HYPERTHERMIA
CLINICS INTERNATIONAL

Hyperthermia Treatment for Breast Cancer

LEVEL 1A EVIDENCE

Table of Contents

Summary of Research

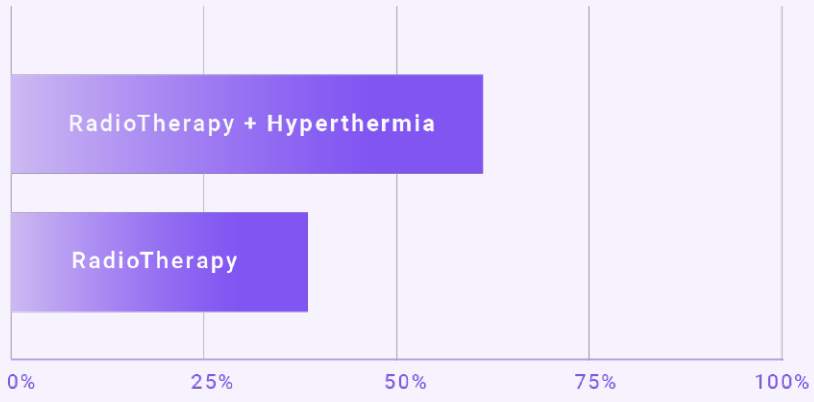
Treatment Response Improved by 60% when Combining Radiotherapy with Hyperthermia for Recurrent Breast Cancer

Complete Response was 38.1% with Standard Radiotherapy Treatment Compared with 60.2% when Radiotherapy was Combined with Biweekly Hyperthermia; and up to a 72% Complete Response for Localised Chest Wall Recurrence.

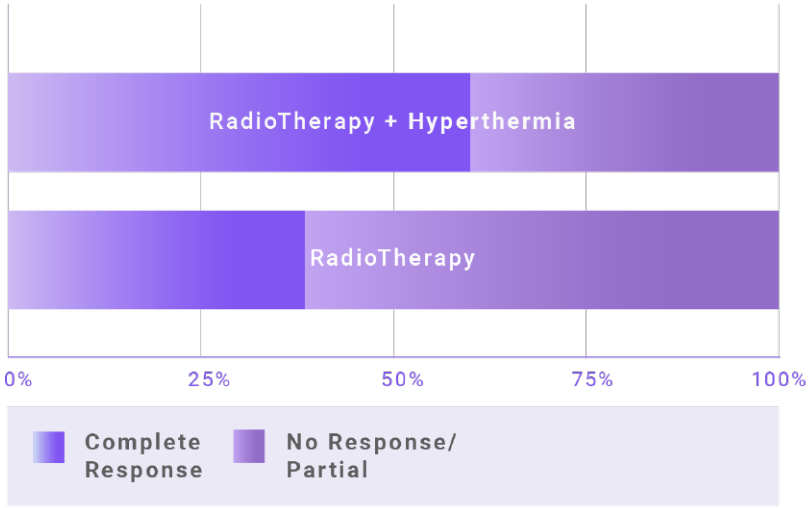
Results Show that the Addition of Hyperthermia to Radiotherapy and/or Chemotherapy for the Treatment of Breast Cancer Enhances Treatment Response and Can Increase Local Control.

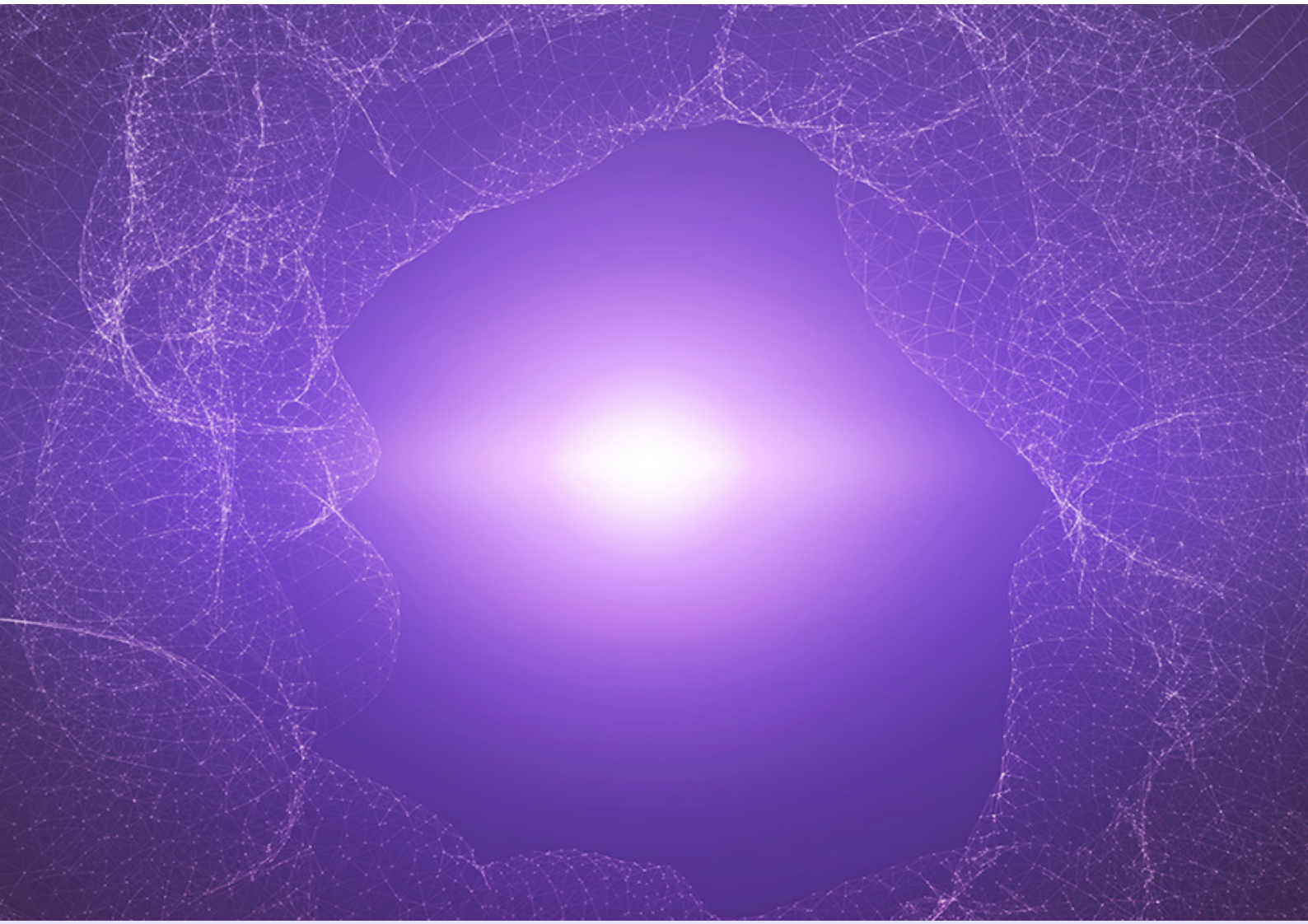
Hyperthermia Is Now Included in the NCCN Clinical Practice Guidelines for Breast Cancer Recurrences.

Complete Response %



Complete Response %



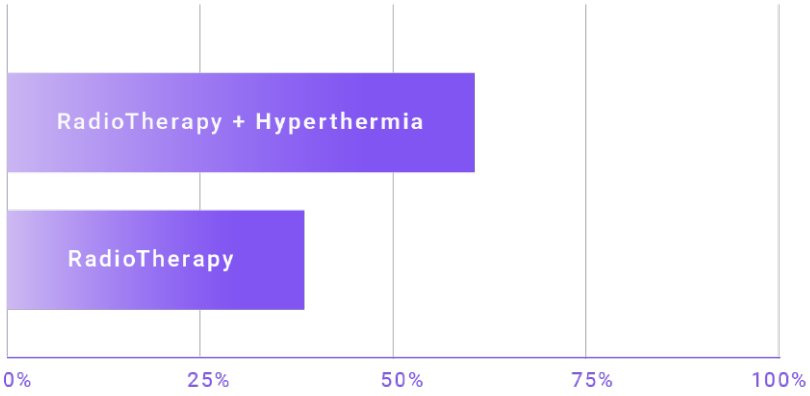


Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: a Systematic Review and Beta-analysis.

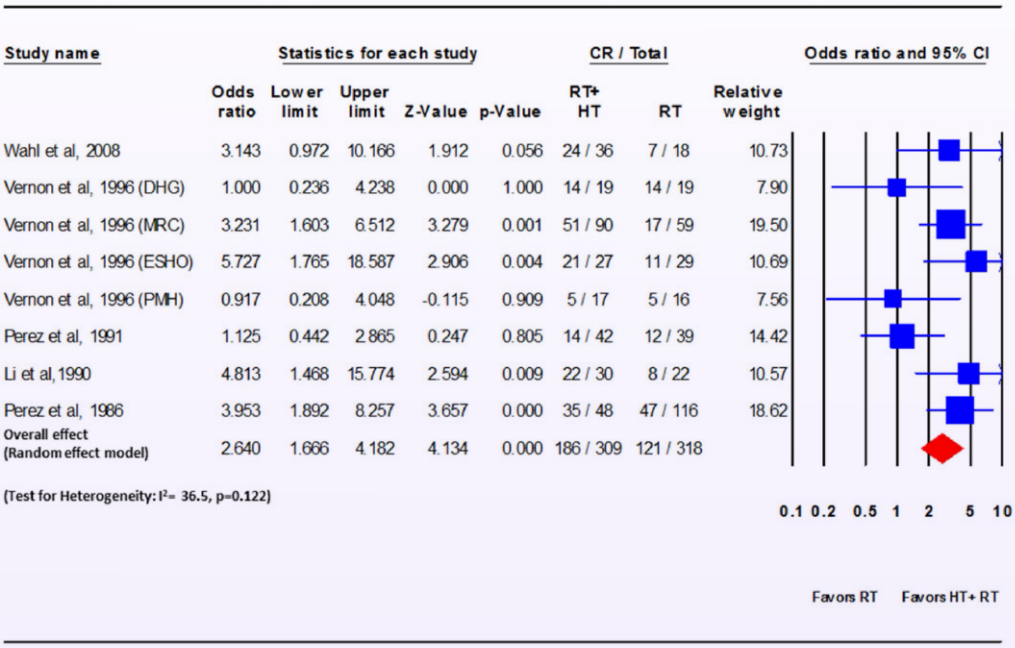
In all, 627 patients were enrolled in 2-arm and 1483 in single-arm studies. Patients were treated with a median of 7 HT sessions, and an average temperature of 42.5°C was attained. Mean RT dose was 38.2 Gy (range, 26-60 Gy). Hyperthermia was most frequently applied after RT.

In the 2-arm studies, a CR of 60.2% was achieved with RT + HT versus 38.1% with RT alone (odds ratio 2.64, 95% confidence interval [CI] 1.66-4.18, P<.0001). Risk ratio and risk difference were 1.57 (95% CI 1.25-1.96, P<.0001) and 0.22 (95% CI 0.11-0.33, P<.0001), respectively. In 26 single-arm studies, RT + HT attained a CR of 63.4% (event rate 0.62, 95% CI 0.57-0.66). Moreover, 779 patients had been previously irradiated (696 from single-arm and 83 from 2-arm studies). A CR of 66.6% (event rate 0.64, 95% CI 0.58-0.70) was achieved with HT and reirradiation (mean 3 SD dose: 36.7 3 7.7 Gy). Mean acute and late grade 3/4 toxicities with RT + HT were 14.4% and 5.2%, respectively.

2nd Arm Complete Response %



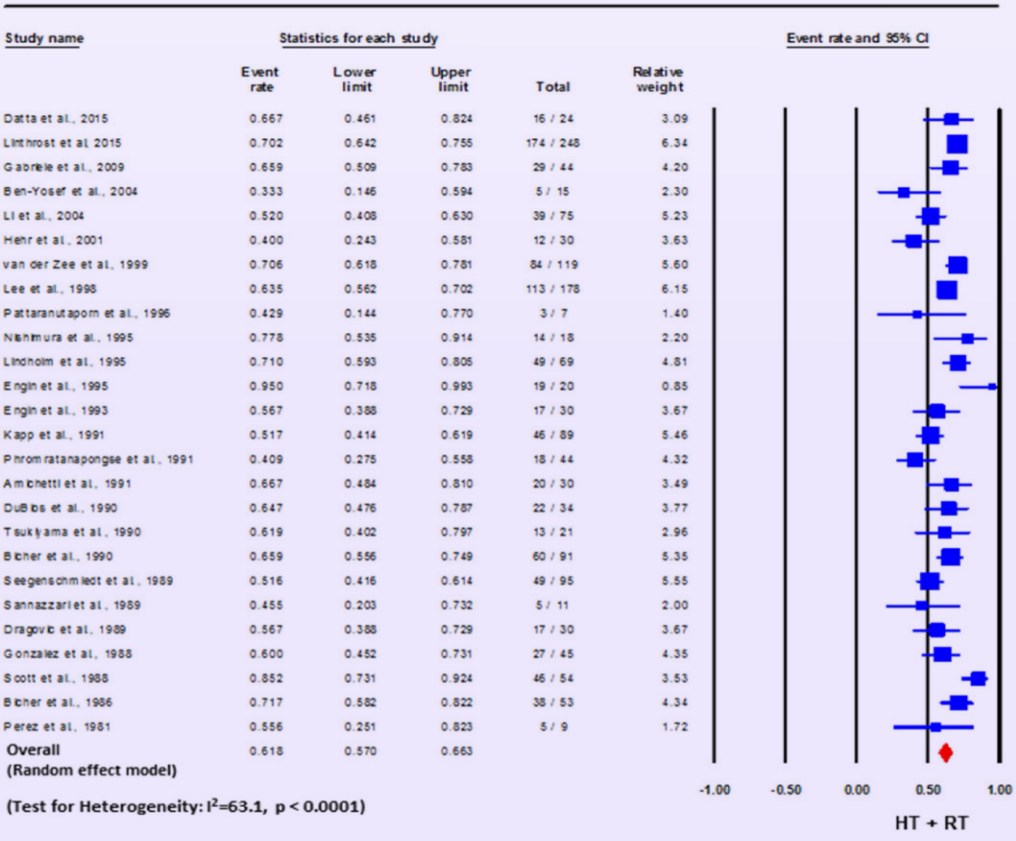
(a) Odds Ratio (Hyperthermia + Radiotheraphy vs. Radiotherapy alone)



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	RT+ HT	RT	Relative weight
Wahl et al, 2008	3.143	0.972	10.166	1.912	0.056	24 / 36	7 / 18	10.73
Vernon et al, 1996 (DHG)	1.000	0.236	4.238	0.000	1.000	14 / 19	14 / 19	7.90
Vernon et al, 1996 (MRC)	3.231	1.603	6.512	3.279	0.001	51 / 90	17 / 59	19.50
Vernon et al, 1996 (ESHO)	5.727	1.765	18.587	2.906	0.004	21 / 27	11 / 29	10.69
Vernon et al, 1996 (PMH)	0.917	0.208	4.048	-0.115	0.909	5 / 17	5 / 16	7.56
Perez et al, 1991	1.125	0.442	2.865	0.247	0.805	14 / 42	12 / 39	14.42
Li et al, 1990	4.813	1.468	15.774	2.594	0.009	22 / 30	8 / 22	10.57
Perez et al, 1986	3.953	1.892	8.257	3.657	0.000	35 / 48	47 / 116	18.62
Overall effect (Random effect model)	2.640	1.666	4.182	4.134	0.000	186 / 309	121 / 318	

(Test for Heterogeneity: I^2= 36.5, p=0.122)

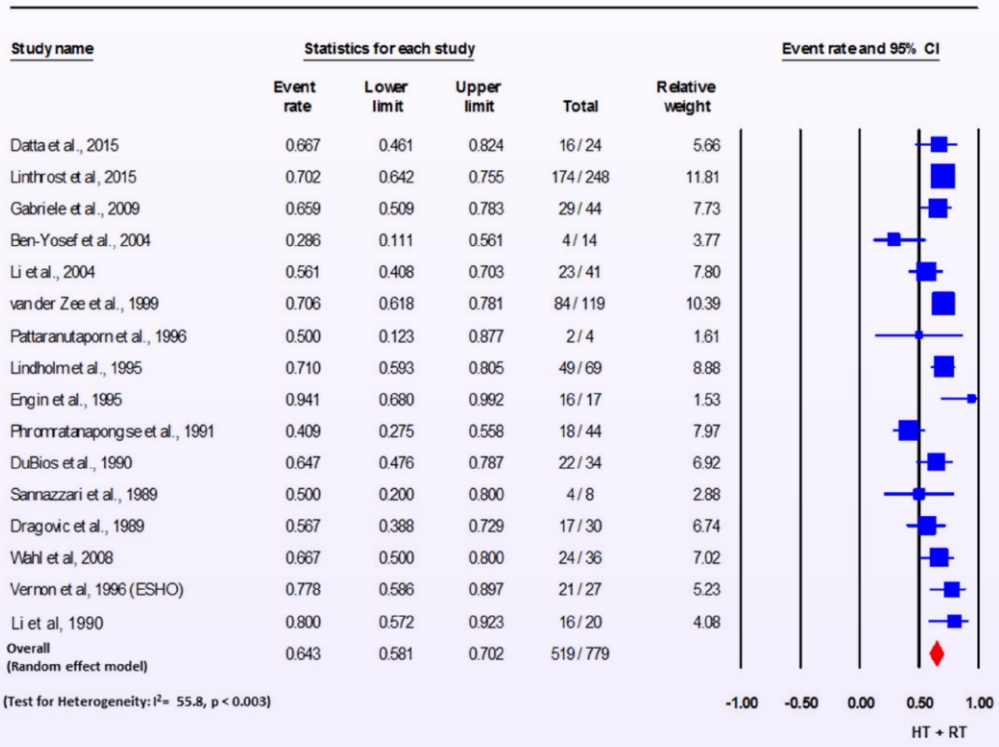
Event Rate: Single arm Studies (Hyperthermia and Radiotherapy)



Study name	Event rate	Lower limit	Upper limit	Total	Relative weight
Datta et al., 2015	0.667	0.461	0.824	16 / 24	3.09
Linthrost et al. 2015	0.702	0.642	0.755	174 / 248	6.34
Gabriele et al., 2009	0.659	0.509	0.783	29 / 44	4.20
Ben-Yosef et al., 2004	0.333	0.146	0.594	5 / 15	2.30
Li et al., 2004	0.520	0.408	0.630	39 / 75	5.23
Hehr et al., 2001	0.400	0.243	0.581	12 / 30	3.63
van der Zee et al., 1999	0.706	0.618	0.781	84 / 119	5.60
Lee et al., 1998	0.635	0.562	0.702	113 / 178	6.15
Pattaranutaporn et al., 1996	0.429	0.144	0.770	3 / 7	1.40
Nishimura et al., 1995	0.778	0.535	0.914	14 / 18	2.20
Lindholm et al., 1995	0.710	0.593	0.805	49 / 69	4.81
Engin et al., 1995	0.950	0.718	0.993	19 / 20	0.85
Engin et al., 1993	0.567	0.388	0.729	17 / 30	3.67
Kapp et al., 1991	0.517	0.414	0.619	46 / 89	5.46
Phromratanapongse et al., 1991	0.409	0.275	0.558	18 / 44	4.32
Amichetti et al., 1991	0.667	0.484	0.810	20 / 30	3.49
DuBois et al., 1990	0.647	0.476	0.787	22 / 34	3.77
Tsukiyama et al., 1990	0.619	0.402	0.797	13 / 21	2.96
Bicher et al., 1990	0.659	0.556	0.749	60 / 91	5.35
Seegenschmiedt et al., 1989	0.516	0.416	0.614	49 / 95	5.55
Sannazzari et al., 1989	0.455	0.203	0.732	5 / 11	2.00
Dragovic et al., 1989	0.567	0.388	0.729	17 / 30	3.67
Gonzalez et al., 1988	0.600	0.452	0.731	27 / 45	4.35
Scott et al., 1988	0.852	0.731	0.924	46 / 54	3.53
Bicher et al., 1986	0.717	0.582	0.822	38 / 53	4.34
Perez et al., 1981	0.556	0.251	0.823	5 / 9	1.72
Overall (Random effect model)	0.618	0.570	0.663		

(Test for Heterogeneity: I^2=63.1, p < 0.0001)

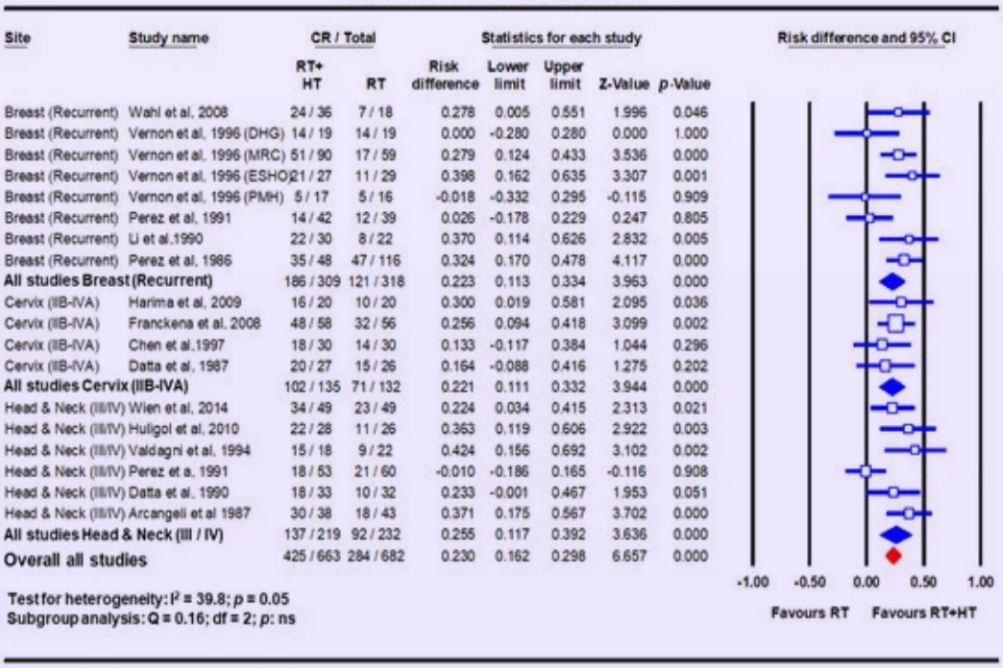
Event Rate: Reirradiation and Hyperthermia



Study name	Event rate	Lower limit	Upper limit	Total	Relative weight
Datta et al., 2015	0.667	0.461	0.824	16 / 24	5.66
Linthrost et al, 2015	0.702	0.642	0.755	174 / 248	11.81
Gabriele et al., 2009	0.659	0.509	0.783	29 / 44	7.73
Ben-Yosef et al., 2004	0.286	0.111	0.561	4 / 14	3.77
Li et al., 2004	0.561	0.408	0.703	23 / 41	7.80
van der Zee et al., 1999	0.706	0.618	0.781	84 / 119	10.39
Pattaranutaporn et al., 1996	0.500	0.123	0.877	2 / 4	1.61
Lindholm et al., 1995	0.710	0.593	0.805	49 / 69	8.88
Engin et al., 1995	0.941	0.680	0.992	16 / 17	1.53
Phromratanapongse et al., 1991	0.409	0.275	0.558	18 / 44	7.97
DuBios et al., 1990	0.647	0.476	0.787	22 / 34	6.92
Sannazzari et al., 1989	0.500	0.200	0.800	4 / 8	2.88
Dragovic et al., 1989	0.567	0.388	0.729	17 / 30	6.74
Wahl et al, 2008	0.667	0.500	0.800	24 / 36	7.02
Vernon et al, 1996 (ESHO)	0.778	0.586	0.897	21 / 27	5.23
Li et al, 1990	0.800	0.572	0.923	16 / 20	4.08
Overall (Random effect model)	0.643	0.581	0.702	519 / 779	

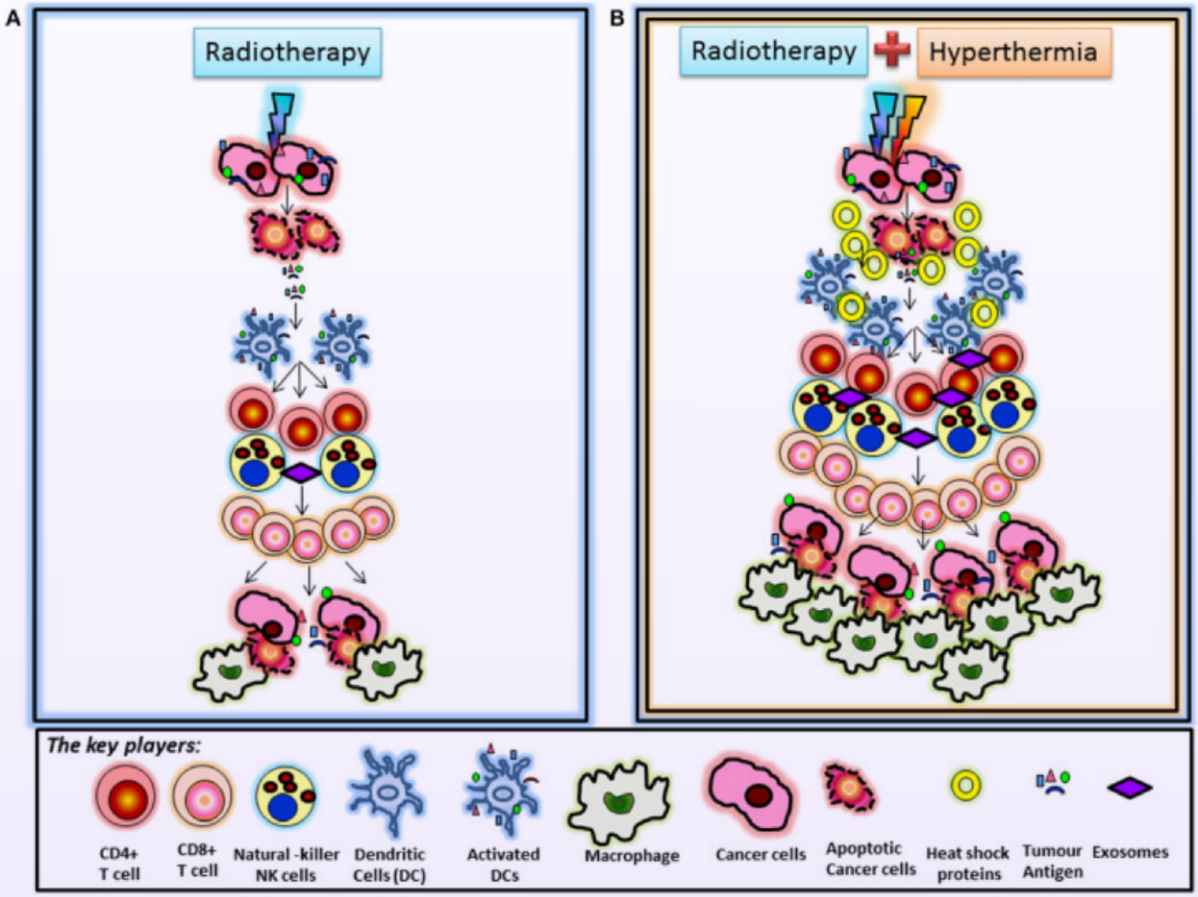
(Test for Heterogeneity: I^2= 55.8, p < 0.003)

Risk Difference: RT + HT vs RT



Site	Study name	CR / Total RT+ HT	CR / Total RT	Risk difference	Lower limit	Upper limit	Z-Value	p-Value
Breast (Recurrent)	Wahl et al, 2008	24 / 36	7 / 18	0.278	0.005	0.551	1.996	0.046
Breast (Recurrent)	Vernon et al, 1996 (DHG)	14 / 19	14 / 19	0.000	-0.280	0.280	0.000	1.000
Breast (Recurrent)	Vernon et al, 1996 (MRC)	51 / 90	17 / 59	0.279	0.124	0.433	3.536	0.000
Breast (Recurrent)	Vernon et al, 1996 (ESHO)	21 / 27	11 / 29	0.398	0.162	0.635	3.307	0.001
Breast (Recurrent)	Vernon et al, 1996 (PMH)	5 / 17	5 / 16	-0.018	-0.332	0.295	-0.115	0.909
Breast (Recurrent)	Perez et al, 1991	14 / 42	12 / 39	0.026	-0.178	0.229	0.247	0.805
Breast (Recurrent)	Li et al.1990	22 / 30	8 / 22	0.370	0.114	0.626	2.832	0.005
Breast (Recurrent)	Perez et al, 1986	35 / 48	47 / 116	0.324	0.170	0.478	4.117	0.000
All studies Breast (Recurrent)		186 / 309	121 / 318	0.223	0.113	0.334	3.963	0.000
Cervix (IIB-IVA)	Harima et al, 2009	16 / 20	10 / 20	0.300	0.019	0.581	2.095	0.036
Cervix (IIB-IVA)	Franckena et al, 2008	48 / 58	32 / 56	0.256	0.094	0.418	3.099	0.002
Cervix (IIB-IVA)	Chen et al.1997	18 / 30	14 / 30	0.133	-0.117	0.384	1.044	0.296
Cervix (IIB-IVA)	Datta et al, 1987	20 / 27	15 / 26	0.164	-0.088	0.416	1.275	0.202
All studies Cervix (IIB-IVA)		102 / 135	71 / 132	0.221	0.111	0.332	3.944	0.000
Head & Neck (II/IV)	Wien et al, 2014	34 / 49	23 / 49	0.224	0.034	0.415	2.313	0.021
Head & Neck (II/IV)	Huligol et al, 2010	22 / 28	11 / 26	0.363	0.119	0.606	2.922	0.003
Head & Neck (II/IV)	Valdagni et al, 1994	15 / 18	9 / 22	0.424	0.156	0.692	3.102	0.002
Head & Neck (II/IV)	Perez et a, 1991	18 / 53	21 / 60	-0.010	-0.186	0.165	-0.116	0.908
Head & Neck (II/IV)	Datta et al, 1990	18 / 33	10 / 32	0.233	-0.001	0.467	1.953	0.051
Head & Neck (II/IV)	Arcangeli et al 1987	30 / 38	18 / 43	0.371	0.175	0.567	3.702	0.000
All studies Head & Neck (III / IV)		137 / 219	92 / 232	0.255	0.117	0.392	3.636	0.000
Overall all studies		425 / 663	284 / 682	0.230	0.162	0.298	6.657	0.000

Test for heterogeneity: I^2 = 39.8; p = 0.05
Subgroup analysis: Q = 0.16; df = 2; p: ns



Conclusions

Thermoradiation therapy enhances the likelihood of CR rates in LRBCs over RT alone by 22% with minimal acute and late morbidities. For even those previously irradiated, reirradiation with HT provides locoregional control in two-thirds of the patients. Thermoradiation therapy could therefore be considered as an effective and safe palliative treatment option for LRBCs.

Niloy R. Datta, Emsad Puric, Dirk Klingbiel, Silvia Gomez, Stephan Bodis. **Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis.** International Journal of Radiation Oncology. 2016. Volume 94, Issue 5.

Clinical Study of Modulated Electrohyperthermia for Advanced Metastatic Breast Cancer

mEHT was examined in 10 patients with advanced metastatic breast cancer and recurrent disease, who were considered incurable by standard therapy protocols. Of the 10 patients, partial response was achieved in 3, disease stability in 3, and progressive disease in 4; however, their quality of life was improved based on their subjective reports.

No adverse effects were observed in any of the 10 patients. The present study demonstrated the feasibility of mEHT as a possible therapy for advanced breast cancer cases when standard therapies fail. Moreover, mEHT had no side effects and may be combined with various treatments for long-term therapy.

Nagata T, Kanamori M, Sekine S, Arai M, Moriyama M and Fujii T: **Clinical study of modulated electrohyperthermia for advanced metastatic breast cancer.** Mol Clin Oncol 14: 103, 2021

Reirradiation + Hyperthermia for Recurrent Breast Cancer en Cuirasse

Background and Purpose

Patients with irresectable locoregional recurrent breast cancer en cuirasse (BCEC) do not have effective curative treatment options. Hyperthermia, the elevation of tumor temperature to 40–45 °C, is a well-established radio- and chemotherapy sensitizer. A total of 196 patients were treated with reirradiation and hyperthermia (reRT+HT) at two Dutch institutes from 1982–2005. The palliative effect was evaluated in terms of clinical outcome and toxicity.

Patients and Methods

All patients received previous irradiation to a median dose of 50 Gy. In all, 75% of patients received 1–6 treatment modalities for previous tumor recurrences. ReRT consisted of 8x4 Gy given twice a week or 12x3 Gy given four times a week. Superficial hyperthermia was added once or twice a week. Tumor area comprised ≥ of the ipsilateral chest wall.

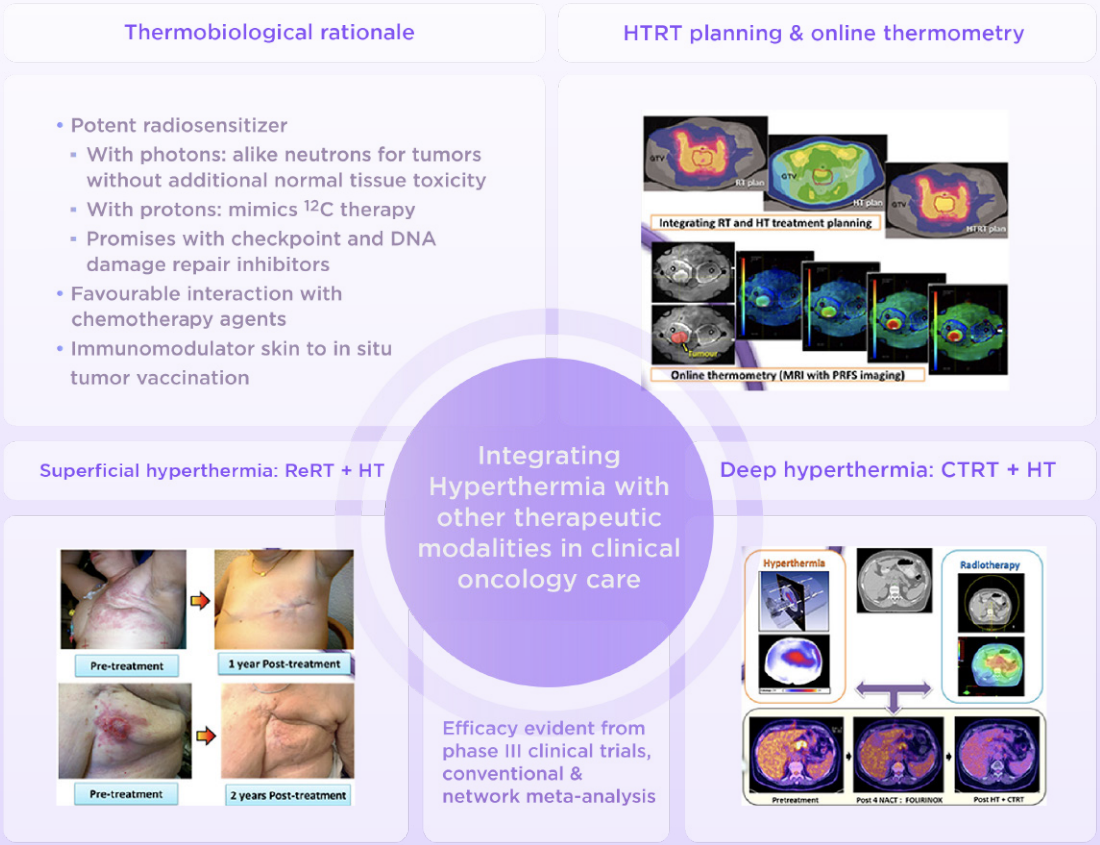
Results

Overall clinical response rate was 72% (complete response [CR] 30%, partial response [PR] 42%, stable disease [SD] 22%, progressive disease [PD] 6%). The local progression-free rate at 1 year was 24%. Median survival was 6.9 months. Forty-three percent of our patients with CR, PR, SD after treatment remained infield progression-free until death or last follow-up. Acute ≥grade 3 toxicity occurred in 33% of patients, while late ≥grade 3 toxicity was recorded in 14% of patients. Tumor ulceration prior to treatment had a negative impact on both clinical outcome and toxicity.

Conclusions

ReRT+HT provides sustainable palliative tumor control, despite refractory, extensive tumor growth. Compared to currently available systemic treatment options, reRT+HT is more effective with less toxicity.

Oldenborg, S., Rasch, C.R.N., van Os, R. et al. **Reirradiation + hyperthermia for recurrent breast cancer en cuirasse.** Strahlenther Onkol 194, 206–214 (2018). https://doi.org/10.1007/s00066-017-1241-7



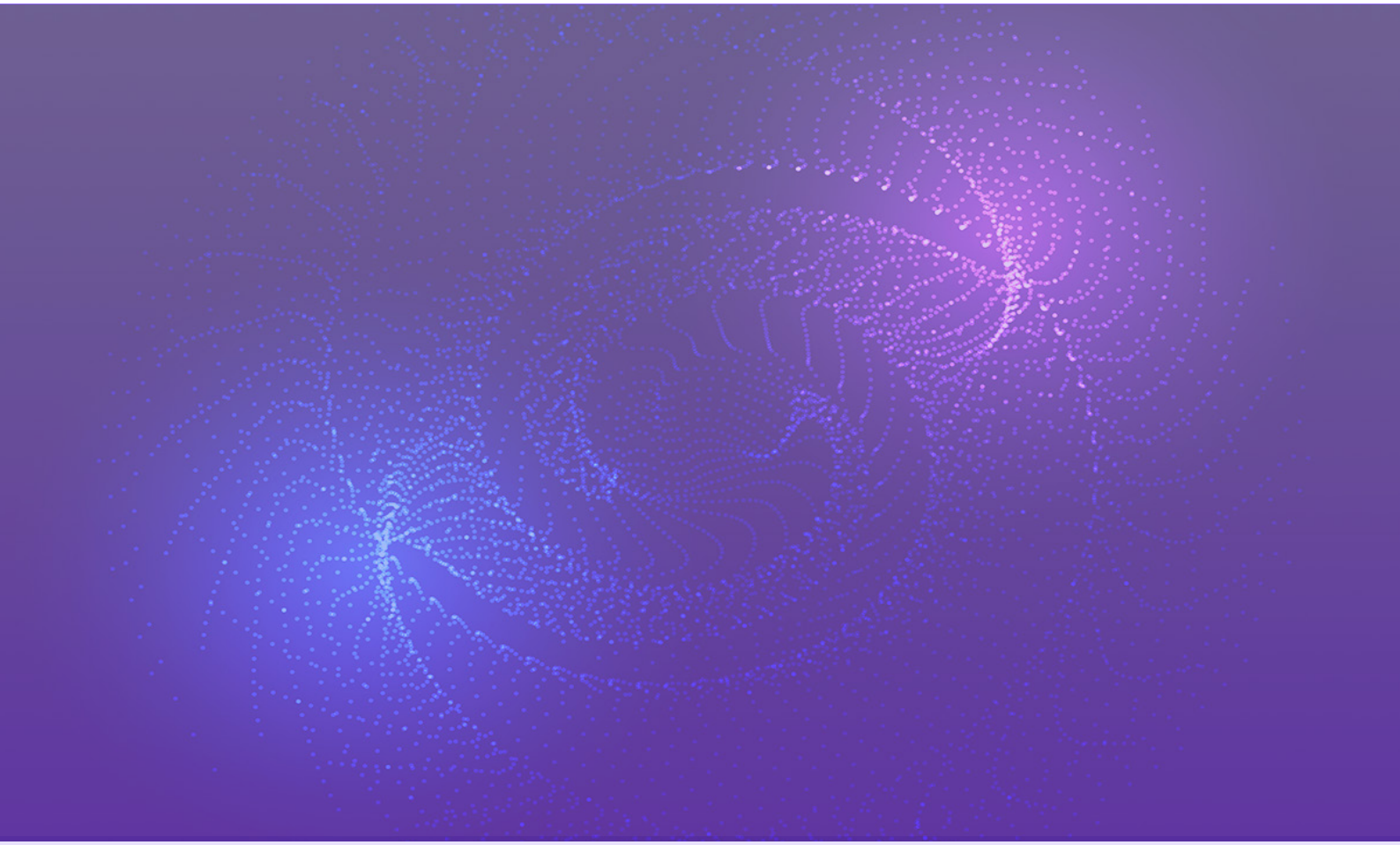
Integration of hyperthermia in clinical practice along with other treatment modalities is supported by its thermobiological rationale and clinical evidences reported from various phase III randomized trials and meta-analysis of various tumors sites. ReRT, reirradiation; HT, hyperthermia; RT, radiotherapy; HTRT, thermoradiotherapy; CTRT, chemoradiotherapy; NACT, neoadjuvant chemotherapy; PRFS, proton resonance frequency shift. The images of RT, HT, and HTRT plans have been modified and reproduced with permission from van Leeuwen et al.

Datta NR, Kok HP, Crezee H, Gaipl US, Bodis S. **Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses.** Front Oncol. 2020 Jun 12;10:819. doi: 10.3389/fonc.2020.00819. PMID: 32596144; PMCID: PMC7303270.

Chemotherapy + Radiation & Hyperthermia for Locally Advanced Breast Cancer

As preoperative chemotherapy has been shown to improve outcomes in the setting of LABC, it seems intuitive to intensify preoperative therapy so as to further improve these outcomes. The addition of HT to preoperative chemoradiotherapy has been shown to increase cCR and pCR rates more so than chemotherapy alone in small series and is similar to some reports of concurrent chemoradiation. Cooperative randomised trials need to be performed that look at HT + chemotherapy versus HT + chemoradiotherapy or chemoradiotherapy alone, in the neoadjuvant setting to see if HT adds an advantage.

Zagar TM, Oleson JR, Vujaskovic Z, Dewhirst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL. **Hyperthermia for locally advanced breast cancer.** Int J Hyperthermia. 2010;26(7):618-24. doi: 10.3109/02656736.2010.501051. PMID: 20849257; PMCID: PMC2949291.



Safety & Cost Effective Analysis

The Oncotherm EHY2000 device used for the proposed mEHT treatment for Sarcoma, and in combination with standard of care, is the same model and device used in many of the clinical trials published around CRT + mEHT combination.

Oncologic Hyperthermia has been included into the ESMO and NCCN guidelines for certain cancers.

In the South African setting, mEHT was proven successful in a Phase 3 clinical trial for an unrelated tumor type, Cervical Cancer, using the EHY2000 device in JHB. The number of patients who were disease free at 3 years was 32% more in the hyperthermia group than in the chemoradiation group alone, more than double the amount of disease-free patients after 3 years. Level 1 evidence. (C Mienaar, et al. 2022). Preliminary data suggests a >30% increase in 5 year survival when mEHT is combined with standard CRT for Cervical Ca.

A cost effectiveness analysis was performed using a Markov model, the results of which showed that CRT combined with mEHT dominated over CRT alone, thus was more effective and less costly that CRT alone. (C Mienaar, et al. 2022)

Patients reported an improved quality of life in the hyperthermia group, and with increased compliance to treatment verse the patients receiving only chemoradiation. Hyperthermia treatment revealed no increased toxicity whilst improving outcomes and enhancing the systemic anti-cancer immune response (abscopal effect). (C Mienaar, et al. 2022)

Please note that treatment options for this challenging condition are limited and adjunctive treatments proven to augment quality of life and overall survival should receive special consideration and inclusion into the management protocol for breast cancer.

We find no substantive reason why mEHT treatment should not be indicated in this clinical setting, and thus we are hopeful for medical aid assistance.

References

Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. **Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis.** International Journal of Radiation Oncolog, 2016. Vol 94, Issue 5.

Datta NR, Kok HP, Crezee H, Gaipl US, Bodis S. **Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses.** Front Oncol. 2020 Jun 12;10:819. doi: 10.3389/fonc.2020.00819. PMID: 32596144; PMCID: PMC7303270.

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Minnaar CA, Maposa I, Kotzen JA, Baeyens A. **Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients.** Cancers (Basel). 2022;14(656):1-20.

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Nagata T, Kanamori M, Sekine S, Arai M, Moriyama M and Fujii T: **Clinical study of modulated electrohyperthermia for advanced metastatic breast cancer.** Mol Clin Oncol 14: 103, 2021

Oldenborg, S., Rasch, C.R.N., van Os, R. et al. **Reirradiation + hyperthermia for recurrent breast cancer en cuirasse.** Strahlenther Onkol 194, 206–214 (2018). https://doi.org/10.1007/s00066-017-1241-7

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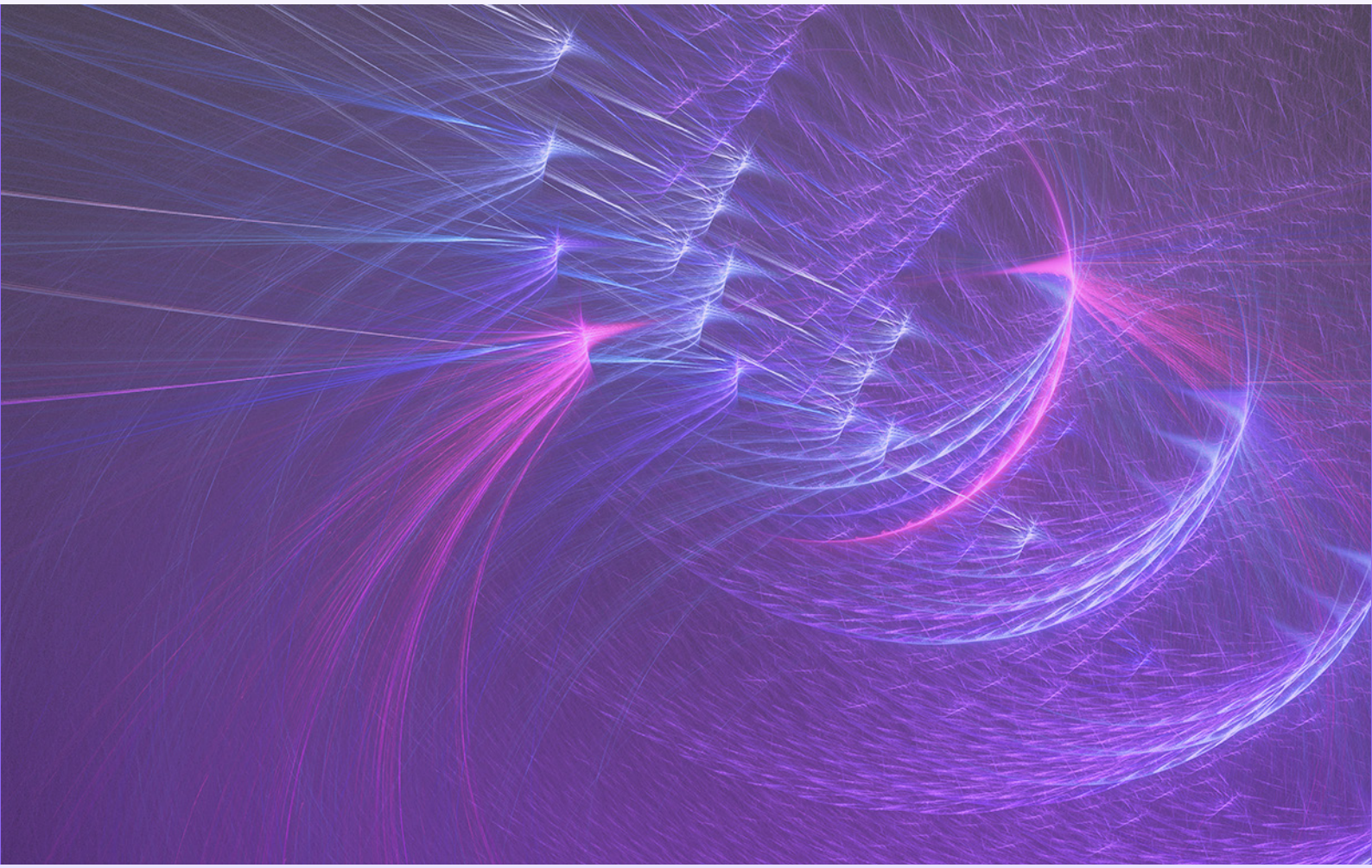
Zagar TM, Oleson JR, Vujaskovic Z, Dewhirst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL. **Hyperthermia for locally advanced breast cancer.** Int J Hyperthermia. 2010;26(7):618-24. doi: 10.3109/02656736.2010.501051. PMID: 20849257; PMCID: PMC2949291.



Medical Device Details

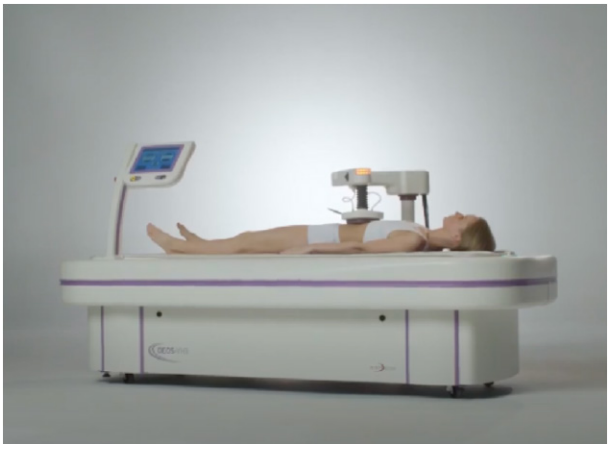
Oncotherm EHY2000 & EHY2030

The Oncotherm EHY2000 and most recent model EHY 2030 are both manufactured in Hungary with CE certification, registered with SAHPRA in South Africa as a medical device, and contracted into a rigorous maintenance plan with auto-calibration following each treatment session.

The EHY2000 has been operational in South Africa for over 8 years adjacent the Wits Donald Gordon Radiation Oncology Unit; and first trialled in a phase III clinical study at the Charlotte Maxeke Johannesburg Academic Hospital from 2014-2017 with excellent clinical results. Additionally the study reported on easy integration into the workflow, affordability and a favourable safety and tolerability profile. This included vulnerable and high risk population groups such as HIV-positive and obese patients.

Mechanism of Action

The method transfers energy using the principle of capacitive coupling radio waves of 13,56 MHz over through the region of tumor tissue with heterogenous targeting of malignant tissue and the surrounding tumor microenvironment. This results in improved oxygenation and radiosensitisation at the core of solid tumors, improved drug delivery and drug reaction rate / chemo-sensitization, destabilizing thermal stress on tumor lipid raft membranes leading to necrosis and apoptosis, immune recognition and documented abscopal effects; further modified immune response within the TME with the release of HSP and increased NK cell activity; and significantly impaired DNA repair mechanisms following chemoradiation.



Accepted Hyperthermia Protocols

- Oncotherm EHY2000 is a registered medical device with SAHPRA
- Patient lies supine on de-ionized waterbed with a locoregionally positioned applicator 20-30cm with energy output at 150W for 60-90min, modulated
- Applicator, size of probe and duration of treatment are dependent on site of Ca.

Simplified:

- One cycle is 4 weeks. The first 2 cycles, 8 weeks, requires 3 x 60-90min sessions per week, 48hrs apart.
- Hereafter 4 further cycles are considered as maintenance, 2 x 60-90min / week. A total of 6 cycles is generally recommended.
- In certain clinical settings, such as Glioblastoma, ongoing treatment > 6 cycles is recommended. In other settings, as with Cervical, only 2 initial cycles are recommended c/w CRT.

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