Redefining Hyperthermia: A Not Temperature-Dependent Solution of The Temperature Problem

Sergey Roussakow, MD, PhD
Galenic Research Institute

Presented at 35th ICHS, Guangzhou, 2017

Cite this article as:
Roussakow S. (2018): Redefining Hyperthermia: A Not Temperature-Dependent Solution of The Temperature Problem; Oncothermia Journal 22: 116-150
www.oncothermia-journal.com/journal/2018/Redefining_Hyperthermia.pdf

Redefining Hyperthermia: A Not Temperature-Dependent Solution of The Temperature Problem

Sergey Roussakow, MD, PhD
Galenic Research Institute

Joint Conference of ICHS & WFCMS-SCNT
35th Annual Conference of International Clinical Hyperthermia Society
"Hyperthermia, Natural Medicine and Health Maintenance & Cancer Rehabilitation"
Clifford Hospital
24-26th 2017
Guangzhou, China

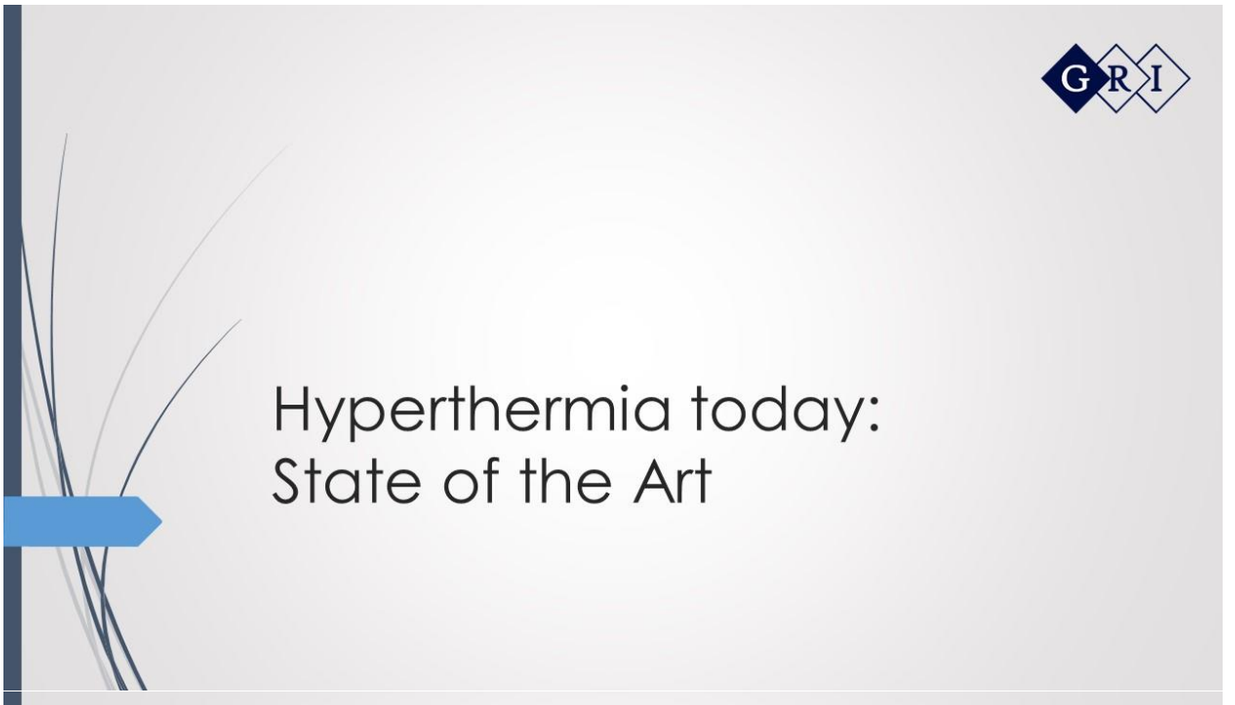
I didn't need this concept ...

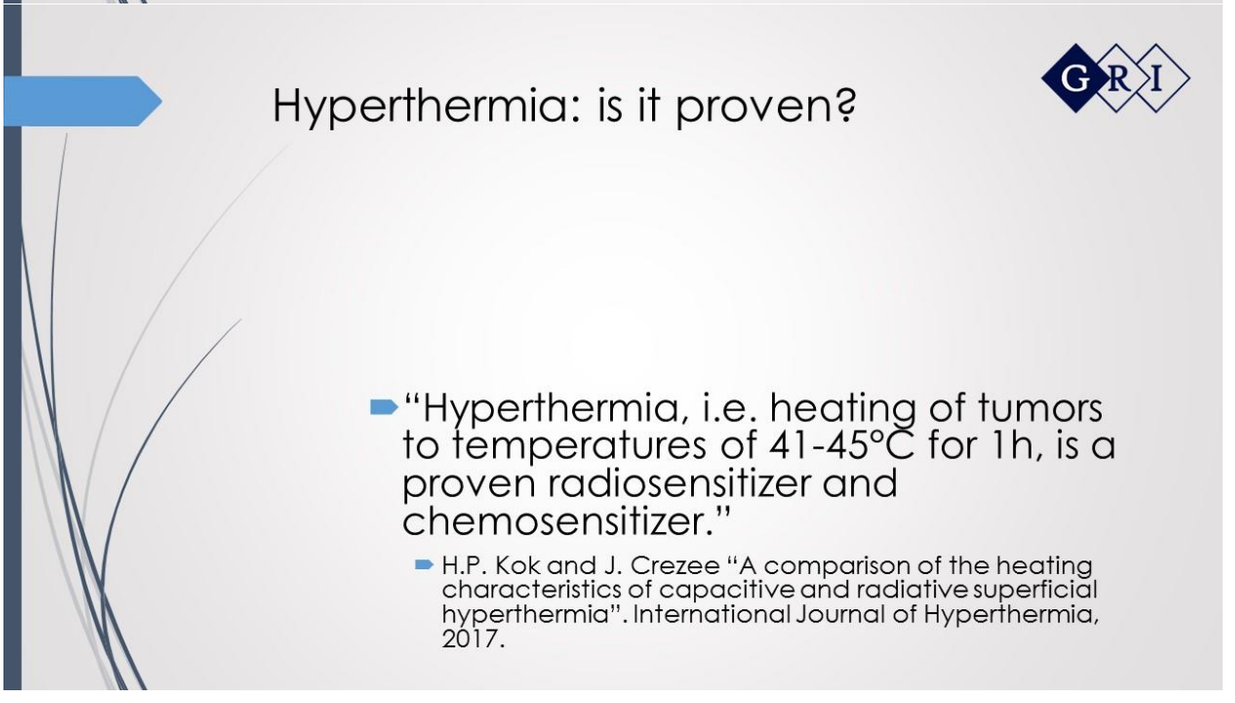
Napoleon Bonaparte
(1769 – 1821)

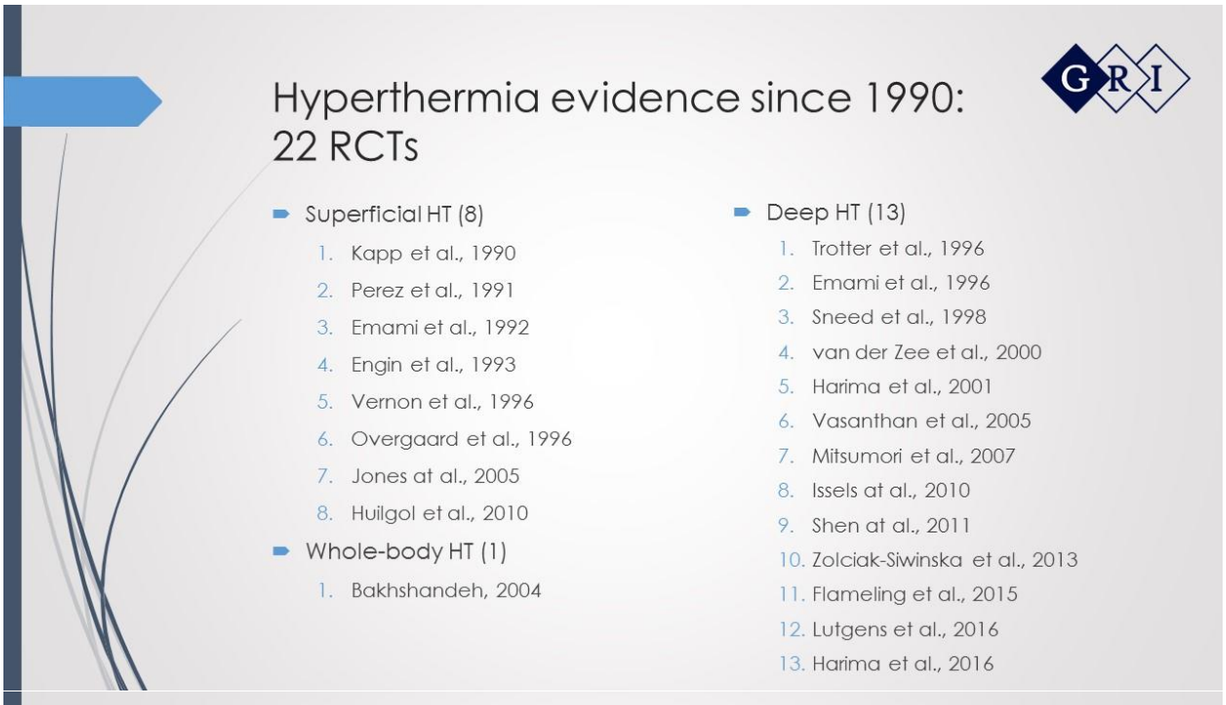
I was talking to Laplace, I was congratulating him upon a book he had just published and I asked him how it was that the name of God, which was so incessantly repeated in the writings of Lagrange, did not appear even once in his work. 'The reason,' he replied, 'is that I had not had occasion to make use of that hypothesis'.

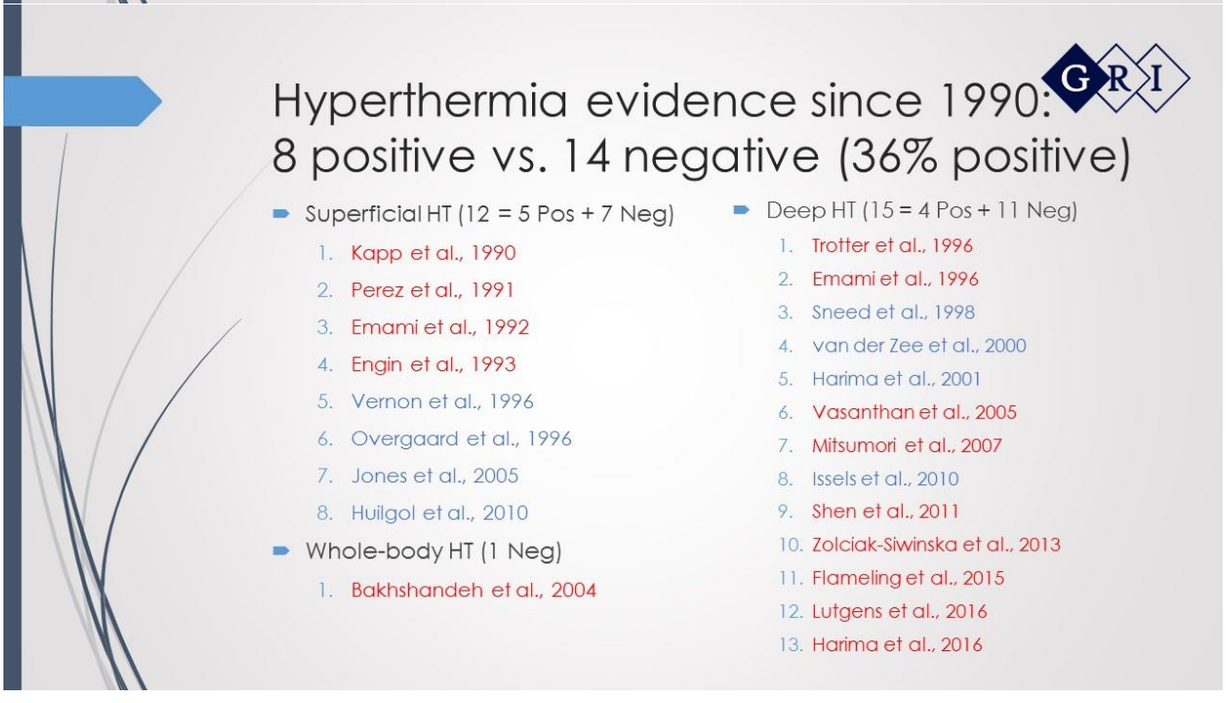
Antommarchi F. Mémoires. — Paris, 1825, t. 1, p. 282.

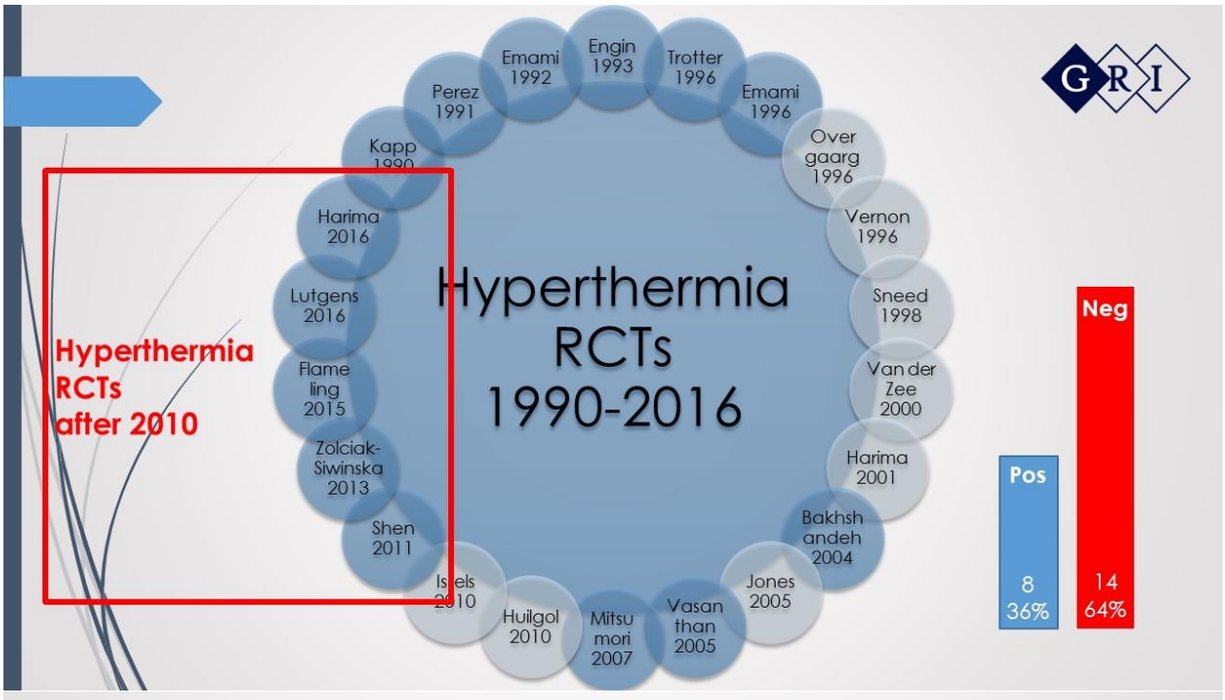
Pierre-Simon Laplace
(1749 – 1827)

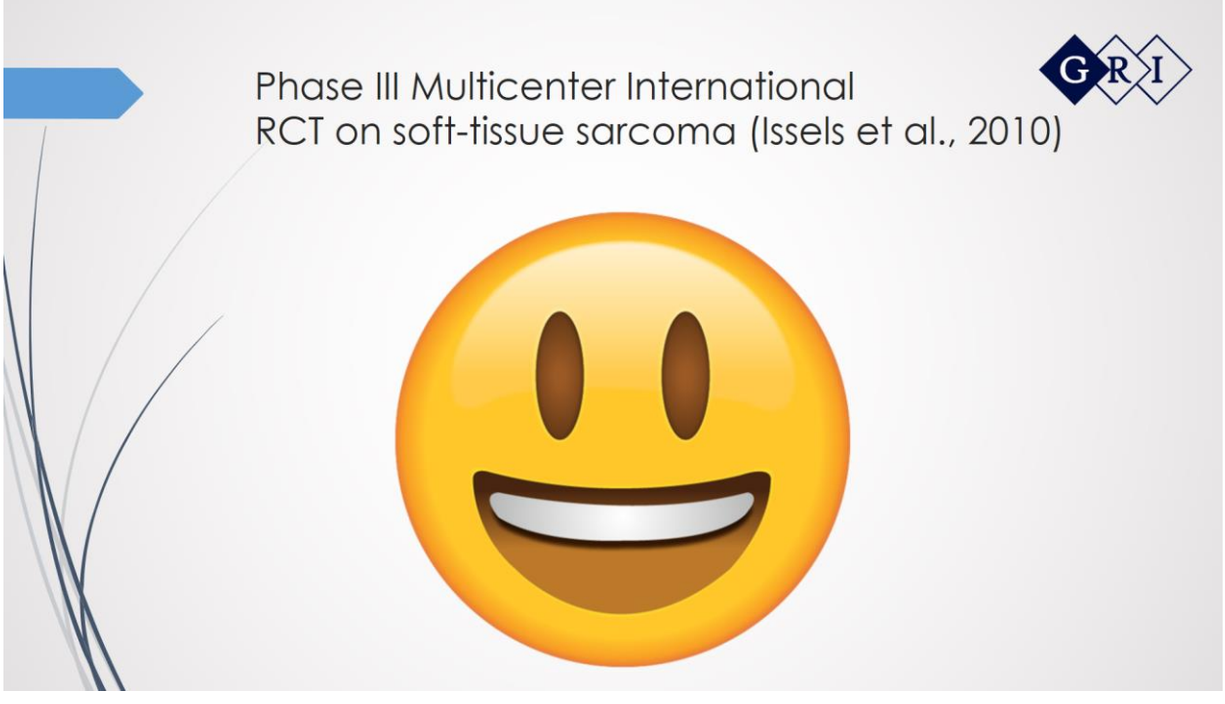

Hyperthermia today:
State of the Art


Hyperthermia: is it proven?
"Hyperthermia, i.e. heating of tumors to temperatures of 41-45°C for 1h, is a proven radiosensitizer and chemosensitizer."
H.P. Kok and J. Crezee "A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia". International Journal of Hyperthermia, 2017.


Hyperthermia evidence since 1990:
22 RCTs
Superficial HT (8)
1. Kapp et al., 1990
2. Perez et al., 1991
3. Emami et al., 1992
4. Engin et al., 1993
5. Vernon et al., 1996
6. Overgaard et al., 1996
7. Jones at al., 2005
8. Huilgol et al., 2010
Whole-body HT (1)
1. Bakhshandeh, 2004
Deep HT (13)
1. Trotter et al., 1996
2. Emami et al., 1996
3. Sneed et al., 1998
4. van der Zee et al., 2000
5. Harima et al., 2001
6. Vasanthan et al., 2005
7. Mitsumori et al., 2007
8. Issels at al., 2010
9. Shen at al., 2011
10. Zolciak-Siwinska et al., 2013
11. Flameling et al., 2015
12. Lutgens et al., 2016
13. Harima et al., 2016


Hyperthermia evidence since 1990:
8 positive vs. 14 negative (36% positive)
Superficial HT (12 = 5 Pos + 7 Neg)
1. Kapp et al., 1990
2. Perez et al., 1991
3. Emami et al., 1992
4. Engin et al., 1993
5. Vernon et al., 1996
6. Overgaard et al., 1996
7. Jones et al., 2005
8. Huilgol et al., 2010
Whole-body HT (1 Neg)
1. Bakhshandeh et al., 2004
Deep HT (15 = 4 Pos + 11 Neg)
1. Trotter et al., 1996
2. Emami et al., 1996
3. Sneed et al., 1998
4. van der Zee et al., 2000
5. Harima et al., 2001
6. Vasanthan et al., 2005
7. Mitsumori et al., 2007
8. Issels et al., 2010
9. Shen et al., 2011
10. Zolciak-Siwinska et al., 2013
11. Flameling et al., 2015
12. Lutgens et al., 2016
13. Harima et al., 2016

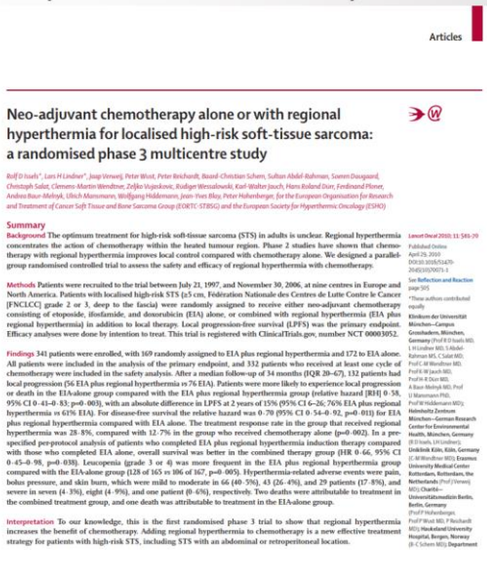

Hyperthermia RCTs 1990-2016
Hyperthermia RCTs after 2010
Engin 1993
Trotter 1996
Emami 1996
Over gaarg 1996
Vernon 1996
Sneed 1998
Van der Zee 2000
Harima 2001
Bakhsh andeh 2004
Jones 2005
Vasan than 2005
Mitsu mori 2007
Huilgol 2010
Issels 2010
Shen 2011
Zolciak-Siwinska 2013
Flame ling 2015
Lutgens 2016
Harima 2016
Kapp 1990
Perez 1991
Emami 1992
Neg
14
64%
Pos
8
36%


Phase III Multicenter International RCT on soft-tissue sarcoma (Issels et al., 2010)

Phase III Multicenter International RCT on soft-tissue sarcoma (Issels et al., 2010)

Phase III Multicenter International RCT on soft-tissue sarcoma (Issels et al., 2010)

- 9 leading oncology centers
  - Universitätsklinik Graz, Graz, **Austria**
  - Rigshospitalet, Copenhagen, **Denmark**
  - Centre Leon Berard, Lyon, **France**
  - Charité—Universitätsmedizin Berlin, Berlin, **Germany**
  - Klinikum der Universität München—Campus Grosshadern, München, **Germany**
  - Universitätsklinikum Düsseldorf, Düsseldorf, **Germany**
  - Haukeland University Hospital, Bergen, **Norway**
  - Erasmus University Medical Center Rotterdam, Rotterdam, the **Netherlands**
  - Duke University Medical Center, Durham, NC, **USA**



Articles

Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

Rolf D Issels*, Lars H Lindner*, Jaap Verweij, Peter Wust, Peter Reichardt, Bernd-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter Hohenberger, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and the European Society for Hyperthermic Oncology (ESHO)

Summary

Background The optimum treatment for high-risk soft-tissue sarcoma (STS) in adults is unclear. Regional hyperthermia concentrates the action of chemotherapy within the heated tumour region. Phase 2 studies have shown that chemotherapy with regional hyperthermia improves local control compared with chemotherapy alone. We designed a parallel-group randomised controlled trial to assess the safety and efficacy of regional hyperthermia with chemotherapy.

Methods Patients were recruited to the trial between July 23, 1997, and November 30, 2006, at nine centres in Europe and North America. Patients with localised high-risk STS (≥5 cm, Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade 2 or 3, deep to the fascia) were randomly assigned to receive either neo-adjuvant chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone, or combined with regional hyperthermia (EIA plus regional hyperthermia) in addition to local therapy. Local progression-free survival (LPFS) was the primary endpoint. Efficacy analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT 00003052.

Findings 341 patients were enrolled, with 169 randomly assigned to EIA plus regional hyperthermia and 172 to EIA alone. All patients were included in the analysis of the primary endpoint, and 332 patients who received at least one cycle of chemotherapy were included in the safety analysis. After a median follow-up of 34 months (IQR 20–67), 132 patients had local progression (56 EIA plus regional hyperthermia vs 76 EIA). Patients were more likely to experience local progression or death in the EIA-alone group compared with the EIA plus regional hyperthermia group (relative hazard [RH] 0·58, 95% CI 0·41–0·83; p=0·003), with an absolute difference in LPFS at 2 years of 15% (95% CI 6·26; 76% EIA plus regional hyperthermia vs 61% EIA). For disease-free survival the relative hazard was 0·78 (95% CI 0·54–0·92, p=0·011) for EIA plus regional hyperthermia compared with EIA alone. The treatment response rate in the group that received regional hyperthermia was 28·8%, compared with 12·7% in the group who received chemotherapy alone (p=0·002). In a pre-specified per-protocol analysis of patients who completed EIA plus regional hyperthermia induction therapy compared with those who completed EIA alone, overall survival was better in the combined therapy group (HR 0·66, 95% CI 0·45–0·98, p=0·038). Leucopenia (grade 3 or 4) was more frequent in the EIA plus regional hyperthermia group compared with the EIA-alone group (128 of 165 *vs* 106 of 167, p=0·005). Hyperthermia-related adverse events were pain, bolus pressure, and skin burn, which were mild to moderate in 66 (40·5%), 43 (26·4%), and 29 patients (17·8%), and severe in seven (4·3%), eight (4·9%), and one patient (0·6%), respectively. Two deaths were attributable to treatment in the combined treatment group, and one death was attributable to treatment in the EIA-alone group.

Interpretation To our knowledge, this is the first randomised phase 3 trial to show that regional hyperthermia increases the benefit of chemotherapy. Adding regional hyperthermia to chemotherapy is a new effective treatment strategy for patients with high-risk STS, including STS with an abdominal or retroperitoneal location.

Lancet Oncol 2010; 11: 561–70
Published Online April 29, 2010
DOI:10.1016/S1470-2045(10)70071-1

See Reflection and Reaction page 505

*These authors contributed equally

Klinikum der Universität München—Campus Grosshadern, München, Germany (Prof R D Issels MD, L H Lindner MD, S Abdel-Rahman MS, C Salat MD, Prof C-M Wendtner MD, Prof B W Jauch MD, Prof H-R Dürr MD, A Baur-Melnyk MD, Prof U Mansmann PhD, Prof W Hiddemann MD); Helmholtz Zentrum München—German Research Center for Environmental Health, München, Germany (P D Issels, I H Lindner); Uniklinik Köln, Köln, Germany (C-M Wendtner MD); Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands (Prof J Verweij MD); Charité—Universitätsmedizin Berlin, Berlin, Germany (Prof P Wust MD, P Reichardt MD); Haukeland University Hospital, Bergen, Norway (B-C Schem MD); Department

Phase III Multicenter International RCT on soft-tissue sarcoma (Issels et al., 2010)

Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

Rolf D Issels, Lars H Lindner*, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter Hohenberger, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and the European Society for Hyperthermic Oncology (ESHO)*

- 20 authors, incl. 16 Professors
- European Organisation for Research and Treatment of Cancer, Soft Tissue and Bone Sarcoma Group (EORTC-STBSG)
- European Society for Hyperthermic Oncology (ESHO)
- 351 patients
- Published in Lancet Oncology

ft-tissue sarcoma (STS) in adults is unclear. Regional hyperthermia heated tumour region. Phase 2 studies have shown that chemo- ontrol compared with chemotherapy alone. We designed a parallel- and efficacy of regional hyperthermia with chemotherapy.

Phase III Multicenter International RCT on soft-tissue sarcoma (Issels et al., 2010)

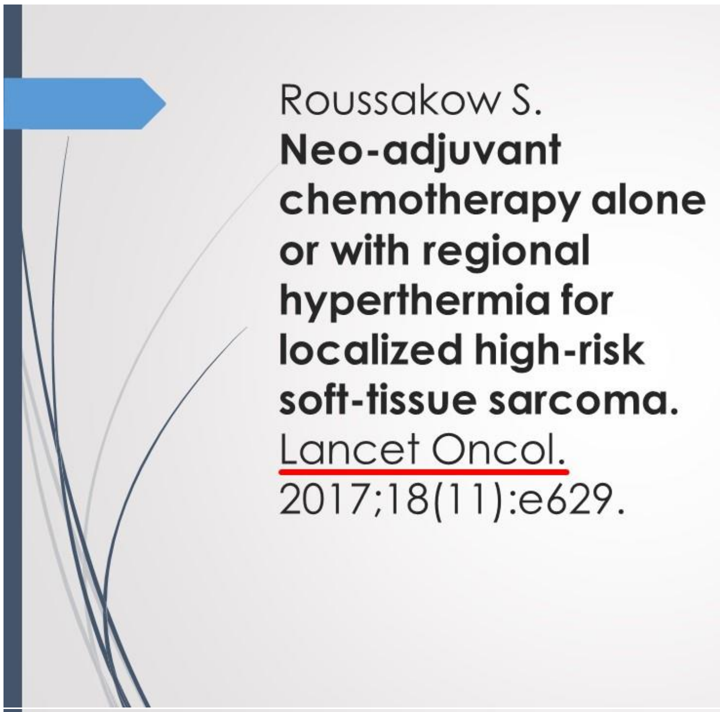
Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

EVIDENCE

- 20 authors, incl. 16 Professors
- European Organisation for Research and Treatment of Cancer, Soft Tissue and Bone Sarcoma Group (EORTC-STBSG)
- European Society for Hyperthermic Oncology (ESHO)
- 351 patients
- Published in Lancet Oncology

RESULTS

- **Significantly better 4-year LPFS (p = 0.003) and DFS (p = 0.011) in the thermochemotherapy group.**
- **No effect to OS (p = 0.43)**



Doctopic: Analysis and Interpretation

THELANCETONCOLOGY-D-17-01129

S1470-2045(17)30643-5

[Embargo: date—time (GMT/BST)]

PROOF (not for distribution)

Correspondence

Neo-adjuvant chemotherapy alone or with regional hyperthermia for soft-tissue sarcoma

A randomised, controlled, phase 3 trial by Rolf Issels and colleagues[1] on neo-adjuvant chemotherapy alone or with regional hyperthermia for localised, high-risk, soft-tissue sarcoma published in 2010 in *The Lancet Oncology* is currently the only level 1 evidence in favour of regional hyperthermia for the treatment of soft-tissue sarcoma.[2] I believe a bias is present in this analysis because the combined treatment group received more chemotherapy than the chemotherapy alone group (median 8·0 cycles vs 5·0 cycles). Transformation of the medians into means by the Hozo algorithm[3] returns the mean values of 6·0 (SD 2·6) for the combined treatment group versus 4·5 (2·3) for the chemotherapy alone group with a relative increase of 1·33 (95% CI 1·22–1·45; p<0·0001) in the combination treatment group, with a power of 98%. There was also a significant difference between the groups in post-induction treatment (53% for the combined treatment group vs 41% for the chemotherapy alone group who completed chemotherapy; p=0·027). Therefore, one cannot conclude that chemotherapy plus hyperthermia is superior to chemotherapy alone, because the difference in chemotherapy received outweighs the effect of the addition of hyperthermia.

Moreover, I believe there is also information bias, because the reported advantage of chemotherapy plus hyperthermia versus chemotherapy alone regarding the endpoints of tumour response, local progression-free survival, and disease-free survival is based on the analysis of a subgroup of measurable tumours (n=244 [72%]) but not the total randomised sample (n=341). 118 (35%) patients were excluded from evaluation of the primary endpoint (local progression-free survival), including 21 patients with measurable tumours. Because the number of patients with a complete or partial response was different between the groups (34 in the combined treatment group vs 16 in the chemotherapy alone group), the progression-free survival difference is unreliable. Additionally, the external validation of tumour response did not exclude the possibility of misclassification, because it was applied only to patients who were locally assessed as responders. The validity of the trial is arguable since its overall results are substantially worse than those reported by the Sarcoma Meta-analysis Collaboration.[4] Because I believe that these potential biases are concealed by understatement, I am concerned about the results of this trial. I highlight these issues to prevent the ongoing misinterpretation of this trial and to avoid unproven treatments being used in clinical practice.

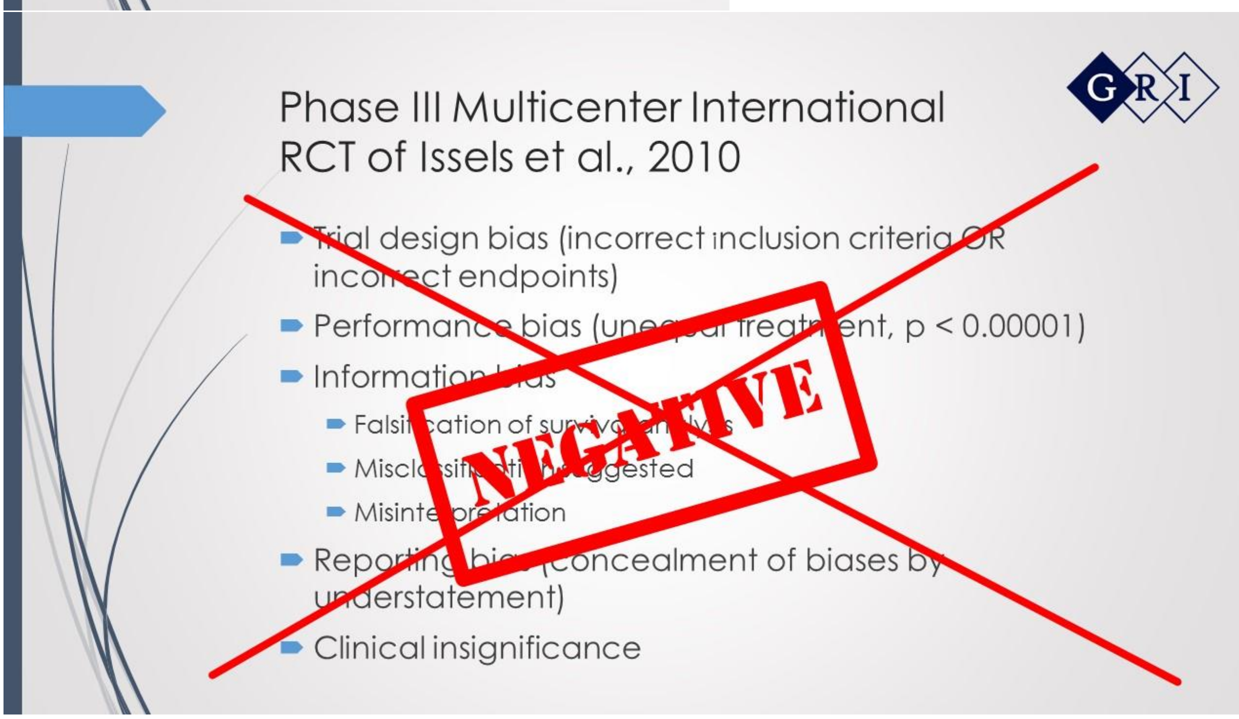
I declare no competing interests.

Sergey Roussakow
roussakow@gmail.com

Galenic Research Institute, Moscow, 127051, Russia

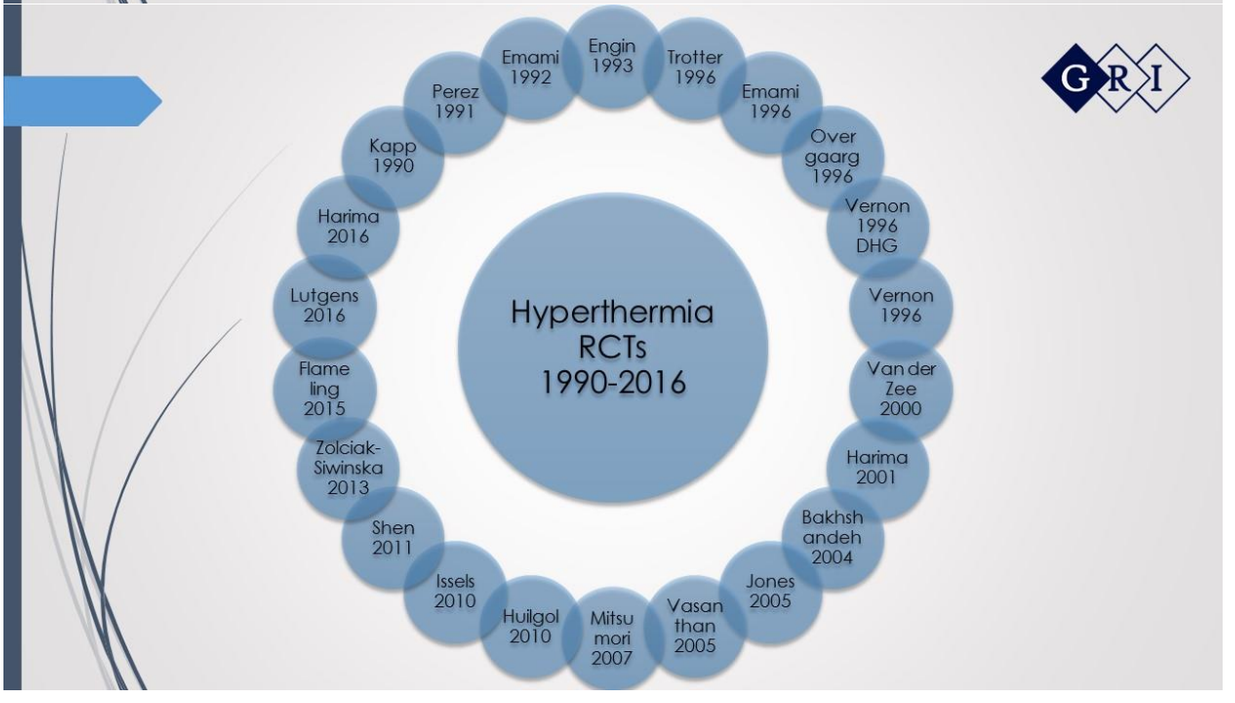
1 Issels RD, Lindner LH, Verweij J, et al, European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG); European Society for Hyperthermic Oncology (ESHO). Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol 2010; 11: 561–70.
2 Lindner LH, Issels RD. Hyperthermia in soft tissue sarcoma. Curr Treat Options Oncol 2011; 12: 12–20.
3 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
4 Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997; 350: 1647–54.

www.thelancet.com/oncology Vol 18 October 2017 1



Other submissions

- Roussakow S. *"A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma" of Yoko Harima et al. (2001): multiple biases and no advantage of hyperthermia."* **Int J Hyperthermia**. 2017. Submitted.
- Roussakow S. *"About incorrectness of the report of the randomized trial of Y. Harima et al. "A multicentre randomized clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer": multiple biases and evidence of scientific misconduct."* **Int J Hyperthermia**. 2017. Submitted.
- Roussakow S. *"Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours."* **The Lancet**. 2017. Submitted.



Hyperthermia evidence: Systematic reviews

1. Review Committee on Microwave Cancer Therapy. Review of the Use of Microwave Therapy for the Treatment of Patients with Cancer. Final Report to the Minister for Health and Ageing, National Health and Medical Research Council, Australia Government, **2005**.
2. G-BA [Joint Federal Committee: Hyperthermia (including whole-body hyperthermia, regional hyperthermia, superficial hyperthermia and hyperthermia in combination with radiotherapy and / or chemotherapy)]. **2005**.
3. De Haas-Kock DFM et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database of Systematic Reviews **2009**,
4. Lutgens et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database of Systematic Reviews **2010**,
5. Mathis S, Johnasson T. Hyperthermie. Systematic review. Wien: Ludwig Boltzmann Institut für Health Technology Assessment. **2010**.
6. Kirisits et al. Efficacy of Hyperthermia treatment in combination with radio- or chemotherapy in Breast- Bladder- Cervix carcinoma and Soft tissue sarcoma patients. Wien: Ludwig Boltzmann Institut fur Health Technology Assessment. **2012**
7. Datta et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia. **2016**.
8. Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. **2016**.
9. Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. **2016**.

Hyperthermia evidence: Systematic reviews: 4 negative vs 6 positive

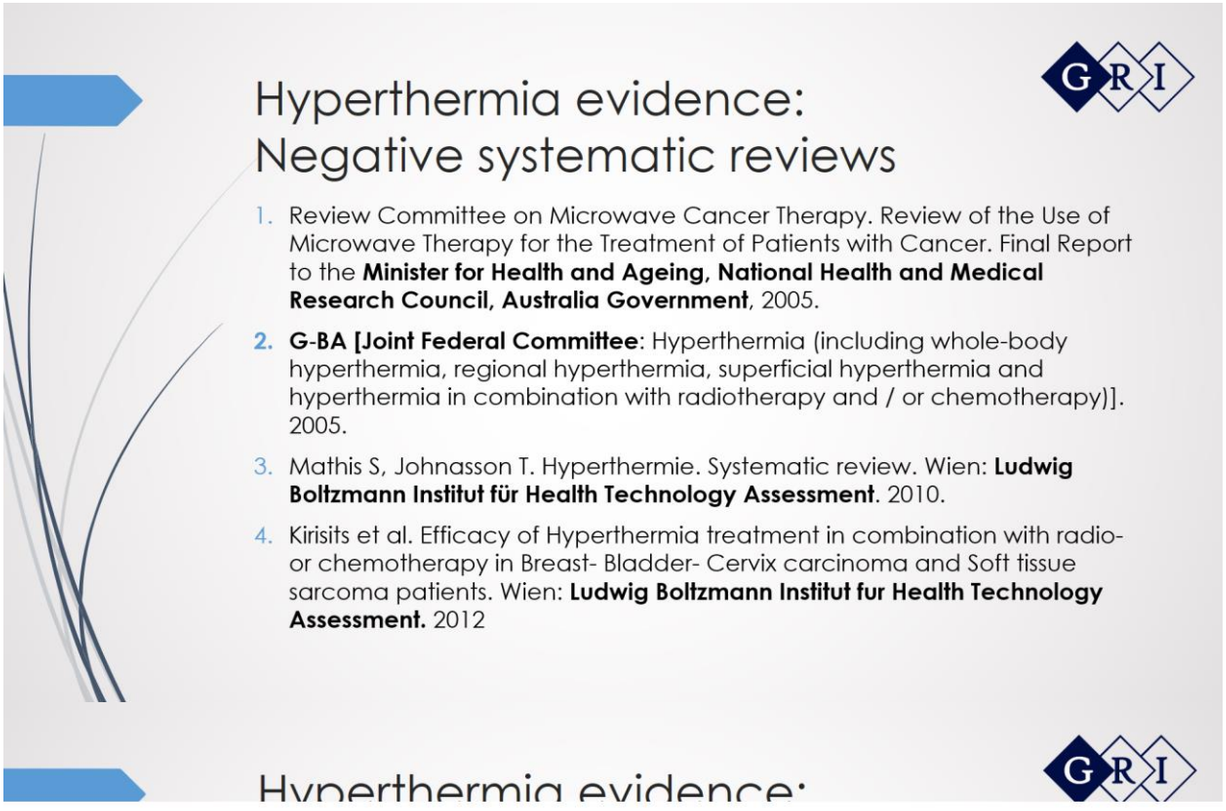
1. Review Committee on Microwave Cancer Therapy. Review of the Use of Microwave Therapy for the Treatment of Patients with Cancer. Final Report to the Minister for Health and Ageing, National Health and Medical Research Council, Australia Government, 2005.
2. G-BA [Joint Federal Committee: Hyperthermia (including whole-body hyperthermia, regional hyperthermia, superficial hyperthermia and hyperthermia in combination with radiotherapy and / or chemotherapy)]. 2005.
3. De Haas-Kock DFM et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database of Systematic Reviews 2009,
4. Lutgens et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database of Systematic Reviews 2010,
5. Mathis S, Johnasson T. Hyperthermie. Systematic review. Wien: Ludwig Boltzmann Institut für Health Technology Assessment. 2010.
6. Kirisits et al. Efficacy of Hyperthermia treatment in combination with radio- or chemotherapy in Breast- Bladder- Cervix carcinoma and Soft tissue sarcoma patients. Wien: Ludwig Boltzmann Institut fur Health Technology Assessment. 2012
7. Datta et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia. 2016.
8. Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016.
9. Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016.

Hyperthermia evidence: Systematic reviews: 4 negative vs 6 positive

1. Review Committee on Microwave Cancer Therapy. Review of the Use of Microwave Therapy for the Treatment of Patients with Cancer. Final Report to the Minister for Health and Ageing, National Health and Medical Research Council, Australia Government, 2005.
2. G-BA [Joint Federal Committee: Hyperthermia (including whole-body hyperthermia, regional hyperthermia, superficial hyperthermia and hyperthermia in combination with radiotherapy and / or chemotherapy)]. 2005.
3. **De Haas-Kock DFM et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database of Systematic Reviews 2009,**
4. **Lutgens et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database of Systematic Reviews 2010,**
5. Mathis S, Johnasson T. Hyperthermie. Systematic review. Wien: Ludwig Boltzmann Institut für Health Technology Assessment. 2010.
6. Kirisits et al. Efficacy of Hyperthermia treatment in combination with radio- or chemotherapy in Breast- Bladder- Cervix carcinoma and Soft tissue sarcoma patients. Wien: Ludwig Boltzmann Institut fur Health Technology Assessment. 2012
7. Datta et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia. 2016.
8. Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016.
9. Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016.

Hyperthermia evidence: Systematic reviews: 4 negative vs 6 positive

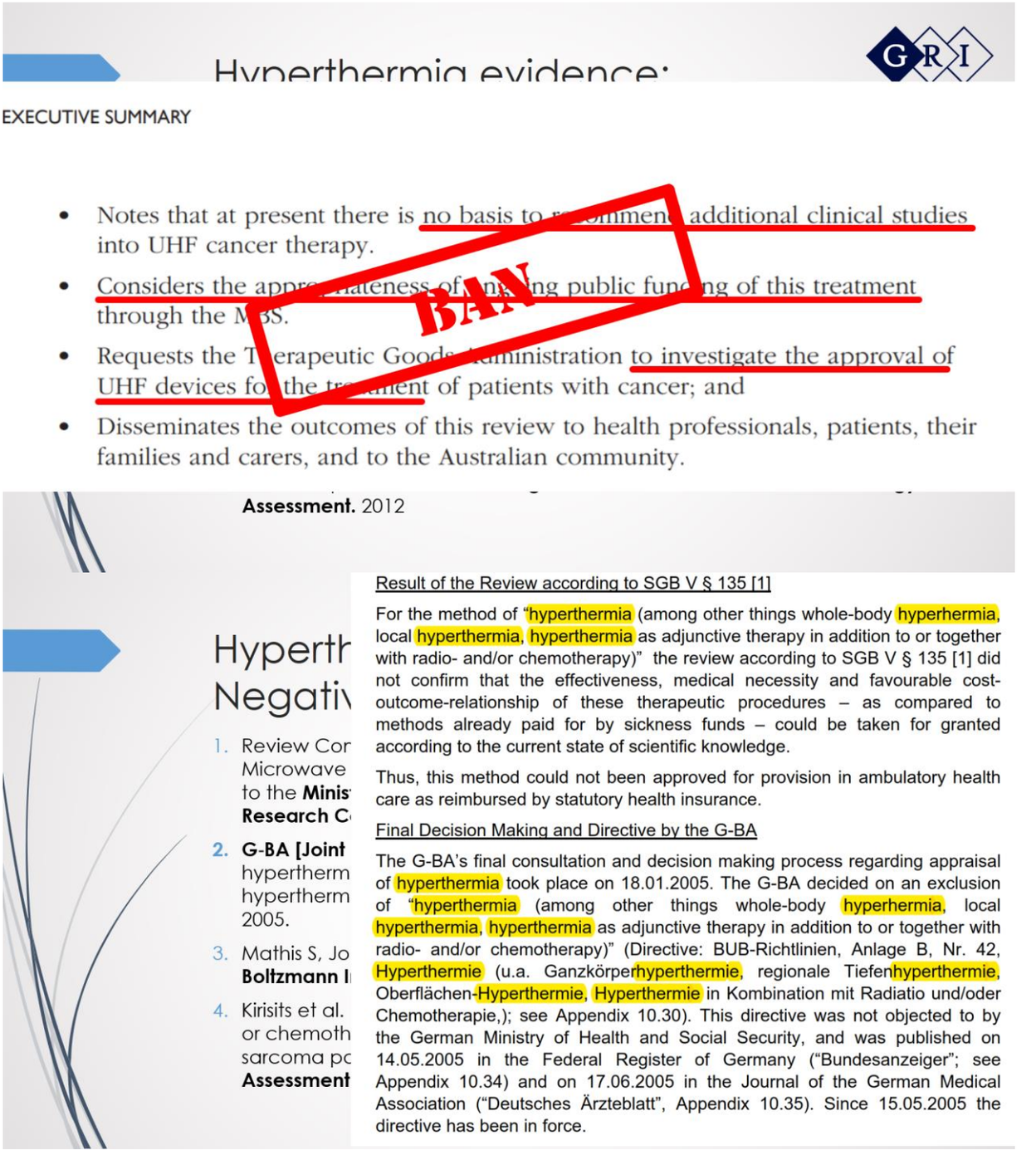
1. Review Committee on Microwave Cancer Therapy. Review of the Use of Microwave Therapy for the Treatment of Patients with Cancer. Final Report to the Minister for Health and Ageing, National Health and Medical Research Council, Australia Government, 2005.
2. G-BA [Joint Federal Committee: Hyperthermia (including whole-body hyperthermia, regional hyperthermia, superficial hyperthermia and hyperthermia in combination with radiotherapy and / or chemotherapy)]. 2005.
3. **De Haas-Kock DFM et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database of Systematic Reviews 2009,**
4. **Lutgens et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database of Systematic Reviews 2010,**
5. Mathis S, Johnasson T. Hyperthermie. Systematic review. Wien: Ludwig Boltzmann Institut für Health Technology Assessment. 2010.
6. Kirisits et al. Efficacy of Hyperthermia treatment in combination with radio- or chemotherapy in Breast- Bladder- Cervix carcinoma and Soft tissue sarcoma patients. Wien: Ludwig Boltzmann Institut fur Health Technology Assessment. 2012
7. **Datta et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia. 2016.**
8. **Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016.**
9. **Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016.**



EXECUTIVE SUMMARY

- Notes that at present there is no basis to recommend additional clinical studies into UHF cancer therapy.
- Considers the appropriateness of ongoing public funding of this treatment through the MBS.
- Requests the Therapeutic Goods Administration to investigate the approval of UHF devices for the treatment of patients with cancer; and
- Disseminates the outcomes of this review to health professionals, patients, their families and carers, and to the Australian community.

Assessment. 2012



Hyperthermia evidence:

EXECUTIVE SUMMARY

- Notes that at present there is no basis to recommend additional clinical studies into UHF cancer therapy.
- Considers the appropriateness of ongoing public funding of this treatment through the MBS.
- Requests the Therapeutic Goods Administration to investigate the approval of UHF devices for the treatment of patients with cancer; and
- Disseminates the outcomes of this review to health professionals, patients, their families and carers, and to the Australian community.

BAN

Assessment. 2012

Hyperth
Negati

1. Review Cor
Microwave
to the **Minis**
Research C
2. **G-BA [Joint**
hypertherm
hypertherm
2005.
3. Mathis S, Jo
Boltzmann I
4. Kirisits et al.
or chemoth
sarcoma pc
Assessment

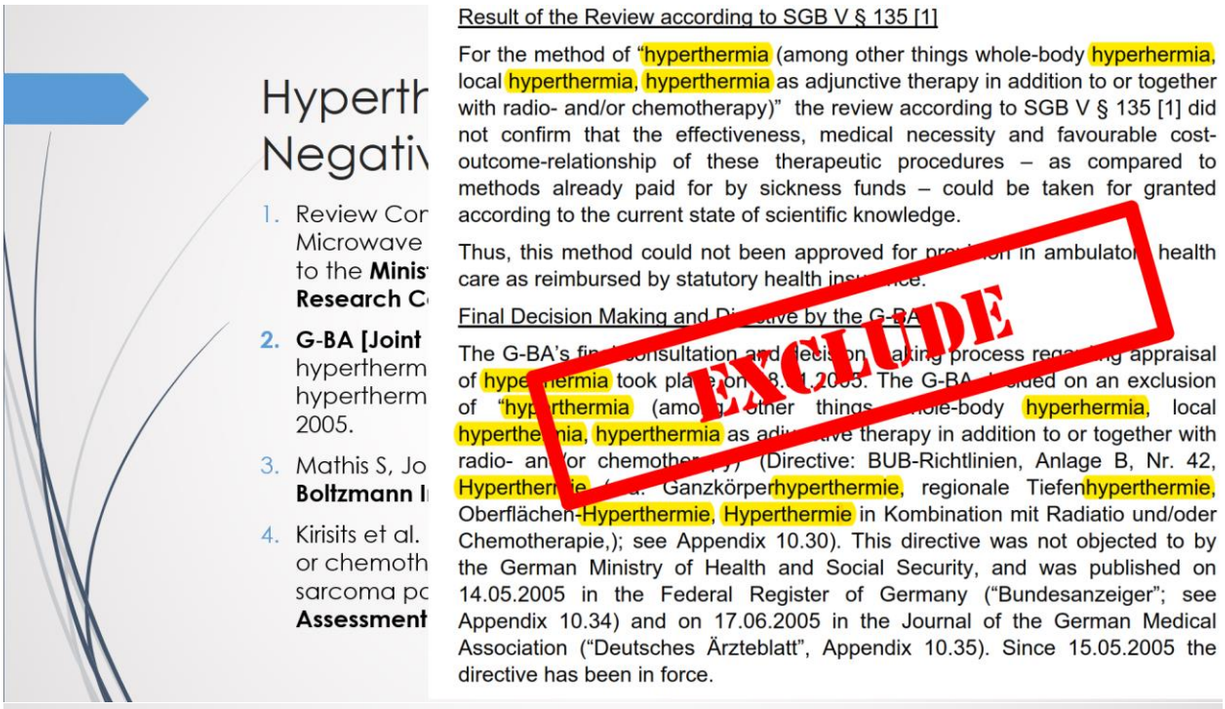
Result of the Review according to SGB V § 135 [1]

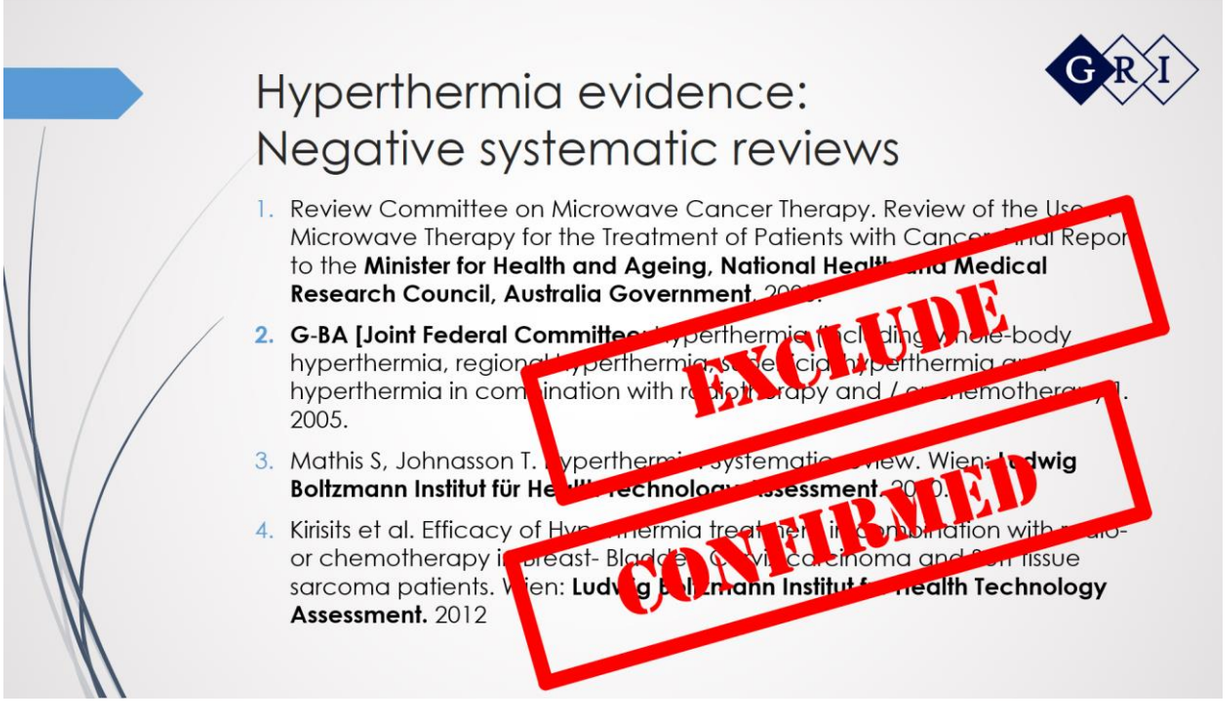
For the method of "hyperthermia (among other things whole-body hyperhermia, local hyperthermia, hyperthermia as adjunctive therapy in addition to or together with radio- and/or chemotherapy)" the review according to SGB V § 135 [1] did not confirm that the effectiveness, medical necessity and favourable cost-outcome-relationship of these therapeutic procedures – as compared to methods already paid for by sickness funds – could be taken for granted according to the current state of scientific knowledge.

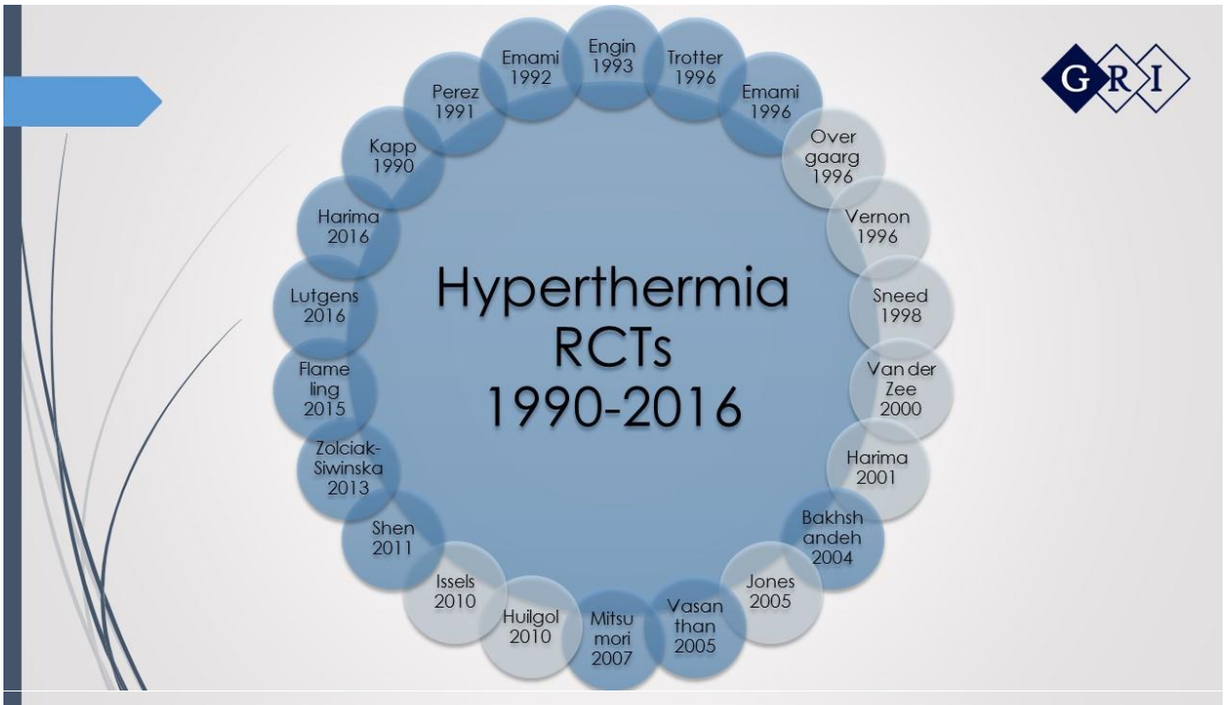
Thus, this method could not been approved for provision in ambulatory health care as reimbursed by statutory health insurance.

Final Decision Making and Directive by the G-BA

The G-BA's final consultation and decision making process regarding appraisal of hyperthermia took place on 18.01.2005. The G-BA decided on an exclusion of "hyperthermia (among other things whole-body hyperhermia, local hyperthermia, hyperthermia as adjunctive therapy in addition to or together with radio- and/or chemotherapy)" (Directive: BUB-Richtlinien, Anlage B, Nr. 42, Hyperthermie (u.a. Ganzkörperhyperthermie, regionale Tiefenhyperthermie, Oberflächen-Hyperthermie, Hyperthermie in Kombination mit Radiatio und/oder Chemotherapie,); see Appendix 10.30). This directive was not objected to by the German Ministry of Health and Social Security, and was published on 14.05.2005 in the Federal Register of Germany ("Bundesanzeiger"; see Appendix 10.34) and on 17.06.2005 in the Journal of the German Medical Association ("Deutsches Ärzteblatt", Appendix 10.35). Since 15.05.2005 the directive has been in force.

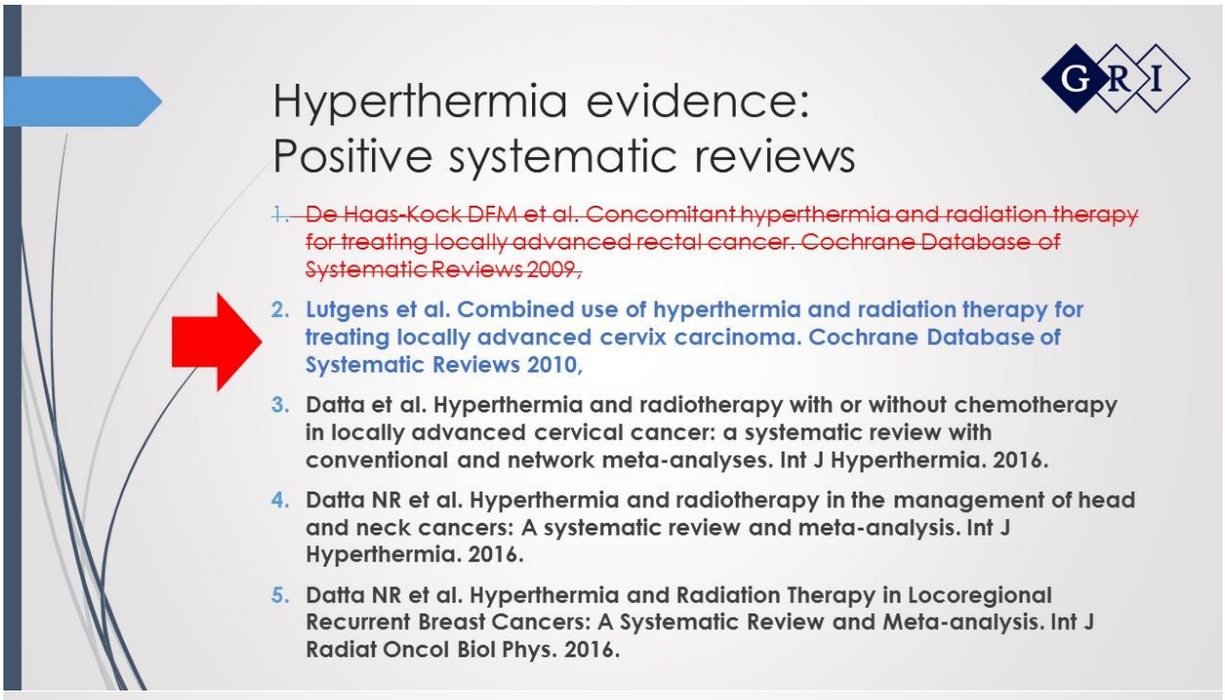

Hyperth
Negati
1. Review Cor
Microwave
to the Minis
Research C
2. G-BA [Joint
hypertherm
hypertherm
2005.
3. Mathis S, Jo
Boltzmann I
4. Kirisits et al.
or chemoth
sarcoma pc
Assessment
Result of the Review according to SGB V § 135 [1]
For the method of "hyperthermia (among other things whole-body hyperhermia, local hyperthermia, hyperthermia as adjunctive therapy in addition to or together with radio- and/or chemotherapy)" the review according to SGB V § 135 [1] did not confirm that the effectiveness, medical necessity and favourable cost-outcome-relationship of these therapeutic procedures – as compared to methods already paid for by sickness funds – could be taken for granted according to the current state of scientific knowledge.
Thus, this method could not been approved for
health care as reimbursed by statutory health
Final Decision Making and
The G-BA's
of hyperthermia took pla
of "hyperthermia (amo
hyperthermia, hyperthermia as
radio- an
Hyperther
Oberflächen-Hyperthermie, Hyperthermie in Kombination mit Radiatio und/oder Chemotherapie,); see Appendix 10.30). This directive was not objected to by the German Ministry of Health and Social Security, and was published on 14.05.2005 in the Federal Register of Germany ("Bundesanzeiger"; see Appendix 10.34) and on 17.06.2005 in the Journal of the German Medical Association ("Deutsches Ärzteblatt", Appendix 10.35). Since 15.05.2005 the directive has been in force.
EXCLUDE


Hyperthermia evidence:
Negative systematic reviews
1. Review Committee on Microwave Cancer Therapy. Review of the Use
Microwave Therapy for the Treatment of Patients with Cancer
to the Minister for Health and Ageing, National Health
Research Council, Australia Government.
2. G-BA [Joint Federal Committee
hyperthermia, regional
hyperthermia in com
2005.
3. Mathis S, Johnasson T.
Boltzmann Institut für He
4. Kirisits et al. Efficacy of Hyp
or chemotherapy i
sarcoma patients. W
Assessment. 2012
EXCLUDE
CONFIRMED



Hyperthermia evidence: Positive systematic reviews

1. **De Haas-Kock DFM et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database of Systematic Reviews 2009,**
2. **Lutgens et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database of Systematic Reviews 2010,**
3. **Datta et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia. 2016.**
4. **Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016.**
5. **Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016.**



PROSPERO

International prospective register of systematic reviews

NHS National Institute for Health Research

Print | PDF

The effectiveness and cost-effectiveness of conventional radiofrequency hyperthermia with concurrent chemo and/or radiotherapy in the treatment of locally advanced cervical cancer: a systematic review of randomized trials with meta-analysis and economical evaluation

Sergey Roussakow

Citation

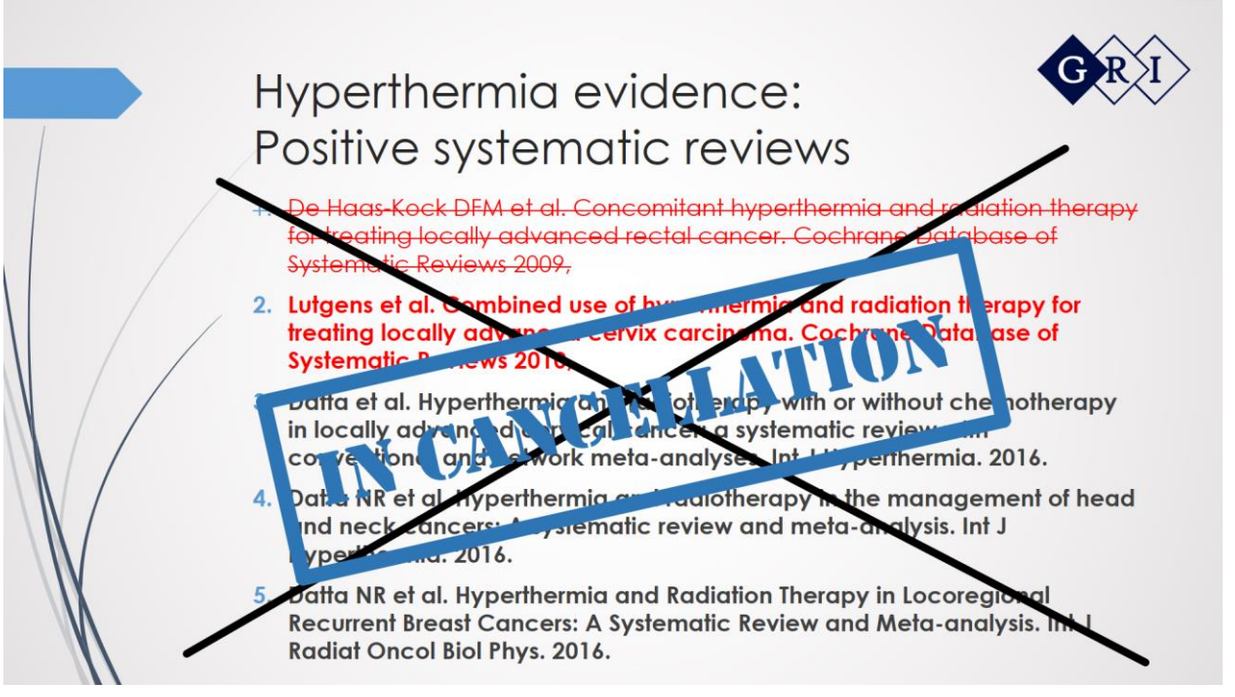
Sergey Roussakow. The effectiveness and cost-effectiveness of conventional radiofrequency hyperthermia with concurrent chemo and/or radiotherapy in the treatment of locally advanced cervical cancer: a systematic review of randomized trials with meta-analysis and economical evaluation. PROSPERO 2017 CRD42017072520 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017072520

Review question

Does conventional radiofrequency hyperthermia enhance the standard chemo and/or radiotherapy in the

Hyperthermia evidence: Positive systematic reviews

1. ~~De Haas-Kock DFM et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database of Systematic Reviews 2009,~~
2. **Lutgens et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. Cochrane Database of Systematic Reviews 2010,**
3. Datta et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia. 2016.
4. Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016.
5. Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016.



Hyperthermia approval: NCCN Breast Cancer Guideline

- The guideline includes consideration of the addition of hyperthermia to irradiation for localized recurrences / metastasis.
- The addition of hyperthermia generated substantial discussion and controversy among the panel.
- It is the category 3 recommendation (i.e. based on any level of evidence with substantial controversy.)

That's all.

50th anniversary of hyperthermia: still an experimental technology

- American Cancer Society
  - Hyperthermia is a promising way to improve cancer treatment, but it is largely an experimental technique at this time.
- US National Cancer Institute
  - A number of challenges must be overcome before hyperthermia can be considered a standard treatment for cancer.

FAILURE

- 1976
  - "The discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia" (Manfred von Ardenne)
- 2017
  - >10,000 publications
  - >50 monographs
  - >1,000 published studies
  - >30 RCTs
  - >10 phase III RCT

Hyperthermia: is it proven?

"Hyperthermia, i.e. heating of tumors to temperatures of 41-45°C for 1h, is a proven radiosensitizer and chemosensitizer."

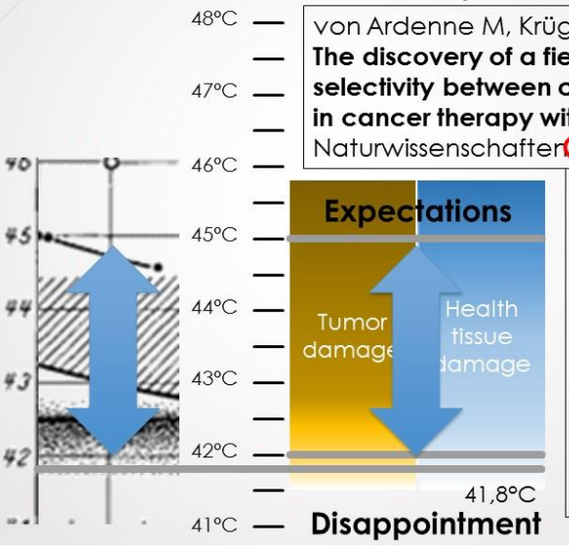
UNPROVEN

The Reasons of Hyperthermia Failure

Oncological hyperthermia is not an ancient treatment

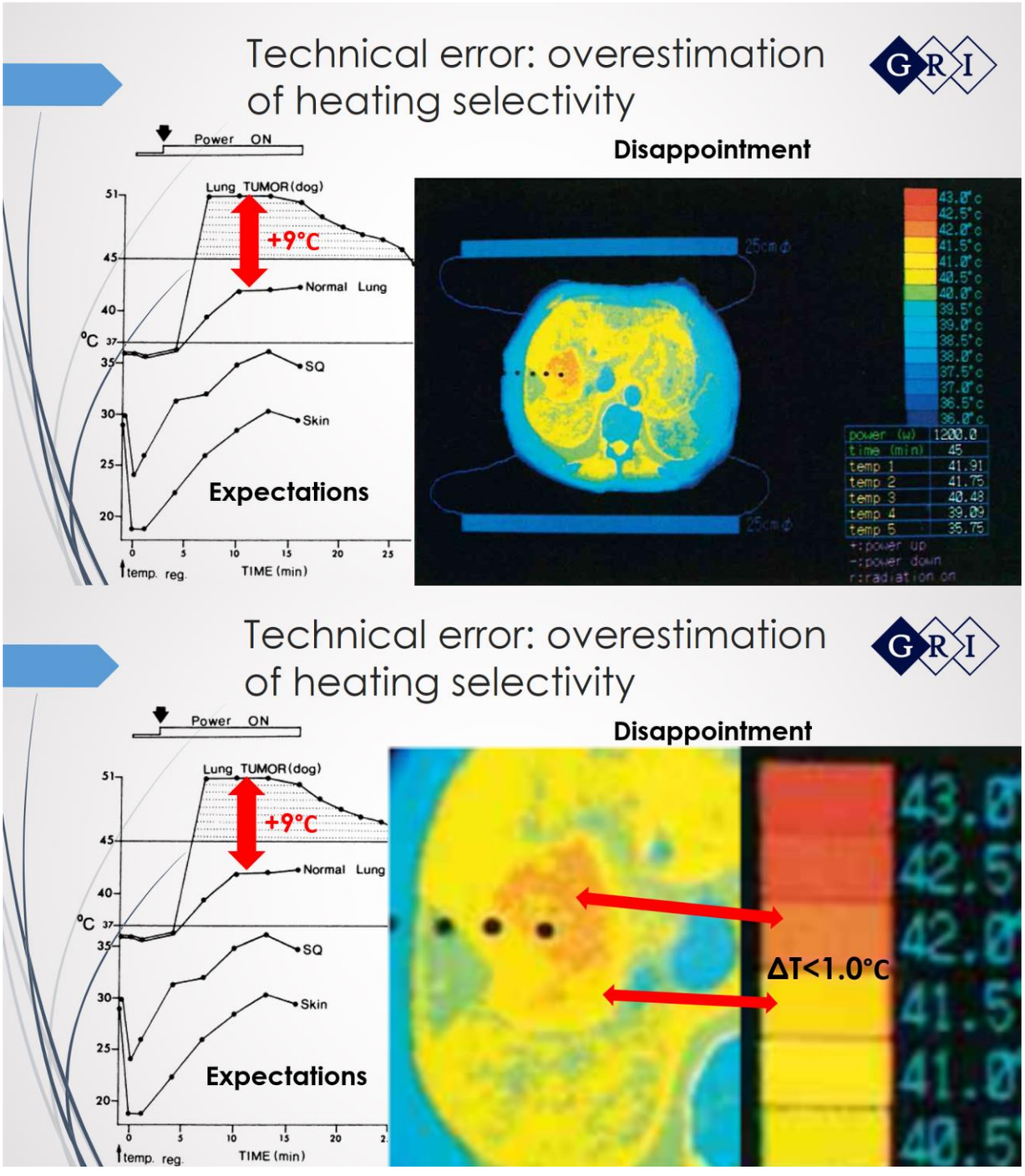
- 1898
  - Westermark F. **On the treatment of the ulcerating cervical carcinoma by constant heating.** Zentralbl Gynaekol 1898; 22:1335-1337.
- 1895
  - Discovery of X-rays (W. Roentgen)
- 1898
  - Discovery of radium (Pierre & Marie Curie)

Biological error: overestimation of thermal sensitivity difference

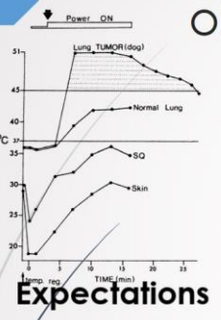


von Ardenne M, Krüger W. **The discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia.** Naturwissenschaften **1966**; 53:436-437.

«There is no difference in response of normal and tumor cells for hyperthermia in vitro». Kelleher DH, Vaupel P. Vascular Effects of Localized Hyperthermia. In: Baronzio GF, Hager ED. Hyperthermia in Cancer Treatment: a Primer. Landes Bioscience, **2006**: 219-228.


Technical error: overestimation of heating selectivity
Power ON
Lung TUMOR(dog)
+9°C
Normal Lung
SQ
Skin
Expectations
°C
TIME (min)
temp. reg.
Disappointment
power (w) 1200.0
time (min) 45
temp 1 41.91
temp 2 41.75
temp 3 40.48
temp 4 39.09
temp 5 35.75
+:power up
-:power down
r:radiation on
Technical error: overestimation of heating selectivity
Power ON
Lung TUMOR(dog)
+9°C
Normal Lung
SQ
Skin
Expectations
°C
TIME (min)
temp. reg.
Disappointment
ΔT<1.0°C

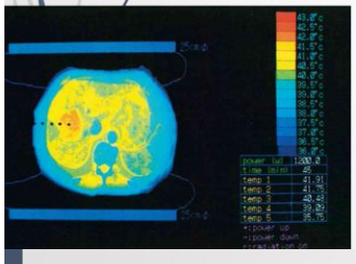
Technical error: overestimation of heating selectivity

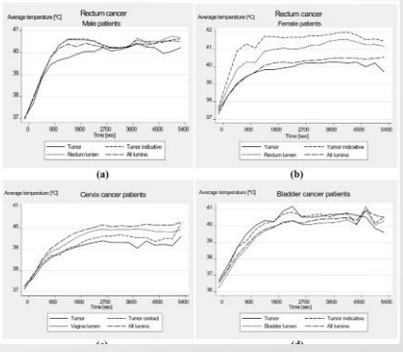


Expectations

Disappointment

Heating selectivity doesn't exceed 1°C with capacitive heating and absent or negative with radiative heating





The main problem of hyperthermia

No Difference in Thermal Sensitivity

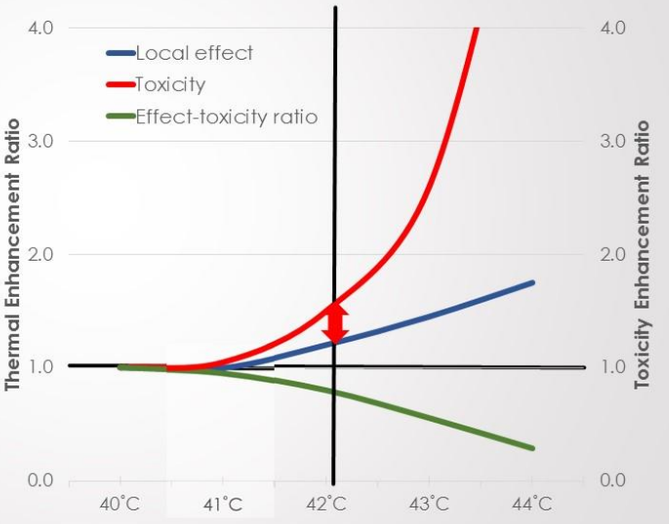
+

No Selectivity of Heating

=

No Therapeutic Range

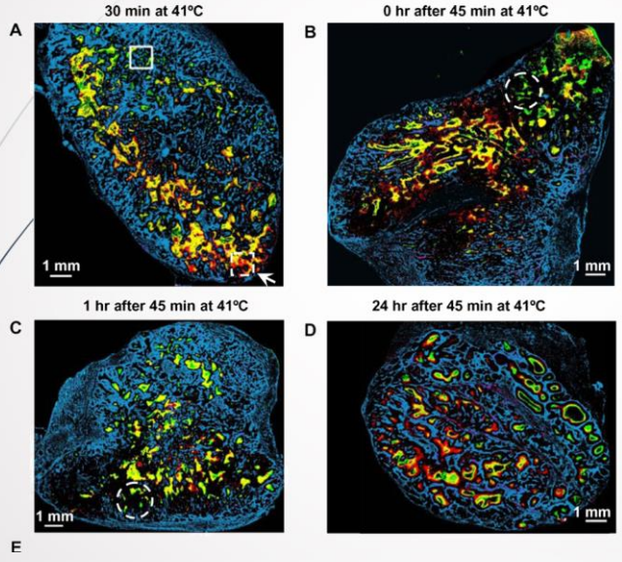
The main problem of hyperthermia: absence of therapeutic range



The "moderate re-setting" of hyperthermia

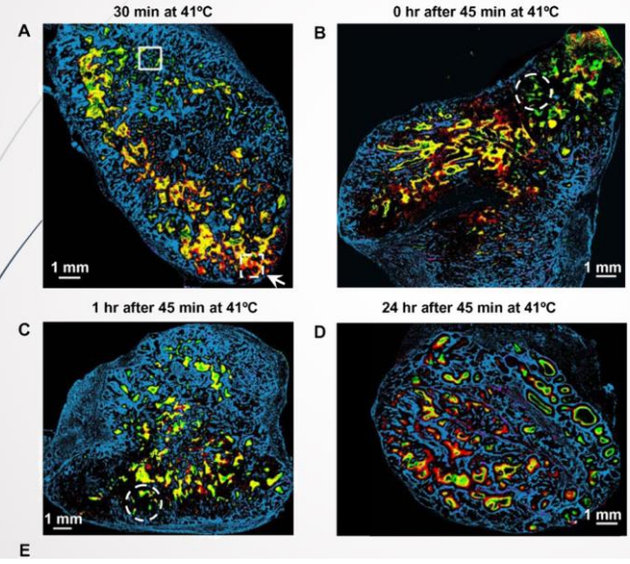
- Dewhirst MW, Vujaskovic Z, Jones E, Thrall D. **Re-setting the biologic rationale for thermal therapy**. Int J Hyperthermia. 2005 Dec;21(8):779-90.
  - Moderate hyperthermia (<42°C) is the main modality
  - Enhancement of tumor perfusion is the main mechanism
  - 'Thermal dose' is the key parameter

Physiological error: overestimation of chemo- and radiotherapy enhancement



Sun X et al.
Changes in tumor hypoxia induced by mild temperature hyperthermia as assessed by dual-tracer immunohistochemistry. Radiother Oncol. Aug 2008; 88(2):269-276.

Physiological error: overestimation of chemo- and radiotherapy enhancement



Since clinically relevant increases in oxygenation induring beyond the heating period were rarely seen, it would apper that an improvement in the efficacy of oxygen-dependent cancer therapy is unlikely to be achieved in post-hyperthermia period.

Kelleher DK, Vaupel P.
No sustained improvement in tumor oxygenation after localized mild hyperthermia. Advances in Experimental Medicine and Biology. 2010;662(4):393–8.

Thermal dose failure
Temperature failure

No correlation of thermal dose with histologic response was observed. Prospective control of CEM43 degrees T90 failed to achieve the projected pCR rate following pre-operative thermoradiotherapy for high-grade soft tissue sarcomas, despite excellent local control.

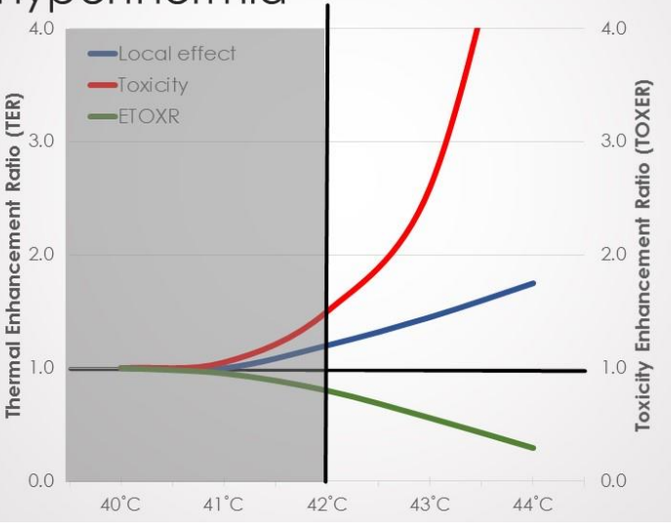
Maguire PD et al. A phase II trial testing the thermal dose parameter CEM43 degrees T90 as a predictor of response in soft tissue sarcomas treated with pre-operative thermoradiotherapy. Int J Hyperthermia. 2001;17(4):283-90.

CONCLUSION: In this retrospective study, no clear CEM43 degrees CT90 thermal dose targets or associations with clinical endpoints could be established.

de Bruijne M et al. Evaluation of CEM43 degrees CT90 thermal dose in superficial hyperthermia: a retrospective analysis. Strahlenther Onkol. 2010 Aug;186(8):436-43.

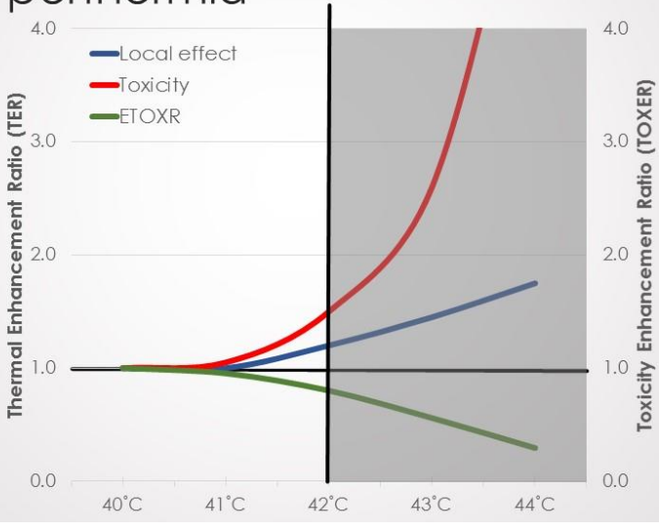
No temperature-based parameter was predictive.

The futility of the moderate hyperthermia

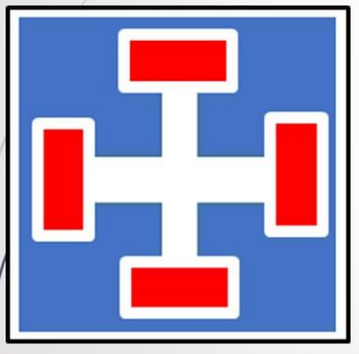


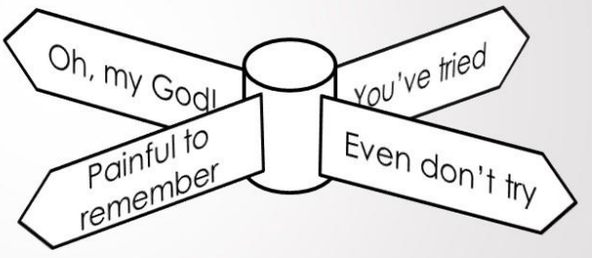
The Second Coming of the Extreme Hyperthermia: No way out.

The futility of the extreme hyperthermia

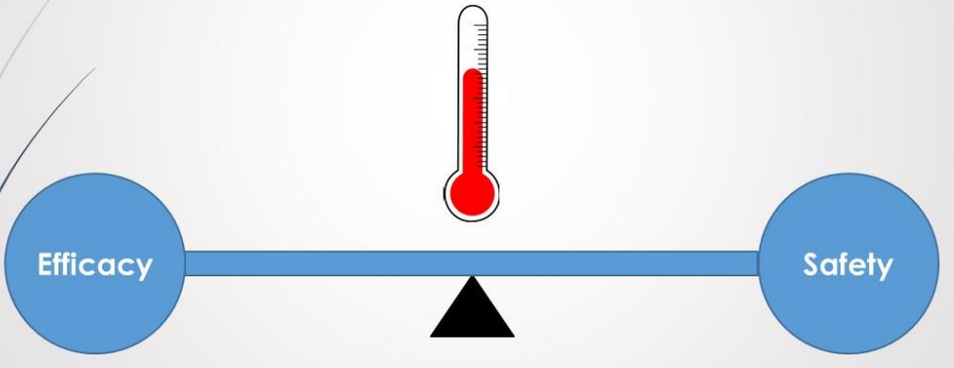


Temperature hyperthermia crossroad

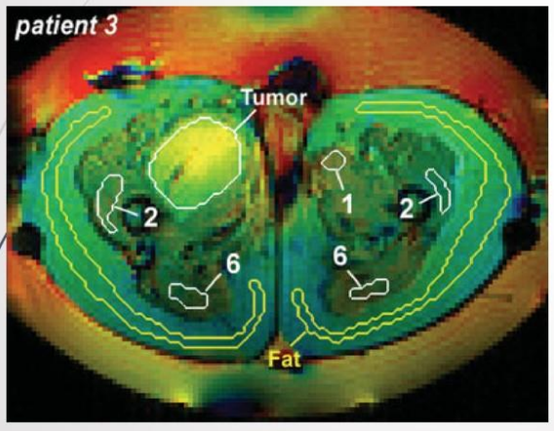


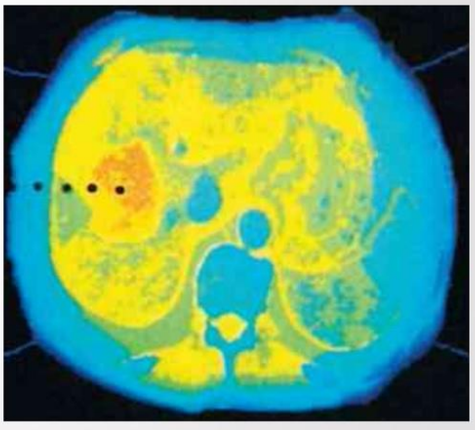


Thermometry in hyperthermia: A useless necessity

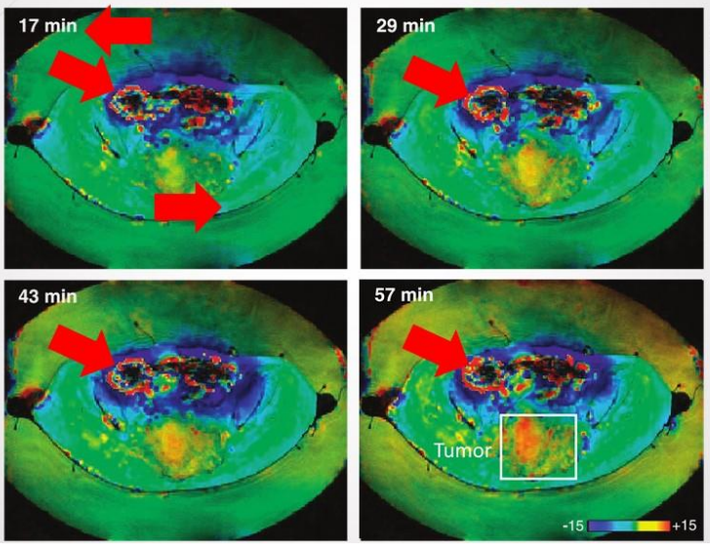


The problem of focusing: no temperature solution





The problem of "hot spots"



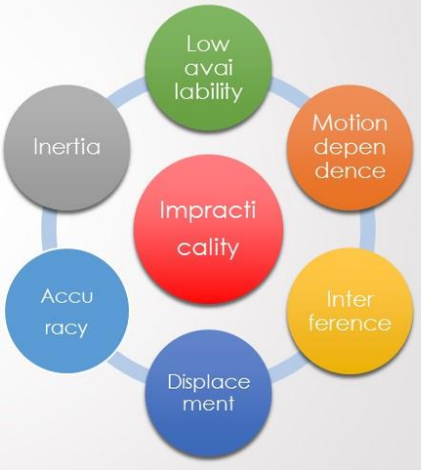
Sigma-Eye aplicator BSD-2000 system

Gellermann J et al. **Noninvasive magnetic resonance thermography of recurrent rectal carcinoma in a 1.5 Tesla hybrid system.** Cancer Res. 2005;65(13):5872-80.

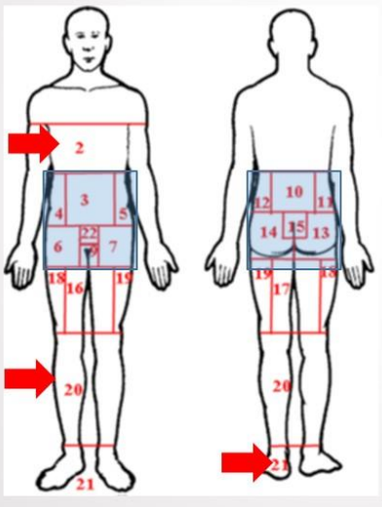
Thermometry problem: no solution

In view of the possible severe complications and the limited clinical value of the information achieved by interstitially placed thermometry catheters, interstitial thermometry was not found to routinely benefit the individual patient.

van der Zee J et al. Practical limitations of interstitial thermometry during deep hyperthermia. Int J Radiat Oncol Biol Phys. 1998;40(5):1205-12.



Hyperthermia thermal planning (HTP): one more dead-end.



Region (regions as in figure 2)	Complaint occurrence (%)	Average DTC (±SE)
Abdomen mid	27.6	3.5 ± 0.1
Lower back mid	18.8	3.2 ± 0.1
Tailbone/anus	8.0	2.1 ± 0.2
Buttocks left	7.9	4.9 ± 0.2
Buttocks right	6.4	5.7 ± 0.2
Bladder	3.2	2.8 ± 0.2
Groin/Hip left	3.1	7.4 ± 0.3
Abdomen left	3.0	5.7 ± 0.7
Abdomen right	1.4	5.5 ± 0.5
Lower back left	1.1	6.9 ± 0.4
Thigh left	0.9	9.0 ± 0.1.6
Legs	0.7	NaN (outside HTP models)
Stomach/upper abdomen	0.7	9.7 ± 1.3
Feet	0.5	NaN (outside HTP models)
Thigh right	0.4	7.7 ± 3.0
Thigh top	0.3	10.8 ± 0.8
Systemic	0.3	NaN (no fixed region)
Lower back right	0.1	7.4 (no SE, single complaint)

Average displacement was 7 cm (4 – 10 cm)

Hyperthermia thermal planning (HTP): one more dead-end.

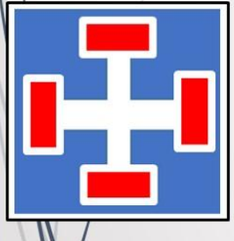
Replacing the Sigma-60 by the Sigma-Eye applicator resulted in a higher SAR in the tumor by 24% ($p < 0.001$), and higher temperatures (T90: +0.4°C, $p < 0.001$; T50: +0.6°C, $p < 0.001$) … Based on this uncertainty analysis, significant and clinically relevant improvements in HTQ and tumor temperature were achieved when replacing the Sigma-60 by the Sigma-Eye applicator.

Canters at al. Benefit of replacing the Sigma-60 by the Sigma-Eye applicator. A Monte Carlo-based uncertainty analysis. Strahlenther Onkol. 2013;189(1):74-80.

Because the efficacy of the SIGMA-Eye applicator is lower than that of the SIGMA-60, we applied the range of from 1000 W to 1600 W amplifier power, which roughly corresponds to 400 to 600 W in the SIGMA-60.

Gellermann J et al. Noninvasive magnetic resonance thermography of soft tissue sarcomas during regional hyperthermia: correlation with response and direct thermometry. Cancer. 2006;107(6):1373-82.

Temperature hyperthermia: State of the Art

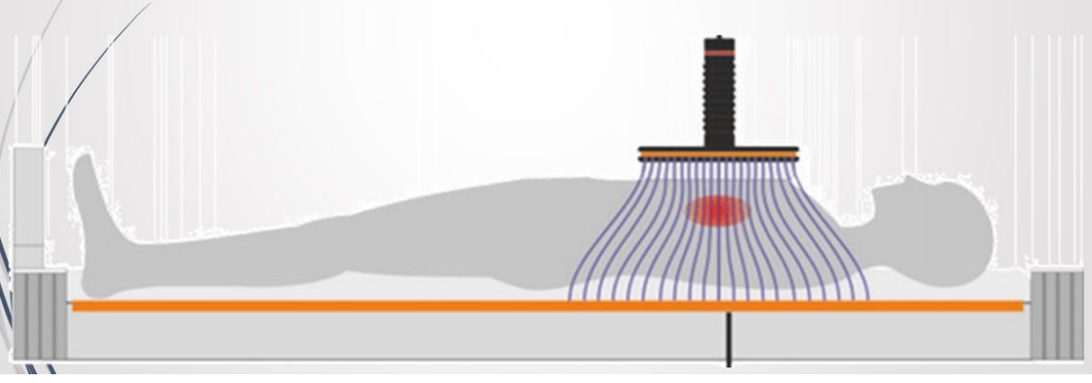


- No definition
- No concept
- No therapeutic range
- No clinical evidence
- No acceptance
- No approval
- No prospects
- No thermal dose evidence
- No temperature evidence
- No temperature control
- No thermal planning
- No focusing
- No extreme HT
- No moderate HT
- No radiosensitization
- No chemopotentiation

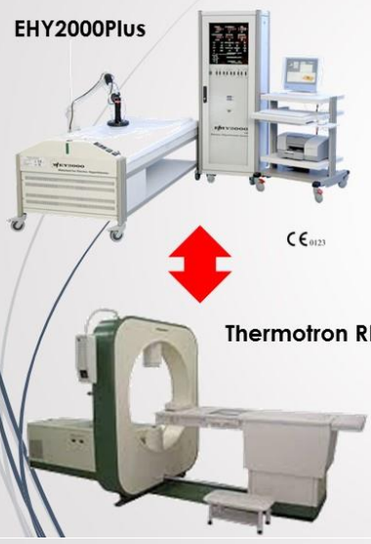
Non-temperature-dependent solution of the temperature problem

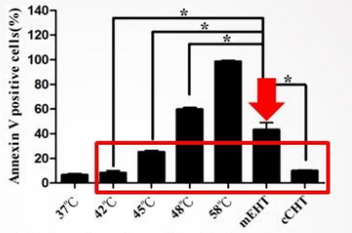
Modulated electrohyperthermia (mEHT, Oncothermia™)

Modulated electro-hyperthermia is a novel method of treatment for solid malignant tumours by the local application of a high-frequency electromagnetic field (13.56 MHz), modulated by 0–5 kHz flicker noise, by virtue of impedance-coupled functionally asymmetric electrodes.

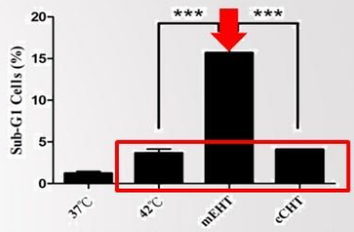


mEHT and Hyperthermia: A Difference in Effects



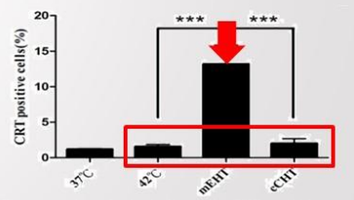


The fraction of annexin-positive cells after mEHT at 42°C (43.1 ± 5.8%) is significantly higher than after CHT at 42°C (10.0 ± 0.6%), and approximately corresponds to HT at 46°C.



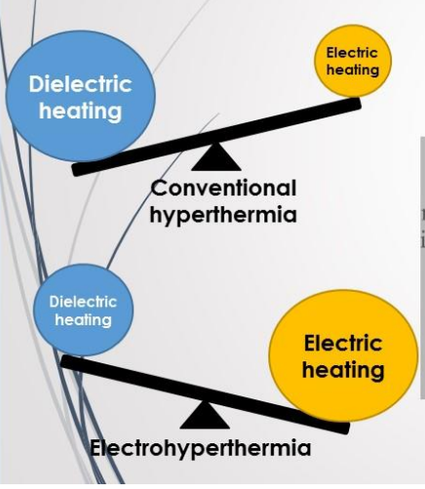
The fraction of cells with fragmented DNA (sub-G1) after mEHT at 42°C was 15.67 ± 1.76% against 4.1 ± 0.0% after CHT at 42°C and 3.65 ± 0.49% after HT at 42°C.

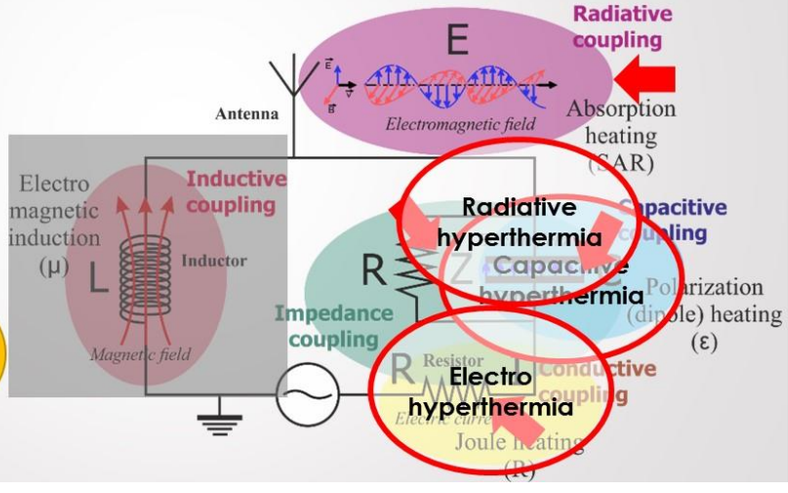
Significant increase in activation of caspase-3,-8 and -9 at 24 hours after exposure to mEHT at 42°C, compared to CHT and HT at 42°C.



The expression of calreticulin after mEHT at 42°C was 13.2 ± 2.65% compared to 2.03 ± 0.67% after CHT at 42°C and 1.57 ± 0.31% after HT at 42°C.

Types of electromagnetic coupling

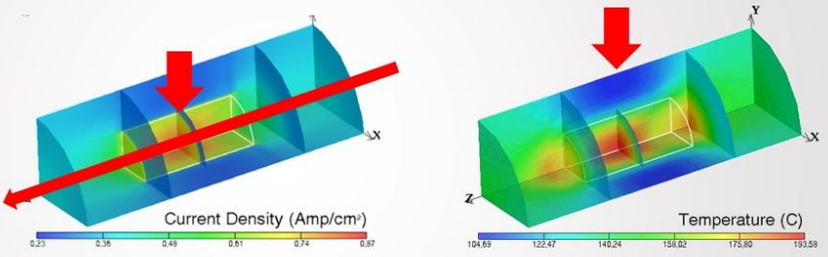




Impedance selectivity: Solution of the focusing problem

Color mapping of current density distribution in an impedance heater; time t = 150 sec.

Salengke S, Sastry SK. **Experimental investigation of ohmic heating of solid–liquid.** J Food Engineering. 2007;83(3):324-36.

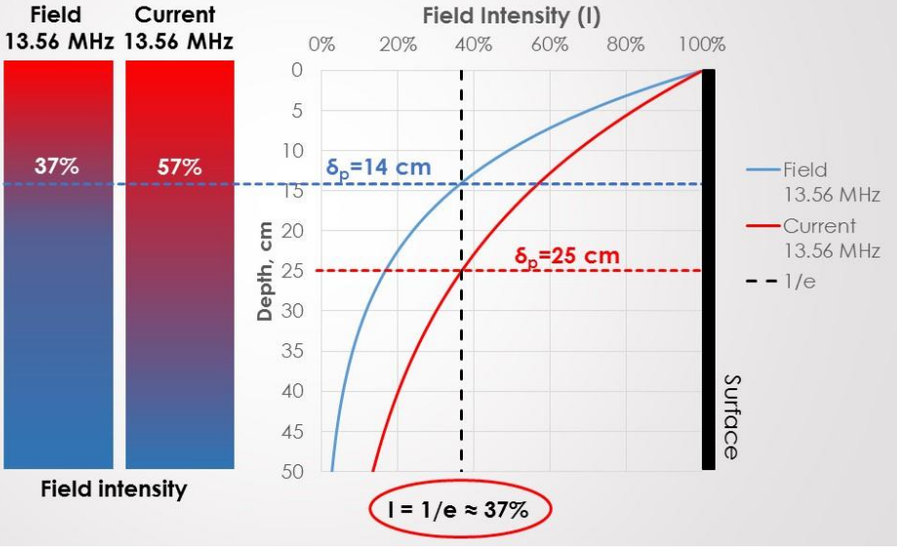


σ = 2

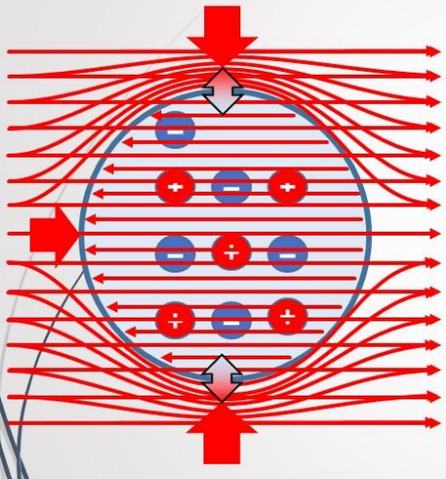
Conductance of the insert is twice the surrounding medium

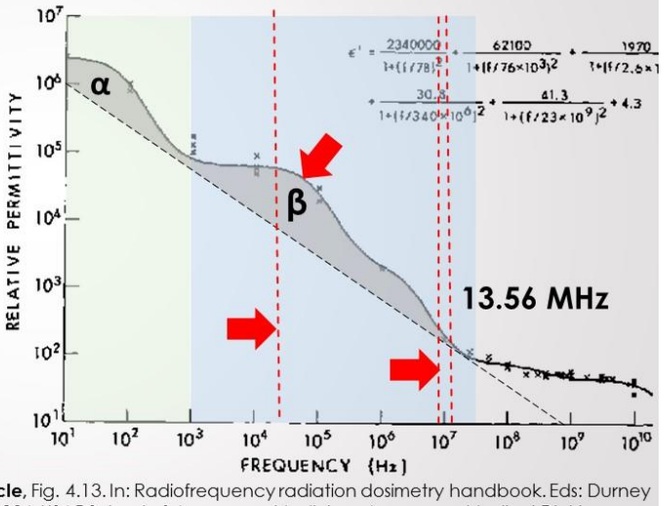
Penetration depth

Szasz O, Szigeti GP, Vancsik T, Szasz A. **Hyperthermia dosing and depth of effect.** Open J Biophys, 2017. Forthcoming.



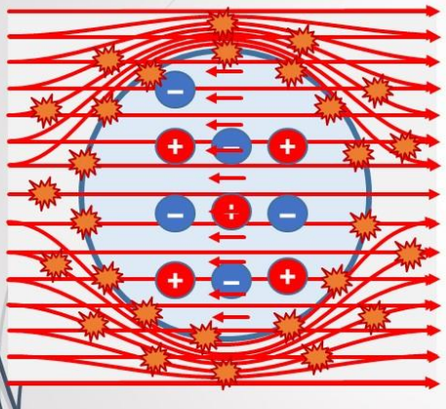
Beta-dispersion and membrane heating

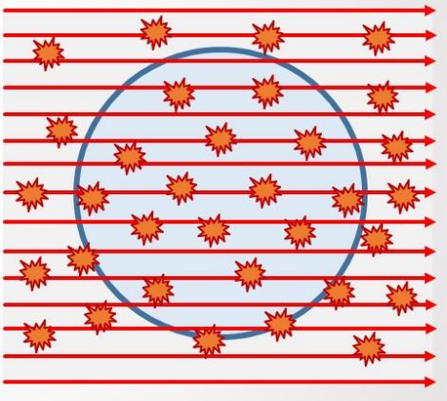


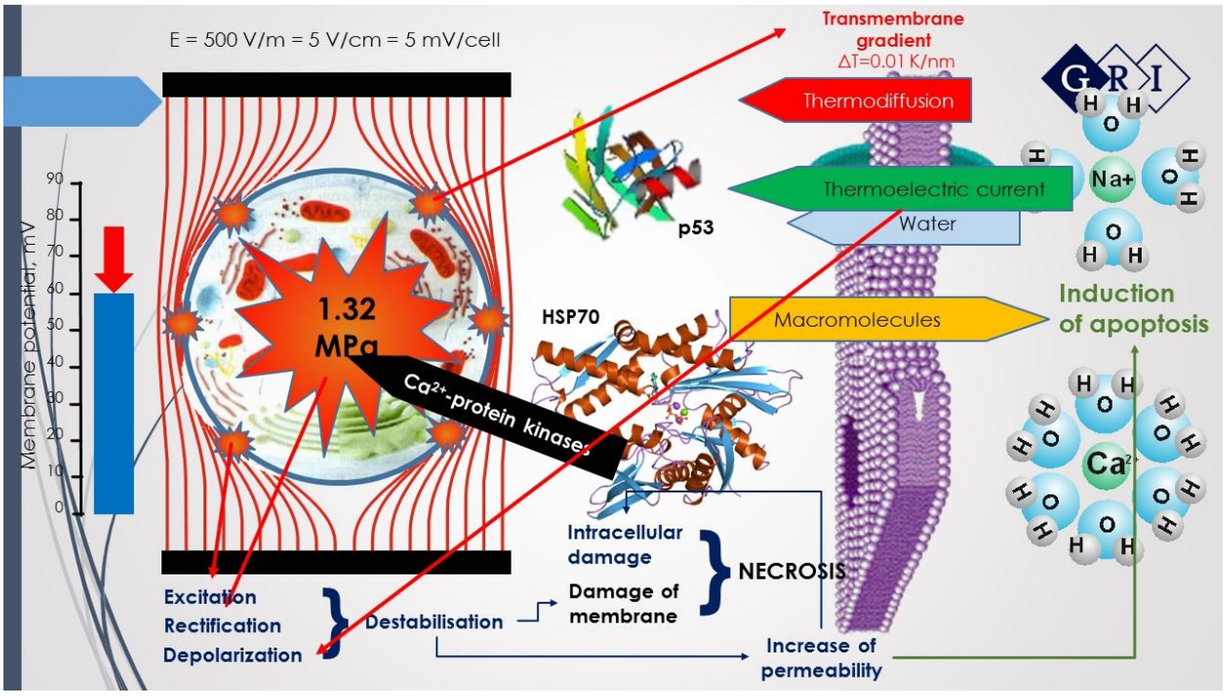


Hurt WD. **Relative dielectric permittivity for muscle**, Fig. 4.13. In: Radiofrequency radiation dosimetry handbook. Eds: Durney CH, Massoudi H, Iskandef MF. 4th ed., October 1986. USAF School of Aerospace Medicine, Aerospace Medical Division (AFSC), Brooks Air Force Base, TX 78235-5301, USA. 505 p.

Beta-dispersion and membrane heating






E = 500 V/m = 5 V/cm = 5 mV/cell
Transmembrane gradient
ΔT=0.01 K/nm
Thermodiffusion
Thermoelectric current
Water
Macromolecules
Induction of apoptosis
Membrane potential, mV
90
80
70
60
50
40
30
20
10
0
1.32 MPa
Ca²⁺-protein kinases
p53
HSP70
Na+
Ca²⁺
Intracellular damage
Damage of membrane
NECROSIS
Excitation
Rectification
Depolarization
Destabilisation
Increase of permeability