistake or something else, it doesn't' 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 70th and 80th, 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 hadn't a machine, heated with any suitable warmer[341,342]. Near 1980, US National Cancer Institute (NCI) 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 started.

The first wake-up calls sounded in late-80th when institutional reports on NCI contract were reported. Heating is not enough, toxicity is limiting, 43°C in unreachable in view of toxicity – this was a resume of Stanford report[205]. Impossibility of extreme temperatures questioned the entire concept of extreme hyperthermia. 'Thermal dose' concept[343] was 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 dependence of heat-damage to living tissues. To that date it looked grounded, because difference in gain rate over and under 43°C was known since 60th. To the moment, futility of this parameter is obvious[284].

Though hyperthermia problems were already obvious to the most advanced users and scientists[210], it still looked very strong before 1990. Extreme hyperthermia concept was finally furnished after explanation of tumor bloodflow[274]: heating over 42.5°C causes 'cut-off' of tumor bloodflow with subsequent hypoxia, acidosis and following necrosis of tumor tissue. Hyperthermic activity reached its maximum: the record number of 8 monographs and 350 papers were published in 1990. Ten big randomized III phase 'trials for recognition' sponsored by RTOG and leading US universities were launched. Hyperthermia triumph was almost in hands – but it didn't happen.

Instead of the triumph, the huge disappointment awaited the hyperthermic community: all the trials[222,223,224,225,226] failed to show hyperthermia benefit. Nothing was confirmed: thermal parameters mainly didn't correlate with the endpoints, heating was not enough in frame of the extreme HT concept, toxicity was too high and number of sessions didn't 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 because 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 of this structure – this couldn't fall in a day. And – may be the most significant factor, – hyperthermia was already included in advance in the base manuals on radiotherapy. As the time has shown, may be 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 were no the cardinal resume. Whereas earlier Stanford institutional report conclusion was simple and clear, these conclusions 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 to the industry a possibility to recover them. Then, RTOG attempted to recover the situation and had launched the new deep hyperthermia trial[246] with 'second generation' equipment before the first negative trial[226] was published. This phase I/II trial results were negative again, and RTOG left the topic forever.

This was the turnover point. After independent sponsors – RTOG and the big universities, - finally left hyperthermia trials in 1996, and hyperthermic societies took the trials in their hands, the trend momentarily turned out. Since the 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's 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 is an 'open secret' – it's enough just to visit ESHO web-site. Even without respect to these interrelations, both industry and hyperthermic societies that time were united with the common aim – survival, - though had common interests. Our earlier critical analysis displayed 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 negative result. Surprisingly, in 1996 a 'very positive' trial was published from this merge. Though 3 of 5 arms remained negative1, this fact even didn't get the abstract. Simultaneously published 'positive' Overgaard et al trial[252] was clinically insignificant1 in view of inadequate control. Surprisingly, the fundamental Seegemschmiedt et al. monograph[248] was published in 1996 'like nothing happened'.

Understatement of negative results is a common problem, which forms a 'positive bias' in the entire modern medicine: because nobody interested in negative results, they are poorly published and quoted. Often, negative trials even not published. The published papers are usually brief and of lower quality. They are never reprinted and very rarely commented. Contrary, positive trials are usually often quoted and referred, they are reprinted and commented, 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 isn't mentioned, it's absent.

1996 was the turnover year in one more meaning: this was the last year of scientific hyperthermia. As it clear from the above, before 90th the hyperthermia was a scientific hypothesis, albeit with a touch of belief, though it's quite usual for a nice and promising hypothesis. In 90th, 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, pre-selection of patients, selective data reporting, incorrect analysis, selective data publication, systematic bias, etc[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 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 since 1996 to 2005 were a decade of the gradual and cautious hyperthermia revanche. Only 3 randomized clinical trials on external electromagnetic hyperthermia were held during this decade[254,257,258]. 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[275,344,264], 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's not enough just to say 'Nine randomized studies failed to show a significant benefit from addition of hyperthermia'[264] – this should be explained. Anyway, even such weak evidences allowed hyperthermia to reach some acceptance: it was once mentioned in NCCN guidelines in US and agreed for advanced cervix cancer treatment in Dutch.

On the other side of Pacific Ocean everything went well. Thermotron obtained an acceptance in Japan without III phase trials. Government supported it with grants, the treatments were covered with insurance. After US hyperthermia 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 catastrophe of 90th. Though consensus 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 90th were nearly forgotten, new trials were accepted, Japan looked as a bright example.
As usual, a fly in the ointment didn't hesitate to appear. In 2004, a grand failure of the first and the only randomized trial on whole-body hyperthermia happened: the result in hyperthermia arm was twice worse than in chemotherapy control[260]. It could be a burst but everything was done to blow off steam without explosion. These preliminary results were 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 never was commented or referred. ISHOW had dissolved silently. The result should be erased by understatement.

Nobody awaited that it is Japan where the next powerful blow will come from soon. New ugly facts came in 2005 from the old trouble-maker – independent trials. In late 90th, two big randomized clinical international multicenter trials[271,272] were 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 published in 2005 was the most painful. First, the highest temperature was reached in this trial but results in HT group were for worse than in RT-control, and it was impossible to explain. Second, the design of the trial was close to two previous 'positive' trials[254,257] which were already included in the 'golden database' of HT evidences. Therefore, these evidences were becoming questionable. It's not surprising therefore, that hyperthermic opinion-leaders rushed to explain why their trials were successful whereas Vasanthan trial failed, but it was inconclusive[345]. Third, all the old 'sins' of hyperthermia were remembered.

This ugly fact was impossible to ignore any more. The situation demanded urgent actions – and in 2005 hyperthermic opinion-leaders announced the 'resetting of hyperthermia rationale'[273] at last: extreme hyperthermia is impossible – moderate (mild) hyperthermia (MHT) based on thermal dose calculation was announced the actual concept.

The name of the event is demonstrative itself. Not 'reassessment', not 'correction' – it was a remarkable attempt of exactly the 'reset': to cancel everything happened before with one action and start from zero without any burden of former sins. And – this is principal, - without necessity to change anything; the same equipment, the same procedures, just less temperatures. Taking into account that 'hyperthermic temperatures' were in fact moderate already for more than decade (and in some meaning from just the beginning[346]), 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 hypothesis to disappointment or acceptance. With this reset, hyperthermia which time was up 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 were scientific action. 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[282]. New rationale looked obvious and visible. Number of publications had been rising. Publication of the second

negative IAAE trial[272] in 2007 already didn't hurt hyperthermia too much – it looked like a '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 frame of the old and ineffective extreme concept[287]. New evidences were slow to emerge. It was an obvious contradiction. Second, it was many times showed that thermal parameters are not connected with endpoints in any way and thermal dose is of lowest significance. Next, nothing changed in the hyperthermia practice. In Erasmus Medical center nothing had been changing since 1985, and hyperthermia remained extreme[251] – they just hadn't noticed any 'resetting' of the rationale. Manufacturers still recommend to heat tumors from 40°C to 45°C[347]. 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[274,348,349,283] 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[348]. According to Song et al., this rise of oxygenation at MHT was stronger than at extreme HT (16 mmHg vs 12 mmHg[274]), and MHT was more potent radiosensitizer than carbogen breathing and nicotinamode[348], and this effect is a stable platform for using MHT as general-purpose radio- and chemo sentisizer[349]. This was a discovery of one more magic ‘almost endless’ effect of hyperthermia and once more it seems to be fallacious.

First, the effect of the significant, sustained and long-lasting improvement of tumor oxygenation by MHT was revealed only by Song laboratory and was not supported by other groups, which haven’t revealed a sustained increase of both tumor bloodflow and oxygenation after MHT[280,350]. According to Vaupel and Kelleher, the real effect of MHT on tumor bloodflow and oxygenation is limited and transient, and can’t be used for radio sensitization. These are contrary points of view. Second, Song’s effect is very controversial because in fact ‘better oxygenation without better perfusion’ concept was declared without any satisfactory explanation of the effect. The offered explanation[349] is extremely weak and was entirely built on wrong premises and unwarranted suggestions. Understanding of tumor physiology could help in explaining of 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 dominates 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[351]. 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[352] which rises as tumor grows[353], is the obvious feature of a tumor. Alongside with the enhanced vascular permeability, 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[354]. The tumor shunting capacity could be so great that causes refractory hypoxemia at lung tumors in view of great intrapulmonary shunting[355,356]. 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 are always dilated and atonic[355].

Let's hypothesize, what happens in a tumor during mild hyperthermia. Tumor hasn't 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 a 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 (sladge). As a result, the major part of the enhanced bloodflow is just shunted through the tumor shunting vessels. Second, the speed-up 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 speed-up of capillary bloodflow significantly worsens the situation: due to the limited time of passage, the gas exchange is limited, and functional shunting[357] develops alongside with abovementioned anatomic shunting, looking like 'arterialization' of tumor blood-flow. Turbulent sladge of blood cells could block capillaries at all. As a result, bidirectional changes of tumor microcirculation at MHT could both to improve tissue oxygenation or have no changes, or to deteriorate hypoxia. Also, it could be supposed that perfusion and oxygenation at MHT significantly rise in the initially wellvasculated regions and clusters, whereas in the previously hypoxic and hypoperfused badly vasculated regions and clusters, the bloodflow doesn't rise or even decreases. 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 mm3. This is a too big scale to register a real microcirculation changes but it's 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 lympogenous dissemination.

Fortunately, there is an excellent paper of Sun et al.[281] 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's 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, 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: it seems that 24 hrs after a 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 doesn't lead to 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[354].

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[280]. 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 re-oxygenation.

For seven years since the re-setting, there is no any evidence of MHT efficacy. Surprisingly, in the later work[283] Song et al. once again operate with extreme 42.5°C heating though calling it 'mild hyperthermia'. This is a 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 extreme hyperthermia was replaced with inconsistent and controversial MHT rationale. This is the essence of mid-00th 'resetting maneuver': impossibility of extreme HT and 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 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 negative trials of 90th.

The results of experiments on combination of whole-body and local heating (WBH+LH) deny this opinion. It was obviously shown in 90th that this combination really provided much better heating up to 42.9°C vs. 41.3-41.7°C at WBH and 39.9°C at LH (p=0.0012), and WBH+LH heating was much more uniform[358]. Thermal dose CEM 43° T90 in combination group was 12 times higher than in local HT group (49 min vs. 4 min)359. Unexpectedly, this near to ideal heating led to much worse experimental results at dog sarcomas than LH only: time of local control didn't 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[359]. 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's 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 at >43°C204, von Ardenne 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 outweights its benefits.

As it discussed in details above, 'the last crusade' of hyperthermia in form of Issels et al. tremendous STS trial[277] led to fiasco1. Despite the official 'positive' result of the trial, the huge systematic bias in view of the doubled treatment power in HT-arm vs. 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's 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'll see the fourth basic method of cancer treatment at last. Possibly, it will be associated with hyperthermia-range heating, but let it don't deceive you: the 'temperature hyperthermia' is over.

Conflict of interests

The author is the General Consultant of OncoTherm Group in Russia and CIS countries and the Secretary Treasurer of International Clinical Hyperthermia Society.

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