4. Clinical trials and literature regarding tumour entities, 06/21

Clinical results on local hyperthermia:
Investigations consistently show noticeably higher rates of complete remission when radiotherapy is combined with hyperthermia, compared to radiotherapy on its own. In over 28 randomised controlled clinical trials, the addition of hyperthermia to radiotherapy or chemotherapy was investigated. In 36 clinical trials, significantly improved results were achieved by combining the treatment with hyperthermia. In particular when treating patients with highly malignant tumours, in the case of patients who had reached an advanced stage of the disease, with therapy-resistant tumours, partial rates of remission were achieved, that are very promising and clearly superior to the previous methods.

INDICATIONS with clinical results for <u>LOCAL</u> HYPERTHERMIA:

1. Brain tumours and metastases
2. Head/neck tumours
3. Oesophageal carcinoma/gastric carcinoma
4. Mammary carcinoma/relapses
5. Pulmonary carcinoma
6. Hepatic carcinoma/metastasis
7. Pancreatic carcinoma
8. Colorectal tumours
9. Pelvic tumours
- Cervix/ovary carcinoma
- Bladder carcinoma
10. Sarcomas
11. Peritoneal carcinomas
12. Melanomas
13. Bone metastases

A **selection** of clinical **randomised** trials on local combined hyperthermia:

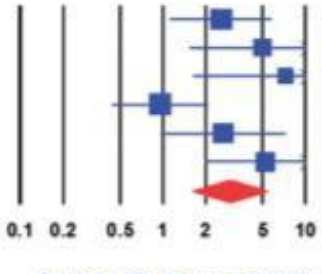
Review by Datta:

(a) **Odds ratio (Radiotherapy + Hyperthermia vs. Radiotherapy alone)**

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Local CR / Total RT+HT	Local CR / Total RT alone	Weight (Random) Relative weight
Wen et al, 2014	2.56	1.12	5.86	0.026	34 / 49	23 / 49	19.89
Hulgol et al, 2010	5.00	1.52	16.46	0.008	22 / 28	11 / 26	14.36
Valdagni et al, 1994	7.22	1.61	32.46	0.010	15 / 18	9 / 22	10.90
Perez et al, 1991	0.96	0.44	2.08	0.908	18 / 53	21 / 60	20.75
Datta et al, 1990	2.64	0.96	7.28	0.061	18 / 33	10 / 32	16.85
Arcangeli et al, 1987	5.21	1.94	13.98	0.001	30 / 38	18 / 43	17.26
Overall effect	2.92	1.58	5.42	0.001	137 / 219	92 / 232	

Test for heterogeneity, $I^2 = 55.38$, $p = 0.047$

Odds ratio and 95% CI

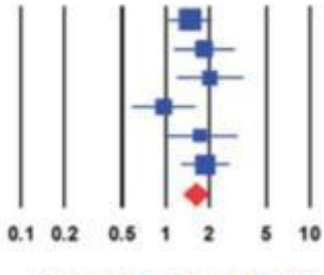


(b) **Risk ratio (Radiotherapy + Hyperthermia vs. Radiotherapy alone)**

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Local CR / Total RT+HT	Local CR / Total RT alone	Weight (Random) Relative weight
Wen et al, 2014	1.48	1.04	2.10	0.029	34 / 49	23 / 49	26.11
Hulgol et al, 2010	1.86	1.14	3.03	0.013	22 / 28	11 / 26	15.00
Valdagni et al, 1994	2.04	1.18	3.51	0.010	15 / 18	9 / 22	12.44
Perez et al, 1991	0.97	0.58	1.62	0.908	18 / 53	21 / 60	13.93
Datta et al, 1990	1.75	0.96	3.18	0.069	18 / 33	10 / 32	10.35
Arcangeli et al, 1987	1.89	1.28	2.78	0.001	30 / 38	18 / 43	22.16
Overall effect	1.61	1.32	1.97	0.000	137 / 219	92 / 232	

Test for heterogeneity, $I^2 = 13.37$, $p = 0.329$

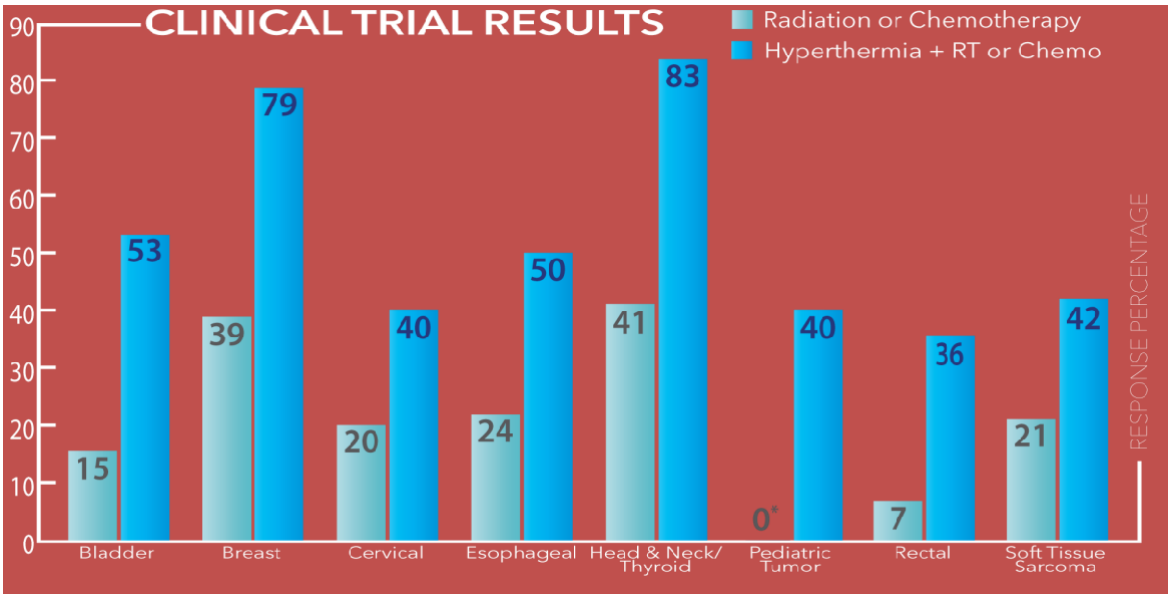
Risk ratio and 95% CI



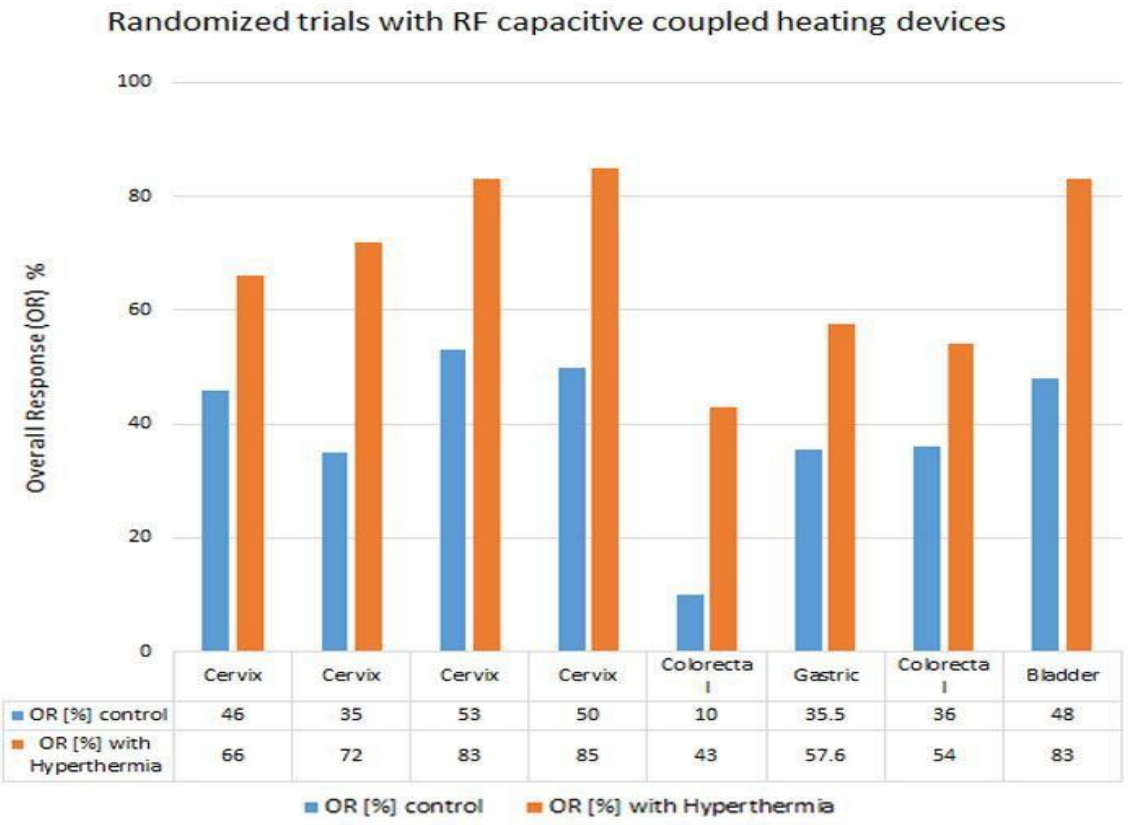
2

The en 31.3% and 46.9% across the six trials. With thermoradiotherapy, the overall CR reported was 62.5% (137/219), (range 33.9–83.3%). The odds ratio was 2.92 (95% CI: 1.58–5.42, p¼0.001); the risk ratio was 1.61 (95% CI: 1.32–1.97, p50.0001) and the risk difference was 0.25 (95% CI: 0.12–0.39, p50.0001), all in favour of combined treatment with hyperthermia and radiotherapy over radiotherapy alone. Acute and late grade III/IV toxicities were reported to be similar in both the groups.

A **selection** of clinical **randomised** trials on local combined hyperthermia:

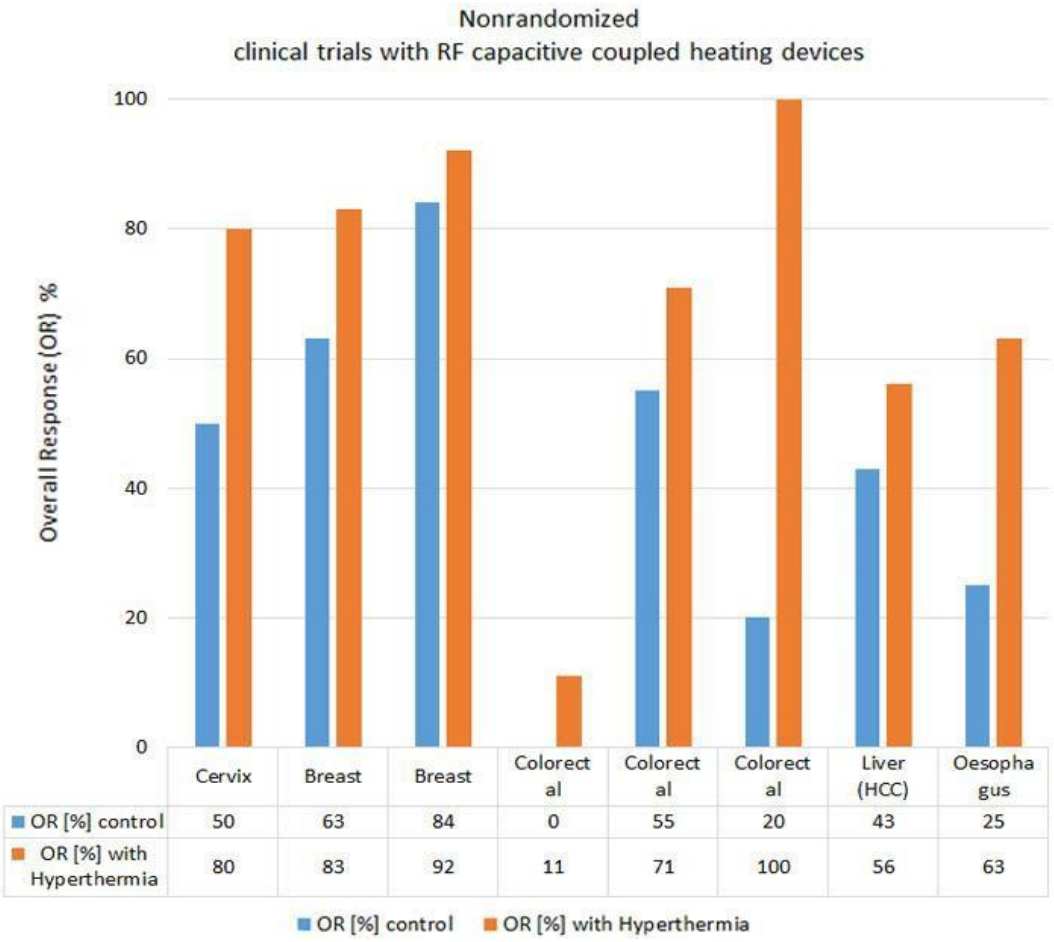


A **selection** of clinical **randomised** trials on local combined hyperthermia by means of capacitive coupling (8 or 13 MHz):



	Cervix	Cervix	Cervix	Cervix	Colorectal	Gastric	Colorectal	Bladder
OR [%] control	46	35	53	50	10	35.5	36	48
OR [%] with Hyperthermia	66	72	83	85	43	57.6	54	83

A **selection** of clinical **<u>non</u>-randomised** trials on local combined hyperthermia



4

<u>Literature concerning individual tumour entities:</u>

1. Brain tumours and metastases:

A. Fiorentini G, et al, „A phase II clinical study on relapsed malignant gliomas treated with electro-hyperthermia" PMID: 17203754 [PubMed - indexed for MEDLINE]

B. Fiorentini G., Sarti D., Milandri C., Dentico P., Mambrini A., Guadagni S. (2018): Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-hyperthermia Oncothermia Journal 22:32-45

C. Ryabova A.I., Novikov V.A., Choinzonov E.L., Gribova O.V., Startseva Zh.A.; „Local Hyperthermia in Multimodal Therapy of Malignant Glioma", Tomsk Cancer Research Institute; 5th Russian-Japanese Neurosurgical Symposium (RJNS2016)

D. Hager, D., Sahinbas,H., Groenemeyer, D.H. 2008; Prospective phase II trial for recurrent high-grade gliomas with low radiofrequency (LRF) hyperthermia; Journal of Clinical Oncology, 2008 ASCO AnnualMeeting Proceedings,Vol. 26, No. 155, 2008: 247

E: Anastasiya I. Ryabova, Valery A. Novikov, Olga V. Gribova, et al; "Concurrent Thermochemoradiotherapy in Glioblastoma Treatment: Preliminary Results" 08/2017 http://dx.doi.org/10.5772/intechopen.76264

F: D. Hager, H. Dziambor, E. M. App et all. The treatment of patients with high-grade malignant gliomas with RF-hyperthermia. 39th ASCO Annual Meeting. May 31-June 3, 2003 (Abstract No. 470).

G: Tanaka R, Kim CH, ,et all. Radiofrequency hyperthermia for malignant brain tumors: preliminary results of clinical trials. Neurosurgery. 1987 Oct;21(4):478-83.

H: Sahinbas H, Groenemeyer DHW. Boecher E, Lange S. Hyperthermia treatment of advanced relapsed glioma and astrocytoma. 9th ICHO 2004.page;85.

I: Stahl H, Wust P, Maier-Hauff K et all. The use of an early postoperative interstitial-hyperthermia combination therapy in malignant gliomas. Strahlenther Onkol. 1995 Sep;171(9):510-24.

J: H. Bühler, P. Nguemgo-Kouam, H. Sahinbas [...] I.A. Adamietz, Article: 610 Clonogenic survival as well as motility of malignant cells is reduced by hyperthermia alone or in combination with irradiation , Article, Sep 2015

K: Sahinbas H. Retrospective clinical study for advanced brain-gliomas by adjuvant electro-hyperthermia treatment, Review Article, Cancer Therapy Vol 8, 139-149, 2012

L: Sneed PK, Stauffer PR, 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 Jan 15;40(2):287-295

u.v.m.

2. Head/neck tumours:

Review von Datta et al.-Schweiz, Huigol in Mumbai:
Niloy R. Datta, Susanne Rogers, Silvia Gómez Ordóñez, Emsad Puric & Stephan Bodis (2015): Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis, International Journal of Hyperthermia, DOI: 10.3109/02656736.2015.1099746

Non resectable Head & Neck Cancer (Huilgol, Mumbai Indien. USA 2004)
60 patients; combining radiation therapy with hyperthermia (1x/week 45 – 90 Min.) initial results: 46 patients CR complete remission ; 14 patients PR partial remission. Overall Survival (OS) after 6 months 84 % after 24 months 66 %.

Non resectable Head & Neck Cancer (Huilgol, Mumbai Indien; ESHO 2007)
23 patients; after common treatment with radiation (70 Gy) and chemo (either 60 mgs Paclitaxel or 50 mg Cisplatin/week) combining radiation with HT applied after radiation (30-50 min). This three base treatment concept was accepted well by all patients. Initial Results: 10 patients CR; 13 patients PR.

Nagraj G. Huilgol, et al; „Chemoradiation with hyperthermia in treatment of head and neck cancer"; Inter. J. hyperthermia Febr. 2010; 26(1): 21-25

6 Valdagni R, Amichetti M. Report of a long-term follow-up in a randomised trial comparing radiation therapy and radiation plus hypertherrnia to metastatic lymph nodes in stage IV head and neck cancer patients. Int J Radiat Oncol 1993; 28:163-69
„Nonresectable head/neck tumors Stage IV with metastasis in lymphnods
randomized phase III trial (Valdagni und Amichelli, Italy)"
Radiotherapy (RT) + regional Deep Location Hyperthermia (HT); n= 41 Patients

RESULTS:	Complete Remission :	41 % in solo arm RT
		83 % in arm of combining RT + HT
	5-years Survival Rate:	0 % in solo arm RT
		53 % in combining RT + HT

Datta NR, Bose Ak, Kapoor HK, et al. Head and nech cancers: results of thermoradiotherapy versus radiotherapy. Int J Hyperthermia 1990; 6:479-86

u.v.m.

3. Oesophageal carcinoma/gastric carcinoma

Tumor site	Experi-mental	Con-trol	No. of Pts-	OR [%] Control	OR [%] with HT	Survival benefit	Remarks	Ref.
Oesophagus	CT + HT	CT	40	19	41	No	RCT	28
Oesophagus	RT + HT		53	8	70		RCT	29
Oesophagus	RT + CT + HT		53	8	27		RCT	30
Oesophagus	RT + HT	RT	313	25	63	Yes	RCT	31
Oesophagus	RT + CT + HT	Rt+ CT	66	59	81,2	Yes	RCT	47
Oesophagus	Ext. RT MW + HT	ext. RT	66			Yes	OT	32

Abbreviations: RT: radiotherapy; CT: chemotherapy; MW: microwaves; RCT: randomised controlled trial- OT: open-label observational study; CR: complete response; Rec: recurrence after adjuvant treatment; neoadj.: neoadjuvant; adj.: adjuvant

Sugimachi K, Kuwano H, Ide H et al. Chemotherapy combined with or without hyperthermia for patients with oesophageal carcinoma: a prospective randomised trial. Int J Hyperthermia 1994, 4:485-493

Sugimachi K, Kitamura K, Baba K: Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus: a prospective randomised trial. Int J Hyperthermia 1992, 8:289-295

Sugimachi K, Kitamura K, Baba K, lkebe M, Morita M, Matsuda H, Kuwano H: Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus - A prospective randomised trial. Int J Hyperthermia 1992, 8:289-295

Muratkhozhaev NK, Svetitsky PV, Kochegarov AA, Alimnazarov SA, Kuznetsov VN, Shek BA: Hyperthermia in therapy of cancer patients. Med. Radiol. (Russian) 1987, 32:30-36

Wang J, Li D, Chen N.: Intracavitary microwave hyperthermia combined with external irradiation in the treatment of esophageal cancer [Article in Chinese) Zhonhua Zhong Liu Za Zhi 1996 Jan, 18(1):51-54

Shchepotin IB, Evans SR, Chorny V, Osinsky S, Buras RR, Maligonov P, Shabahang M, Nauta RJ.: „Intensive preoperative radiotherapy with local hyperthermia for the treatment of gastric carcinoma“., Surg Oncol 1994 Feb;3(1):37-44

Fang H, Zhang Y, Wu Z, Wang X, Wang H, Wang Y, et al. Regional hyperthermia combined with chemotherapy in advanced gastric cancer. Open medicine (poland) 2019;14(1):85-90.

Lu C,LiL, Luo Z, Cui Y, Fu P, Zhou J, et al. Clinical efficacy of type-B ultrasound-guided intraperitoneal hyperthermic chemoperfusion combined with systemic chemotherapy in advanced gastrice cancer patients with malignant ascites. Neoplasma 2016;63(2):299-303**.**

4. Mammary carcinoma/relapses

For the first time in 2007, the National Comprehensive Cancer Network (**NCCN**) incorporated the combined treatment of radiotherapy and hyperthermia into its Guidelines for Breast Cancer (Relapses). Since 2012 and 2013 it has been listed the Category 1b(B) Breast Cancer Guidelines.
It has also been incorporated by the **AGO** (*Arbeitsgemeinschaft Gynäkologische Onkologie e.V.*) as a relapse therapy, in the form of a combined therapy with radiotherapy and/or chemotherapy. In some countries, it ranks among the primary therapy concepts.

1. Markus Notter, H. Piazena, P. Vaupel (2016): Hypofractionated re-irradiation of large-sized recurrent breast cancer with thermography-controlled, contactfree water-filtered infra-red-A hyperthermia: a retrospective study of 73 patients, International Journal of Hyperthermia, DOI: 10.1080/02656736.2016.1235731

2. Sherar M, van der Zee J, Gonzalez DG et al: Relationship between thermal dose and outcome in thermoradiotherapy treatments for superficial recurrences of breast cancer: data from a phase III trial., Int J Radiat Oncol Biol Phys 1997 Sep 1;39(2):371-380

3. Vernon CC, Hand JW, Field SB 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: 731-744.

4. En cuirasse Brustkrebs (Oidenburg et al, Ams.terdam, Holland, ESHO Verona 2009), 80 Patienten re-RT+HT; davon 17 nacherfassbar 32Gy/8 Fraktionen gemeinsam mit HT; Ansprechrate 76,5% ; wenn Tumorgrösse dec!kungsgleich zu Elektrode sogar 88,2% bei einem progressionsfreien Intervall von 6 Monaten. Keine schweren Nebenwirkungen.

5. Jones et al. (Jones et. al., Journal of Clinical Oncology Vol. 23, No 13, May 1, 2005.), 109 Patients with **breast CA** close to skinsurface compr. response rate of 68,1 % (radiation + HT) vs. 42,3% (radiation alone), most significant difference with patients previously radiated: **68,2% in radiation+ HT vs. 23,5 % radiation alone**

etc.

5. Pulmonary carcinoma

Tumorentität	RT	CxT	OR%	OR% mit HT	N	Ref.
Lungenkarzinom; (Wholebody HT)	nein	ja	36	68	44	[1]
Lungenkarzinom (nicht kleinzellig)	ja	nein	20	73	49	[2]
Lungenkarzinom (nicht kleinzellig)	ja	nein	-	100	13	[3]

Engelhardt R, Neumann H, M-ller U, L0hr GW. Clinical studies in whole body hyperthermia. In Sugahara T, Saito M (eds): Hyperthermic Oncology Volume 2. London: Taylor and Francis 1989;509-51

Karasawa K, Muta N, Nakagawa K, Hasezawa K, Terahara A, Onogi Y, Sakata K I, Aoki Y, Sasaki Y, Akanuma A: Thermoradiotherapy in the treatment of locally advanced nonsmall cell lung cancer, Int. J. Radiol. Oncol. Biol. Phys, Vol. 30., 1994, pp. 1171-1177

Imada H, Nomoto S, Tomimatsu A, Kosaka K, Kusano S, Ostapenko VV, Terashima H: Local control of Nonsmall cell lung cancer by radiotherapy combined with high power hyperthermia using an 8MHz RF capacitive device, Japn. J. Hyperthermic Onco 1999, 15:19-24

S. Sakao, Y. Takiguchi, K. Nemoto, et al; Japan; “Thermoradiotherapy for local control of chest wall invasion in patients with advanced non-small cell lung cancer”

6. Hepatic carcinoma/metastasis

Maeta M et al: a case-matched control study of intrahepatoarterioal chemotherapy in combination with or without regional hyperthermia for treatment of primary and metastatic hepatic tumors. Int J Hyperthermia 1994; 10 (1):51-58

Sugiyama A. et al: Hepatic arterial infusion chemotherapy combined with hyperthermia for metastatic liver tumors of colorectal cancer. Semin Oncol 1997; 24 (2 Suppl 6): S6-135-8

Kurpeshhey O. et al: Immeadiate results of loco-regional hyperthermia and chemotherapy for liver metastases of colo-rectal cancer. Presentation at ESHO conference 2010 Rotterdam, May 22, 2010

Hager ED et al: Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Research 1999; 19 (4C):3403-8

Kim BS et al: Phase II trial for combined external radiotherapy and hyperthermia for unresectable hepatoma. Cancer Chemother Pharmacol 1992; 31 (Suppl):S119-27

Moffat FL et al: effect of radiofrequency hyperthermia and chemotherapy on primary and secondary hepatic malignancies when used with metronidazole. Surgery 1983; 94 (4): 536-42

Moffat FL et al: further experience with regional radiofrequency hyperthermia and cytotoxic chemotherapy for unresectable hepatioc neoplasia. Cancer 1985; 55 (6): 1291-5, (n =178patients)

Nagata Y, Hiraoka M, Nishimura Y et al: Clinical results of radiofrequency hyperthermia for malignant liver tumors. Int J Radiat Oncol Biol Phys (1997) 38:359-365

Nagata Y, Hiraoka M, Akuta K et al: Radiofrequency thermotherapy for malignant liver tumors, Cancer 65(8) 1990: 1730-1736

Alexander HR, Libutti SK, Pingpank JF et al:Hyperthermic isolated hepatic perfusion using melpha- tan for patients with ocular melanoma metastatic to liver. Clin Cancer Res (2003) 9: 6343-6349

Kasianenko IV, Osinsky SP, Pivnyuk VM et al: Thermochemotherapy for liver matastases in patients with mammary carcinoma and gastrointestinal tumors. Oncol UKR (2000) 2:34-36

Yamamoto K, Tanaka Y: Radiofrequency capacitive hyperthermia for unresectable hepatic cancers. J Gastroenterol 1997; 32:361-366

Seong J, Lee HS, Han KH et al: Combined Treatment of Radiotherapy and Hyperthermia for Unresectable Hepatocellular Carcinoma. Yonsei Med J 35(3) (1994):252-259

Ohguri T, Imada H, Yahara K et al: Effect of 8-MHz radiofrequency-capacitive regional hyperthermia with strong superficial cooling for unresectable or recurrent colorectal cancer. Int J Hyperthermia 2004; 20(5):465-475

Nishimura Y, Hiraoka M, Abe M: Thermoradiotherapy of locally advanced colorectal cancer. In: Matsuda T (ed) Cancer Treatment by Hyperthermia, Radiation and Drugs. Taylor Francis, London,
1993. 278-289

Nishimura Y, Hiraoka M, Akuta K et al: Hyperthermia combined with radiation therapy for primarily unresectable and recurrent colorectal cancer. Int. J Rad Onc Biol (1992) 23(4):759-768

Berdov BA, Menteshashvili GZ: Thermoradiotherapy of patients with locally advanced carcinoma of the rectum. Int J Hyperthermia (1990) 6(5):881-890

Etc. .

7. Pancreatic carcinoma

Review: Astrid van der Horst, Eva Versteijne, Marc G. H. Besselink, Joost G. Daams, Esther B. Bulle, Maarten F. Bijlsma, Johanna W. Wilmink, Otto M. van Delden, Jeanin E. van Hooft, Nicolaas A. P. Franken, Hanneke W. M. van Laarhoven, Johannes Crezee & Geertjan van Tienhoven (2017): The clinical benefit of hyperthermia in pancreatic cancer: a systematic review, International Journal of Hyperthermia, DOI: 10.1080/02656736.2017.1401126. –
Link to this article: https://doi.org/10.1080/02656736.2017.1401126

Table 1. Patient characteristics. Number of patients, median age, disease stage per study, fraction of adenocarcinomas and whether histological confirmation was obtained.

Study	n	Median age (year) Total (HT/control)	Locally advanced disease (stage III) HT	Locally advanced disease (stage III) Control	Metastatic disease (stage IV) HT	Metastatic disease (stage IV) Control	PDAC	Histology Confirmation
Kouloulias et al. 2002 [57]	37	62 (62/60)	6/10 (60%)	19/27 (70%)	4/10 (40%)	8/27 (30%)	37/37	Yes
Ohguri et al. 2008 [60]	29	64 (62/65)	20/20 (100%)	9/9 (100%)	0/20 (0%)	0/9 (0%)	29/29	14/29
Yamada et al. 1992 [54]	73	60.6[b] (NR/NR)	11/17 (65%)[d]	32/56 (57%)[d]	6/17 (35%)	24/56 (43%)	43	52/73
Maluta et al. 2011 [62]	68	64.3 (66.6/65.7)	34/40 (85%)	26/28 (93%)	6/40 (15%)[f]	2/28 (7%)[f]	68/68	Yes
Ashayeri et al. 1993 [55]	24	NR (62/61)	5/5 (100%)	19/19 (100%)[e]	0/5 (0%)	0/19 (0%)	24/24	NR
Maebayashi et al. 2017 [66]	13	78 (62/NR)	5/5 (100%)	8/8 (100%)	0/5 (0%)	0/8 (0%)	4/13	4/13
Douwes 2006 [58]	30	59.8 (59.8/–)	5/30 (17%)[g]	–	25/30 (83%)	–	NR	NR
Tschoep-Lechner et al. 2013 [64]	23	60 (60/–)	2/23 (9%)	–	21/23 (91%)	–	22/23	Yes
Volovat et al. 2014 [65]	19	NR (NR/–)	0/19 (0%)	–	19/19 (100%)	–	11/19	Yes
Ishikawa et al. 2012 [63]	18	64 (64/–)	6/18 (33%)	–	12/18 (67%)	–	18/18	Yes
Bakshandeh-Bath et al. 2009 [61]	13	57 (57/–)	0/13 (0%)	–	13/13 (100%)	–	13/13	Yes
Kouloulias et al. 2001 [56]	7	65 (65/–)	7/7 (100%)	–	0/7 (0%)	–	7/7	Yes
Kakehi et al. 1990 [53][a]	34	NR (NR/–)	6/34 (18%)	–	28/34 (82%)	–	23/34	23
Bull et al. 2008 [59][a]	7	62 (62/–)	0/7 (0%)	–	7/7 (100%)	–	NR	Yes
Overall	395	57–78[c]	107 (43%)	113 (77%)	141 (57%)	34 (23%)		

n: number of patients; –: not applicable; NR: not reported.
[a]The pancreatic cancer patients are part of a larger cohort [53,59].
[b]Average age.
[c]Range of median age.
[d]This includes 12 patients (4 HT, 8 control) with stage I and II.
[e]Control cohort is a comparable group treated a decade earlier than the HT cohort.
[f]Note: for the overall survival analysis, the 8 patients with metastatic disease were excluded [62].
[g]Four patients had stage II disease.

Further **review works** on pancreatic carcinoma

- Martin Roesch & Boris Mueller-Huebenthal; Indian Journal of Surgical Oncology; ISSN 0975-7651; Indian J Surg Oncol; DOI 10.1007/s13193-014-0316-5

Table 1 Survey trials on pancreatic cancer treatments including hyperthermia

Trials on advanced pancreatic cancer	Center	Hyperthermia method	No of patients	Control arm (%)	Arm adding hperth. (%)	Overall Survival (OS) benefit in arm including hyperthermia	Benefit OS odds ratio	Benefit quality of life
Kouloulias et al. 2002 [6]	Athens, Greece	Intrasurgery surface heating	65	85 %	15 %	11 months (SE 2.4 months)	p=0.029	Better: p=0.031
Yamada et al. 1992 [5]	Sendai, Japan	Intrasurgery surface heating	69	80 %	20 %	1 year OS:plus 6.9 % 2. year plus 4.2 %		Only marginally better
Mi et al. 2013 [10]	Meta-analysis for adv. gastric cancers	Intraoperative HIPEC-thermoenhanced Chemotherapy	1906 in 16 rand. trials			1. year OS	2.99 (95 % CI) 2.21 to 4.05; p<0.00001	No higher risks; but increase incidences of abdominal pain
Hager et al. 2006 [24]	Bad Bergzabern, Germany	Non-invasive loco-reg. heating	46		100 %	Median OS: 10.8 months 1. year OS: 41 %		QoL improvement & pain decrease (56 %)
Zhang et al. (2008) [30]	China	Non-invasive loco-reg. heating	75	49 %	51 %	1. year OS plus 13 % 2. year OS plus 50 %		No serious complicat.
Mueller-Huebenthal 2010 [25]	Stuttgart, Germany	Non-invasive loco-reg. heating	25		100 %	Median OS 12.2 months 1. year OS: 51 %		Pain reduction observed
Maluta et al. 2011 [31]	Verona, Italy	Non-invasive loco-reg. heating	60	50 %	50 %	OS plus 4 months=+36 %	p=0.025	No increased toxicity
Ishikawa et al. 2012 [32]	Multicentre Japan	Non-invasive loco-reg. heating	18		100 %	Median OS: 8 months; 1 year OS: 33 %		No added toxicity except mild pain & skin rush
Tschoep-Lechner 2013 [33]	Munich, Germany	Non-invasive loco-reg. heating	23		100 %	Median OS 12.9 months		

- K. E. TSCHOEP-LECHNER[1], V. MILANI[1],& R.-D. ISSELS[1] ; Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer"; Klinikum Grosshadern Munich, Germany, Int. J. Hyperthermia, February 2013; 29(1): 8–16; (Received 30 July 2012; Revised 8 October 2012; Accepted 13 October 2012)

8. Colorectal tumours

1. Fang H, Zhang Y, Wu Z, Wang X, Wang H, Wang Y, et al. Regional hyperthermia combined with chemotherapy in advanced gastric cancer. Open medicine (poland) 2019;14(1):85-90.

2. Sun JJ, Fan GL, Wang XG, Xu K. The research on the influences of hyperthermal perfusion chemotherapy combined with immunologic therapy on the immunologic function and levels of circulating tumor cells of the advanced colorectal cancer patients with liver metastasis. Eur Rev Med Pharmacol Sci 2017;21(13):3139-3145.

3. Min Kyu Kang, MD1*, Myung Se Kim1, Jae Hwang Kim2 ; “Clinical outcomes of mild hyperthermia for locally advanced rectal cancer (235 patients) treated with preoperative radiochemotherapy”; large prospective randomised trial; 2011, Vol. 27, No. 5 , Pages 482-490 (doi:10.3109/02656736.2011.563769)

4. De Haas-Kock DF, Buijsen J, Pijls-Johannesma M, Lutgens L, Lammering G, van Mastrigt GA, De Ruysscher DK, Lambin P, van der Zee J. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database Syst Rev 2009; CD006269

5. Furuta K, Konishi F, Kanazawa K, Saito K, Sugawara T. Synergistic effects of hyperthermia in preoperative radiochemotherapy for rectal carcinoma. Dis Colon Rectum 1997; 40: 1303–1312

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7. Wust P, Rau B, Gellerman J, Pegios W, Loffel J, Riess H, Felix R, Schlag PM. Radiochemotherapy and hyperthermia in the treatment of rectal cancer. Recent Results Cancer Res 1998; 146: 175–191

8. Anscher MS, Lee C, Hurwitz H, Tyler D, Prosnitz LR, Jowell P, Rosner G, Samulski T, Dewhirst MW. A pilot study of preoperative continuous infusion 5-fluorouracil, external microwave hyperthermia, and external beam radiotherapy for treatment of locally advanced, unresectable, or recurrent rectal cancer. Int J Radiat Oncol Biol Phys 2000; 47: 719–724

9. Maluta S, Romano M, Dall'oglio S, Genna M, Oliani C, Pioli F, Gabbani M, Marciai N, Palazzi M. Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum. Int J Hyperthermia 2010; 26: 108–117

Most of the trials currently running concern colorectal carcinoma,
etc., …….

9. Pelvic tumours

- **Cervix/ovary carcinoma:**

1. Niloy R. Datta, E. Stutz,S. Gomez, et al; Radiation Oncology, University Hospital Zurich, Switzerland; Review: Efficacy and Safety Evaluation of the Various Therapeutic Options in Locally Advanced Cervix Cancer: "A Systematic Review and Network: Meta-Analysis of Randomized Clinical Trials"; Radiation Oncology, International Journal of biology physics; Received May 29, 2018, and in revised form Sep 21, 2018. Accepted for publication Sep 25, 2018.

2. Niloy R. Datta, Susanne Rogers, Silvia Gómez &Stephan Bodis (2016) Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses“ ; International Journal of Hyperthermia, 32:7, 809-821, DOI: 10.1080/02656736.2016.1195924
Link to this article: http://dx.doi.org/10.1080/02656736.2016.1195924

3. Yoko Harima, Takayuki Ohguri, et al (2016); „A multicentre randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer“, International Journal of Hyperthermia, 32:7, 801-808, DOI: 10.1080/02656736.2016.1213430
Link to this article: http://dx.doi.org/10.1080/02656736.2016.1213430

4. He L, Wang J, Chen H, Wu X, Tang L, Wang X, et al. Hyperthermia as an adjuvant therapy to chemotherapy for the treatment of advanced ovarian cancer complicated by ascites. Biomedical research (india) 2017;28(18):8115-8120.

5.. Van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. New England journal of medicine 2018;378(3):230-240.

etc..

- **Urinary bladder carcinoma**

1. Ba M, Cui S, Wang B, Long H, Yan Z, Wang S, et al. Bladder intracavitary hyperthermic perfusion chemotherapy for the prevention of recurrence of non-muscle invasive bladder cancer after transurethral resection. Oncology reports 2017;37(5):2761-2770.

2. Colombo R, Salonia A, Leib Z, Pavone-Macaluso M, Engelstein D. Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). BJU Int 2011;107(6):912-918.

3. Wittlinger M, Rödel CM, Weiss C, Krause SF, Kühn R, Fietkau R, Sauer R, Ott OJ.: Quadrimodal treatment of high-risk T1 and T2 bladder cancer: transurethral tumor resection followed by concurrent radiochemotherapy and regional deep hyperthermia. In: Radiotherapy and Oncology 2009 Nov;93(2):35

10. Sarcomas

- Issels RD, Lindner LH, Verweij J, Wessalowski R, Reichardt P, Wust P, et al. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk **Soft Tissue Sarcoma**: the EORTC 62961-ESHO 95 Randomized Clinical Trial. JAMA oncology 2018;4(4):483-492.

- Lindner LH[1], Angele M, Dürr HR, Rauch J, Bruns C.; **„Systemic therapy and hyperthermia for locally advanced soft tissue sarcoma“;** Chirurg. 2014 May;85(5):398-403. doi: 10.1007/s00104-013-2687-5; PMID: 24740176 --; Medizinische Klinik III, Klinikum der Universität München - Campus Grosshadern, Marchioninistr. 15, 81377, München, Deutschland,

11. Peritoneal carcinomas:

Here most trials are targeted at individual, organ-related peritoneal metastases, mostly within the scope of an invasive surgery setting (e.g. HIPEC and PIPAC), and are not described further here.

12. Melanomas

Due to the use of modern immunotherapeutics, the significance of hyperthermia has tended to recede into the background.

Previous clinical trials:

1. Dewhirst MW, Pronitz L, Thrall D, Prescott D, Clegg S, Charles C, MacFall J, Rosner G, Samulski T, Gilette E, LaRue S. Hyperthermic treatment of malignant diseases: current status and view toward the future. Semin Oncol. 1997; 24: 616-25.
2. Gonzalez Gonzalez D, van Dijk JD, Blank LE, Rumke p. Combined treatment with radiation and hyperthermia in metastatic malignant melanoma. Radiother Oncol. 1986; 6: 105-13.
3. Overgaard J, Gonzalez Gonzalez D, Hulshof MCCM, Arcangeli G, Dahl O, Mella O, Bentzen SM, Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. Lancet. 1995; 345: 540-43.
4. Richtig E, Hoff M, Rehak P, Kapp K, Hofmann-Wellenhof R, Zalaudek I, Poschauko J, Uggowitzer M, Kohek P, Smolle J. Efficacy of superficial and deep regional hyperthermia combined with systemic chemotherapy and radiotherapy in metastatic melanoma. JDDG. 2003; 1: 635-42.

13. Bone metastases

- Kong F, Nie Z, Liu Z, Hou S, Ji J. Effects of thermal therapy combined with pamidronate disodium on pain associated with **bone metastases**: a randomized control trial (RCT) study. Biomedical research (india) 2017;28(21):9286-9290.

- Chi MS, Yang KL, Chang YC, Ko HL, Lin YH, Huang SC, et al.; Department of Radiation Therapy and Oncology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; Biomedical Science and Engineering, National Chiao-Tung University, HsinChu, Taiwan; Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With **Painful Bony Metastases**: a Phase 3 Prospective, Randomized, Controlled Trial. International journal of radiation oncology, biology, physics 2018;100(1):78-87.

- Pirus Ghadjar, Peter Wust, Volker Budach, Wilfried Budach; Klinik für Radioonkologie und Strahlentherapie, Charité, Universitätsmedizin Berlin; „Die kapazitive Hyperthermie scheint das Schmerzansprechen bei der palliativen Bestrahlung von **schmerzhaften Knochenmetastasen** zu verbessern“; Strahlenther Onkol; https://doi.org/10.1007/s00066-018-1376-1; Springer-Verlag GmbH Germany, part of Springer Nature 09/2018

17 • Chow E, Harris K, Fan G et al (2007) Palliative radiotherapy trials for bone metastases: A systematic review. J Clin Oncol 25:1423–1436

- Agarawal JP, Swangsilpa T, van der Linden Y et al (2006) The role of external beamradiotherapy in the management of bone metasta- ses. Clin Oncol 18:747–760

- Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM (2002) Hyperthermia in combined treatment of cancer. Lancet Oncol 3:487–497

- Wust P (2016) Thermotherapy in Oncology. UNI-MED Science, Bremen, London, Boston

Whole-body hyperthermia (WBHT): See DGHT Guidelines 10/2018

Whole-body hyperthermia
General definition
WBHT is the controlled increase in the core body temperature by supplying external energy, in line with the currently favoured apportionment specified above. It is also termed “passive hyperthermia”.

Stages of whole-body hyperthermia (WBHT):

	Milde GKHT		Moderate GKHT		Extreme GKHT
Zieltemperatur Körperkern, T(rektal)	**< 38,5 °C** x)		**38,5 °C - 40,5 °C** x)		**> 40,5 °C** x)
Anwendungsdauer im angegebenen Temperaturbereich	≤ 30 min	> 30 min	≤ 180 min	> 180 min	i.d.R. ≥ 60 min
Patientenbelastung	Schwitzen, kein thermoregulatorischer Streß	Schwitzen, kein thermoregulatorischer Streß	thermoregulatorischer Streß, unsediert / leicht sediert	thermoregulatorischer Streß, leicht / stark sediert	thermoregulatorischer Streß, tiefe intravenöse Anästhesie oder Vollnarkose
Patientenüberwachung	ohne Betreuung,	pflegerische Betreuung T(axillär) oder T(rektal) oder T(sublingual) oder T(tympanal)	pflegerische Betreuung mit ärztlicher Aufsicht xx) kontinuierlich T(rektal) +) ± T(axill / tymp) + HF/SpO2 ± EKG sporadisch ± NIBP („±“ bedeutet wahlweise)	pflegerische Betreuung mit ärztlicher Aufsicht kontinuierlich T(rektal) +) + T(axill) + HF/SpO2 + EKG/RESP sporadisch + NIBP	ärztlich geleitete Behandlung Intensiv-Überwachung
Indikationsbereich (Auswahl)	Entspannung, Wellness	Rehabilitation, Physiotherapie, Rheumatologie, Orthopädie	Rheumatol., Dermatol., Onkologie, Psychiatrie, Immunologie, Umweltmedizin	Onkologie chronische Infektion	Onkologie, chronische Infektion
Pflichten des Geräteherstellers	CE-Kennzeichnung als Medizinprodukt unter Mitwirkung einer „Benannten Stelle“ und behördlicher Überwachung				

x) Die Temperaturgrenzen zwischen den Stufen der GKHT haben nur orientierenden Charakter, da sie individuellen Schwankungen unterliegen
xx) In Deutschland auch unter Aufsicht von Heilpraktikern
+) Falls rektale Temperaturmessung nicht möglich ist, kann die Körperkerntemperatur auch vesikal oder vaginal gemessen werden

Fig.: Three stages of whole-body hyperthermia: (WBHT) 10/2018 (DGHT Guidelines)

1. Mild and moderate whole-body hyperthermia

1.1. Definition

Mild WBHT comprises an increase in the core body temperature to target temperatures up to 38.5 C. The period of application is divided into two chronological intensity stages, a short duration of < 30 mins and a longer duration of > 30 mins (Fig.).

Moderate WBHT comprises increasing the core body temperature to target temperatures of 38.5°C to 40.5°C. The period of use in the field of the target temperatures specified is likewise divided into two chronological intensity stages, a short duration of < 120 mins and a longer duration of > 120 mins (see above).

1.2. Technical requirements

1.2.1. Hyperthermia technology

18 Within the scope of the WBHT in the mild and moderate temperature range, the contact heat, e.g. in the water bath, and the radiative heating by means of infra-red radiation, are used. As an especially agreeable method, the use of water-filtered infra-red-A has gained acceptance, from a physical and physiological perspective. This involves a considerable proportion of the infra-red radiation first being absorbed at the depth where the circulating blood transports the heat energy absorbed with the blood flow into all regions of the body. The most widespread methods, currently, in Germany are the hyperthermia techniques of Heckel (in earlier systems, with infra-red-A+B radiation, in the current system regionally with water-filtered infra-red-A radiation and C radiation), and the application of the IRATHERM® technique according to von Ardenne (exclusively with water-filtered infra-red-A radiation).

1.2.2 Temperature monitoring

19 In the case of the mild WBHT, it is obligatory to control the temperature as from a period of use of > 30 mins. This can be done axillary, rectally, sublingually, tympanically or chronologically selectively, in regard to which the measured values are to be documented, inclusive of the measuring technology used. To be preferred, however, are measurement systems with permanent temperature recording, which can be done by keeping track of the recorded temperature on a PC using data processing.

20

21 As from the temperature level of moderate WBHT, thermoregulatory stress arises for the patient with an increasing temperature level, which necessitates nursing care subject to medical supervision, as noted in Fig. 1. As from temperatures of 38.5°C, the minimum requirement is ongoing rectal temperature measurement, as well as the recording of the heart rate and SpO2. There is broad general consensus that the temperature measured rectally is considered the core body temperature. When the period of application is extended to > 120 mins over 38.5°C, in addition a continuous second temperature measurement is required, axillary or tympanically, and also an ECG/RESP measurement, as well as sporadic measurement of the blood pressure. Should a rectal measurement not be possible (e.g. in the case of anus praeter), a vesical or vaginal temperature recording may be taken into consideration. It is to be borne in mind that the axillary and, even more so, the tympanically measured temperature in the late heating-up phase may deviate from the temperature measured rectally by around 0.5 - 1 degree Celsius.

Phase I and Phase II trials on whole-body hyperthermia exist up to now, which provide evidence that the method is feasible, and lead to the expectation of a better response, in particular in the case of tumours that are refractive and resistant to therapy (pancreatic and colon, as well as ovarian, carcinomas, sarcomas).

Evidence levels:

Evidence Level	
1a	At least one **meta-analysis** based on methodologically high quality randomised, controlled trials (RCTs)
1b	At least **one** sufficiently large **RCT**
2a	At least **one trial without CT randomisation**
2b	At least one trial of another type, quasi-**experimental trial**
3	More than one **non-experimental trial**, such as, for instance, comparative trials, correlative trials, case control trials or clinical pilot studies
4	**Responses of** expert committees; descriptive trials
5	A **case series** or one or more expert opinions

Indications or areas of indication in three main groups are listed below:

A High evidence (Levels 1 + 2);
B Medium to low evidence (Levels 3 + 4); and
C Low evidence (Level 5)

CT Controlled Trial
RCT Randomised Controlled Trial

A Indications, based on at least **CT** or **RCT** (Evidence levels 1 + 2)[1]

Indication	**Clinical trial**	**Literature**
• Fibromyalgia syndrome	RCT + CT + CT + pilot study	**[11, 12, 13, 14]**
• Chronic backache	RCT + pilot study	**[15, 16]**
• Ankylosing spondylitis	RCT + pilot study	**[17, 18, 19]**
• Axial spondyloarthritis	CT	**[20]**
• Psoriatic arthritis	RCT	**[21]**
• Arterial hypertension	RCT + pilot study	**[22, 23]**
• Depressive disorder, severe depression	RCT + RCT + pilot study	**[24, 25, 26]**

B Indications, based on comparative trials, case control trials, clinical pilot studies (Evidence Levels 3 + 4)

• Immune activation pilot study		**[27, 28, 29, 30, 31]**
• **Cancerous disease, increase in the efficacy of standard treatments**	**Pilot study**	**[32]**
• **Cancerous disease at the palliative stage, alleviating pain and fatigue syndrome**	**Pilot study**	**[32]**
• Bronchial asthma	Pilot study	**[33]**
• Osteoarthritis	Pilot study	**[34]**
• Systemic sclerosis	Pilot study + pilot study	**[23, 35, 36]**
• Irritable bowel syndrome	RC pilot study	**[37]**

[1] In regard to the indications cited in the highest evidence group, **A**, the associated treatment schemes of the WBHT carried out as documented in the publication which involves the highest evidence are specified in Appendix 1.

C Indications and areas of indication, based on case series or expert opinions (Evidence Level 5)

• Maintenance treatment following curative cancer therapy		**[38, 39]**
• Allergic rhinitis/hay fever		**[40]**
• Chronic prostatitis		**[40]**
• Osteoarthritis		**[34]**
• Ulcerative colitis and Crohn's disease	Case series	**[41]**
• Borreliosis		**[42, 43]**
• Post-traumatic regeneration		**[40]**
• Detoxification		**[44]**

Summary of the INDICATIONS for <u>WHOLE BODY</u> HYPERTHERMIA:

1. Bowel cancer with metastasis
2. Head/neck tumours
3. Advanced stage pancreatic carcinoma

➔ Cancerous diseases in **metastasized/advanced diseases** that are treated with chemotherapy.

Literature concerning WBHT:

Brockow T, Wagner A, Franke A, Offenbächer M, Resch KL. A Randomized Controlled Trial on the Effectiveness of Mild Water-Filtered Near Infrared Whole-body Hyperthermia as an Adjunct to a Standard Multimodal Rehabilitation in the Treatment of Fibromyalgia. Clin J Pain 2007; 1:67-75

11 Walz J, Hinzmann J, Haase I, Witte T. Ganzkörperhyperthermie in der Schmerztherapie - eine kontrollierte Studie an Patienten mit Fibromyalgiesyndrom. Schmerz 2013; 1:38-45

12 Romeyke T, Stummer H. Multi-modal pain therapy of fibromyalgia syndrome with integration of systemic whole-body hyperthermia – effects on pain intensity and mental state: A non-randomised controlled study. J Musculoskel Pain 2014; 4:341-55

13 Schleenbecker HG, Schmidt KL. Zur Wirkung einer iterativen milden Ganzkörperhyperthermie auf den Fibromyalgieschmerz. Phys. Rehab. Kur Med 1998; 8:113-117

14 Ettrich U,·Konrad B, Prate K, Seifert J, Krummenauer F. Milde Ganzkörperhyperthermie in Kombination mit stationärer multimodal orientierter Schmerztherapie - Evaluation bei Patienten mit chronischem unspezifischem lumbalem Rückenschmerz. Orthopäde 2014; 2:165-74

15 Weller E, Ullrich D. Infrarot-A-Hyperthermie-Anwendung bei Patienten mit Analgetica-Abusus wegen chronischer Rückenschmerzen. Vortrag auf dem 95. Kongress der Gesellschaft für Phys Med und Rehab 5.10.1990

16 Lange U, Müller-Ladner U, Dischereit G. Wirkung iterativer Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei ankylosierender Spondylitis – eine kontrollierte, randomisierte, prospektive Studie. Akt Rheumatol 2017; 2:122-28

17 Zauner D, Quehenberger F, Hermann J, Dejaco C, Stradner MH, Stojakovic T, Angerer H, Rinner B, Graninger WB. Whole body hyperthermia treatment increases interleukin 10 and toll-like receptor 4 expression in patients with ankylosing spondylitis: A pilot study. Int J Hyperthermia 2014; 6:393-401

18 Tarner IH, Ladner UM, Uhlemann C, Lange U. The effect of mild whole-body hyperthermia on systemic levels of TNF-alpha, IL-1 beta and IL-6 in patients with ankylosing spondylitis. Clin Rheumatol 2009; 4:397-402

19 Stegemann I, Hinzmann J, Haase I, Witte T. Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei Patienten mit axialer Spodyloarthritis. Orthopäd & Unfallchirurg Praxis 2013; 10:458-63

20 Lange U, Schwab F, Müller-Ladner U, Dischereit G. Wirkung iterativer Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei Arthritis psoriatica – eine kontrollierte, randomisierte, prospektive Studie. Akt Rheumatol 2014; 5:310-16

21 Mischke M. Wirkungen einer einmaligen bzw. seriellen Infrarot-A-Hyperthermie bei Patienten mit arterieller Hypertonie der WHO-Stadien I und II. Diss. Humboldt-Universität Berlin 18.07.1991
22 Meffert H, Scherf HP, Meffert B. Milde Infrarot-A-Hyperthermie: Auswirkungen von Serienbestrahlungen mit wassergefilterter Infrarotstrahlung auf Gesunde und Kranke mit arterieller Hypertonie bzw. systemischer Sklerodermie. Akt Dermatol 1993; 19:142-48
23 Janssen CW, Lowry CA, Mehl MR, Allen JJB, Kelly KL, Gartner DE, Medrano A, Begay TK, Rentscher K, White JJ, Fridman A, Roberts LJ, Robbins ML, Hanusch KU, Cole SP, Raison CL. Whole-Body Hyperthermia for the Treatment of Major Depressive Disorder – A Randomized Clinical Trial. JAMA Psychiatry 2016; 8:789-95
24 Naumann J, Grebe J, Kaifel S, Weinert T, Sadaghiani C, Huber R: Effects of hyperthermic baths on depression, sleep and heart rate variability in patients with depressive disorder: a randomized clinical pilot trial BMC Complement Altern Med 2017; 17:172
25 Hanusch KU, Janssen CH, Billheimer D, Jenkins I, Spurgeon E, Lowry CA, Raison CL. Whole-Body Hyperthermia for the Treatment of Major Depression: Associations With Thermoregulatory Cooling. Am J Psychiatry 2013, 170:7
26 Kobayashi Y, Ito Y, Ostapenko VV, Sakai M, Matsushita N, Imai K, Shimizu K, Aruga A, Tanigawa K. Fever-range whole-body heat treatment stimulates antigen-specific T-cell responses in humans. Immunology Letters 2014; 162:256-61
27 Mace TA, Zhong L, Kokolus KM, Repasky EA. Effector CD8+T cell IFN-γ production and cytotoxicity are enhanced by mild hyperthermia. Int J of Hyperthermia 2012; 1:9-18
28 Gaipl U. Immunologische Wirkungsmechanismen der Hyperthermie. 22. Jahrestag der Deutschen Gesellschaft für Radioonkologie 16.06.2016. Mannheim
29 Weigelin B. Activating serial killers of cancer cells with artificial fever: Hyperthermia as supporting strategy for immunotherapy of cancer. Symposium - Modern Hyperthermia 14.11.2015. Krakow
30 Skitzki JJ.Repasky EA, Evans SS. Hyperthermia as an immunotherapy strategy for cancer. Curr Opin Investig Drugs 2009; 6: 550-58
31 Bull JMC, Scott GL, Strebel FR, Nagle VL, Oliver D, Redwine M, Rowe RW, Ahn CW, Koch SM. Fever-range whole-body thermal therapy combined with cisplatin, gemcitabine and daily interferon-α: A description of a phase I-II protocol. Int J Hyperthermia 2008; 8:649-62
33 Zaltenbach G. Erfahrungen bei Asthma bronchiale und anderen Atemwegserkrankungen mit Sauerstoff-Mehrschritt-Therapie und Hyperthermie. Erfahrungsheilkunde 1988; 2:79-82
34 Brockow T, Beck I, Müller H, Resch KL: Applicability auf effectiveness of mild infrared whole body hyperthermia in symptomatic osteoarthritis - a pilot study. Abstract, 9th Annual Symposium on Complementary Health Care, 4th - 6th December 2002 Exeter, UK
35 Förster J, Fleischanderl S, Wittstock S, Storch A, Meffert H. Letter to the Editor: Infrared-Mediated Hyperthermia is Effective in the Treatment of Scleroderma-Associated Raynaud's Phenomenon. J Investig Dermatol 2005; 6:1313-16
36 Förster J, Storch A, Fleischanderl S, Wittstock S, Pfeiffer S, Riemekasten G, Worm M. Neutrophil respiratory burst is decreased in scleroderma and normalized by near-infrared mediated hyperthermia. Clin Exp Dermatol 2006; 6:799-806
37 Sachse C. Studie der Charité Berlin: Ganzkörperhyperthermie bei Reizdarmsyndrom. VII. Hyperthermie-Kongress der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2016:11
38 Wey S: Mammakarzinom - komplementäre Praxis. EHK 2017; 66:302-14
39 Wey S: 14 Jahre Fiebertherapie / Ganzkörperhyperthermie in der onkologischen Rezidivprophylaxe. Abstract
VII. Hyperthermie-Kongress der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2016
40 Heckel M, Heckel I: Beobachtungen an 479 Infrarothyperthermiebehandlungen - Beitrag zur Methode der Ganzkörperüberwärmung. Med Welt 1979; 30:971-75
41 Lexer G: Hyperthermie bei entzündlichen Darmerkrankungen. Abstract "Hyperthermie einst und heute – Symposium aus Anlass des 80. Jahrestages der Verleihung des Nobelpreises für Medizin an Julius Wagner-Jauregg. GAMED Wien, 2007
42 Zais ODA. Hyperthermie und Borreliose – Verschiedene Therapiestrategien. Abstract VIII. Hyperthermie-Symposium der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2017:6
43 Douwes F: Augmentierte Thermo-Eradikation der chronischen Borreliose - Ein neuer Therapieansatz.
VI. Hyperthermie-Kongress der Deutschen Gesellschaft für Hyperthermie, Berlin Okt 2015
44 Kleef R: Hyperthermie und Entgiftung. OM & Ernährung 2011; 135:7

APPENDIX:

The following **trials reported** are currently being carried out with hyperthermia **in Germany:**

See the information at this link: https://dktk.dkfz.de/de/klinische-plattformen/studienregister

Kurztitel (Status)	Titel	
1	AArau-Studie (Aktiv)	A Phase IIB study of the tetramodal therapy of T2-T4 Nx MO bladder cancer with hyperthermia combined with chemoradiotherapy following TUR-BT
2	GKH-TMM (Aktiv)	The aim of the study is to determine the feasibility and efficacy of moderate weekly whole Body hyperthermia Treatment during radiochemotherapy for pre-irradiated locally or regionally recurrent head and neck squamous cell carcinomas. The Primary aim of the study is feasibility, defined as 80% of patients completing at least four applications of hyperthermia
3	HEAT (Aktiv)	Hyperthermia European Adjuvant Trial
4	HT-01 (Rekrutierung beendet)	Preoperative Radiochemotherapy With Hyperthermia for Locally Advanced Rectal Cancer
5	HT-02 (Aktiv)	Registry of perioperative hyperthermia and radiochemotherapy in soft tissue sarcomas
6	HT-03 (Aktiv)	Prospective registry of hyperthermia combined with radiotherapy of recurrent breast cancer
7	Hyper TET (Aktiv)	Hyper-Thermia Enhanced Anti-tumor Efficacy of Trabectedin
8	HyRec (Aktiv)	Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxalliplatin combined with deep regonal hyperthermia
9	NEOPAMAIN (Aktiv)	Pazopanib Maintenance Phase II

DKTK-Studienregister
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5. Summary of the results of the current research and prospects:

Hyperthermia has – rightly – acquired the reputation of **being a potent sensitiser for radiotherapy and chemotherapies.**
Hyperthermia itself likewise has the effect of **promoting the body's own immune system.**
The arguments according to which this supplementary thermal therapy option is also synergistically conducive for the new generation of immunotherapies are likewise plausible, and it is to be expected that this can actually be proven, based on evidence, by means of trials in the next few years.
In this respect, it is also interesting that, in the case of this supplementary therapy option, **no additional further adverse side effects** are to be expected.
Hyperthermia has so much more potential than it is presently given credit for, in clinical relevance. Fortunately, this perspective is slowly, but constantly, changing more from year to year, and - at least in regard to the combination with radiotherapy - **these days it can already be stated that hyperthermic therapy is being accepted**. The same potential also, in any case, appears to be predictable when it is combined with the newly emerging immune therapeutic concepts.

Altogether, 16 RCTs are presently running in Germany, which could, in principle, be suitable for a cross-sector benefit assessment of hyperthermia.
Research identified RCTs in the indications cervical carcinoma, colorectal carcinoma, ovarian carcinoma, gastric carcinoma, soft tissue sarcomas and malignant liver and bladder tumours. The ongoing trials include potentially relevant trials in the indications of pulmonary carcinoma (NSCLC) and pancreatic carcinoma.
As a "new" indication, in this year's research two RCTs on the treatment of pain in the case of bone metastases have been identified.
Depending upon the research, further clinical trials can be identified in other countries. The publications have been constantly increasing over the past few years.

The **long medical tradition of targeted heating of the body** or sub-areas in the treatment of various diseases vouches for the safe application and broad therapeutic potential of such methods of treatment. Today, the basic immunological research is, with increasing penetration of the complex immunological modes of action, to an increasing extent providing the rationale for a systemic, hyperthermic stimulation of the human organism.

New pharmacological therapies in the fields of rheumatology and oncology, which are targeted at selectively influencing immunological processes and sometimes achieve astonishing alleviation of symptoms and cancer-diminishing processes, are sometimes associated with considerable risks and side effects. Here it is worth taking a look (back) at forms of treatment which likewise have an effect upon the immune system, and in an unusual way, reinforce **the efficiency of the radiotherapy and many forms of chemotherapy**, **and do so with an exceedingly low incidence of risk and side effects**. A suitable combination of such approaches should increasingly be the subject of future research.

Hyperthermia (local or the mild and moderate WBHT) can be used in combination with other methods of treatment. With individual indications, **significant positive results** could already be evidenced within the scope of **prospective clinical trials**. Through careful documentation of treatment results targeted in the routine application, further controlled clinical trials should be launched, which gradually increases the evidence level of hyperthermia in various areas of indication.

In the oncological application, an impartial review of the method and results of hyperthermia and similar concepts with chemotherapy, as well as the treatment results that have been achieved with the latter to date, is pending.

The published data situation in regard to the deployment of hyperthermia, as shown in this summary, in the treatment of chronic illnesses and cancerous diseases, **presents positive, sufficient, adequate treatment results, including improved quality of life**.

A **stay on the ward** (**in hospital**) is **NOT necessary** in order to carry out these local hyperthermia procedures (LHT) and mild/moderate whole body hyperthermia (WBHT). Hospitalising the people concerned is avoided.

The **therapeutic procedures** described above and the technical **development have their origin in Germany** and are now being operated worldwide.

In our opinion, hyperthermia is a very **potent additional therapy option** in order to be able to better assist those seeking help.

Bochum, June 2021

H. Sahinbas

On behalf of DGHT e.V., reg. assoc.
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