International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: http://www.tandfonline.com/loi/ihyt20

Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry

Nikola Cihoric, Alexandros Tsikkinis, Gerard van Rhoon, Hans Crezee, Daniel M. Aebersold, Stephan Bodis, Marcus Beck, Jacek Nadobny, Volker Budach, Peter Wust & Pirus Ghadjar

To cite this article: Nikola Cihoric, Alexandros Tsikkinis, Gerard van Rhoon, Hans Crezee, Daniel M. Aebersold, Stephan Bodis, Marcus Beck, Jacek Nadobny, Volker Budach, Peter Wust & Pirus Ghadjar (2015) Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry, International Journal of Hyperthermia, 31:6, 609-614, DOI: 10.3109/02656736.2015.1040471

To link to this article: http://dx.doi.org/10.3109/02656736.2015.1040471

Published online: 15 May 2015.

International Journal of Hyperthermia

http://informahealthcare.com/hth
ISSN: 0265-6736 (print), 1464-5157 (electronic)

Int J Hyperthermia, 2015; 31(6): 609–614
 DOI: 10.3109/02656736.2015.1040471

informa healthcare

RESEARCH ARTICLE

Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry

Nikola Cihoric[1], Alexandros Tsikkinis[1], Gerard van Rhoon[2], Hans Crezee[3], Daniel M. Aebersold[1], Stephan Bodis[4], Marcus Beck[5], Jacek Nadobny[5], Volker Budach[5], Peter Wust[5], & Pirus Ghadjar[5]

[1]*Department of Radiation Oncology, Inselspital, Bern University Hospital, and University of Bern,* [2]*Erasmus MC Cancer Institute, Department of Radiation Oncology, Rotterdam, The Netherlands,* [3]*Academic Medical Centre, Department of Radiation Oncology, Amsterdam, The Netherlands,* [4]*Kantonsspital Aarau Radio-Onkologie, Aarau, Switzerland, and* [5]*Charité Universitätsmedizin, Berlin, Germany*

Abstract

Purpose: Hyperthermia has been shown to improve the effectiveness of chemotherapy and radiotherapy in the treatment of cancer. This paper summarises all recent clinical trials registered in the ClinicalTrials.gov registry. *Materials and methods*: The records of 175,538 clinical trials registered at ClinicalTrials.gov were downloaded on 29 September 2014 and a database was established. We searched this database for hyperthermia or equivalent words. *Results*: A total of 109 trials were identified in which hyperthermia was part of the treatment regimen. Of these, 49 trials (45%) had hyperthermic intraperitoneal chemotherapy after cytoreductive surgery (HIPEC) as the primary intervention, and 14 other trials (13%) were also testing some form of intraperitoneal hyperthermic chemoperfusion. Seven trials (6%) were testing perfusion attempts to other locations (thoracic/pleural $n = 4$, limb $n = 2$, hepatic $n = 1$). Sixteen trials (15%) were testing regional hyperthermia, 13 trials (12%) whole body hyperthermia, seven trials (6%) superficial hyperthermia and two trials (2%) interstitial hyperthermia. One remaining trial tested laser hyperthermia. *Conclusions*: In contrast to the general opinion, this analysis shows continuous interest and ongoing clinical research in the field of hyperthermia. Interestingly, the majority of trials focused on some form of intraperitoneal hyperthermic chemoperfusion. Despite the high number of active clinical studies, HIPEC is a topic with limited attention at the annual meetings of the European Society for Hyperthermic Oncology and the Society of Thermal Medicine. The registration of on-going clinical trials is of paramount importance for the achievement of a comprehensive overview of available clinical research activities involving hyperthermia.

Keywords

Cancer, heat, hyperthermia, trials

History

Received 17 January 2015
Revised 15 March 2015
Accepted 8 April 2015
Published online 15 May 2015

Introduction

Hyperthermia is a procedure which raises the temperature of tumour-loaded tissue to 39.5–43 °C and is generally applied as an additive treatment to established non-surgical cancer treatments, namely chemotherapy and radiation therapy [1]. The temperature elevation can be achieved by different methods including superficial hyperthermia, regional hyperthermia, interstitial hyperthermia, whole body hyperthermia and hyperthermic isolated limb perfusion [1]. Moreover, in patients with peritoneal carcinomatosis hyperthermic intraperitoneal chemotherapy after cytoreductive surgery (HIPEC) has been investigated [2]. Even though some evidence from clinical trials on the use of hyperthermia could be gained, hyperthermia is not yet an established player in the multimodal treatment set-up of solid tumours [3,4]. Several reasons have been suggested to explain the lack of wide clinical use. Arguments such as that the application of hyperthermia is considered to be time consuming, technologically complex and demanding to the patient, are used to explain the hesitation. Others have challenged the evidence of positive hyperthermia trials from the last century by criticising these as being small or technically outdated and claiming that hardly any new clinical studies are being performed [5,6]. Past phase III trials have been extensively discussed in multiple reviews [7–12], including Cochrane analysis [13,14], and authorities in many countries have been convinced to accept adjuvant hyperthermia for radiotherapy and chemotherapy as regular treatment for specific cancer indications as summarised by Sauer et al. [8]. To our knowledge an inventory on all clinical trials is not available, whereas in our opinion such an overview could provide a good insight in the dynamics of the clinical interest in hyperthermia. To obtain such an inventory we used ClinicalTrials.gov. ClinicalTrials.gov is a publicly available database established and maintained by the US National Institutes of Health. Registration of an interventional clinical trial is obligatory in the USA and regulated by several US federal laws as well as laws of the European Union and it is required for funding from the World Health Organization. Trials must be registered

Correspondence: Pirus Ghadjar, MD, Department of Radiation Oncology, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30 450 657055. Fax: +49 30 450 7527152. E-mail: pirus.ghadjar@charite.de

before patient recruitment. Editors of numerous clinical journals published a joint statement that trial registration is obligatory before results publication. Results of trials without registration may not be published. The registration process and database structure are well described on the website and medical and technical literature regarding ClinicalTrials.gov are publicly available. Clinicaltrials.gov is the most recognised trial registry worldwide. It is the only database that provides the possibility to download trial data [15–19].

We analysed all clinical trials starting from 2000 using some form of hyperthermia for cancer treatment, which have been registered in the ClinicalTrials.gov registry to summarise this information for clinicians and investigators.

Materials and methods

The methods used for the registration process of a trial at the ClinicalTrials.gov registry have previously been described [20]. The records of 175,538 clinical trials registered at ClinicalTrials.gov were downloaded on 29 September 2014 including all the available fields in the form of an extensible mark-up language (xml) format and a database was established with the contents of the 'xml' file datasets (MS SQL Database). We searched this database for the word hyperthermia including abbreviations and word variations (e.g. hyperthermic). We also used the list of Medical Subject Headings (MeSH; http://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?mode=&term=HYPERTHERMIA,+INDUCED) terms for database search. All trials addressing diseases other than cancer were excluded from this analysis. Identified trials were grouped according to their primary intervention such as superficial hyperthermia, regional hyperthermia, interstitial hyperthermia, whole body hyperthermia, HIPEC, other intraperitoneal hyperthermic chemotherapy approaches, isolated limb perfusion. Other features of the identified trials were compared (trial condition, trial phase, estimated enrolment, outcome measures).

Results

A total of 109 trials were identified (Figure 1). Trial characteristics are summarised in Table 1. Of these 49 trials (45%) had HIPEC as the primary intervention and 14 other trials (13%) were also testing some form of intraperitoneal hyperthermic chemoperfusion. Seven trials (6%) were testing perfusion attempts to other locations (thoracic/pleural $n = 4$, limb $n = 2$, hepatic $n = 1$). Sixteen trials (15%) were testing regional hyperthermia, 13 trials (12%) whole body

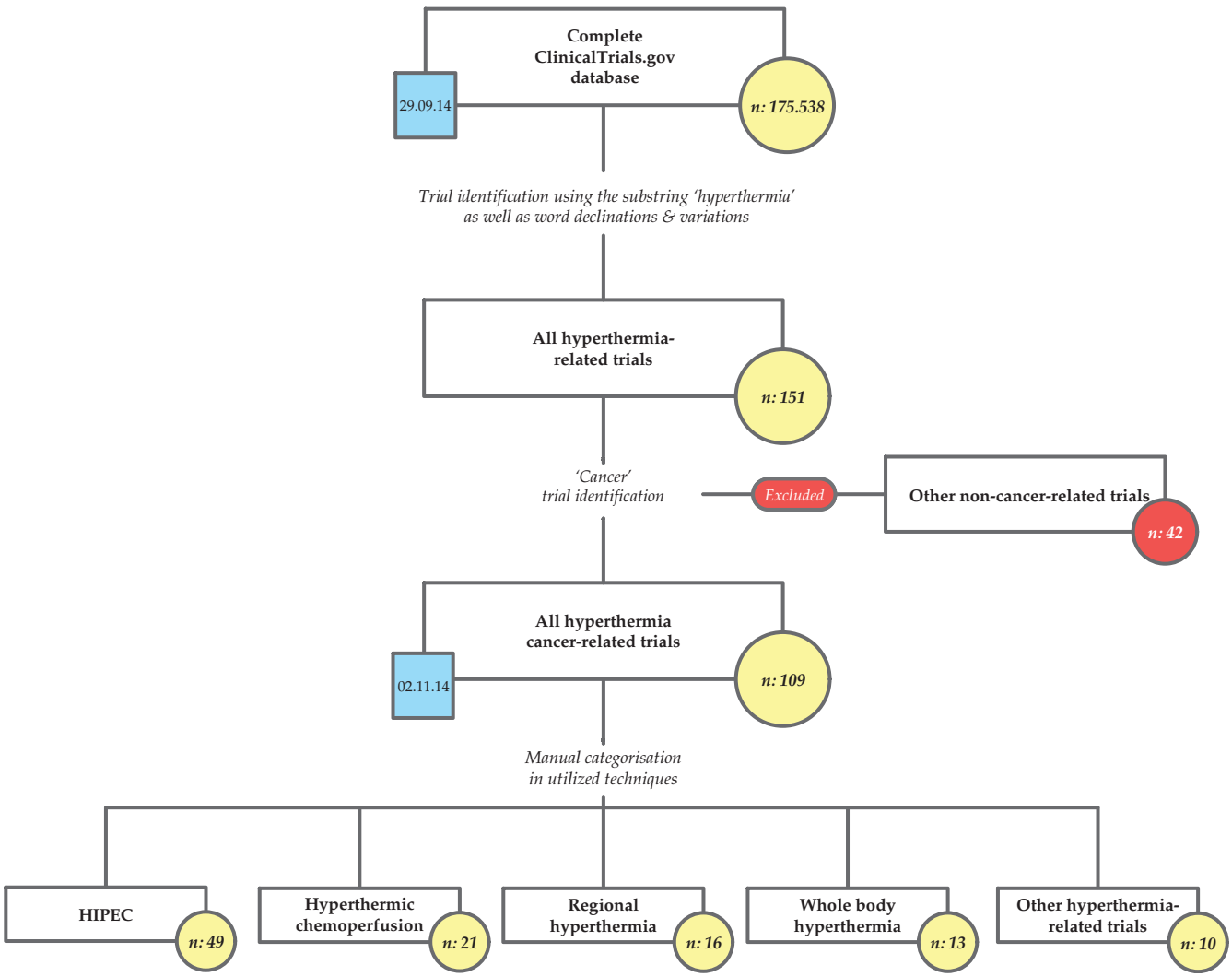

Figure 1. Consort diagram.

Table 1. Trial characteristics.

	Trials (%)						
			Hyperthermic chemoperfusion				
Trial attribute	All ($n = 109$)	HIPEC ($n = 49$, 45%)	Intraperitoneal ($n = 14$, 13%)	Other locations ($n = 7$, 6%)	Regional ($n = 16$, 15%)	Whole body ($n = 13$, 12%)	Other** ($n = 10$, 9%)
Lead sponsor							
Industry	5	1	1	0	1	0	2
NIH	9	0	4	4	0	0	1
Other	95	48	9	3	15	13	7
Masking							
Open	84	42	11	4	12	7	8
Single blind	3	1	0	0	0	2	0
Double blind	3	2	0	0	1	0	0
NA	19	4	3	3	3	4	2
No. of arms							
1	49	23	5	3	5	7	4
2	34	18	5	1	0	3	3
3	2	1	1	0	7	0	0
≥4	1	1	0	0	4	0	0
NA	23	6	3	3	0	3	3
Enrolment*							
0–50	55	24	9	3	5	10	4
51–100	16	9	3	0	4	1	0
101–200	13	6	1	1	3	1	1
>200	16	8	1	1	2	1	3
Location							
N. America	57	21	10	7	5	9	5
S. America	1	1	0	0	0	0	0
Europe	38	21	4	0	7	2	4
Asia	13	6	0	0	4	2	1

*In eight trials the enrolment is not stated; **includes seven superficial, two interstitial and one laser; NA, not available; NIH, US National Institutes of Health.

hyperthermia, seven trials (6%) superficial hyperthermia and two trials (2%) interstitial hyperthermia. One remaining trial tested laser hyperthermia.

A total of 103 trials (94%) were interventional trials, with the remaining six being observational trials. Of the interventional trials 17 trials (16%) were phase I, nine trials (9%) were phase I/II, 38 trials (37%) were phase II, two trials (2%) were phase II/III and 22 trials (21%) were phase III, for the remaining 15 trials phase was not available.

Only five of all identified trials (<5%) were sponsored by an industrial partner, the remaining ($n = 104$; 95%) were investigator driven trials.

Most trials were executed in North America ($n = 57$; 52%), Europe ($n = 38$; 35%) and Asia ($n = 13$; 12%) (Table 2). Figure 2 shows the number of trials registered according to the year started. Note the steep (4×) increase of trials started in 2014, with again most trials started on HIPEC.

Table 2. Locations of trial conduction.

Country	Trial count
USA	55
France	10
Germany	9
China	7
Belgium	4
Italy	4
Netherlands	4
Korea	3
Canada	2
Switzerland	2
Taiwan	2
Austria	1
Brazil	1
Greece	1
Israel	1
Poland	1
Sweden	1
UK	1

Discussion

More than half of hyperthermia-related clinical trials on cancer treatment identified in the ClinicalTrials.gov registry focused on some form of intraperitoneal hyperthermic chemoperfusion. The combination of radical cytoreductive surgery followed by intraoperative hyperthermic chemoperfusion, also referred to as HIPEC, was studied frequently. Regional hyperthermia was only the second most commonly used technique followed by whole body hyperthermia and superficial hyperthermia. The majority of the identified trials were phase II and III trials. Only a small minority of all trials was industrially sponsored (<5%), reflecting the currently limited interest of electro-mechanic companies for this type of treatment. North America and Europe were the two most common geographic sites for trial execution. The steep increase in number of registered clinical trials in 2014 reflects in our opinion the growing interest in hyperthermia as a promising modality to enhance the effectiveness of radiotherapy and chemotherapy (Figure 2).

The ClinicalTrials.gov registry is only available for 2000 onwards, hence hyperthermia trials before this date are not

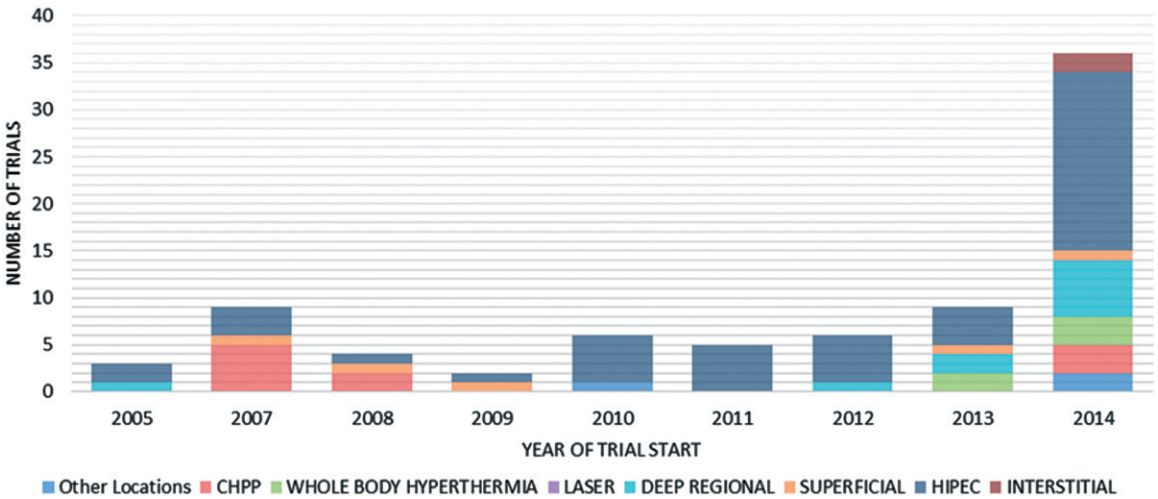

Figure 2. Clinical trials distribution according to the year the trial was started.

Table 3. Summary of all positive randomised phase III trials using an external radiofrequency heating device.

Reference	Treatment	Tumour	End point	Lesions	−HT	+HT
Hua (2011) [21]	RT + CT	Nasopharynx	5 years PFS	180	63%	73%
Huilgol (2010) [22]	RT	Head and neck	CR	54	42%	79%
Issels (2010) [23]	CT	Soft tissue sarcoma	median DFS	340	162 months	317 months
Jones (2005) [24]	RT	Various	CR	109	42%	64%
		Previously irradiated		39	24%	68%
Colombo (2003) [25]	CT	Bladder	2 years OS	75	40%	83%
Verwaal (2003) [26]	CT (HIPEC)	Colorectal peritoneal carcinomatosis	median S	105	126 months	223 months
Harima (2001) [27]	RT	Cervix	CR	40	50%	85%
Van der Zee (2000) [28]	RT	Bladder, cervix, rectum	3 years OS	358	24%	30%
Sneed (1998) [29]	RT	Glioblastoma	2 years S	112	15%	31%
Vernon (1996) [30]	RT	Breast	CR	308	41%	59%
		Previously irradiated		39	39%	79%
Wang (1996) [31]	RT	Oesophagus	3 years S	125	24%	42%
Overgaard (1995) [32]	RT	Melanoma	2 years NED	134	28%	48%
Kitamura (1995) [33]	RT, CT	Oesophagus	CR	66	6%	25%
You (1993) [34]	RT, surgery	Rectum	response	122	5%	23%
Sugimachi (1992) [35]	RT, CT, surgery	Oesophagus	Palliation	53	8%	70%
Strotsky (1991) [36]	RT, surgery	Bladder	3 years S	102	67%	94%
Berdov (1990) [37]	RT, surgery	Rectum	5 years S	115	7%	36%
Kakehi (1990) [38]	RT	Rectum	Response	14	20%	100%
Engelhardt (1989) [39]	CT	Lung	Response	44	36%	60%
Egawa (1989) [40]	RT	Various	Response	92	63%	82%
Valdagni (1988) [41]	RT	Head and neck	CR	44	41%	83%
Datta (1987) [42]	RT	Cervix	CR	64	31%	55%
Kohno (1984) [43]	CT	Vulva/vagina	Response	65	19%	59%

RT, radiation therapy; CT, chemotherapy; HT, hyperthermia; +HT, either RT, CT or both combined with HT; −HT, either RT, CT or both without HT; DFS, disease-free survival; PFS, progression-free survival; NED, no evidence of disease; S, survival; OS, overall survival; CR, complete response.

available in our current analysis, which is a major limitation. Therefore it is worth looking at the evidence for certain types of hyperthermia being generated by published clinical trials which were not registered within ClinicalTrials.gov, as they were conducted before the ClinicalTrials.gov registry became popular. Several review articles addressing clinical trials using hyperthermia have suggested that there are at least 32 randomised clinical phase III trials, 31 using an external radiofrequency heating device and just one using the HIPEC technique [7,10]. Twenty-three of these 32 phase III trials showed a positive effect by adding hyperthermia to standard radiation therapy or chemotherapy in terms of treatment outcome (expressed in various end points) (Table 3). Seventeen out of 23 trials listed in the mentioned review articles were conducted prior to 2000.

In contrast to this older evidence, our present inventory clearly shows a strong clinical research interest for hyperthermic chemoperfusion approaches, which can be easily handled by the surgeons and medical oncologists involved. The use of external radiofrequency heating devices is associated with substantial additional costs (for dedicated technical equipment and staff), which limited its propagation and use within clinical trials. In contrast, additional expenses for hyperthermic intraperitoneal chemoperfusion are decent when compared to normothermic intraperitoneal chemoperfusion, facilitating the spread of this approach in clinical

practice and trials. A similar development is noticed for the application of hyperthermia in non-muscle-invasive bladder cancer. The recent introduction of relatively easy to use hyperthermia devices draws the attention of interested urologists to this field, who have initiated new clinical trials [44,45]. Despite the relatively low costs and easy handling of chemoperfusion approaches over more sophisticated ones such as regional hyperthermia, we also have to take into account whether important oncological end points can actually be improved by chemoperfusion approaches. This has been better described for regional hyperthermia in the past (Table 3) and results of current ongoing trials are therefore awaited. Based upon this ClinicalTrials.gov registry inventory one could consider that HIPEC and chemoperfusion are rather under-represented in the programmes of the annual meetings of the European Society for Hyperthermic Oncology and the Society of Thermal Medicine.

The current inventory focused only on those trials registered in the ClinicalTrials.gov registry and provides only information from 2000 until present. As shown above not all clinical studies for phase III trials are registered, and many more phase I and II studies have been published or are active that are not included in ClinicalTrials.gov [7,9,10]. Moreover, since 2007 a research group under the auspices of the European Society for Hyperthermic Oncology (the Atzelsberg Circle) is actively initiating clinical studies using radiofrequency devices for regional hyperthermia. As an example, the activities of the Atzelsberg Circle have resulted in the open-label, non-randomised, single-institution, phase II study of regional hyperthermia by Wessalowski et al. for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours, demonstrating an objective response rate of 86% [46].

Therefore, as a follow up of the results presented here, we are currently working on an inventory of all clinical trials of the past decades falling within the scope of the ClinicalTrials.gov registry to provide an updated overview on data from all clinical trials related to hyperthermia in oncology.

Conclusions

This inventory shows that there is substantial active and ongoing clinical research addressing the potential of adjuvant hyperthermia. This is in contrast to the general opinion. Almost half of trials focused on some form of intraperitoneal hyperthermic chemoperfusion. Registration of on-going clinical trials is essential for the generation of future comprehensive overviews of clinical research activities in the field of hyperthermia.

Acknowledgements

We would like to thank Branislav Trninic and Tomislav Cuk from KapitalSoft, Trebinje for technical support and advice for data processing.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, et al. Hyperthermia in combined treatment of cancer. Lancet Oncol 2002;3:487–97.
2. Ahmed S, Stewart JH, Shen P, Votanopoulos KI, Levine EA. Outcomes with cytoreductive surgery and HIPEC for peritoneal metastasis. J Surg Oncol 2014;110:575–84.
3. Overgaard J. Editorial. The heat is (still) on – The past and future of hyperthermic radiation oncology. Radiother Oncol 2013;109: 185–7.
4. Januszewski A, Stebbing J. Letter. Hyperthermia in cancer: Is it coming of age? Lancet Oncol 2014;15:565–6.
5. Mathis S, Johansson T. Hyperthermia. Decision Support Document 36. Vienna: Ludwig Boltzmann Institut für Health Technology Assessment, 2010, 1992–0496. Available at http://eprints.hta.lbg.ac.at.
6. Wild C. Should hyperthermia be included in the benefit catalogue for oncologic indications? Commercial interests are presumed behind the editorial of R. Sauer et al. Strahlenther Onkol, 2013, 189:81–86.
7. van der Zee J, Vujaskovic Z, Kondo M, Sugahara T. The Kadota Fund International Forum 2004 – clinical group consensus. Int J Hyperthermia. 2008;24:111–22.
8. Sauer R, Crezee H, Hulshof M, Issels R, Ott O, van Rhoon G. The letter of the Ludwig Boltzmann Institute is unnecessarily polarizing to the discussion on whether or not hyperthermia is evidence based. Strahlenther Onkol, 2013;189:84–6.
9. Issels RD. Hyperthermia adds to chemotherapy. Eur J Cancer 2008; 44:2546–54.
10. Horsman MR, Overgaard J. Hyperthermia: A potent enhancer of radiotherapy. Clin Oncol (R Coll Radiol) 2007;19:418–26.
11. Lammers RJ, Witjes JA, Inman BA, Leibovitch I, Laufer M, Nativ O, Colombo R. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: A systematic review. Eur Urol 2011;60: 81–93.
12. Mi D, Li Z, Yang K, Cao N, Lethaby A, Tian J, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: A systematic review and meta-analysis of randomised controlled trials. Int J Hyperthermia 2013; 29:156–67.
13. De Haas-Kock DF, Buijsen J, Pijls-Johannesma M, Lutgens L, Lammering G, van Mastrigt GA, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database Syst Rev 2009;3:CD006269.
14. Lutgens L, van der Zee J, Pijls-Johannesma M, De Haas-Kock DF, Buijsen J, Mastrigt GA, et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database Syst Rev 2010;3:CD006377.
15. Inrig JK, Califf RM, Tasneem A, Vegunta RK, Molina C, Stanifer JW, et al. The landscape of clinical trials in nephrology: A systematic review of Clinicaltrials.gov. AmJ Kidney Dis 2014;63: 771–80.
16. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007–2010. JAMA 2012;307:1838–47.
17. Subramanian J, Madadi AR, Dandona M, Williams K, Morgensztern D, Govindan R. Review of ongoing clinical trials in non-small cell lung cancer: A status report for 2009 from the ClinicalTrials.gov website. J Thorac Oncol 2010;5:1116–19.
18. Todd JL, White KR, Chiswell K, Tasneem A, Palmer SM. Using ClinicalTrials.gov to understand the state of clinical research in pulmonary, critical care, and sleep medicine. Ann Am Thorac Soc 2013;10:411–17.
19. Hirsch BR, Califf RM, Cheng SK, Tasneem A, Horton J, Chiswell K, et al. Characteristics of oncology clinical trials: Insights from a systematic analysis of ClinicalTrials.gov. JAMA Intern Med 2013; 173:972–9.
20. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database – update and key issues. N Engl J Med 2011;364:852–60.
21. Hua Y, Ma S, Fu Z, Hu Q, Wang L, Piao Y. Intracavity hyperthermia in nasopharyngeal cancer: A phase III clinical study. Int J Hyperthermia 2011;27:180–6.

22. Huilgol NG, Gupta S, Sridhar CR. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial. J Cancer Res Ther 2010;6:492–6.
23. Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem BC, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: A randomised phase 3 multicentre study. Lancet Oncol 2010;11:561–70.
24. Jones EL, Oleson JR, Prosnitz LR, Samulski TV, Vujaskovic Z, Yu D, et al. Randomized trial of hyperthermia and radiation for superficial tumors. J Clin Oncol 2005;23:3079–85.
25. Colombo R, Da Pozzo LF, Salonia A, Rigatti P, Leib Z, Baniel J, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. J Clin Oncol 2003;21:4270–6.
26. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43.
27. Harima Y, Nagata K, Harima K, Ostapenko VV, Tanaka Y, Sawada S. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int J Hyperthermia 2001;17:97–105.
28. van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 2000;355:1119–25.
29. Sneed PK, Stauffer PR, McDermott MW, Diederich CJ, Lamborn KR, Prados MD, et al. Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost ± hyperthermia for glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1998;40:287–95.
30. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: Results from five randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys 1996;35:731–44.
31. Wang J, Li D, Chen N. Intracavitary microwave hyperthermia combined with external irradiation in the treatment of esophageal cancer. Zhonghua Zhong Liu Za Zhi, 1996;18:51–4.
32. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, Arcangeli G, Dahl O, Mella O, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. Lancet 1995;345:540–3.
33. Kitamura K, Kuwano H, Watanabe M, Nozoe T, Yasuda M, Sumiyoshi K, et al. Prospective randomized study of hyperthermia combined with chemoradiotherapy for esophageal carcinoma. J Surg Oncol 1995;60:55–8.
34. You QS, Wang RZ, Suen GQ, Yan FC, Gao YJ, Cui SR, et al. Combination preoperative radiation and endocavitary hyperthermia for rectal cancer: Long-term results of 44 patients. Int J Hyperthermia 1993;9:19–24.
35. Sugimachi K, Kitamura K, Baba K, Ikebe M, Morita M, Matsuda H, et al. Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus – a prospective randomized trial. Int J Hyperthermia 1992;8:289–95.
36. Strotsky A, Fradkin S, Zhavrid E, Karpovich U. Combined therapy of bladder cancer with the use of hyperthermia. Strahlenther Onkol 1991;167:346.
37. Berdov BA, Menteshashvili GZ. Thermoradiotherapy of patients with locally advanced carcinoma of the rectum. Int J Hyperthermia 1990;6:881–90.
38. Kakehi M, Ueda K, Mukojima T, Hiraoka M, Seto O, Akanuma A, et al. Multi-institutional clinical studies on hyperthermia combined with radiotherapy or chemotherapy in advanced cancer of deep-seated organs. Int J Hyperthermia 1990;6:719–40.
39. Engelhardt R, Neumann H, Müller U, Löhr G. Clinical studies in whole body hyperthermia. In: Sugahara T, Saito M, eds. Hyperthermic Oncology Vol 2. London: Taylor and Francis, 1989. pp. 509–10.
40. Egawa S, Tsukiyama I, Kajiura Y, Akine Y, Ogino T, Takayasu K, et al. Characteristics of the response of soft tissue sarcoma to hyperthermia: The correlation between temperature distribution, radiological examination and histology. Int J Hyperthermia 1989;5: 23–35.
41. Valdagni R, Amichetti M, Pani G. Radical radiation alone versus radical radiation plus microwave hyperthermia for N3 (TNM-UICC) neck nodes: A prospective randomized clinical trial. Int J Radiat Oncol Biol Phys 1988;15:13–24.
42. Datta N, Bose A, Kapoor H. Thermoradiotherapy in the management of carcinoma of the cervix (IIIB): A controlled clinical study. Indian Med Gazette 1987;121:68–71.
43. Kohno I, Kaneshige E, Fujiwara K, Sekiba K. Thermochemotherapy (TC) for gynecologic malignancies. In: Overgaard J, ed. Hyperthermic Oncology Vol 1. London: Taylor and Francis, 1998. pp. 753–6.
44. Synergo. Radiofrequency induced thermo-chemotherapy effect for the treatment of non-muscle invasive bladder cancer. Ongoing clinical trials. Available at: http://www.synergo-medical.com/#!ongoing-clinical-trials-en/cx81.
45. Combat Medical. Combat Medical leading the current investigation in thermotherapy device assisted therapies for NMIBC. Available at: http://www.hivec.co.uk/index.php/clinical-information.
46. Wessalowski R, Schneider DT, Mils O, Friemann V, Kyrillopoulou O, Schaper J, et al, for the MAKEI study group. Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: An open-label, non-randomised, single-institution, phase 2 study. Lancet Oncol 2013;14:843–52.