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Critical analysis of randomized trials on hyperthermia: dubious effect and multiple biases

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Abstract

Hyperthermia in oncology still remains an experimental treatment with no realistic future in clinical cancer therapy, though declaration of the undisputed efficacy of hyperthermia is a common place in every hyperthermia paper. We've studied available randomized trials on hyperthermia from the position of 'null hypothesis' to confirm or refuse the efficacy and safety of clinical hyperthermia, taking into account also the possible biases. Unfortunately, the careful analysis of 14 randomized clinical trials doesn't confirm a clinical benefit of hyperthermia independently of its type: superficial, deep of whole-body. We haven't found any positive trial not affected with biases. With correction to distortions, there is no trial with obvious long-term positive effect of hyperthermia. Effect of hyperthermia could be shown in an experimentally designed clinical trial or versus inadequate comparator. In clinical setting and provided that the study design is correct, hyperthermia is not effective at all or not effective enough to justify its obvious disadvantages: toxicity and labor-intensity. Thermal concept of hyperthermia seems to be irrelevant. Nevertheless, multiple publications of positive trials, reviews and meta-analyses create an impression of hyperthermia renaissance.

Modern hyperthermia starts from the first paper on local hyperthermia of F. Westermark1 published in 1898, more than 110 years ago. 80 years ago in the early 30s, electromagnetic hyperthermia started with Whitney Radiotherm. 50 years ago, studies of Selawry and Crile launched the modern period of hyperthermia history, and almost 40 years have already passed since von Ardenn and LeVeen introduced local electromagnetic hyperthermia. Regardless of the starting point, hyperthermia is one of the oldest known treatment modalities in oncology.

In 2007, Horsman and J Overgaard[2] started their meta-analysis with the words: "Hyperthermia is generally regarded as an experimental treatment with no realistic future in clinical cancer therapy. …", and then added: «… This is totally wrong». Thus, the eminent hyperthermicians voiced the general opinion of the medical community on hyperthermia. This opinion was articulated by Hornback3 already in 1987 when he 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, and 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». Nowadays, clinical hyperthermia is still a time-consuming procedure, done with relatively crude tools, and is an inexact treatment method that has many inherent technical problems; it's an interesting, challenging, exasperating, not-too scientific field; it's already far not innovative, but is still an experimental form of therapy about which we have much to learn. If nothing changed for 25 years, something is wrong with hyperthermia.

Horsman and Overgaard[2] wrote then: «Although the role of hyperthermia alone as a cancer treatment may be limited, there is extensive preclinical data showing that in combination with radiation it is one of the most effective radiation sensitizers known. Moreover, there are a number of large randomized clinical trials in a variety of tumor types that clearly show the potential of hyperthermia to significantly improve both local tumor control and survival after radiation therapy, without a significant increase in side-effects». The simple question: if this is true, why is hyperthermia still not a standard method of treatment in oncology?

To answer this question, we studied all randomized clinical trials on hyperthermia published after 1990. We didn't include non-randomized clinical trials taking into account the well-known fact that such trials usually show much higher effect. It was clearly demonstrated, for instance, in the famous RTOG trial on thermoradiotherapy of superficial tumors when 68% complete response rate was reported in phase I/II non-randomized trial[4] and only 32% in phase III randomized trial[5]. Editorial of Brizel[6] clearly shows inconsistency of such non-randomized trials.

We reviewed 14 randomized clinical trials: 7 on superficial local hyperthermia (see Table 1.), 6 on deep loco-regional hyperthermia (see Table 5.) and 1 on whole-body hyperthermia. We proceeded from the "null

hypothesis", i.e. considering hyperthermia not effective and/or not safe. From this point of view, we analyzed trials for 1) efficacy by endpoints, 2) toxicity, 3) biases. With the "null hypothesis", the negative trial result does not need any explanation. Therefore, only positive trials were subjects to our analysis.

Superficial hyperthermia clinical trials

The clinical trial of Perez et al.[5] (RTOG protocol 8104) published in 1991 compared thermoradiotherapy (TRT) versus radiotherapy only (RT) in a well-designed and large (307 patients with tumors of chest wall, neck nodes and melanoma) randomized trial sponsored by Radiation Therapy Oncology Group (RTOG). Complete local response (CLR) was reached in 32% of patients in TRT arm and in 30% of RT arm; the difference was statistically insignificant. There was no effect to overall survival. Despite the demonstration of stronger thermal enhancement of RT in tumors <3 cm, the result was disappointing.

Three clinical trials with similar design were published nearly simultaneously from 1990 to 1993, comparing efficacy of different TRT protocols: Kapp et al.[7] compared the effect of 2 and 6 hyperthermia sessions; Emami et al.[8] and Engin et al.[9] compared the effect of 4 and 8 sessions (see Table 1). The difference between 'short' and 'long' protocols was negligible, and Engin et al. even showed lower efficacy of 'long' protocol: CLR was 55% in 8 sessions arm and 59% in 4 sessions arm (not significant).

Trial		Kapp et al.[7]	Perez et al.[5]	Emami et al.[8]	Engin et al.[9]	Vernon et al.[10]	Overgaard J[11]	Jones et al.[12]
Organization		Stanford University	Mallinckrodt Institute of Radiology	Mallinckrodt Institute of Radiology	Thomas Jefferson University	Some European and Canadian centers	Danish Cancer Society	Duke University
Country		USA	USA	USA	USA	Europe/Canada	Europe	USA
Year of publication		1990	1991	1992	1993	1996	1996	2005
Design		Monocenter	Monocenter	Monocenter	Monocenter	Multicenter	Multicenter	Monocenter
Nr of patients		70	307	173	41	236	70	108
Nr of tumors		179	N/D	240	44	N/D	134	N/D
Type of tumors		Chest wall, neck nodes, melanoma	Chest wall, neck nodes, melanoma	Superficial	Chest wall, neck nodes	Chest wall	Melanoma	Chest wall, neck nodes, melanoma
Therapy	HT+	RT + HT 42.5°C (6 HTs)	RT + HT 42.5°C x 45-60' (2 HTs)	RT + HT 42.5°C (8 HTs)	RT + HT 42.5°C (8 HTs)	RT + HT 42.5°C	RT + HT 43°C x 60' (3 HTs)	RT + HT 10<CEM43°C T_{90}<100 (10 HTs)
	HT-	RT + HT 42.5°C (2 HTs)	RT only	RT + HT 42.5°C (4 HTs)	RT + HT 42.5°C (4 HTs)	RT only	RT	RT
Complete local response (%)	HT+	52%	32%	57.8%	55%	59%	62% (immed.) /46% (2yr)	66%
	HT-	51%	30%	54.7%	59%	41%	35% (immed.)/ 28% (2 yr)	42%
Overall survival	HT+	N/D	Statistically insignificant	Statistically insignificant	N/D	Statistically insignificant	Statistically insignificant	Statistically insignificant
	HT-							
Disease-free survival	HT+	N/D	Enhanced	N/D	N/D	Enhanced	N/D	Enhanced
	HT-							
Burns	HT+	N/D	30%	N/D	40%	11%	N/D	46%
	HT-		0%		40%	2%		5.7%
Complications (overall)	HT+	5% needed medication, 3% needed surgery	N/D	18% of severe complications	N/D	Pain	27% pain, incl. 8% moderate and 6% severe	16% needed pause of treatment
Authors estimation		Negative	Negative	Negative	Negative	Positive	Positive	Positive
Final estimation		Negative	Negative	Negative	Negative	Dubious	Dubious	Dubious

Table 1. Randomized clinical trials on superficial local hyperthermia published after 1990

In 1996, Vernon et al.[10] a trial was published showing significantly better CLR rate for TRT arm (59%) than for RT only arm (41%) without any effect to survival. Unfortunately, despite the big enough sample size, this result couldn't be considered relevant because of the incorrect trial design. This was a combination of 5 different European and Canadian clinical trials merged to reach statistical significance. Different protocols are hard to compare, and choice of patients is not excluded, and there are controversial data. For example, Vernon et al. report only 11% of burns whereas other trials report 30-45% burns, but at the same time "some" patients in Vernon et al. trial didn't fulfill the protocol due to pain whereas there were no such patients in other trials with much higher share of burns. We consider this trial "semi-randomized" and consider its result dubious because of low reliability.

In the same year, a clinical trial of Overgaard et al.[11] was published. It was multicenter (11 centers in 6 countries) randomized controlled trial on 70 patients with metastatic or recurrent skin melanomas. 128 lesions were evaluated (63% ≤ 4 cm, 37% > 4 cm). RT was applied by 3 large fractions (8/9 Gy) with subsequent hyperthermia (43°C, 60 min) directly following the RT. Immediate CLR rate in TRT arm was 62% versus 35% in RT only arm (gain 77%, p=0.003), and 2 year local control rate (LCR) in TRT arm was 46% versus 28% in RT only arm (gain 64%, p=0.008).

Despite being good at first sight, Overgaard et al. trial leads to many questions. The sample of the trial is too small, especially considering its multicenter design: 11 European cancer centers enrolled only 70 patients for 6.5 years, i.e. less than 1 patient per center annually. Taking into account that melanoma is a quite frequent tumor, this creates ideal terms for pre-selection of patients, on the one hand, and for special attention to treatment of hyperthermia arm, which usually leads to much better clinical results. Though the trial seems to be well-randomized, the latter bias should obviously be presented with such a small sample. And, surely, such a small sample is not representative. The authors justify that such a small sample as it is, is enough for the statistically significant result but the approach which is correct for experimental trial is not suitable for clinical trial where the sample size and especially its proportion to general sample is a significant factor of the representativeness of the results. Additionally, in this trial not the patients but the tumors were subject to randomization. This is also typical for a rather experimental design. As a result, the trial looks like in vivo radiobiology experiment in clinical trial shell.

The main bias of the study is an incorrect comparator which is known as a typical bias in clinical trials. The best or at least standard control treatment is the implied demand for clinical trials. The usual RT dose for skin melanoma treatment, as well for other superficial lesions, is 40-50 Gy per site[5,9] with common dose not more than 100 Gy, and it's commonly known that low doses significantly reduce the effect of RT[26]. 24/27 Gy total doses (TD) used in this trial are certainly low, especially considering the well-known radioresistance of melanoma. The median number of tumors per patient was 2; therefore there was no reason to lower dose per site because of high common dose. Also, the usual fractionation for skin melanoma is 10-20 fractions of 2-5 Gy each. Hypofractionation used in this trial (3 fractions 8-9 Gy each) is rare. Such choice of comparator has only one logical explanation: this protocol is ideal for thermal modification. With three doses only, each dose is modified and it's simpler to coordinate HT and RT; and the larger single RT dose is, the better modification effect is. Low common dose allows showing hyperthermia effect because standard high-dose radiotherapy usually makes hyperthermia effect insignificant[19]. This once again demonstrates that this is not a clinical trial but in vivo radiobiology experiment without clinical significance.

This impression is enforced by lack of proper survival analysis. Of course, survival analysis is a core for any clinical trial but not for radiobiological experiment. All known in this trial is that immediate local control in hyperthermia arm was better and remained better after 2 years, but it's still unknown, which overall survival was in both groups 2 years later. Overall, 5-year survival was 19% which is far worse than the average level for metastatic skin melanoma, but there is no answer to the main question – which survival was in TRT and RT arms and which group had a better survival rate? There is a very detailed survival analysis by local response, number of tumors, sex, even by general control of all diseases – everything except the primary goal of the trial, the survival by groups – and it looks like hiding the negative results. There is another reason to suppose that negative results in this trial are incompletely reported: for instance, there is not a word about burns, though these are obviously reported in other trials, and it is usually more than 30%.

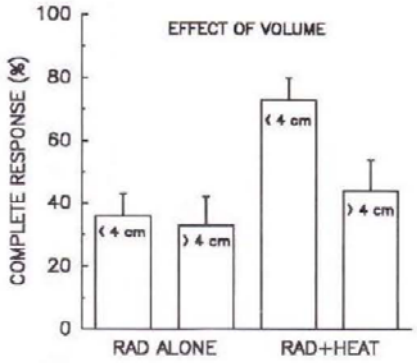


Figure 1. Effect of tumor volume on complete response rate (Overgaard et al., 1996[11])

It's also not clear, why 4 cm was used as a border for small tumor size? All the other randomized studies for superficial tumors used 3 cm as a border size, and this is absolutely correct because superficial tumors generally considered as so, if they are less than 3 cm deep. In RTOG 8104 trial[5], 77% of tumors were more than 3 cm. In Overgaard et al. trial, 63% of tumors were less than 4 cm and this distribution couldn't be compared with other trials because of the different criteria of tumor size. Therefore, it's impossible to say

exactly, whether there was pre-selection of small tumors in this trial. It was already known to that moment that TRT is significantly more effective in small tumors. The authors tried to prove that tumor size impact was statistically insignificant (p=0.21), but it seems to be not correct. As it's seen in Figure 1, the impact of tumor volume is much stronger in TRT arm, and the only reason why it's not statistically significant is the 4 cm limit. With a 3 cm limit, this difference would be higher and probably statistically more significant, as it is in other trials.

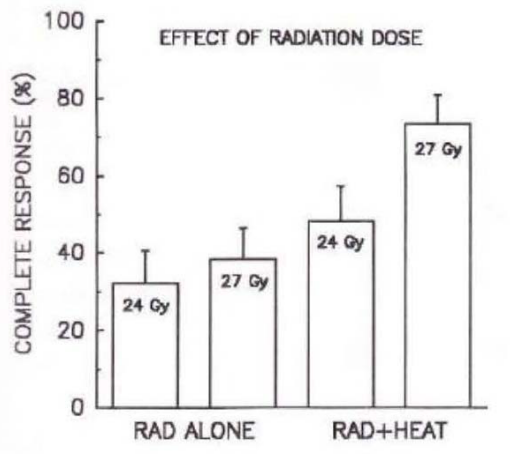


Figure 2. Effect of radiation dose on complete response rate (Overgaard et al., 1996[11])

Moreover, 2 different RT protocols with TD 24 and 27 Gy were used in the trial. There was no reason to include two RT protocols to examine HT efficacy: in this case all other factors should be equal. It's obvious that authors intended to show that thermal enhancement rises with the increase of TD (Figure 2) with subsequent extrapolation of the conclusion to the higher (normal) doses. This is an absolutely incorrect approach. The results of other trials show that with normal/high TD, the effect of thermal modification becomes insignificant or disappears[5,7,8,9] or even reverses[19], therefore the extrapolation is incorrect. RT strength in this trial was much higher than HT strength: CLR rate was 56% for 27 Gy vs. 25% for 24 Gy (Gain 124%, p=0.05), i.e. twice stronger than HT effect (Gain 64%). This also supposes that with rise of TD of RT, the relative thermal enhancement will diminish soon. The displayed thermal effect was rather the effect of single dose difference (9 Gy vs 8 Gy) than the effect of TD because the higher thermal effect to higher single doses is well-known in radiobiology. Finally, statistics do not look correct because the authors report only 1.17 odds ratio for RT versus 1.73 for HT.

The above mentioned is enough for drawing the conclusion:

- The trial is in fact in vivo radiobiological study without clinical significance.
- The trial seems to be especially designed for demonstration of hyperthermia efficacy to the detriment of practical value.
- The trial uses an incorrect comparator.
- The actual survival outcome of the study is hidden.
- Negative data seems to be reported incompletely.

Apparently, this is the reason why the study had no consequences: further studies on TRT of malignant melanoma are absent and there is not any clinical application. That is why we consider this trial result as dubious.

Characteristic	No HT (n = 52)		HT (n = 56)	
	No. of Patients	%	No. of Patients	%
Age				
Median	59.3	-7 years	52.4	
Range	38.4-83.8		18.2-90.9	
Sex				
Male	13		14	
Female	39		42	
Site of disease				
Breast/chest wall	33	63	37	66
Head and neck	6	12	8	14
Melanoma	6	12	5	9
Other	7	13	6	11
Multiple HT fields	7	13	18	32
Prior XRT	17	33	22	39
RT dose, Gy (given on protocol)				
Median	50	+10%	55	
Range	18-70		20-70	
Metastasis at enrollment	17 of 51	33	16 of 52	31
Additional systemic therapy	34	65	33	59
Hyperthermia dose, CEM 43°C T_{90}				
Median	0.74		14.3	
Range	0.07-1.49		0.57-36.21	

Abbreviations: HT, hyperthermia; XRT, external radiation therapy; RT, radiation therapy; CEM, cumulative equivalent minutes.

Table 2. Patient characteristic and treatment summary from Jones et al.[12] clinical trial

In 2005, the most famous and the most cited superficial hyperthermia study of EL Jones at al.[12] from Duke University was published. This trial deserves a very careful analysis because of its impact on hyperthermia application. This was a prospective, randomized, controlled, and monocentric study on 108 patients with superficial tumors of chest wall, neck nodes and melanoma. TRT with CEM43°C T90 =10-100 was studied versus fractionated RT alone (single dose 1.8-2 Gy, total dose 30-70 Gy). CLR was the main endpoint and it was significantly higher in TRT arm – 66.1% vs. 42.3% than in RT alone arm (p=0.02).

Even the first look at the patient characteristic (Table 2) reveals biases. The median age for TRT arm was 7 years less than for the RT only arm (52.4 vs. 59.3 years). Such difference is impossible with proper randomization for a more than 100 person sample. Incorrect randomization is a well-known defect of randomized trials. Some other points also suggest improper randomization: e.g., radiation dose in TRT arm was 10% higher. As it is shown above, 10% increase of RT dose in Overgaard et al.[11] trial led to 124% gain of 2 year local control rate. This improper randomization was further distorted by pre-selection of "heatable" patients: after test heating, 13 patients from 122 (11%) were considered "non-heatable" and didn't enter the trial. This pre-selection could not be considered as a defect if trial conclusion refers to "heatable" patients only, but it doesn't include such remark.

Factor	Value	Possible CLR Gain
Pre-selection of "heatable" patients	11%	+10%
Pre-selection of RT-resistant patients	36%	+10%
RT dose bias	10%	+50-100%
Median age	-7 years	Unpredictable gain
Tumor size	Unknown	+30-50%[5,7-9]
Total weight:		**>60%**

Table 3. Analysis of impact of biases in Jones et al[12] clinical trial

There is no tumor size data in the trial, though tumor size analysis is always present in any clinical trial as one of the major predictors of RT success. Taking into account the obvious defects of randomization, lack of tumor size data, pre-selection of "heatable" patients and slow enrollment (122 patients per 7 years, i.e. 1.5 patients per month), selection of patients with small tumors is highly probable. One more distortion factor is the high percentage of RT-pretreated patients (36%).

These patients were radioresistant: whereas in TRT arm their CLR rate was virtually equal (68.2% in pre-treated and 65% in not pre-treated), CLR rate in RT only arm was significantly lower in the pre-irradiated group (23.5% vs. 51%). Simple analysis shows that 36% share of RT-pretreated patients adds 10% difference in favor of TRT arm. This is not an obvious defect but well-designed trials usually exclude such known disturbing factors, enrolling either pretreated or not pretreated patients.

We tried to analyze the possible impact of all the above mentioned biases on CLR rate (see Table 3). The result shows that only accountable factors – pre-selection of "heatable" and RT-resistant patients and RT dose bias, – could add at least 60% to the effect in TRT arm, whereas the measured CLR gain in the trial is

57%. With regard to the known younger age of TRT arm and possible tumor size bias, the total impact of biases could be even stronger. In other words, it's possible that hyperthermia really didn't improve the radiotherapy effect but, vice versa, it worsened that. Taking into account the results of the previously reviewed trials, this conclusion doesn't look impossible.

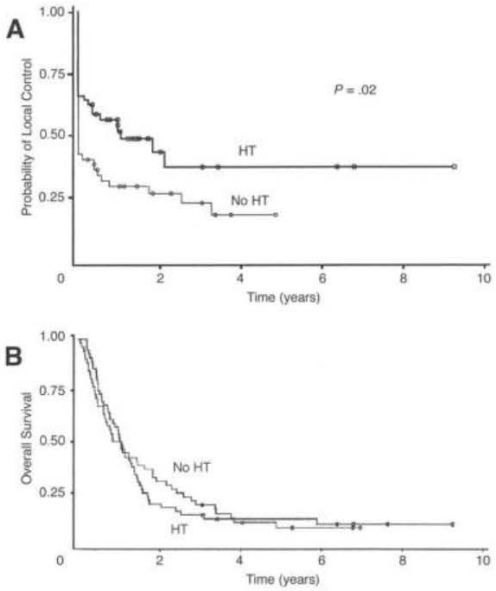
Local Control Rate (LCR) was the only positive (+57%) and statistically significant (p=0.02) effect of the study (see Figure 3, A). Long-term LCR is fully explained by initial LCR gain because the hazard of progression had become equal in both arms already in the 1st year (see Figure 3, C). Overall survival (see Figure 3, B) was the most disappointing endpoint: it was worse in TRT arm from the 1st year to the end of the trial, though statistically insignificant (p=0.84). With respect to known significant biases in favor of TRT arm, these results are threatening. This negative impression is further aggravated by attempts to hide the negative course of the trial. Table 4 is demonstrative in this respect. In fact, patients in TRT arm more patients died but with perfect local control (see Figure 3, A-B). In the table, a very favorable picture of better local control in TRT arm is shown but without detailed information which could spoil the impression. This is an obvious example of data manipulation. Finally, safety in this trial was the worst among all previous trials: 46% of burns, incl. 3% of 3rd degree; 11% of complications of catheterization, incl. 3% of grade 3 toxicity. 16% of patients had to pause the treatment due to toxicity.

Status	No HT (n = 52)		HT (n = 56)	
	No. of Patients	%	No. of Patients	%
Local recurrence				
Less than CR	30	58	19	34
Later failure	9	17	10	18
Death (without local treatment failure)	11	21	21	37
Alive with local control	1	2	5	9
Censored: additional local surgery	1	2	1	2

Abbreviations: HT, hyperthermia; CR, complete response.

Table 4. 2yr Local Control Status from Jones et al.[12] clinical trial

The authors' conclusion - "Adjuvant hyperthermia with a thermal dose more than 10 CEM 43°C T_{90} confers a significant local control benefit in patients with superficial tumors receiving radiation therapy", - seems irrelevant. We consider the result of the trial dubious. The observed local control benefit could be fully explained by the reported biases, and with regard to the biases survival gain in TRT arm seems to be negative.



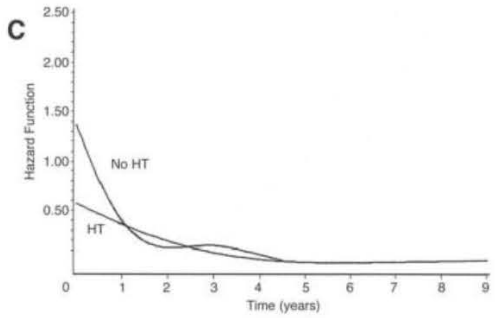


Figure 3. Clinical results of Jones et al[12] clinical trials. A – Probability of Local Control. B – Overall Survival. C – Hazard Function

In 2007, a paper of Jones et al.[13] was published advocating the use of hyperthermia as a radiotherapy sensitizer for treatment of chest wall recurrences: "Data from several randomized trials suggest that the addition of hyperthermia to radiation can increase the response rate for such local recurrences". The same year, the 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 if the radiation failed. The NCCN guidelines stated that, "while there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone (Jones et al., 2005[12])". The NCCN guidelines noted that the addition of hyperthermia generated substantial discussion and controversy among the NCCN panel members and is a category 3 recommendation (the recommendation is based upon any level of evidence but reflects major disagreement). The counterpoint was stated by B McCormick[14] from Department of Radiation Oncology of Memorial Sloan-Kettering Cancer Center who said: "Although HT in chest wall recurrences has been used for several decades, recent reports are few. Unresolved issues of radiation dose, optimal temperature and timing of HT, and quality assurance problems with thermometry are apparent from these studies. Although clearly an effective treatment option in this clinical scenario, more research on HT and radiation is needed before this treatment combination can be considered standard care".
Thus, from 7 reviewed randomized clinical trials on superficial hyperthermia, 4 are considered negative by the authors themselves (Perez et al.[5], Emami et al.[8], Kapp et al.[7] and Engin et al.[9]). Of the 3 remaining trials which are considered positive by their authors, Jones et al. trial was biased and dubious, Vernon et al. trial had incorrect design and controversial data and Overgaard et al. trial was not representative, it was biased and clinically insignificant.

These trials showed that superficial TRT is effective:
- for small tumors only (≤3 cm, thermal enhancement ratio (TER)=1.2-2) with no effect for big tumors (≥3 cm, TER=0.9-1.1);
- for those tumors only which are possible to heat adequately (20'≤Tmin 42.5°C);
- for 'heatable' tumors only;
- only with effective thermal control;
- with large RT fractions but much less effective or not effective with typical hyperfractionated protocols;
- only in special setting – HT shortly after RT.

Even in this setting, HT statistically significantly improves only the CLR rate (+30-60%) and the short-term local control rate (1-2 years). Total local control rate (complete + partial local remission) improvement and long-term local control rate (>2 years) are generally statistically insignificant. The major prognostic factors for duration of local control were tumor histology, then RT dose, then tumor size, then minimum temperature in the tumor (much less significant). The recent retrospective study of de Bruijne et al.[53] showed that with respect to tumor volume, thermal dose was not associated with any clinical endpoint. There is no influence on overall survival; sometimes it tends to be worse with HT[12]. Even these small and partial successes of superficial hyperthermia look clinically insignificant because small tumors represent smaller part (25-35%) of superficial tumors and could be easily ablated or removed by surgery (methods of choice). These are big superficial tumors, which are interesting for hyperthermia treatment, but it is ineffective in this regard. Major part of these tumors is hardly heatable because of localization, body shape, sensitivity, etc. Hard thermal control used in 'positive' clinical trials is impossible in clinical practice (for example, 24-channel thermometry is routinely used in Erasmus university HT center); bad thermal control

significantly reduces both efficacy and safety – up to reversal of the ratio. Hypofractionated RT protocols, which are optimal for thermal modification, are much less used in practice. Optimal sequence of RT and HT is hard or impossible to manage in real practice; suboptimal sequence makes the combination much less effective or ineffective. The level of toxicity (≥30% of burns), which is applicable in clinical trials, is impossible in clinical practice.

Conclusion on superficial hyperthermia:

- There has been no clear evidence of overall efficacy of hyperthermic radiotherapy modification of superficial tumors so far.
- Existing positive results are biased and/or clinically insignificant.
- Superficial hyperthermia is still an experimental treatment with limited applicability in clinical practice.

The conclusion of hyperthermia society opinion leaders is vague: "In a select group of patients, the addition of hyperthermia to radiotherapy increases the eradication of local tumor, with a modest increase in largely self-limited toxicity. While attainment of CR is a worthwhile study endpoint, one must also consider the need to address palliation of symptoms, in that the majority of these patients will ultimately succumb to their distant disease. In the modern era of 'targeted' therapy, the issue of local control will increasingly become more important. Future applications of hyperthermia combined with radiotherapy should include the addition of targeted biological agents in the hopes of increasing the CR rate and hopefully translating into prolonged disease-free survival. Liposomal doxorubicin has been combined with radiotherapy and hyperthermia by one group and warrants further evaluation in the future. Efforts must be taken to provide reproducible, efficacious heating of tumors so that the synergistic effect of combining radiotherapy and hyperthermia can be optimized. With rigorous thermal dosimetry and careful treatment technique, the addition of heat to radiotherapy can result in long-term local control of breast cancer chest wall recurrences"[15].

Having been translated from Aesopian language, this means that hyperthermic radiotherapy modification is effective only in a selected group of patients, and it causes primarily palliation of symptoms by improved local control without any effect to survival, because metastatic process is not affected by this treatment, and this local effect could be achieved only upon conditions of effective heating, rigorous thermal dosimetry and careful treatment technique, and hyperthermia increases the toxicity of the treatment, and its future application of TRT depends on the targeted biological agents which could increase its effect. Thus, this conclusion also contains a hidden confession of insufficient efficacy of superficial TRT of breast cancer and chest wall recurrences, and these limitations would keep hyperthermia far from clinical practice.

Clinical Trial		Emami et al.[16]	van der Zee et al.[17]			Mitsumori et al.[18]	Vasanthan et al.[19]	Issels et al.[20]	Harima et al.[28]
Sponsor		RTOG	Dutch Deep Hyperthermia Group			IAAE	IAAE	ESHO, EORTC, NIH	N/A
Year of publication		1996	2000			2007	2005	2010	2001
Enrollment period		1986-1992 6.5 years	1990-1996 6 years			1988-2002 3.5 years	1998-2002 3.5 years	1997-2006 9.5 years	1994-1999
Nr of patients		184 (173)	358			80	110	341	40
			114	143	101				
Age	HT+		51	62	73		50	51	65
	HT-		50	64	69		45	52	62
Tumor type		Deep-seated tumors of head & neck and pelvis	Loc. adv. cervical cancer	Loc. adv. rectal cancer	Loc. adv. bladder cancer	Locally advanced NSCLC	Locally advanced carcinoma of the uterine cervix	Soft tissue sarcoma	Loc. adv. cervical cancer
Pretreatment		Heavy: 84% RT, 45% surg, 34%ChT	No			No	No	No	No
Comparison		TRT vs. RT alone	TRT vs. RT alone			TRT vs. RT alone	TRT vs. RT alone	TChT vs. ChT in complex treatment	TRT vs. RT alone
Base treatment		EBRT TD ≤100 Gy	EBRT+BT TD=65Gy	EBRT TD 66-70 Gy	EBRT TD 66-70Gy	EBRT	EBRT + BT TD=84 Gy	ChT (EIA) → surgery → RT → ChT (EIA)	EBRT + BT TD=82.2 Gy
HT unit(s)		N/A	3 units: BSD2000, TEM, 4-guide			Thermotron-RF8	Thermotron-RF8	BSD2000	Thermotron-RF8
HT protocol		42.5°C x 30-60', 1 (before RT) or 2 (bef/aft RT) HTs	42°C x 60', 5 HTs after RT 1/week			42°C x 60', 5 HTs after RT 1/week	42°C x 60', 5 HTs after RT 1/week	42°C x 60', 16 HTs interval 3 days	42°C x 60', 3 HTs after RT 1/week

Complete Local Response (CLR)	HT+	CLR 55%	CLR 55% (p<0.001)			Statistically insignificant (p=0.49)		CLR+PLR=34% (p=0.02)	80%
			CLR 83%	St.insign.					
	HT-	CLR 53%	CLR 39% (p<0.001)					CLR+PLR=16% (p=0.02)	50%
			CLR 57%	St.insign.					
Overall Survival (OS)	HT+	34% (2 y)	51% (3y)			Statistically insignificant (p=0.868)	73.2% (3y) (p=0.19)	79 mnth (p=0.43)	58% (3y)
	HT-	33% (2 y)	27% (3y)					74 mnth (p=0.43)	48% (3y)
Local Progres-sion Free Survival (LPFS)	HT+					significantly better (p=0.036)	68.5% (3yrs) (p=0.58)	66% (4y) (p=0.003)	
	HT-							55% (4y) (p=0.003)	
Progression Free Survival (PFS)	HT+							32 mn (p=0.011)	
	HT-							18 mn (p=0.011)	
Common toxicity	HT+	3-4 Grade - 22%					17% Gr2, 1% Gr3	96.4% (p=0.005)	
	HT-	3-4 Grade - 12%					4% Grade 2	78.5% (p=0.005)	

Table 5. Randomized clinical trials on deep local hyperthermia published after 1990

Hyperthermia of deep-seated tumors

The phase III RTOG clinical trial on deep hyperthermia of Emami et al. was published in 1996[16]. This was a prospective, randomized, controlled, multicenter trial. 184 heavily pre-treated patients with deep-seated tumors of head & neck and pelvis were enrolled. TRT with HT 42.5°C for 30-60' applied after RT vs. RT alone (cumulative dose ≤100 Gy) was tested. CLR rate was 55% in TRT arm and 53% in RT only arm. 2-year overall survival was 34% in TRT arm and 33% in RT only arm. Acute 3-4 grade toxicity was 22% vs. 12% and late toxicity 20% vs. 12% in TRT and RT arms respectively. Thus, complete response rate increment was negligible and statistically insignificant; toxicity increment was substantial, both acute and late, but statistically not significant.

The authors concluded that "Interstitial hyperthermia did not show any additional beneficial effects over interstitial RT alone. Delivery of HT remains a major obstacle. The benefit of HT in addition to RT still remains to be proven in properly randomized prospective clinical trials after substantial technical improvements in heat delivery and dosimetry are achieved".[16]

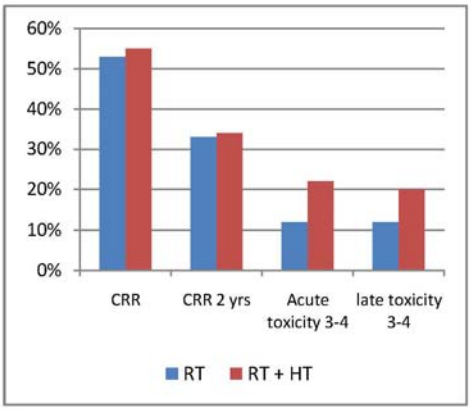


Figure 4. Clinical results of Ememi et al.[16] trial. (CRR – Complete Response Rate)

In 2000, Dutch Deep Hyperthermia Group (DDHG) published a prospective, randomized, controlled, multicenter phase III trial of Van der Zee J et al.[12]. 358 not pretreated patients were enrolled in 11 Dutch centers and randomized for TRT (182 patient) and RT only (176 patient). RT was applied as External Beam RT (EBRT) + Brachytherapy (BT) with total dose 65 Gy. 5 sessions of deep HT (42°C for 60' up to 90' of total time) was administered weekly 1-4 hrs after RT. CLR rate and Local Disease-Free Survival (LDFS) were the endpoints.

The trial included three sub-groups (see Figure 5.):

- Advanced cervical cancer 8114 patients)
- Advanced rectal cancer (143 patients)
- Advanced bladder cancer (101 patients)

Though overall CLR rate was statistically significantly increased in TRT arm (55% vs. 39%, p<0.001) and duration of local control in TRT arm was also significantly longer (p=0.04), there were great differences between the subgroups. There was no statistically significant effect in rectal cancer group, and OS in TRT

arm was worse there, though being statistically insignificant. In general, the result in rectum cancer group was negative. The bladder cancer result was better but the improved local control disappeared during the follow-up, and there was no effect to OS. In general, this result was dubious.

Cervix cancer group was the only one with statistically significant improvement of all CLR (83% vs. 57%, p=0.003), LDFS (3y LDFS 61% vs. 41%, p) and OS (3year OS 51% vs. 27% in RT only arm, p=0.009). Therefore, only cervix cancer results were further reported[21]. In 2008, Franckena et al.[22] published the impressive result of long-time follow-up: 12-year local control rate was 56% in TRT arm vs. 37% in RT arm (p=0.01); 12-year overall survival in TRT arm was 37% vs. 20% in RT arm (p=0.03). Median overall survival was 2.64 years in TRT arm vs. 1.78 years in RT arm. Local recurrence rate was 25% in TRT arm vs. 31% in RT arm. Distant metastases rates were the same in both arms (31% and 32%).

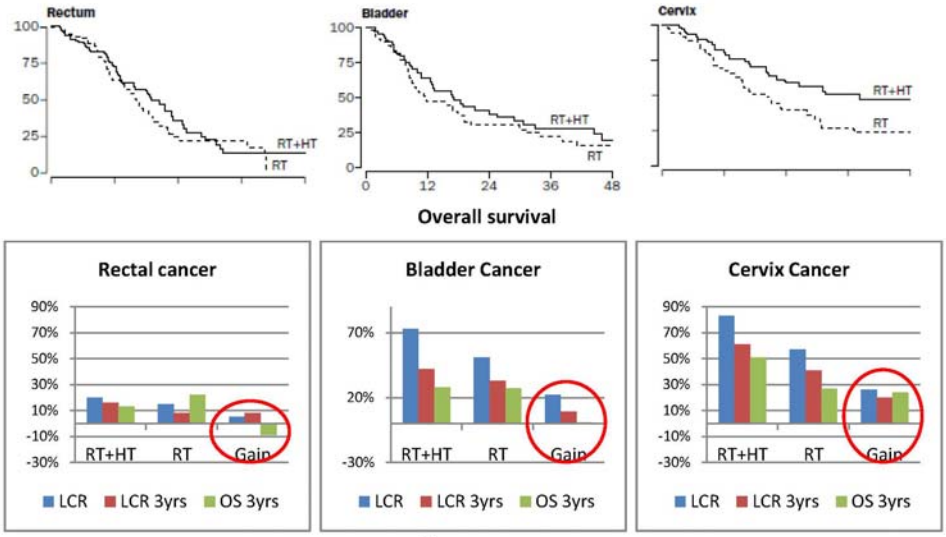


Figure 5. Clinical results of DDHG trial of Van der Zee J et al.[17]: LCR – Local Control Rate, OS – Overall Survival

First of all, interpretation of the trial result provokes disagreement. The statements like "in this trial, a beneficial effect from adding hyperthermia to standard radiotherapy was demonstrated, particularly for patients with cervical cancer"[23] or "the overall result showed a substantial benefit for whole group but only 114 patients with cervical cancer were included in the published reports of this trial"[24] are incorrect. In fact, beneficial effect was demonstrated only in cervical cancer sub-group. Results in the other two sub-groups were negative (rectal cancer) or dubious (bladder cancer).[25] Therefore, for correct analysis of trial results we consider it consisting of three sub-trials where only one was successful.

Secondly, it seems that the trial used incorrect comparator – RT with total dose 67 Gy vs. 75-95 Gy in successful RT trials. It's impossible to say which part of the TD was targeted to tumor mass in this trial because it's not specified. It's known only that "para-aortal nodes were routinely included in the external radiotherapy field"17, therefore TD to tumor mass was less than 67 Gy (estimated not more than 60 Gy). This point was widely criticized and authors' attempts to justify that the comparator look weak. The position that such dose "is considered adequate treatment"23 is unsatisfactory because it was not adequate but it was the best available or standard treatment is demanded by default for control treatment in a III phase trial. Inadequacy of low doses was obviously showed by Perez et al. trial26: in Stage III unilateral lesions, the 10 year pelvic failure rate was about 50% with ≤70 Gy to tumor mass versus 35% with higher doses, and in bilateral or bulky tumors it was 60% with doses ≤70 Gy and 50% with higher doses. Therefore, higher RT dose could add 25-30% and more to long-term local control rate and there is not any ground to consider total dose less than 70 Gy adequate, especially for control group in clinical trial. Combination of an external-beam RT (EBRT) with a brachytherapy (BT) with total dose of 75-85 Gy to tumor mass has been widely accepted since the mid-70s[26,27] whereas enrollment to DDHG trial started in 1990. Advocacy that the low dose was a consequence of the fact that not all patients received full RT is disproved by the study protocol. According to the protocol, EBRT was applied to whole pelvis by 23-28 fractions of 1.8-2.0 Gy to TD 46-50.4 Gy; then HDR BT 17 Gy in 42 patients or LDR BT 20-30 Gy in 49 patients was applied[17,21]. It follows that, at least in 42 patients TD couldn't exceed 67 Gy and in the other 49 patients it could vary in the range of 66-80 Gy. Therefore it seems that the really achieved TD of 67-68 Gy

is a planned target TD of the trial and not a result of a not full RT. Another attempt is to change the focus from the problem of insufficient RT dose to the general change of cervix cancer paradigm to chemoradiotherapy after the start of DDHG trial[25]. This is really true but it doesn't answer the question of RT dose inadequacy in any way. As it's obviously seen from Table 6, the clinical results in DDHG trial control (RT) group were 1.5-2 times worse than the best results available, and even much worse than the old results of Fletcher received in 1954-1963 on the very first megavolt linear accelerators with TD=90 Gy for IIIB stage. That is, it's evident that DDHG trial used incorrect comparator which is considered a serious bias.

The authors explain the worse clinical results by the relatively young age, bulky tumors and nodal involvement. The first reason is not convincing. Median age 50-51 is equal to age of the first diagnosis of cervix cancer in Northern Europe (50-52) and of necessity nearly equal to any other North-European study enrolling non-treated patients. Also, though in this trial the immediate CLR rate was better for older patients[21], other studies show that younger age is associated with better long-term results and survival[30,34]. Two other reasons look acceptable but not evident enough. Though the average tumor size in DDHG trial is really big, in terms of survival this is a significant factor for stage I but not for more advanced stages where parametria involvement and nodal status are significant[26,30]. Nodal involvement in DDHG trial, though seemed to be more extensive than in other trials (70% vs. 30-40%) was assessed in 44% of patients only[21], therefore it is not evident. To summarize, there are some grounds to consider DDHG sample more severe than in other clinical trials but it's not evident. Anyway, the use of stage of disease is valuable and correct for comparison (see Table 6.). And the question remains: why was a so gentle RT schedule used which is obviously inadequate to severity of the sample?

Trial	Van der Zee at al., 2000[17,21,22]		Harima et al., 2001[28]		Vasanthan et al., 2005[19]		Perez et al., 1998[26,29]	Nishiguchi et al., 1994[27]	Barillot et al., 1997[30]		Fletcher, 1968[31]	
Stage	TRT	RT	TRT	RT	TRT	RT	RT	RT	RT		RT	
Parameter	IIIB (IIB-IVA)		IIIB		IIIB (IIB-IVA)		III	III	IIIA	IIIB	IIIA	IIIB
CLR	83%	57%	80%	50%	80%			80%				
3y LDFS	61%	41%	80%	49%	68.5%							
3y OS	51%	27%	58%	48%	73.2%							
5y LDFS	61%	37%							65%	59%		
5y OS	41%	23%						47%	69%	48%	45%	36%
10y LDFS	61%	37%					68%					
10y OS	37%	20%					45%				36%	30%

Table 6. Comparison of clinical results of TRT trials with best results of only RT – trials for cervical cancer CLR – Complete Local Response, LDFS – Local Disease-Free Survival, OS – Overall Survival

However, the most impressive fact is that the clinical results in TRT arm of DDHG trial are also worse than the best results reported with RT only (see Table 6.) with total dose to tumor mass 75-90 Gy. As it was discussed above for Overgaard et al. trial, the use of low RT dose is convenient for radiobiological demonstration of hyperthermia effect but leads to clinical insignificance of any clinical trial. This is what we see in this DDHG trial: it's impressive in demonstration of low-dose radiotherapy modification but clinically insignificant because of low overall effect. As it's obvious from other hyperthermia trials, the effect of hyperthermic RT-modification becomes statistically insignificant or disappears completely in comparison with standard high-dose RT[5,16].

The inadequate comparator is not the only problem of the DDHG trial. There are also huge heterogeneity in RT and HT coupling, difference in the used HT-equipment, poor analysis and incomplete safety analysis. The trial combines data of two independent studies completed by Amsterdam Medical Center (AMC) and by University Hospital Rotterdam (UHR). Whereas the AMC trial was monocentric, the UHR collected patients also from 9 other RT-centers. As a result, if in AMC HT followed RT an hour later, in UHR the usual delay was 3-4 hours because of logistics. It's well-known that RT-modification time interval lasts not longer than 1.5 hours. Thus, there was an RT-modifying coupling in AMC but not in UHR, where concomitant instead of the combined treatment was applied. It seems that efficacy of such different applications should be quite different. The authors indirectly confess inapplicability of classic RT-modification criteria in this case: "Probably the main gain of hyperthermia is a direct effect on the hypoxic tumor cells. This extra cell kill will be clinically relevant in a small proportion of patients only, and studies of more patients are required to establish such an improvement"[17]. This coupling difference is further aggravated by the difference of the equipment used: it was BSD2000 system (BSD Corp., USA) in UHR, 4-

waveguide applicator system in AMC and TEM applicator in Utrecht (all being custom-built). There is not any comparison of the systems except of short phrase "for the three systems, similar energy distribution in human pelvic size phantoms has been demonstrated" [17]. Taking into account the significant difference in technologies (e.g., TEM applicator uses frequency range 10-80 MHz[32] whereas BSD2000 uses 80-120 MHz; these regions have very different properties), there is very low probability that these systems are clinically equal. But no publication on the trial contains separate analysis of efficacy and safety by centers or HT-units. There are no separate data about AMC and UHR, not even about the number of patients in these two trials. But such generalized data are useless from practical point of view because it's unknown, which type of application is effective in such wide range of application modes. It's even unknown, which temperatures were used in the trial because temperature analysis is absent. When Dahl and Mella[24] talk about thermometry data in DDHG trial, they just quote the data from another trial of Harima et al.[28], and this is an obvious confusion. It's also known from another source in Rotterdam (Fatehi, 2000[33]) that intratumoral temperature in cervix carcinoma with BSD2000 system never reaches 40°C, thus the 42°C stated in the trial protocol is a misinformation. Even the tumor-volume dependency analysis is missing which is vital in any HT-trial analyses. In fact, this trial is a 'black box': we know only the input and output parameters but we absolutely don't know 'how it works'. Thus, we don't know how to use it, and that is why DDHG trial is useless from practical point of view.

Additionally, safety analysis seems to be incomplete and biased. This is the only HT-trial which reports more 3-4 grade toxicity in TRT arm (2.2%) than in RT arm (5.9%), which is very dubious. At the same time, authors reports about 12% (20/170) of subcutaneous burns, which needed up to 2 weeks to heal; 3% (5/170) of skin burns, including 1 case (0.58%) of grade 2 burn and 2 cases (1.2%) of grade 3 burn, which demanded the interruption of HT-treatment; and 2 cases (1.2%) of severe deep burns of skin and subskin. Additionally, 'some' patients suffered from catheter-dependent infections17. Therefore, there were at least 18% (30/170) cases of HT-related toxicity which should cause the interruption of HT-treatment, whereas according to the authors' information, treatment was delayed only for 7 patients in TRT arm.
Refusal from treatment is one more source of safety information. It's reported that 41% of patients refused to undergo all 5 HT treatments, 25% received 1-3 treatments only, and 9% didn't receive any HT-session. It's declared that the main reason for refusal is that patients had known about "experimental nature of this treatment"[21]. This is quite a strange explanation because patients were recruited "after verbal informed consent had been obtained" 17, therefore the patients should have been initially informed about experimental nature of treatment; also this doesn't explain 9% of patients (16) who didn't receive any HT session at all. The most probable reason for not receiving HT-treatment is the toxicity. After all considerations, we assess HT-dependent toxicity near 30% with HT-limiting toxicity not less than 10%. These data are hidden.

Therefore, our conclusion on DDHT trial is as follows: Of three DDHT sub-groups, rectum results were clearly negative, bladder results were dubious and only cervix arm showed statistically significant response. This response was received despite the use of an inadequate comparator and was worse than those reported in the best trials with RT only, including long-time control and survival. The study design does not allow speaking about TRT, rather about the HT and RT co-treatment. Poor data presentation and analysis don't allow to understand the reasons of the study results. Toxicity analysis is incomplete. The results of the trial are clinically insignificant and practically inapplicable.

Shortly after the DDHG trial, a small Japanese trial of Harima et al.[28] was published in 2001. It was a prospective, randomized, controlled, and monocentric trial. Between 1994-1999 40 patients with FIGO stage IIIB cervical cancer were enrolled and randomly allocated for TRT and control RT group with 20 patients in each group. RT was applied with 6MV EBRT and iridium-192 HDR BT to TD 82.2 Gy. Hyperthermia was applied within 30 minutes after RT session by Thermotron RF8 capacitive system with the output power of 800-1500W. The trial showed excellent results in favor of TRT arm: CLR rate was 80% in TRT arm vs. 50% in RT only arm, 3 year LDFS and OS were significantly better in TRT arm (80% and 58% respectively) than in RT only arm (49% and 48% respectively).

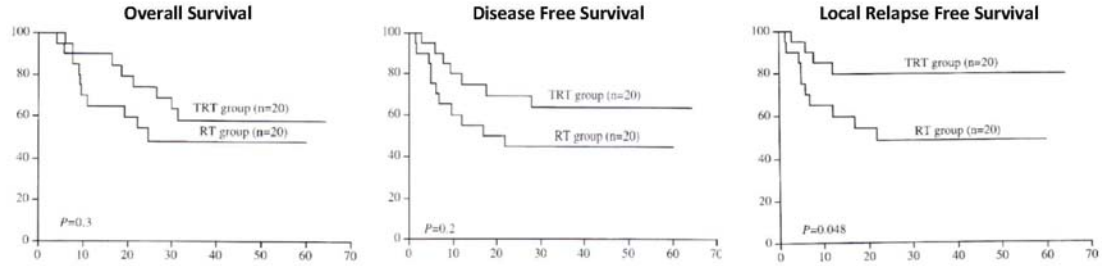


Figure 6. Survival data of Harima et al. clinical trial[28]

The trial stands apart from other trials and is unique in many respects. First, authors calculated the minimum volume of the sample (2x20 patients) from the hypothesis that TRT would give 80% of CLR versus 50% in Rt only. Then, they received the exact as planned result (80% and 50%) with the planned sample volume. Such exact coincidence of trial plan and result is really unique. Secondly, the sample of the trial was the oldest of all mentioned trials: mean age in TRT group was 64.9 years, and these were previously untreated patients. It's very uncommon because according to Ioka et al.[34] trial made on 8966 cases of cervical cancer diagnosed between 1975–1996 (Harima et al. enrolled patients between 1994-1999) who lived in Osaka Prefecture of Japan, the average age in time of the first diagnosis was 54.6 years. It seems that it's hard enough to obtain 10 years older sample of first time diagnosed patients randomly. Thus, pre-selection of aged patients is obvious. The reported fact that local control after TRT is significantly better in older patients[17] could be a reason for selecting such an older sample. At the same time, the average tumor volume in this trial was at least 1.5 times less compared to DDHT trial though the stage of the disease is the same and both trials enrolled previously not treated patients. Moreover, in Harima et al. trial the patients were 14 years younger (64.9 vs 51 years) than in TRT group of DDHT trial. It's well-known that effect is higher for smaller tumors. Third, though TD 82.2 Gy seems to be adequate, in fact it's not so. TD to tumor mass was only 60.6 Gy (30.6 Gy EBRT to whole pelvis and 30 Gy of BT to point A), while 21.6 Gy dose was applied to parametria with central shielding. Therefore, TD to tumor mass was nearly the same as in DDHG trial, but OS in RT group was much better than in DDHG trial (3y OS 48% vs. 27%, 5y OS 48% vs. 23% respectively) and was on the level of the best RT-only trials with TD 75-85Gy to tumor mass (see Table 6.), and it's also amazing. Effect of low-dose comparator and clinical significance of such comparison were discussed above. And, at last, the mentioned trial of Ioka et al.[34] showed that older age is associated with much lower survival: relative 5-year survival for cervical cancer was 88.6% in <30 years, 78.1% in 30–54 years, 67.7% in 55–64 years and 54.4% in 65+ years. In Harima et al. trial, 65-old sample had much higher survival than 15 years younger sample with 1.5 times less tumors in DDHG trial (see Table 6.), and this is once again amazing. We didn't find any reproduction of Harima RT-results with respect to its unique features.

So, there is the unique (not reproduced) small chamber trial made on pre-selected aged sample (10 years older than expected) and with low enough RT dose to tumor mass (60 Gy only, inadequate comparator), but with good result, which is better than in the 15 years younger comparator (van der Zee et al.), and is statistically significant in spite of the extremely low sample (20+20), and this result coincides with the study hypothesis in each and every point. This is an alarming result.

The trial seems to be specially designed to show the effect of TRT like it was shown earlier in the Overgaard et al.[11] trial: much older patients (+10-15 years) and low-dose TD to tumor mass (60.6 Gy) as a comparator with exact RT-HT coupling, and high-dose RT (21.6 Gy) to parametria. Older age and low-dose RT comparator could explain statistical significance of differences. Large dose to parametria, on the one hand, masks inadequacy of the RT-comparator because the total dose 82.2 Gy looks adequate, and, on the other hand, markedly improves overall survival (is improved in both RT and TRT arms compared to van der Zee trial), which is significant because older age favors better local control but doesn't contribute to better survival[34]. To summarize, the trial with so many amazing features should be made on much larger sample and preferably should be reproduced in independent trials for evidence. Until confirmation, the significance of Harima results should be considered as dubious.

It is a reproduction of the effect which is the main problem of Harima et al. trial evidence, because the attempt to reproduce its result was disappointing. In 2005, clinical trial on cervical cancer of Vasanthan et al.19 was published. This was a prospective, randomized, controlled, multicenter phase III trial sponsored

by International Agency of Atomic Energy. Between 1998-2002 110 patients with FIGO IIb-IVa stage of cervical cancer were enrolled in 5 centers in 4 countries. The OS at 3 years was 73.2%, and the local control rate was 68.5%. There were no significant differences between the patients treated with RT and TRT, either with regard to the OS ($p = 0.1893$) or to the rate of local control ($p = 0.58$). At the same time, OS was significantly worse in patients with stage IIb disease in TRT arm ($p = 0.0162$) however, there was no difference in their rate of local control ($p = 0.7988$). Acute Grade 2-3 toxicity was seen in 18% of patients in TRT arm and in 4% in RT arm ($p = 0.01$). Authors concluded that "this study failed to show any benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced carcinoma of the uterine cervix". It's important to note that Vasanthan et al. study had an intermediate design between DDHG and Harima trials: HT was performed in patients with IIb-IVa stage disease with the average age of 50 years, in average 5 times (like in DDHG trial) 1/week by Thermotron RF8 units just after RT (like in Harima trial).

It's interesting to analyze the results of cervical cancer hyperthermia studies because there are many trials which make such analysis possible. It's also interesting because cervical cancer really looks thermosensitive. There was success in cervical cancer treatment, which started an interest in hyperthermia in oncology. In 1898, Swedish gynecologist F Westermark[1] 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 (hot tubs) hyperthermia for treatment of various gynecological diseases. He described several excellent results in inoperable cancer of the cervix. It was the first time when the ability of long-term heating to destroy tumors without damaging of healthy tissues was shown. Gottschalk[35] in 1899 confirmed the success of hyperthermia in cervical cancer. Thus, it is not amazing that at the end of XX century the center of oncologic hyperthermia application returned to cervical cancer.

Authors	Publ.	Country	Type	Design	Nr of patients	Heating	CLR		LPFS		OS		Assessment	
							TRT	RT	TRT	RT	TRT	RT	Authors'	Our
Datta et al.[36]	1987	India	Monocenter	TRT vs. RT	52	Convect.	74%	58%	NR	NR	NR	NR	Positive	NA
Sharma et al.[37]	1989	India	Monocenter	TRT vs. RT	50	Convect.	NR	NR	70%	50%	NR	NR	Positive	NA
Chen et al.[38]	1997	China	Monocenter	TRT vs. TChRT vs. ChRT vs. RT	120	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Negative	NA
Van der Zee et al.[17]	2000	Netherlands	Multicenter	TRT vs. RT	114	EM	83%	57%	61%	41%	27%	51%	Positive	Dubious
Harima et al.[28]	2001	Japan	Monocenter	TRT vs. RT	40	EM	80%	50%	80%	49%	58%	48%	Positive	Dubious
Vasanthan et al.[19]	2005	India-S.Korea-Ukraine-China	Multicenter	TRT vs. RT	110	EM	80%		69%		73%		Negative	Negative

Table 7. Available randomized clinical trials on TRT of cervical cancer

TRT – thermaradiotherapy, RT – radiotherapy, TChRT – thermochemoradiotherapy, ChRT – chemoradiotherapy, N/A – Not Available, NA – Not Assessed, NR – Not Reported, EM – Electromagnetic, Convect. – Convectional

We've found six randomized trials on TRT of cervical cancer (see Table 7). Among them, two early Indian trials of Datta et al. and Sharma et al. were not assessed because they used intravaginal convectional heating, which is clinically insignificant method; additionally, they were too small and reported better local control without effect to survival. The trial of Chen et al. is in Chinese which is a problem. But its result is negative in terms of TRT: the authors reported that of 4 subgroups in this trial, only combination of RT, ChT and HT had shown significant improvement, whereas differences between all other 3 groups (RT only, TRT and ChRT) were not significant. Because of the absence of translation, we haven't included Chen et al. trial in the final record (see Table 14.).

Design and results of the three remaining trials have already been analyzed above and summarized in the table below.

	Harima et al., 2001[28]		Vasanthan et al., 2005[19]		Van der Zee et al., 2000[17]	
Country	Japan		India, S. Korea, China, Ukraine		The Netherlands	
Centers	1		5		11 (2 subtrials)	
Enrollment period	1994-1999 (5y)		1998-2002 (4y)		1990-1996 (6y)	
Submitted for publication	2000 (+1)		2003 (+1)		1999 (+3)	
	TRT arm	**RT arm**	**TRT arm**	**RT arm**	**TRT arm**	**RT arm**
Patients characteristics						
Prior treatment	Not pretreated		Not pretreated		Not pretreated	
Age	64.9	61.6	50	45	51	50
Number of patients						
Total	40		110		114	
By groups	20	20	55	55	58	56
FIGO stage						
IIb			29 (52.7%)	27 (49.1%)	11 (19.0%)	11 (19.6%)
IIIa			6 (10.9%)	3 (5.5%)	0 (0.0%)	1 (1.8%)
IIIb	20 (100%)	20 (100%)	19 (34.5%)	23 (41.8%)	40 (69.0%)	40 (71.4%)
Iva			1 (1.8%)	2 (3.6%)	7 (12.1%)	4 (7.1%)
Tumor characteristics						
Size	5.9	6.1	[4.6]	[4.9]	[7.1]	[7.0]
Volume	[107]	[118]	49.5	60.3	[187]	[179]
Histology						
Squamous cell carcinoma	17 (85.0%)	18 (90.0%)	52 (94.5%)	51 (92.7%)	51 (87.9%)	46 (82.1%)
Adenocarcinoma	3 (15.0%)	2 (10.0%)	1 (1.8%)	3 (5.5%)	4 (6.9%)	7 (12.5%)
Other			2 (3.6%)	1 (1.8%)	3 (5.2%)	3 (5.4%)
Hyperthermia						
Nr of sessions						
0			>0%		7 (12.1%)	
1-3					11 (19.0%)	
3	20 (100%)					
3-7			<100%			
4-6					40 (69.0%)	
Technology						
HT-system	Thermotron RF8		Thermotron RF8		BSD-2000 TEM 4-waveguide	
Technology	Capacitive		Capacitive		APAS, TEM, 4-WG	
Outside heating	100%		100%		100%	
Intracavitary heating			49%			
Frequency	8 MHz		8 MHz		10-120 MHz	
HT treatment parameters						
Power	800-1500W		450-?W		N/A	
RT-coupling	30' after RT		just after RT		1-4 hr after RT	
Heating period	20'		[20']		<30'	
HT-period	60'		60'		60'	
HT sessions	3		5		5	
Frequency	1/week		1/week		1/week	
Thermal control						
Thermosensors	Intratumoral		Intratumoral & Intraluminar		Intraluminar	
Measuring points	4-point		2-point (IL+IT)		1 point	
Measurement	100%		~2.5 times per course		Only part of sessions	
Tmax	41.8		42.1		N/A [40.0][33]	
Tave	40.6		41.6		N/A [39.5][33]	
Tmin	39.6		41		N/A	
Radiotherapy						
Coverage	100%		N/A [90%?]		98%	96%
Total dose (TD)	82.2 Gy		≈84 Gy		68 Gy	67 Gy
to tumor mass (TMD)	60.6 Gy		≈72 Gy		N/A (<68 Gy)	N/A (<67 Gy)
External-beam Radiotherapy (EBRT)						
Technology	6MV		6-18 MV (>70%), ^{60}Co (<30%),		Linear accelerators	
Single dose	1.8 Gy		2 Gy		1.8-2.0 Gy	
Total dose	52.2 Gy		≈62 Gy		46-50.4 Gy	
to whole pelvis	30.6 Gy		≈50 Gy		N/A (<46-50.4 Gy)	
to pelvis wall	21.6 Gy		≈12 Gy		N/A	
Brachytherapy (BT)						
High-dose-rate (HDR)	100%		49%		33%	
Low-dose-rate (LDR)			51%		46%	
Coverage	100%		N/A		79% (for others EBRT boost was used)	
single dose	7.5 Gy					
total dose	30 Gy		22 Gy		17 Gy (LDR), 20-30 Gy (HDR)	
BT % TD/TMD	37%/50%		26%/30%		25-44%	
Clinical results						
CLR	80%	50%	80%		83%	57%
LDFS 3y	80%	49%	69%		61%	41%
OS 3y	58%	48%	73%		51%	27%

Table 8. Analysis of available randomized clinical trials on TRT of cervix cancer

Vasanthan et al. trial, despite the negative results for TRT arm, had an excellent common result: CLR rate 80%, 3y LDFS 69% and 3y OS 73%. As it's seen from Figure 7, Vasanthan LDFS was average between Harima and van der Zee but OS was much better. It's very demonstrative that OS in TRT arm in all three trials was close enough but OS in RT only arms was very different (79% vs. 48% and 27%, respectively).

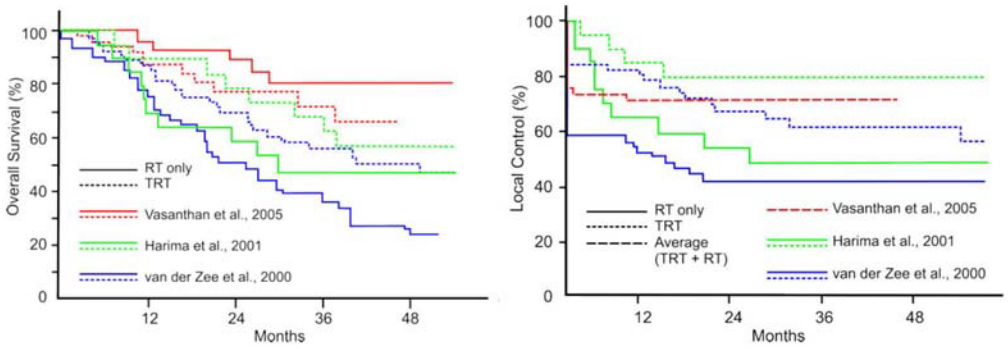


Figure 7. Comparative results of cervical cancer trials

There were two principal differences between Vasanthan trial on the one hand and Harima and van der Zee trials on the other hand: RT dose and tumor volume. In Vasanthan trial, dose to tumor mass was near 72 Gy (with TD=84 Gy), i.e. 20% more than in both Harima and van der Zee trials (TD≈60 Gy). The pattern of these three trials is rather typical: TRT versus low-dose RT gives significant effect, and it's not effective versus high-dose RT.

The second principal point is the tumor volume. As it's seen from Table 8, tumor volume in Vasanthan et al. trial (50-60 cm^3) is two times less than the estimated tumor volume in Harima et al. trial (107-118 cm^3), and is three times less than the estimated tumor volume in van der Zee et al. trial (179-183 cm^3). This is absolutely natural because 50% in Vasanthan trial were patients with IIb stage whereas there were only IIIb stage patients in Harima trial and in van der Zee trial patients could also be considered IIIb stage because IIb and IVa patients were counterbalanced. As anticipated, smaller tumor size led to better local control in Vasanthan et al. trial contemporary to van der Zee at al. trial (see Figure 7.) (the local control in Harima trial seems to be even better but the above-mentioned specificity of the trial design could easily explain it). Local control rates for IIb stage patients were also better than in IIIb stage patients (see Figure 8.). But – suddenly, - the overall survival rate in IIb stage patients was higher and significantly worse compared to both IIIb subgroups and RT control (p=0.016) (see Figure 8.). Therefore, it seems that smaller size is associated with better local control but also with much worse survival rates. Vasanthan et al. didn't analyzed the reasons of enhanced mortality in IIb stage patients saying just "further analysis is necessary to determine if the difference in survival is due to a greater incidence of distant metastases or some other cause"[19]. Significantly higher incidence of distant metastases after TRT (17.3% (4/23) vs. 4.3% (1/23) in RT group) has already been reported earlier by Sharma et al.[37] and it's known also that this trial included both II and III stage patients. It could be hypothesized therefore that in smaller tumors with relatively higher initial perfusion, hyperthermia-induced increase of blood flow could enhance tumor dissemination. On the other hand, neither DDHG[22] nor Harima et al.[28] reports higher metastases rates in TRT group, but they enrolled predominantly advanced stages of the disease (IIIB-IVA).

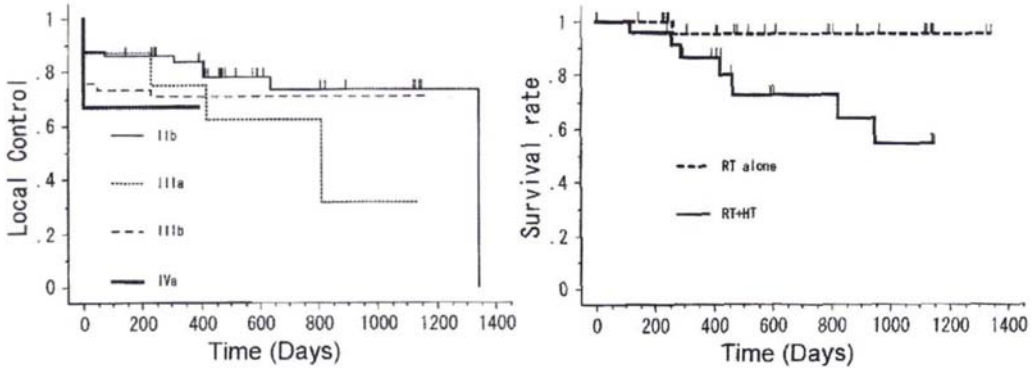


Figure 8. Local control and survival in FIGO IIb stage patients in Vasanthal et al.[19] trial

In 2007, a prospective, randomized, controlled, multicenter phase III trial of Mitsumori et al.[18] made on 80 patients with non-small cell lung cancer (NSCLC) was published. In fact, Vasanthan and Mitsumori trials were two arms of one IAAE sponsored trial. The result was the same: difference between CLR and OS rates in TRT and RT arms was statistically insignificant (p=0.49 and p=0.868, respectively), though Local

Progression Free Survival was significantly better in TRT arm (p=0.036). The authors concluded that "although improvement of LPFS was observed in the RT+HT arm, this study failed to show any substantial benefit from the addition of HT to RT in the treatment of locally advanced NSCLC".

The most recent and the most fundamental randomized trial on deep hyperthermia was published by RD Issels et al.[20] in 2010. This 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) (≥5 cm, FNCLCC grade 2 or 3, deep to the fascia) 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 (NAChT) → definitive surgery → adjuvant RT → adjuvant chemotherapy (AChT). Chemotherapy (ChT) was applied by EIA protocol (etoposide 125 mg/m^2 and ifosfamide 1500 mg/m^2 x 4 days + doxorubicin 50 mg/m^2 on Day 1) in 8 cycles: 4 before surgery and 4 after RT. 169 patient were randomly assigned to receive thermochemotherapy (TChT) instead of ChT. Regional HT (42°C x 60') by virtue of BSD-2000 hyperthermia units were applied on the 1st and 4th day of each ChT cycle. The following results were reported: there was no effect to overall survival (median survival was 79 month in TChT arm vs. 74 month in ChT arm, p=0.43) but short-term local response rate (CLR + PLR) was twice higher in TChT arm (34% vs. 16%, p=0.02), and Local Progression Free Survival (LPFS) was significantly enhanced in TChT arm (32 months vs. 18 months (p=0.011); 76% vs. 61% after 2 years (p=0.003) and 66% vs. 55% after 4 years (p=0.003)).

Unfortunately, careful analysis of the trial gives disappointing results. There is a systematic bias in favor of TChT arm. 5 possible points of possible distortions were identified: Tumor Size, Grade of Disease, Surgery, RT and ChT. All the points were distorted to various extent but unidirectionally in favor of TChT arm, which forms obvious systematic bias. We've attempted to estimate the possible distortion which could be caused by this systematic bias (see Table 9.). The method of estimation is as follows. 'Δ%' is a relative increment of every parameter calculated as a difference between percentages of the parameter for TChT and ChT arms (or the value of the parameter if there is no percentage) divided by the percentage (value) of the less parameter. The impact of a parameter is considered 'direct' if its increase adds to the effect of the treatment, otherwise a parameter has 'reverse' impact. 'Weight' of a parameter is calculated as the sum of patients involved in the parameter assessment in both arms divided by the total number of patients on the sample (341), and represents an impact of this parameter on the general sample. Final distortion ('Dist%') is calculated as a product of 'Δ%' and 'Weight', therefore representing a parameter increment corrected for its weight. Distortion is considered positive if it favors the TChT arm. It's obvious that every parameter has different strength of impact on treatment effect but we didn't do any correction because of its subjectivity. Also, every parameter was assessed by minimum value. For instance, the impact of tumor size, not the tumor volume was assessed, though this 2.7% difference of tumor size means 8.4% difference of tumor volume.

	Arm →	TChT		ChT		Distortion (→TChT)		
	Pat Nr →	Nr	%	Nr	%	Δ%	Weight	Dist%
Factors	Impact ↓	169	49,6%	172	50,4%			
General Factors								
Tumor Size	Reverse	11		11,3		2,7%	100%	2,7%
3 Grade	Reverse	84	49,7%	94	54,7%	10,0%	52%	5,2%
Total						**12,7%**		**7,9%**
Chemotherapy								
Number of ChT-treated	Direct	165	97,6%	167	97,1%	0,6%	97%	0,5%
Median Nr of cycles	Direct	8		5		60,0%	97%	58,4%
Total						**60,0%**		**59,0%**
Surgery								
Overall Surgery (including previous)	Direct	155	91,7%	154	89,5%	2,4%	91%	2,2%
Definitive Surgery	Direct	104	88,9%	102	81,0%	9,8%	60%	5,9%
Measurable Disease without Surgery	Reverse	13	11,1%	24	19,0%	71,4%	11%	7,8%
R0 Surgery + Amputation	Direct	60	35,5%	51	29,7%	19,7%	33%	6,4%
R1 Surgery	Reverse	35	20,7%	36	20,9%	1,1%	21%	0,2%
R2 Surgery	Reverse	9	5,3%	14	8,1%	52,8%	7%	3,6%
Total						**154,9%**		**23,9%**
Radiotherapy								
Nr of Radiotherapies	Direct	108	63,9%	106	61,6%	3,7%	63%	2,3%
Radiotherapy Average Dose	Direct	53,2		52,7		0,9%	63%	0,6%
Total						**4,6%**		**2,9%**
TOTAL:								**93,7%**

Table 9. Estimated distortion of Issels et al.[20] trial results caused by impact of systematic bias

Thus, every parameter of the estimation favors to TChT arm: tumor size (+2.7%), grade of STS (+5.2%), RT (+2.9%), surgery (+23.9%) and ChT (+59%). In surgery, every sub-parameter is also distorted in favor of TChT arm: overall number of patients who underwent surgery, including previous surgery (+2.2%), number of definitive surgeries in this trial (+5.9%), number of patients with measurable disease left without surgery (+7.8%), R0 surgery and amputation (+6.4%), R1 (+0.2%) and R2 (+3.6%) surgeries. It can be assumed that higher percentage of R0 surgery in TChT group is caused by the success of neoadjuvant (induction) treatment but the success of induction treatment also could be contributed to the impact of systematic bias rather than an effect of HT (see Table 10) because total weight of induction distortion is higher than the received effect (18.5% vs. 8.5%). In turn, impact surgery is only a smaller part of the total distortion, which exceeds 90% and greatly overweighs the received increment of LPFS (11-15%).

	Arm →	TChT		ChT		Distortion (→TChT)		
	Pat Nr →	Nr	%	Nr	%	Δ%	Weight	Dist%
Factors	Impact ↓	169	49,6%	172	50,4%			
General Factors								
Tumor Size	Reverse	11		11,3		2,7%	100%	2,7%
3 Grade	Reverse	84	49,7%	94	54,7%	10,0%	52%	5,2%
Total						**12,7%**		**7,9%**
Chemotherapy								
Number of ChT-treated	Direct	165	97,6%	167	97,1%	0,6%	97%	0,5%
4 cycles	Direct	151	89,3%	146	84,9%	5,3%	87%	4,6%
1-3 cycles	Reverse	14	8,3%	21	12,2%	47,4%	10%	4,9%
0 cycles	Reverse	4	2,4%	5	2,9%	22,8%	3%	0,6%
Total						**76,0%**		**10,6%**
TOTAL:								**18,5%**
Immediate Local Response								
No Measurable Disease	Direct	52	30,8%	46	26,7%	15,1%	29%	4,3%
Measurable Disease	Reverse	117	69,2%	126	73,3%	5,8%	71%	4,1%
Total						**20,9%**		**8,5%**

Table 10. Estimated distortion of neoadjuvant (induction) treatment results of Issels et al.[20] trial

It's absolutely obvious that with such significant systematic bias, the effect of the trial cannot be attributed to HT, and it's impossible to exclude that without HT the result in this arm would be even better because HT treatment was associated with high toxicity.

Analysis of toxicity (see Table 11.) shows that toxicity in TChT group increased drastically: general toxicity was 3 times higher (225% vs. 78.5%) and severe toxicity was 20 times higher (24% vs. 1.2%) than in ChT arm. It is especially significant to note that this huge rise of toxicity was minimally conditioned by potentiation of ChT toxicity (factor 1.2-1.5). The major part of toxicity was the own toxicity of hyperthermia: thermometry complications, burns, tissue necrosis, pain, pressure of the bolus and others. In this regard, the authors' conclusion looks irrelevant: "Our results indicate that regional hyperthermia combined with the three-drug-regimen EIA can be given safely with moderate toxicity".

Impact of this 'moderate toxicity' to the course of the trial could be traced. During induction treatment, full HT treatment (7-8 sessions) was performed at 76% patients, 20% of patients received 1-6 sessions and 4% of patients didn't receive any session. During adjuvant HT, full HT treatment was performed at 36% patients, 17% of patients received 1-6 sessions and 38% of patients didn't receive any HT session. Authors declared toxicity as the only reason for non-receipt of the HT treatment. Therefore, this 'moderate' toxicity was HT-limiting in 24% of untreated patients and 55% of impaired patients (factor 2.3). Critical toxicity which forces to cancel HT-treatment became 9,5 times higher (4% to 38%) in impaired patients. This level of toxicity could be unacceptable for clinical practice

Parameter	TChT		ChT	
	total	severe	Total	severe
Common toxicity	96,40%	1,80%	78,50%	1,20%
Thermometry complications	4,30%	1,20%	-	-
Burns	18,40%	0,60%	-	-
Pain	44,80%	4,30%	-	-
Tissue necrosis	6,80%	2,50%	-	-
Pressure of the bolus	31,30%	4,90%	-	-
Other	22,70%	8,60%	-	-
	224,70%	23,90%	78,50%	1,20%
	x3	**x20**		

Table 11. Analysis of toxicity in Issels et al.[20] trial

Finally, we compared the clinical results of the trial with data of Sarcoma Meta-analysis Collaboration (SMAC)[39]. The data are derived from 14 randomized trials made between 1973-1990 on 1568 patients with high-grade sarcomas of extremities and trunk. All the patients had definitive surgery followed by adjuvant RT (47%) and adjuvant doxorubicin-based ChT (100%). Compared to Issels et al. trial, this sample had 14% more STS of extremities (58% vs. 44%), 10% more surgeries (100% vs. 90%), 16% less RT (47% vs. 63%) and didn't have neoadjuvant ChT (see Table 12.). The overall impact of all distortions could be considered as nearly equal.

Factor	Issels[20]	SMAC[39]	Distortion
STS of extremities	44%	58%	14%
Surgery	90%	100%	10%
RT	63%	47%	-16%
Neoadjuvant ChT	97%	0%	-97%
Adjuvant ChT	58%	100%	42%
Total:	**352%**	**305%**	**-47%**

Table 12. Comparison of distortion factors of SMAC and Issels et al. samples

Figure 9. demonstrates that clinical results of Issels et al. trial are uniformly worse than SMAC results. The most impressive fact that even the best results in TChT arm are worse than SMAC results in control arm, despite the fact that this arm didn't have ChT at all. Therefore, the clinical value of Issels et al. result is minor. Thus, it could be concluded that after correction to systematic bias, long-term effects of the Issels et al. trial is dubious and clinically insignificant. Toxicity level of the treatment is unacceptable for clinical practice. But according to the authors' opinion, "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"[40]. This is an extremely doubtful conclusion.

It should be noted that systematic bias of Issels et al. trial was not intended and it was not incorporated in the design of the study initially. In fact, the trial has a brilliant design and is excellently reported. It seems that the problem of the study is rather a common problem of all prospective trials, when investigators pay excessive attention to the study group and much less attention to the control group. As a result, the volume of treatment in control group could decrease so much that the groups become incomparable. Taking into account the hard and complex protocol of Issels trial, its multicenter design, large sample size and long term of the trial, this defect was virtually inevitable. Probably, they designed 'the most effective' treatment protocol which appeared too hard to fulfill. Anyway, this is not an excuse for investigators who just didn't notice this great systematic bias when reporting the results (defect of interpretation).

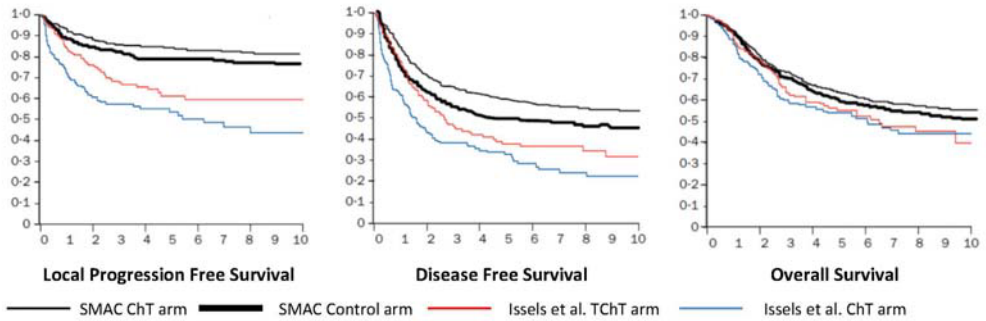


Figure 9. Comparison of clinical results of Issels et al.[20] trial (1997-2006) and SMAC[39] meta-analysis (1973-1990)

As a conclusion, hyperthermia of deep-seated tumors could be effective only versus inadequate comparator. In correct design of a trial, hyperthermia is not effective et all or not effective enough to prove its obvious disadvantages: toxicity and labor-intensity. Clinical efficacy of hyperthermia of deep-seated tumors is still not proven in randomized trials.

Authors	**Bakhshandeh et al. 2003[41]**	**Bakhshandeh et al. 2004[42]**	
Phase	II	III	
Design	Prospective, monocenter, single-arm	Prospective, randomized, controlled	
	TChT	TChT	ChT
Whole-body hyperthermia	Extreme		
Interval between sessions	3-4 weeks		
Number of procedures	4		
Temperature on plateau	41.8°C		
Time on plateau	60′		
Heating method	IR-C		
Unit	Aquatherm		
Anesthesia	IV deep sedation		
Artificial ventilation	No		
Chemotherapy	ICE: ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, etoposide 150 mg/m^2 every 4 weeks	ICE: ifosfamide 4.5 g/m^2, carboplatin 270 mg/m^2, etoposide 135 mg/m^2 every 4 weeks	
Nr of patients	27	31 (27 randomized)	
		14	13
Median age	18-65	58	
Disease	Pleural mesothelioma	Pleural mesothelioma	
Stage	I-III	0-II	
Prior chemotherapy	0%	0%	
Metastases	0%	0%	
Immediate Efficacy (CR+PR)	20%	15%	31%
Complete remission (CR)	0%	0%	0%
Partial remission (PR)	20%	15%	31%
Stable disease (SD)	56%	57%	38%
Progression of disease (PD)	24%	28%	31%
Time to progression	6.9 months	5.6 months	9.2 months
Overall survival	17.9 months	11.5 months	15 months
1 year	68%		
2 year	20%		
Toxicity ¾ grade			
Neutropenia	74%	36%	30%
Thrombocytopenia	33%	37.7%	15.3%
Treatment-related deaths	1 (3.7%), sepsis		

Table 13. Randomized trials on Whole-Body Hyperthermia

Whole-body hyperthermia

The fact that there is only one phase III randomized trial on WBH is very demonstrative itself, because WBH has much longer history of application in oncology than local hyperthermia. Results of multiple phase II WBH trials usually don't justify III phase trial. Bakhshandeh et al[41] trial is demonstrative in this respect. In this II phase trial, 20% of partial remission and 20% 2 year survival in 27 patients with I-II stage malignant pleural mesothelioma was shown after TChT (ICE + WBH); extensive myelosuppression (75%

of 3-4 grade) with 3.7% mortality was reported. Meanwhile, it's known that efficacy of majority of chemotherapies is also 15-20% but on heavier samples, and efficacy of the gemcitabine+cisplatin combination had demonstrated 48% partial remission with less toxicity (not more than 30-40% of 3-4 grade toxicity).[43] Thus, Bakhshandeh et al.[41] phase II study showed more than dubious clinical efficacy with undisputedly higher toxicity, that could hardly be considered a basis for further studies. Anyway, authors had considered these results "promising" and initiated a phase III trial. Preliminary results of this predictably negative randomized phase III study, reported in 2004, exceeded expectations, and was sharply negative[42]. WBH didn't improve the results of chemotherapy, but significantly worsened them in all respects: half less PR, (15% vs. 31% in ChT only arm), significant decrease of OS (11.5 months vs. 15 months) and DFS (5.6 months vs. 9.2 months). It should be mentioned that this phase III trial was done on easier sample than the previous phase II trial (WHO 0-II instead of I-III in phase II trial) and with 10% less ChT dose. This allowed to reduce myelotoxicity significantly (36% vs. 74% in phase II) and to avoid deaths, but it also led to a reversal of clinical results: previously dubious results became clearly negative. Authors concluded that "this preliminary data from a randomized study show little, if any, beneficial effect mediated through hyperthermia" and that "conclusive judgment has to be postponed until completion of this trial" though in fact they just had to stop the trial. Moreover, the results didn't prevent the authors from publishing a review of the current state of WBH, which reports intention of Interdisciplinary Working Group on Hyperthermia to build clinical guidelines on the basis of "promising results of phase II trials" as well as on the basis of this phase III trial in 2005.[44]

The general impression is that the combination of ChT with extreme WBH can, in some cases (20-40%), overcome chemoresistance and provide a partial remission, but without any effect to overall survival. Also, clinical efficacy seems to be reversely connected with toxicity: a clinical benefit is associated with high toxicity; toxicity reduction leads to inefficacy or it worsens the effect of ChT. Since the results obtained in TChT studies have never exceeded the best results without WBH, there is a concern on feasibility of WBH at all, since similar or better effect can be obtained by applying high-dose ChT or polychemotherapy at a lower level of toxicity.

Guidelines on the WBH published by the Universities of Luebeck and Wisconsin in 2000 are more than cautious in terms of efficiency and safety of WBH. In particular, it is postulated that efficiency of WBH is only supposed and is based on very limited clinical data; that separate administration of WBH doesn't make sense because it provides only a minimal increase in overall survival (days, maximum weeks), and only with thermosensitive tumors[45]. These guidelines are intended for research only. The paper of HI Robins, the former head of the WBH program at the University of Wisconsin, immediately preceded these guidelines, was even more skeptical.[46] It is noteworthy that Robins, who was the chairman of the International Working Group on systemic hyperthermia and had published over 80 articles on WBP since 1983, completely stopped his activities in hyperthermia field and hasn't published any paper on the topic since 2003. With such sudden and complete cessation of research activity on WBH, one can assume that the true result of this 20-year activity is not encouraging.

Type	Authors	Year	Localization	Sponsor	Conclusion	
					Resume	Estimation
Superficial HT	Kapp et al. [7]	1990	Superficial	Independent	No Significant Effect	Negative
	Perez et al. [5]	1991	Superficial			Negative
	Emami et al. [8]	1992	Superficial			Negative
	Engin et al. [9]	1993	Superficial			Negative
	Vernon et al. [10]	1996	Superficial	Hyperthermic	Significant Effect	Dubious
	Overgaard et al. [11]	1996	Melanoma			Clinically insignificant
	Jones et al. [12]	2005	Superficial			Dubious
Deep HT	Emami et al. [16]	1996	Deep seated	Independent	No Significant Effect	Negative
	Van der Zee et al. [17]	2000	Rectum	Hyperthermic		Negative
			Bladder			Negative
			Cervix		Significant Effect	Clinically insignificant
	Harima et al.[28]	2001	Cervix			Dubious
	Vasanthan et al. [19]	2005	Cervix	Independent	No Significant Effect	Extremely Negative
	Mitsumori et al. [18]	2007	NSCLC			Negative
	Issels et al.[20]	2010	ST sarcomas	Hyperthermic	Significant Effect	Dubious
WBH	Bakhshandeh et al.[42]	2004	Pleural mesothelioma		No Significant Effect	Extremely Negative

Table 14. Final record of randomized clinical trials on hyperthermia in oncology

Biases of hyperthermia trials

The must common biases of hyperthermia randomized clinical trials are summarized in the table below.

Author	Year	Locali-zation	DIstortions						
			Inadequate comparator	Randomization defects	Pre-selection of patients	Incomplete data presentation	Incorrect design	Systemic distortion	Inadeqate analysis
Vernon et al.[10]	1996	Superficial	?	?	?	X[1]	X[2]	?	?
Overgaard et al.[11]	1996	Melanoma	X[3]	-	?	X[4]	X[5]	-	X[6]
Jones et al.[12]	2005	Superficial	-	X[7]	X[8]	X[9]	-	?	X[10]
Van der Zee et al.[17]	2000	Cervix	X[11]	-	-	X[12]	X[13]	-	X[14]
Harima et al.[28]	2001	Cervix	X[15]	-	X[16]	-	-	-	-
Issels et al.[20]	2010	STS	X[17]	-	-	-	-	X[18]	X[19]

Table 15. Summarized biases of positive randomized clinical trials on hyperthermia

Notes: 1 – incomplete safety data; 2 – combination of some trials with different design; 3 – TD 24/27 Gy; 4 – overall survival by groups is absent; 5 – experimantal design (randomization of tumors instead of patients); 6 – incorrect survival analysis; 7 – median age and TD RT differs >10%; 8 – pre-selection of thermosensitive patients; 9 – tumor size effect analysis is absent; 10 – inadequate analysis of efficacy, ignorance of bad survival; 11 – TD RT 67 Gy, TD to tumor mass <60 Gy; 12 – temperature analysis is absent, safety data are hidden; 13 – combination of two studies with very different protocol; 14 – effects of temperature, tumor volume and protocol are not analysed; 15 – TD to tumor mass 60.6 Gy; 16 – pre-selection of aged patients (+10 years of expected); 17 – volume of base treatment in the control group is twice lower than in the study group; 18 – all the parameters effecting the results are distorted in favor of hyperthermia group (+100%); 19 – masking of systematic distortion, and inadequate toxicity evaluation

Inadequate comparator is the most often and significant bias in RT-based HT trials[11,17,28]. Standard RT has its special efficacy which significantly and not proportionally falls with lowering of the total dose. If HT is added to such low-dose RT, it causes some gain in local the effect but in comparison to effect of the standard high-dose RT, this HT-added effect is at least not better[5,7,8,16] but it is often is worse[9,18], sometimes significantly[19]. At the same time, toxicity of TRT is usually 3-5 times higher than toxicity of RT only. The main problem is that TRT vs standard high-dose RT is not effective because RT itself is a much more potent factor than HT, and HT effect disappears at high-dose RT. The inadequacy of comparator in Issels et al. trial20 is of another nature and caused by the less volume of treatment in the control arm as it was discussed above.

Obvious defect of randomization is revealed only in Jones et al. trial[12], alongside with open pre-selection of patients, which is considered a bias because the resume of the trial refers to all patients and is not limited to 'heatable' patients only. Another hidden type of pre-selection of aged patients was revealed in Harima et al. trial28 where the not pre-treated patients in study group were 10 years older than the expected age of the first diagnosis in Japan. Three trials have incorrect designs. Overgaard et al. trial is in fact a clinical radiobiological trial without clinical significance. Vernon et al. and van der Zee et al. trials combines some different trials with incompatible protocols, different equipment, etc. Also, the data in the majority of the trials are presented incompletely, and virtually all the trials suffer from inadequate analysis. This refers not only to positive trials only. For example, the extremely negative Vasanthan trial is reported and analyzed poorly. For instance, authors just refused to analyze the possible reasons of significantly enhanced mortality in IIb stage group though this is of the great interest. The analysis of reasons of negative trials of 90th was also incomplete and incorrect as it will be discussed below.

The problem of sponsorship influence deserves a special attention. As it known from the literature, the clinical trials sponsored by industry have at least 5 times more probability to be successful (positive) than independent trials. As it is obvious from Table 14, independently sponsored HT clinical trials always reported no significant effect. On the contrary, trials sponsored by hyperthermia societies were successful in majority of cases with only two exclusions. Bladder and rectum cancer groups in van der Zee trial with negative and dubious results were just hidden by low-reporting and by referring to the entire trial as successful. The extremely negative intermediate results of Bakhshandeh et al. trial was reported only once at ASCO meeting. The final result of the trial is absent.

There is a serious interpretational bias. Namely, hyperthermia community tends to consider the negative trials of the early 90s as not significant because of insufficient heating and imperfect technique. This is absolutely incorrect. All the modern hyperthermia technologies were introduced before the 90s: microwave

superficial heating (433 MHz, 915 MHz, 2.4 GHz, etc.) and capacitive 13,56 MHz heating (LeVeen) are in use since late 70s, APAS technology of BSD has been in use since 1982 and 8 MHz capacitive technology of Thermotron has been commercially available since 1985. Erasmus university hyperthermia center has been using 433 MHz technology since 1985 to the date[47]. All the randomized trials of the early 90s 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[7] the minimum temperature in superficial tumors was 40.2°C, the average was 42.5°C and the maximum was 44.8°C. Modern guidelines of Erasmus university[47] for superficial tumors recommends to reach minimum temperature of 40°C and maximum of 43-44°C. It should be considered that in terms of heating and technique the negative trials of the early 90s were absolutely adequate.

Finally, the publication bias is significant. 7 positive trials are well reported, frequently quoted by hyperthermia society and included in all meta-analyses and reviews. Some of them are published sometimes[17,21,22]. On the contrary, the negative trials are poorly quoted and often not mentioned in meta-analises and reviews. This creates the wrong impression of hyperthermia success.

Hyperthermia problems

Despite more than 100 years of development, hyperthermia still doesn't have an acceptable explanation. Current hyperthermia concept is based solely on the temperature concept but clinical results often directly contradict this concept (see Table 16.). Particularly, the significantly stronger radiotherapy modification effect for smaller tumors[5,11] (less than 3-4 cm) is unexplainable from the thermal concept of hyperthermia. Perez et al.[5] explained that "they are easier to heat", and this explanation is commonly accepted now, but already in 1963 G Crile Jr[48] had convincingly demonstrated that, vice versa, bigger tumors could be heated much easier than smaller ones. This difference is very simple to understand because the main predictor of heating is tumor blood flow, which is high enough in small tumors and significantly reduced in big tumors, which play as "heat trap". Also, small tumor is cooled effectively enough by high blood flow of surrounding healthy tissues. Hiraoka et al trials confirmed that bigger tumors are heated better than smaller ones[49] and, at the same time, smaller tumors are cured better with HT[50]. Thus, this phenomenon clearly shows inconsistency of thermal concept of HT: the better heated tumors show worse clinical effect. Instead of initiate discussions about the validity of thermal concept of radiomodification, all the authors[5,8,9,11,16] had made the simplest and presumably wrong conclusion about a better heating of smaller tumors. This wrong conclusion led to logical consequence that insufficient heating is the reason of the trials fail, and that improvement of heating technology could correct a situation.

Results of 3 randomized clinical trials published before 1996 (Kapp et al.[7], Emami et al.[8] and Engin et al.[9]) had blocked the only possible thermal explanation of Perez et al.5 trial fail: one could hypothesize that 2 HT sessions is not enough for demonstration of HT effect. These trials clearly showed that longer protocols with 6 and 8 HT sessions are not more effective and even could worsen effect9. Though Engin et al.[9] had found that some temperature parameters (namely, median minimum tumor temperature, and minimum tumor temperature during the first heat treatment) were prognostic factors predictive of duration of response (though, together with tumor volume), Kapp et al.[7] didn't find such dependence: only tumor histology, radiation dose and tumor volume had correlated with duration of local control. Complete response rate seemed to be not correlated with temperature parameters at all[7,9].

	Hyperthermia theory	Premise	Hypothesis	In fact
1	HT is the most effective in hypoxic areas	Large tumors are mainly hypoxic	Effect of HT should be much stronger in large tumors	Effect of HT is much weaker in large tumors[5,7,31]
2	Higher temperature means stronger effect	Large tumors are easier to heat		
3		In van der Zee et al. trial[17], average temperature in cervix was <40°C and near 1°C lower than in rectum and bladder[33]	Effect of HT in cervix cancer should be worse than in rectum and bladder cancer	Effect of HT in cervix cancer was much stronger than in rectum and bladder cancer[17]
4		In Vasanthan et al. trial[19], the average temperature in cervix was >41°C	Effect of HT in Vasanthan[19] et al. trial should be stronger then in van der Zee et al.[17]	Effect of HT in Vasanthan et al. trial was much worse[17,19]
5		In Vasanthan et al. trial[19], the average temperature in Chennai group was 41.8°C and in Pusan group only 38.1°C	Effect in Chennai group should be much stronger (see Figure 10)	2 year local control was the same[19]
6	HT promotes cell cycle synchronization, thus enhancing the effect of RT	If exists, the synchronization should progress with more sessions	The more HT sessions, the stronger effect should be	Effect of multiple HT sessions is not stronger[8,9]
7	Hyperthermia damages or enhances the RT-damage of malignant tissues	If exists, the damage should accumulate		
8	Moderate HT (<42°C) leads to enhancement of tumor blood flow and oxygenation	Overwhelming majority of trials use HT after RT	Use of HT after RT is not effective because of insufficient temperature and could compensate RT damaging by improving tumor metabolism in view of better blood flow and oxygenation	Thermoradiotherapy trials are mainly unsuccessful[5,7,8,9,16,18,19] but some of them shows remarkable success[11,28]
9	Extreme HT (≥42°C) leads to hypoxia, acidosis, energy deprivation	Average maximum temperature in tumor never exceeds 42°C		
10	Thermal dose (CEM43°C T90) is a main factor of HT success	Thermal dose is a temperature multiplied to duration of exposure	Higher temperature should provide stronger effect	Higher temperature doesn't mean stronger effect (rows 2-5)
11			Longer exposure to heat should provide stronger effect	Effect of multiple HT sessions is not stronger[8,9]

Table 16. The contradictions of the classical theory of hyperthermia and data of randomized clinical trials

These results heavily affected the concept of thermal dose offered by Oleson and developed by Sapareto and Dewey[51] in the mid-80s. The explanation of long protocols fail was extremely weak: thermotolerance was called a reason. It seems to be incorrect because thermotolerance pattern has been well-known since early 60th[48]: it falls to initial level in 72 hours. Therefore, HT sessions 2 times a week, as it was in all the trials, should not be affected by thermotolerance. The subsequent hyperthermia trials of the 2000s[12,20] also used 2 times per week protocols.

Thus, five negative clinical trials of 1990-1996 (see Table 14.) were interpreted incorrectly in terms of reason of the fail: instead of revision of hyperthermia rationale, "insufficient heating" concept was offered. It would be incorrect to say that these results of the randomized trials were surprising: as it's clear from the Hornback paper quoted above[3], clinical oncologists had made their unambiguous decision about hyperthermia on the basis of previous clinical results already in mid-80s. Together with the fail of another RTOG deep hyperthermia trial, these trials' results led to disappointment of the medical community in oncological hyperthermia.

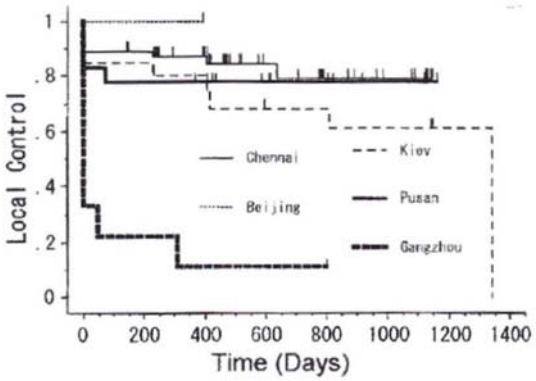


Figure 10. Local control rates in different subgroups of Vasanthan et al.[19] trial

Temperature analysis of cervical cancer studies also gives contradicting results. Average temperature in Vasanthan et al.19 trial was the highest among the main three cervical cancer trials (41.6°C vs. 40.6°C in Harima et al.28 trial and estimated <40°C in van der Zee et al.[17] trial), and the effect of TRT in Vasanthan trial was worse than RT only, though in the other two trials with lower temperature, the effect of TRT was significantly better than in RT control. Also, within Vasanthan et al 19 study, extremely low average temperature was used in the Pusan subgroup (38.1°C) but 2 year local control in this subgroup was the same as in Chennai and better than in the Kiev subgroup, where much higher average temperatures were used (41.8°C and 42.0°C, respectively).

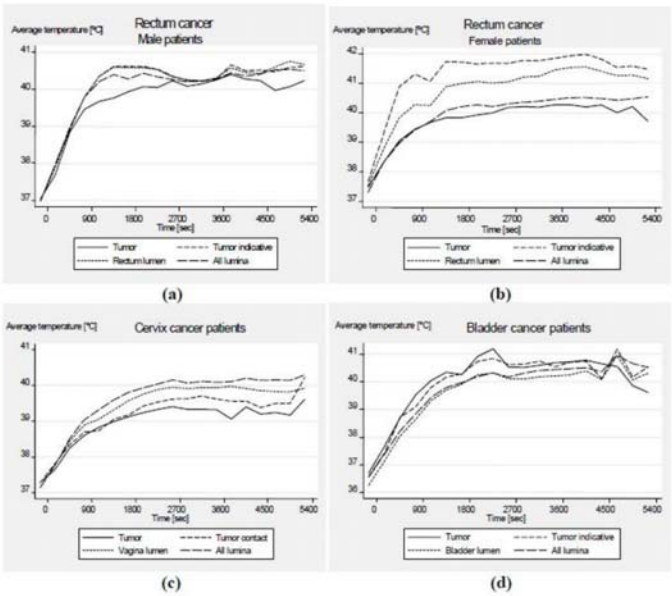


Figure 11. Technical quality of deep hyperthermia using BSD-2000 unit on rectal, bladder and cervical cancer[33]

As it was stated above, there is no temperature analysis in van der Zee et al.[17,21,22] trial but there is a doctoral thesis of D Fatehi[33] from Rotterdam University who was a co-author in later DDHG study[52]. His patients were collected between 2000-2002, i.e. 4 years after completion of the van der Zee trial. This paper refers to technical quality of deep hyperthermia using BSD-2000 unit on rectal, bladder and cervical cancer (see Figure 11.). It's known from the van der Zee paper that it was the Rotterdam University Hospital with its BSD-2000 unit, which was responsible for the larger part of patients enrolled in DDHG study. Therefore, technical results of Fatehi could be considered relevant. It's easy to see that temperature in cervix is less than in rectum and bladder (see Figure 11.), but it was cervical cancer which was effectively treated with TRT whereas TRT of rectum and bladder cancers were not effective[17]. Finally, in 2011 de Bruijne et al.[53] have convincingly demonstrated in a retrospective study that, after the correction of the tumor size, CEM 43°C T90 thermal dose was not associated with any clinical endpoint (CLR, LDFS, OS). Thus, even the central point of hyperthermia concept – the temperature, – has got many contradictions. This means that in fact hyperthermia doesn't have a theoretical base. Clinical results show that hyperthermia is in a dead end. Program papers on hyperthermia show that opinion leaders don't understand what to do and where to move, once again supposing only old thermal solutions[54,55] which should have been discredited already since the mid-90s. Nevertheless, multiple publications of positive trials, reviews and meta-analyses create an impression of hyperthermia renaissance. The most impressive papers report the history of hyperthermia as a history of uniform success, they don't mention the negative results at all and declare heating as the only and exclusive technical problem of hyperthermia[56]. Such approach looks not scientific.

Conclusion

The careful analysis of the 14 randomized clinical trial doesn't confirm a clinical benefit of hyperthermia application independently of its type: superficial, deep or whole-body. We haven't found any positive trial not affected with biases. With correction to distortions, there is no trial with obvious long-term positive effect of hyperthermia. Effects of hyperthermia could be shown in experimental setting and in experimentally designed clinical trials or versus an inadequate comparator. In clinical setting and correct study design, hyperthermia is not effective at all or not effective enough to prove its obvious disadvantages: toxicity and labor-intensity. Hyperthermia thermal concept seems to be irrelevant. Nevertheless, multiple publications of positive trials, reviews and meta-analyses create an impression of hyperthermia renaissance.

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