HYPERTHERMIA
CLINICS INTERNATIONAL

Hyperthermia Treatment for Cervical Cancer

LEVEL 1A EVIDENCE

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Summary of Clinical Evidence

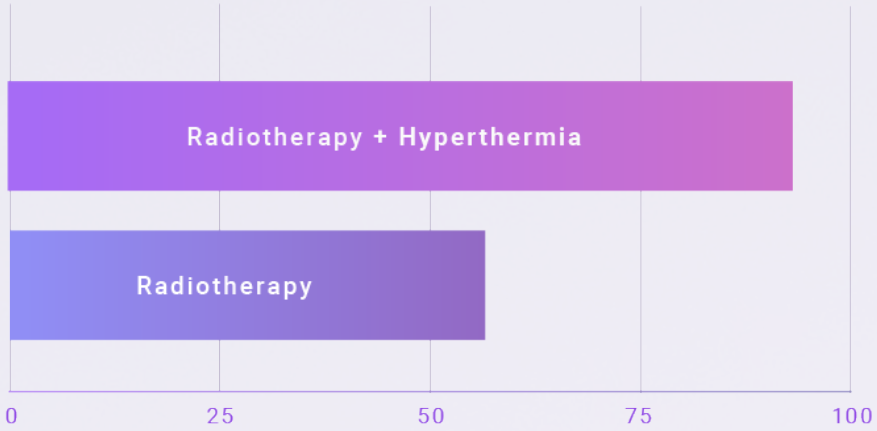
Dutch Deep Hyperthermia Trial (DDHT)

The Dutch Deep Hyperthermia Trial compared radiotherapy plus hyperthermia Vs radiotherapy alone in patients with advanced bladder, cervical, and rectal tumours. The results demonstrate that the addition of Hyperthermia (HT) to Radiotherapy (RT) significantly improves local pelvic control and overall survival rates.

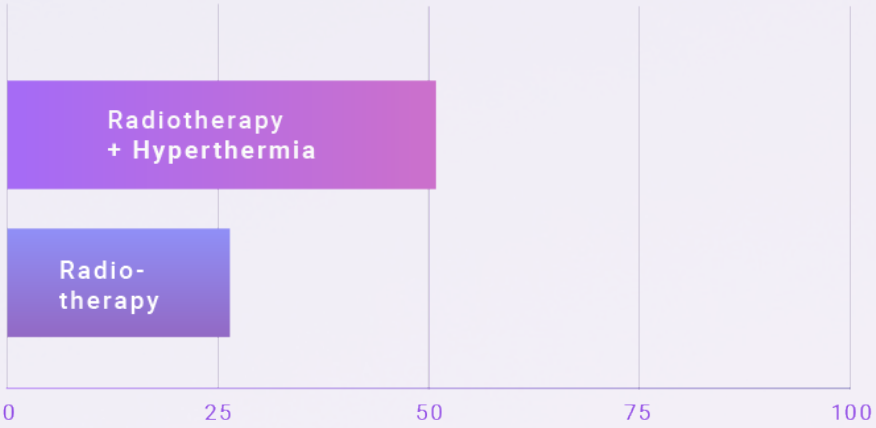
Results from the cervical cancer cohort of 166 patients prospectively randomised into RT (68Gy) + HT vs RT alone; revealed local control rates of 83% (RT+HT) vs 57% (RT), (p=0.003); 3 year Overall Survival was: 51% (RT+HT) vs 27% (RT), (p=0.009);8 and 12 year Overall Survival was 37% (RT+HT) Vs 20% (RT) vs, (p=0.03).3 The combined treatment of Hyperthermia + Radiotherapy has subsequently been recommended in the Netherlands for all patients who are unfit to receive chemotherapy.

This trial also demonstrated the cost effectiveness of HT; the cost per year of life gained was calculated to be Euros 3956 ($5277 USD).

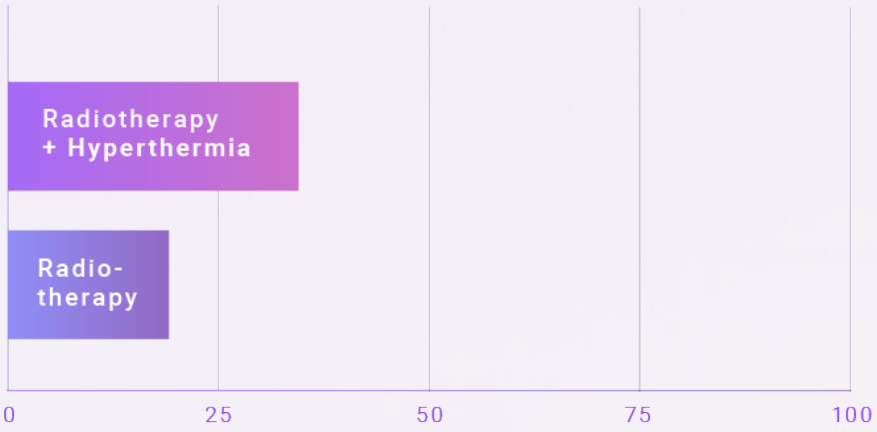
Control Rates %



3 Year Survival Rates %

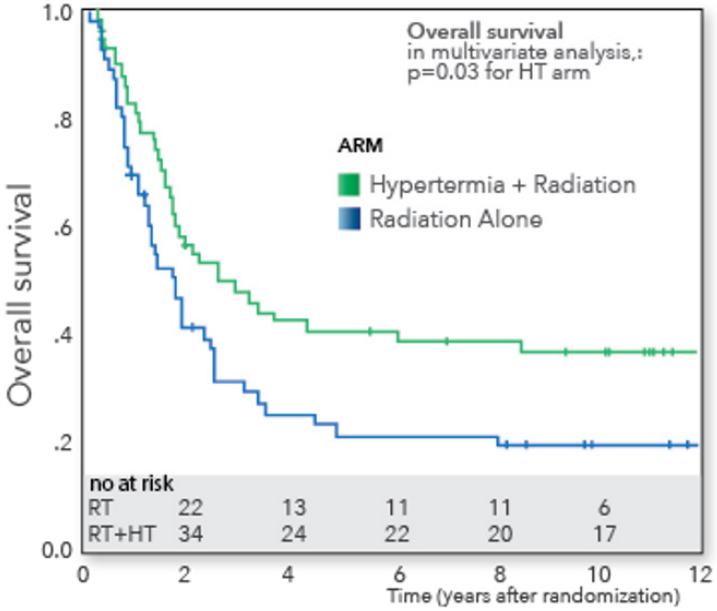


12 Year Survival Rates %

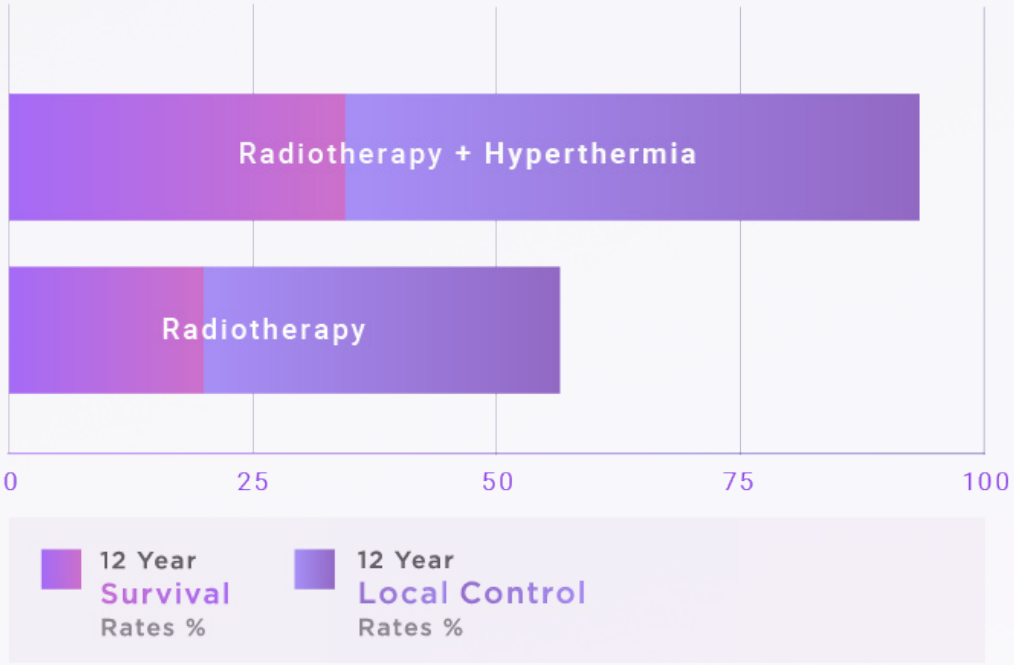


Long-Term Improvement in Treatment Outcome After Radiotherapy and Hyperthermia in Locoregionally Advanced Cervix Cancer: An Update of the Dutch Deep Hyperthermia Trial

Franckena et al confirmed these results in an analyses of 378 locally advanced cervical cancer treated with hyperthermia combined with radiotherapy.4 Thermotherapy technology has improved vastly since the Dutch trial and newer machines should improve outcome even more.



12 Year Follow-up Cervical Cancer FIGO IIB-IVA

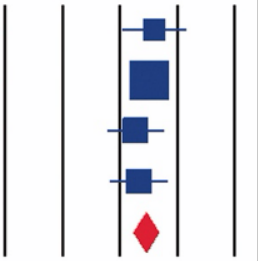


Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses

In a meta-analysis by Datta et al (2016), Six randomised trials with hyperthermia + RT (n=215) vs. RT alone (n=212) were analysed. The risk difference for achieving complete response and local control was greater by 22% (p<.001) and 23% (p<.001), respectively, with the addition of hyperthermia. The authors concluded that the analysis provides level I evidence of a therapeutic benefit of hyperthermia + RT over RT alone.

(a) **Risk difference: Complete response (HTRT vs. RT)**

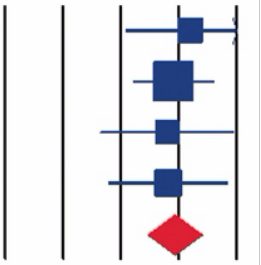
Study name	Risk difference	Lower limit	Upper limit	Z Value	p Value	CR / Total HTRT	CR / Total RT alone	Relative weight
Harima et al.	0.300	0.019	0.581	2.095	0.036	16 / 20	10 / 20	15.38
Franckena et al.	0.256	0.094	0.418	3.099	0.002	48 / 58	32 / 56	46.15
Chen et al.	0.133	-0.117	0.384	1.044	0.296	18 / 30	14 / 30	19.35
Datta et al	0.164	-0.088	0.416	1.275	0.202	20 / 27	15 / 26	19.11
Overall effect	0.221	0.111	0.332	3.944	0.000	102 / 135	71 / 132	



Heterogeneity: $Q = 3.944$, $df = 3$ ($p = 0.764$), $I^2 = 0\%$, $\tau^2 = 0.000$

(b) **Risk difference: Long-term loco-regional control (HTRT vs. RT)**

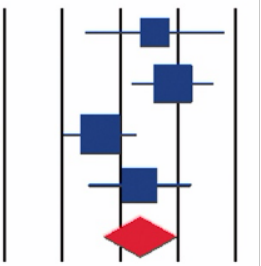
Study name	Risk difference	Lower limit	Upper limit	Z Value	p Value	CR / Total HTRT	CR / Total RT alone	Relative weight
Harima et al.	0.300	0.019	0.581	2.095	0.036	16 / 20	10 / 20	18.00
Franckena et al.	0.228	0.049	0.407	2.498	0.012	36 / 58	22 / 56	44.37
Sharma et al.	0.200	-0.090	0.490	1.353	0.176	14 / 20	11 / 22	16.88
Datta et al	0.205	-0.056	0.467	1.538	0.124	18 / 27	12 / 26	20.75
Overall effect	0.231	0.112	0.350	3.809	0.000	84 / 125	55 / 124	



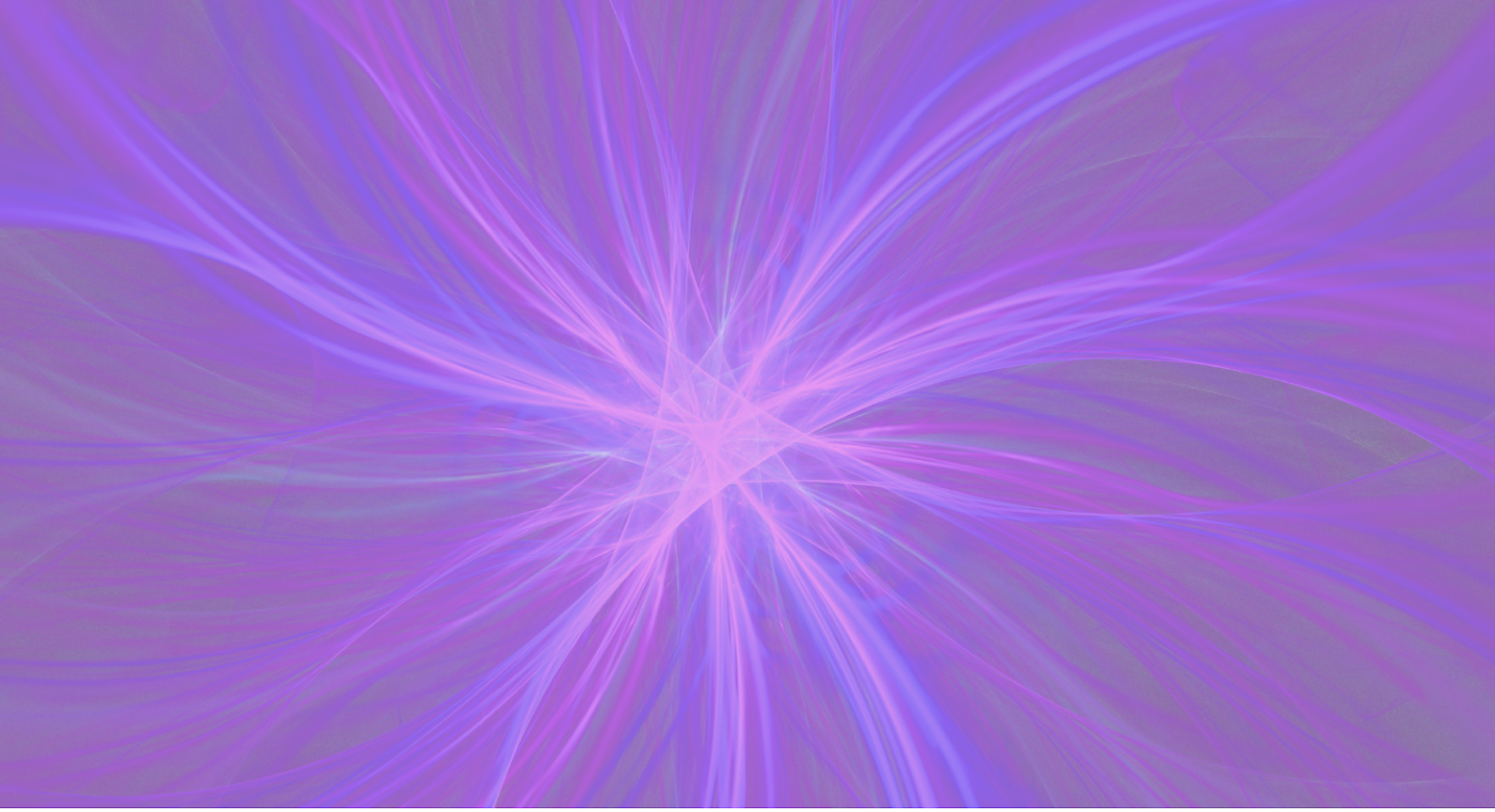
Heterogeneity: $Q = 0.315$, $df = 3$ ($p = 0.957$), $I^2 = 0\%$, $\tau^2 = 0.000$

(c) **Risk difference : Patients alive (HTRT vs. RT)**

Study name	Risk difference	Lower limit	Upper limit	Z Value	p Value	Alive / Total HTRT	Alive / Total RT alone	Relative weight
Harima et al.	0.150	-0.153	0.453	0.971	0.332	13 / 20	10 / 20	17.00
Franckena et al.	0.228	0.049	0.407	2.498	0.012	36 / 58	22 / 56	28.63
Sharma et al.	-0.087	-0.248	0.074	-1.059	0.289	20 / 23	22 / 23	30.76
Datta et al	0.084	-0.141	0.309	0.733	0.464	22 / 27	19 / 26	23.61
Overall effect	0.084	-0.074	0.242	1.039	0.299	91 / 128	73 / 125	



Heterogeneity: $Q = 6.933$, $df = 3$ ($p = 0.074$), $I^2 = 56.7\%$, $\tau^2 = 0.014$



Network meta-analysis for HTC TRT, HTRT, CTRT and RT groups

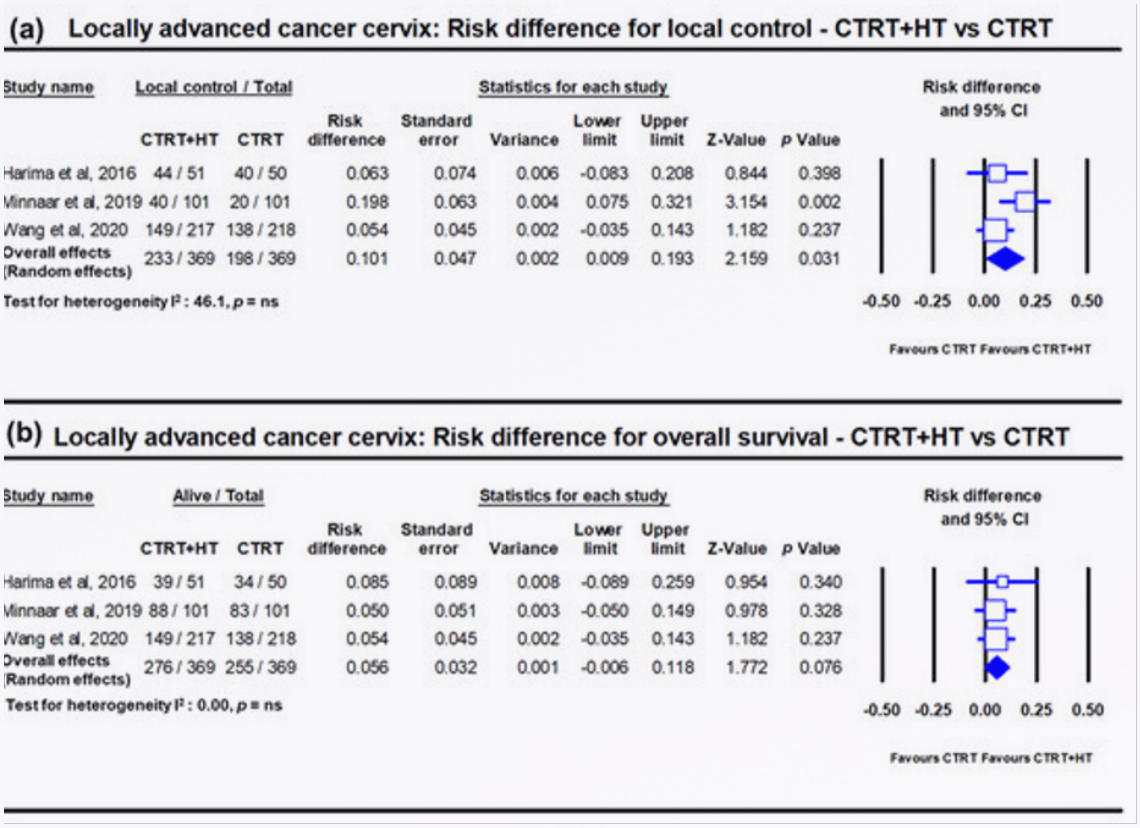
“NMA was performed for two end points (a) CR and (b) patients alive at the end of the study period. For CR, 13 studies with a total of 1000 patients resulted in six possible direct comparisons”

“Based on the corresponding ORs, the league table and forest plots of these groups reveal a significant advantage of HTCTRT over RT (OR: 4.52, 95% Cr.I: 1.93–11.78) and over CTRT (OR: 2.91, 95% Cr.I: 1.97–4.31) for achieving CR. HTRT also demonstrated a significantly higher probability of a CR over RT alone (OR: 2.85, 95% Cr.I: 1.63–5.08).”

Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial

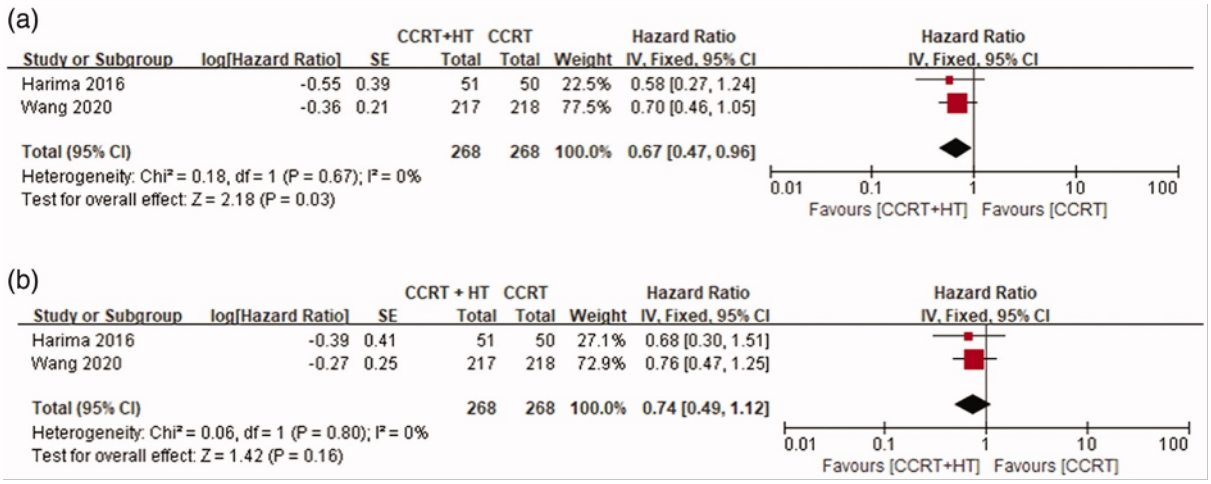
Lutgens et al report on their trial comparing cisplatin versus hyperthermia as a radiosensitiser for LACC patients. The trial was closed prematurely (87 of 376 planned patients enrolled: n=43 in the RT + Cisplatin group; n=44 in the RT + HT group). Median follow-up time was 7.1 years.

Pelvic Recurrence Free Survival: (94; CI 0.36–2.44) and Overall Survival (1.04; CI 0.48–2.23) at 5 years were comparable between both treatment arms, as was grade 3 radiation related late toxicity. Conclusion: Data suggest comparable outcome for RT+ Cisplatin and RT+HT.



Chemoradiotherapy with hyperthermia versus chemoradiotherapy alone in locally advanced cervical cancer: a systematic review and meta-analysis

"Two articles out of 2860 were finally selected for analysis. A total of 536 patients were evaluated (CCRT with HT group: 268, CCRT group: 268). FIGO stages I–II and III–IV were found in 295 (55.0%) and 241 patients (45.0%), respectively. The CCRT with HT group had significantly better five-year OS than the CCRT group (HR 0.67, 95% confidence interval [CI] 0.47–0.96, p = 0.03). LRFS of patients was superior in the CCRT with HT group than in the CCRT group, but without significance (HR 0.74, 95% CI 0.49–1.12; p = 0.16). Moreover, there was no difference between the two groups regarding acute and chronic toxicity."



"HT is known to have a synergic effect with RT and CT. RT causes damage to the DNA of the cancer cells leading to cellular death; in particular, it causes DNA double strand breaks that are extremely lethal. There are repair systems, such as homologous recombination and non-homologous end joining, for these breaks, but heat interferes with these systems.

Combining HT with RT increases unrepaired DNA breaks by inhibiting the repair system, that causes an increase in cell cycle arrest and apoptosis through an increase in transcriptional activation of p53. HT also enhances the cytotoxic effects of cisplatin by increasing absorption that leads to increased intracellular accumulation.

Hyperthermia + Radiotherapy + Chemotherapy

Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients

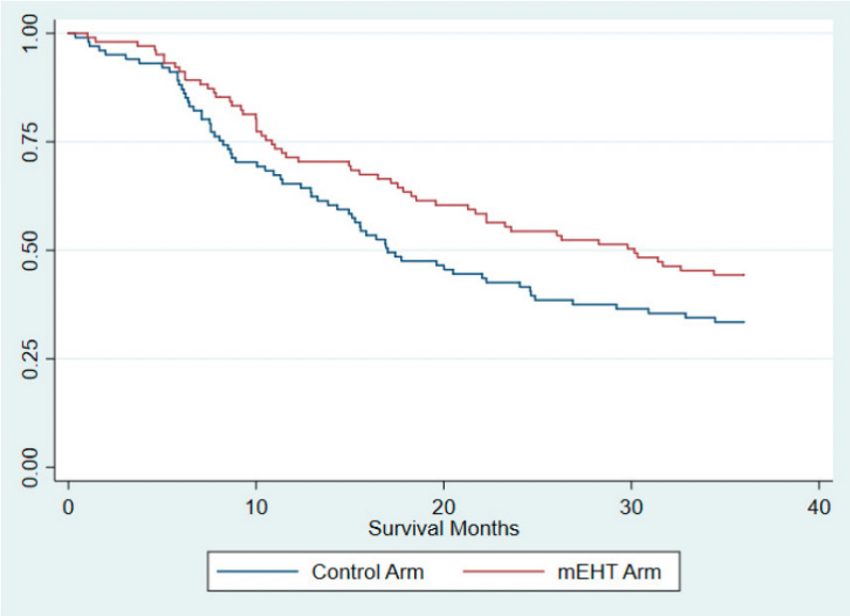
A multicentre study, involving medical centres in Netherlands, Norway and the United States of America, confirmed that the addition of HT to chemoradiotherapy does not increase the treatment-related toxicity. Previously untreated cervical cancer patients were treated with external beam RT, brachytherapy, four doses of cisplatin (40mg/m2) and weekly hyperthermia sessions. After 538 days overall survival was 84%.

In a phase III randomised study at the Charlotte Maxeke Johannesburg Academic hospital, HIV-positive and –negative locally advanced cervical cancer patients were randomised to receive RT + cisplatin or RT + cisplatin + electro-hyperthermia.

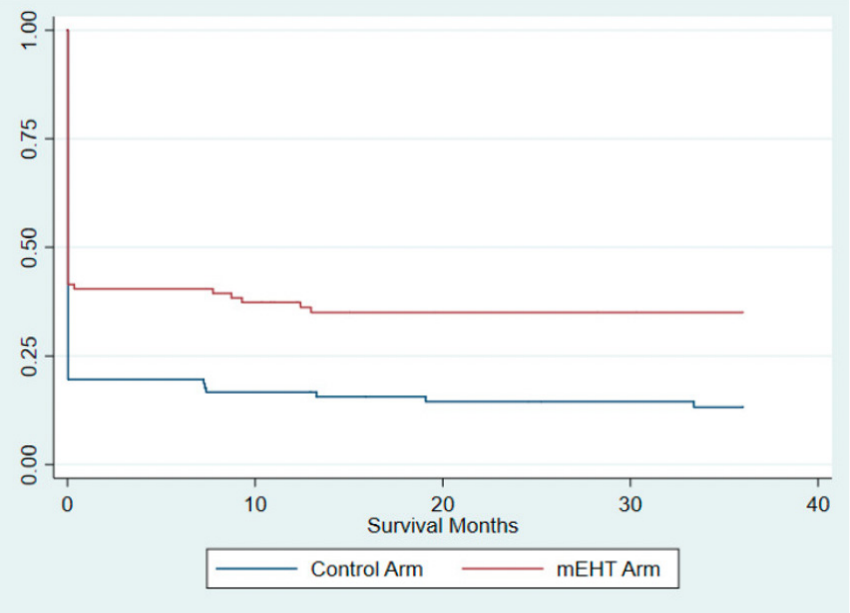
Six month local disease-free survival was higher in the hyperthermia Group (n = 39 [38.6%]), than in the Control Group (n = 20[19.8%]); p = 0.003), and local disease control was also higher in the hyperthermia Group (n = 40[45.5%]) than the Control Group (n = 20[24.1%]); (p = 0.003). Preliminary survival results showed two year disease free survival was significantly higher in the hyperthermia group (52% [33 out of 64]) than in the Control Group (34% [31 out of 91]) (HR: 1.60; p=0.033).

In the participants who have reached three years post-treatment, three year disease free survival is also significantly higher in the mEHT group: 58% [18 out of 31] versus 35% [16 out of 46] (HR: 1.97; p=0.042).

Kaplan–Meier survival curves at three years

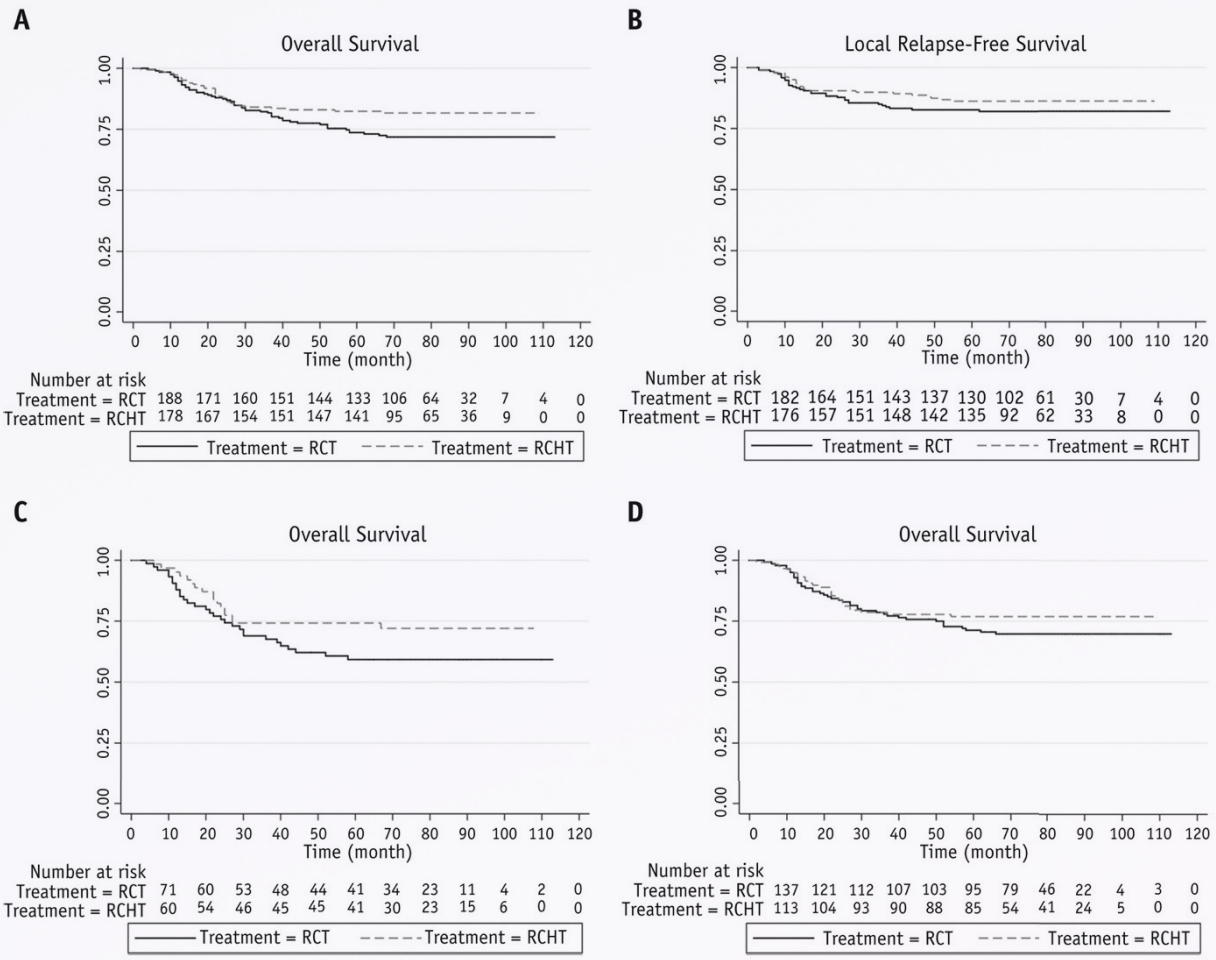


(a) three year overall survival



(b) three year disease free survival.

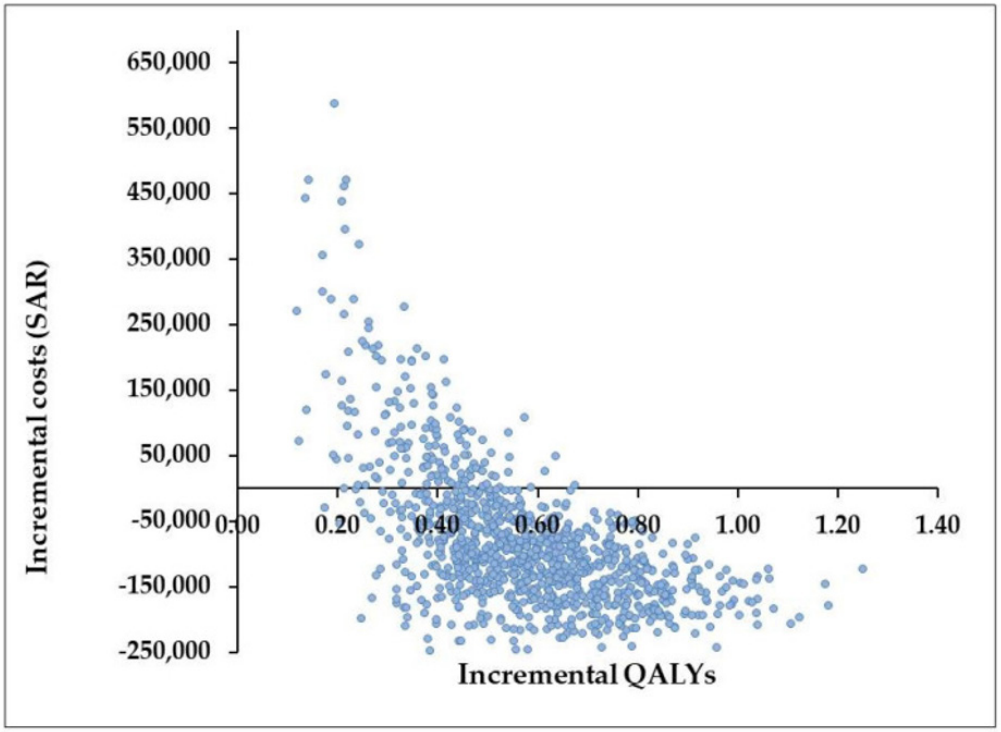
The sharp drop off in DFS rates seen early on in 3b is again a result of the high rate of residual disease at six months post treatment.



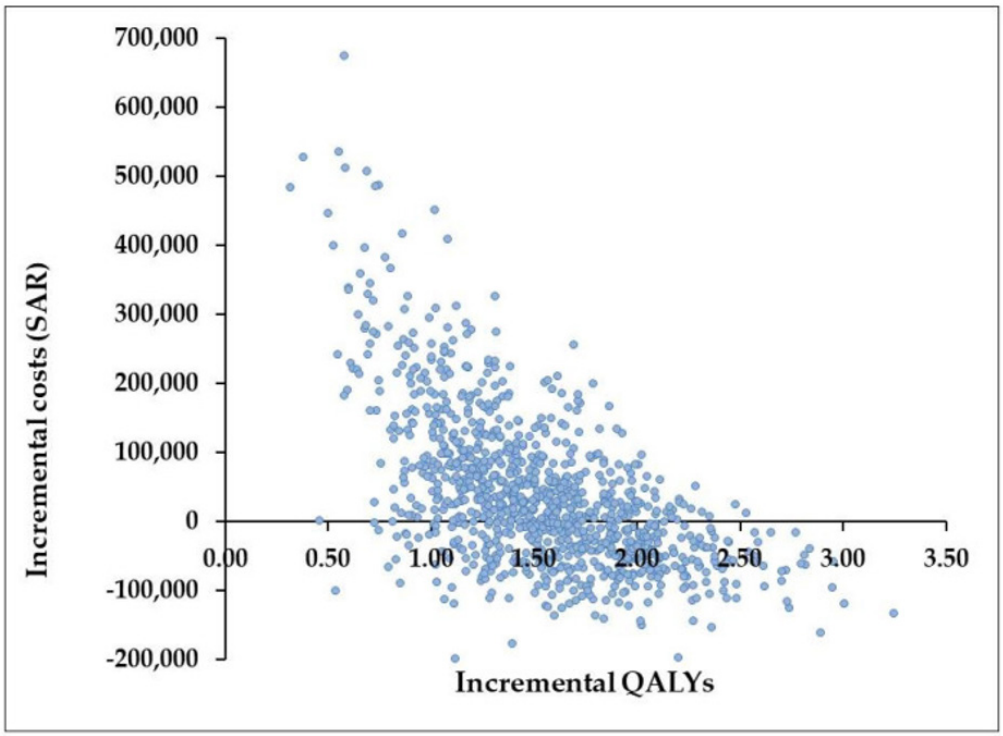
To analyse the addition of electro-hyperthermia to RT + cisplatin for locally advanced cervical cancer, a de novo economic analysis was done with a time horizon of three years and from the perspective of a third party payer using South African costs. A base case analysis showed that the addition of hyperthermia to radiation therapy dominated treatment by radiation therapy alone.

In other words, the addition of hyperthermia was less costly and more effective. This result is driven by the difference in progression free survival, due to the high costs of progressive disease. This model did not assign costs to dying which gives the least effective treatment a cost benefit. The clinical evidence used in this analysis makes a compelling case for this type of intervention. The full analysis, conducted by Dr Deon Oliver, is attached for review. The economic analysis shows that from a cost point of view this intervention should pay for itself or even save a small amount of money. Very few "new" interventions in cancer therapy can make the same claim in an analysis with a time horizon of only three years.

Incremental cost-effectiveness ratio (ICER) plane



(a) government healthcare model;



(b) private healthcare model.

The Cost Effectiveness Analysis was done for both a Government-funded and a privately-funded healthcare model, for the same duration (three years), assuming the same health effects, with the only difference being the input costs. In the Government-funded healthcare model, the QALYs range from 0–1.4, with incremental costs mainly seen in the 4th Quadrant, showing improved clinical benefits and lower costs per QALY with the addition of mEHT. In the Privately funded healthcare model, the QALYs range from 0–3.5 with incremental costs falling in the lower portion of the 1st quadrant and the upper portion of the 4th quadrant, implying a clinical benefit with a high probability of cost saving with the addition of mEHT to chemoradiotherapy.

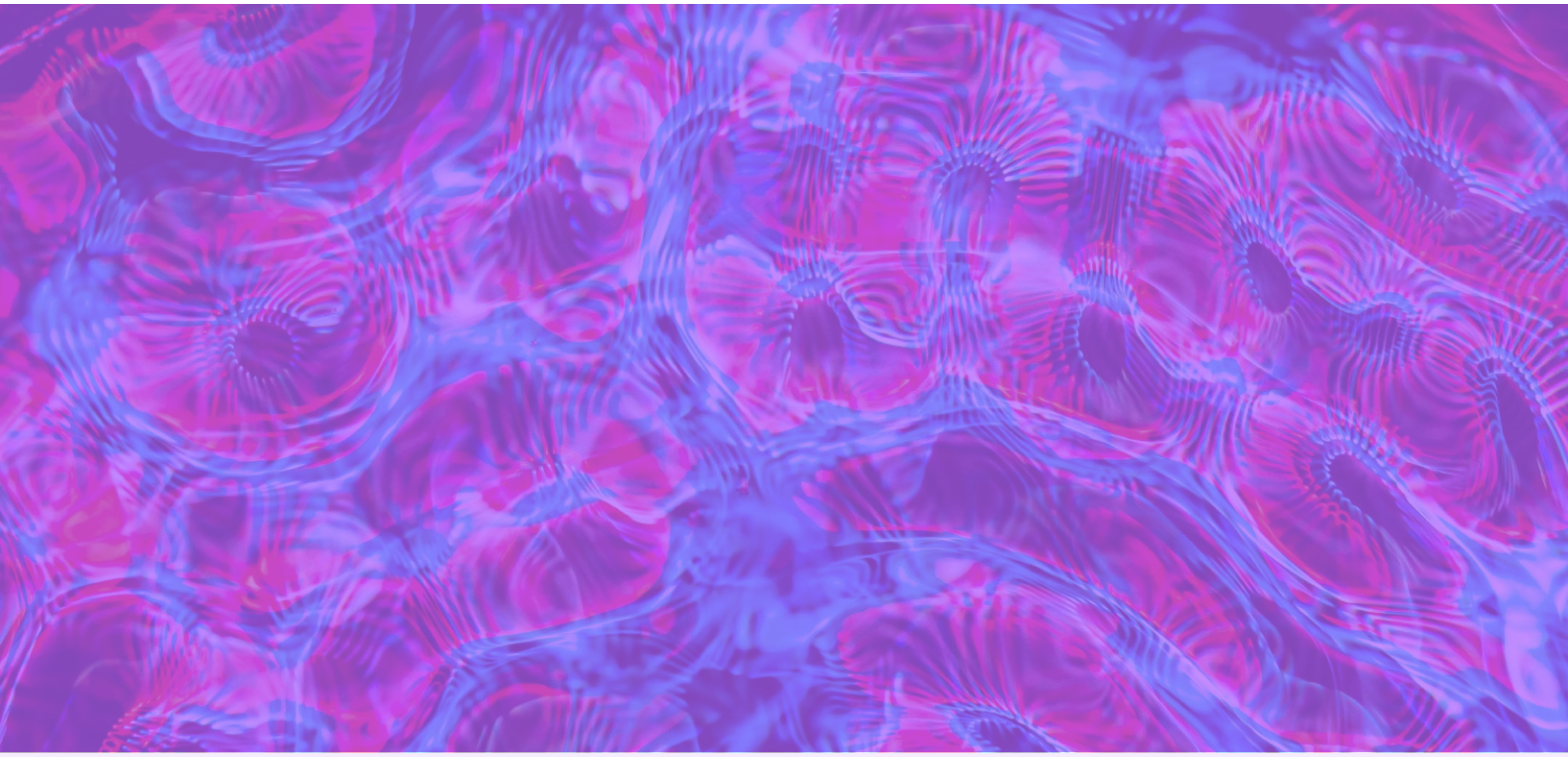
Datta et al showed that for the direct comparison of RT + HT + chemotherapy and RT + chemotherapy, only one study including 68 patients was available. It showed a significantly better complete response for the trimodal treatment arm (RT+ chemotherapy: 46.7%, RT + HT + chemotherapy: 83.3% (risk difference 36.7%, p = 0.0001).The pairwise comparison of various groups showed that HT + RT + chemotherapy was the best option for both complete response and patient survival.

Weekly systemic cisplatin plus locoregional hyperthermia: An effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area

In a study by Franckena et al patients were treated with weekly cisplatin combined with hyperthermia. The excellent results of their study,6 combined with similar results from earlier studies,8 lead to the recommendation by the authors of the inclusion of hyperthermia and cisplatin as standard treatment for patients with residual disease after irradiation to the pelvis.

Abstract

"Purpose: Patients with recurrent cervical carcinoma within a previously irradiated area respond poorly to chemotherapy. We have treated these patients with simultaneous cisplatin and hyperthermia (CDDP+HT) and investigated response, toxicity, palliative effect and survival. Materials and methods: Between 1992 and 2005 47 patients received CDDP+HT. Response was evaluated by gynaecologic examination and CT-scan. The Common Toxicity Criteria (CTC) were used for evaluation of toxicity and palliative effect. The Kaplan-Meier method was used to estimate survival, and Cox regression analysis to evaluate the influence of prognostic factors. Results: The objective response rate was 55%, palliation was achieved in 74% and operability in 19% of patients. Two patients are currently disease free at 9 years and 18 months following treatment and 2 remained disease free until death by other causes. The median survival was 8 months and was influenced by duration of disease free interval and tumour diameter. Grade 3–4 haematological toxicity was observed in 36% of patients and renal toxicity was maximum grade 2. Conclusion: CDDP + HT results in a high response rate and acceptable toxicity in patients with recurrent cervical cancer."



Hyperthermia: A Potential Game-Changer in the Management of Cancers in Low-Middle-Income Group Countries

Locally Advanced Cervical Cancer: Scope for Improvement with Hyperthermia

"Of all the cervical cancer reported globally in 2020, LMICs account for 88.1% of all cases and 91.4% of all mortalities. Thus, the %mortality/incidence in LMICs is estimated at 58.7%. This could be attributed to presentation in most patients in LMICs as locally advanced cervical cancer (LACC). Following the National Cancer Institute guidelines in 1992, chemoradiotherapy (CTRT) using cisplatin as single or in combination is the most common therapeutic intervention in LACC. In a meta-analysis from 14 randomized clinical trials which included 2445 patients, CTRT has been shown to improve the CR (+10.2%, p = 0.027), locoregional control (+8.4%, p < 0.001) and overall survival (+7.5%, p < 0.001) over RT alone . Thus, even though CTRT has shown to improve outcomes over RT alone, it appears that there could still be scope to explore for a possible improvement."

Clinical Outcomes with Hyperthermia in Locally Advanced Cervical Cancer

"HT has also been used along with RT in several randomized clinical trials in LACC. The outcomes as evident on meta-analysis between HTRT vs. RT, shows a distinct improvement with HTRT in terms of CR at the end of treatment and loco-regional control of 22% (p < 0.001) and 23% (p < 0.001), respectively. A non-significant survival advantage of 8.4% with HTRT was also noted without any significant escalation of acute or late morbidities with HT added to RT. Even when HT was used with CTRT, the risk difference from three randomized clinical trials (total patients = 738) for local control and overall survival showed an advantage with HTCTRT over CTRT by 10.1% (p = 0.03) and 5.6% (p: ns), respectively."

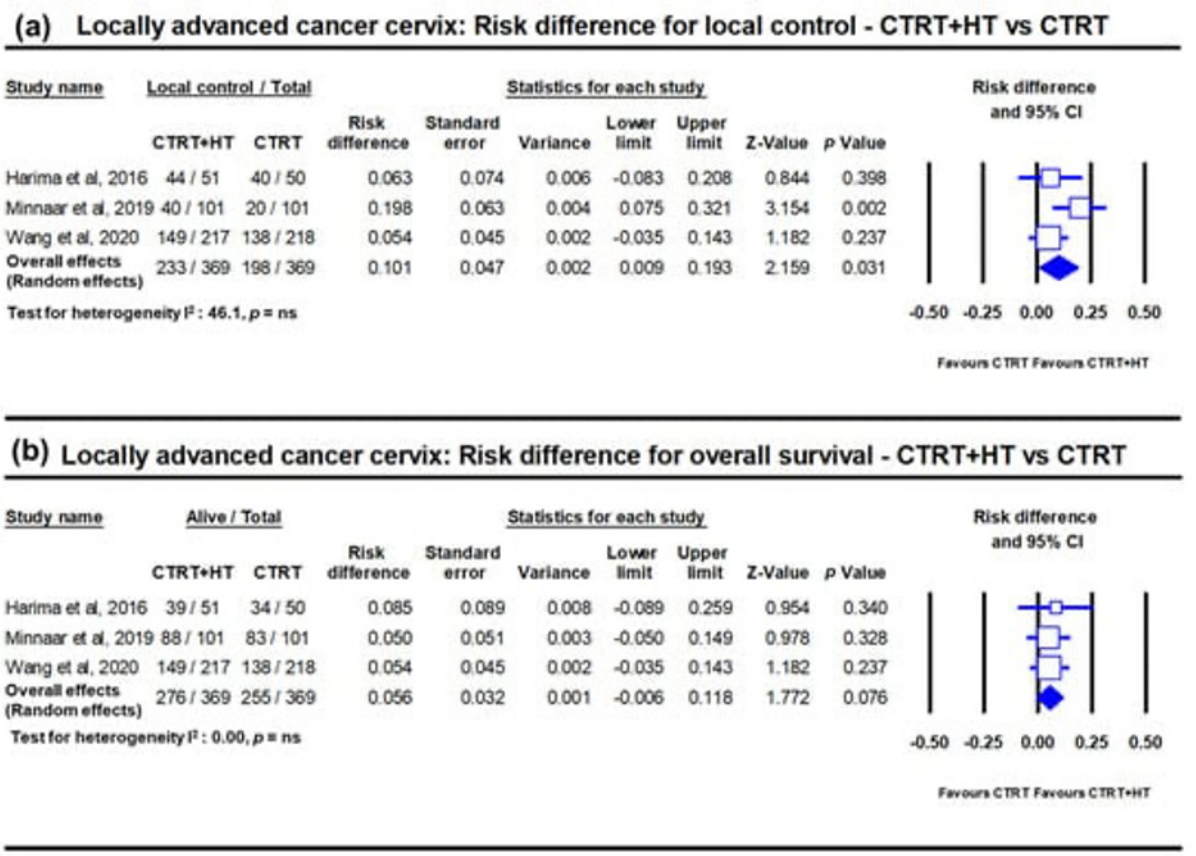


Figure 3. Forest plots depicting the risk difference in locally advanced cancer cervix for (a) local disease control and (b) overall survival with chemoradiotherapy (CTRT) with hyperthermia (HT) versus CTRT alone. Data from Minnaar et al.has been added to the meta-analysis from Yea et al. and replotted. The risk difference for local failure with HT added to CTRT reduces by 10.1% (p = 0.03) while the overall survival improves by 5.6% (p = 0.07). (ns: not significant). For citations of the studies listed, please refer to.

Network meta-analysis, which provides the highest level of clinical evidence, was reported in LACC, in which all the 13 different therapeutic approaches were evaluated from 49 clinical trials totalling 9894 patients. The surface under cumulative ranking curve (SUCRA) estimates provide an objective assessment and ranking of the locoregional control, overall survival, acute and late morbidity. The SUCRA values ranked all the 13 different strategies used in randomized clinical trial settings. Incidentally, the top two approaches evident on SUCRA values were HTRT and HTCTRT.

Thus, based on the highest levels of clinical evidence obtained through both conventional pairwise and network meta-analysis, HT with either RT or CTRT appears to provide a superior therapeutic benefit even when compared to the standard practice of CTRT in LACC. Moreover, HT has been shown to be safe with no significant additional acute or late morbidity to RT or CTRT. It would therefore be pertinent to incorporate HT in the routine clinical management of LACC along with RT or CTRT. This may help to mitigate the high %mortality/incidence seen in cervical cancer in LMICs."

References

Van der Zee, J; González González, D.
The Dutch Deep Hyperthermia Trial: results in cervical cancer.
International Journal of Hyperthermia. 2002, 18:1, 1-12, DOI: 10.1080/02656730110091919. Erratum in: Int J Hyperthermia. 2003 Mar-Apr;19(2):213. PMID: 11820462.

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.

Datta NR, Rogers S, Klingbiel D, Gómez S, Puric E, Bodis S.
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. 2016. 32:7, 809-821.

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

Franckena M, Stalpers LJA, Koper PCM, Wiggenraad RGJ, Hoogenraad WJ, van Dijk JDP, Wárlám-Rodenhuis CC, Jobsen JJ, van Rhoon GC, van der Zee J.
Long-Term Improvement in Treatment Outcome After Radiotherapy and Hyperthermia in Locoregionally Advanced Cervix Cancer: An Update of the Dutch Deep Hyperthermia Trial.
Int J Radiat Oncol Biol Phys. 2008;70(4):1176-1182.

Elming PB, Sørensen BS, Oei AL, Franken NAP, Crezee J, Overgaard J, Horsman MR. **Hyperthermia: The Optimal Treatment to Overcome Radiation Resistant Hypoxia Cancers (Basel)**. 2019 Jan 9;11(1):60. doi: 10.3390/cancers11010060. PMID: 30634444; PMCID: PMC6356970.

Minnaar,C.A.;Kozen,J.A.;Naidoo,T.;Sharma,V.;Vangu,M.;Baeyens,A.;Anne,C.;Kotzen,J.A.; Naidoo,T. **Analysis of the effects of mEHT on the treatment-related toxicity an quality of life of HIV-positive cervical cancer patients.** Int. J. Hyperth. 2020,37,263–272, Cancers2022,14, 65620of 2029

Datta, N.R.; Jain, B.M.; Mathi, Z.; Datta, S.; Johari, S.; Singh, A.R.; Kalbande, P.; Kale, P.; Shivkumar, V.; Bodis, S. **Hyperthermia: A Potential Game-Changer in the Management of Cancers in Low-Middle-Income Group Countries.** Cancers 2022, 14, 315. https://doi.org/10.3390/cancers14020315

Franckena M, Lutgens LC, Koper PC, Kleynen CE, van der Steen-Banasik EM, Jobsen JJ, et al. **Radiotherapy and Hyperthermia for Treatment of Primary Locally Advanced Cervix Cancer: Results in 378 Patients** Int J Radiat Oncol Biol Phys. 2009.73(1):242–50

Franckena M, de Wit R, Ansink AC, Notenboom A, Canters RAM, Fatehi D, et al. **Weekly systemic cisplatin plus locoregional hyperthermia : An effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area**. Int J Hyperth. 2007.23(5):443–50

Ji Woon Yea, Jae Won Park, Se An Oh, Jaehyeon Park. **Chemoradiotherapy with hyperthermia versus chemoradiotherapy alone in locally advanced cervical cancer: a systematic review and meta-analysis.** International Journal of Hyperthermia. 2021. 38:1, pages 1333-1340

Lee S, Lee N, Cho D, Kim J.
Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation.
Oncol Lett. 2017.14(1):73–8

Lutgens LCHW, Koper PCM, Jobsen JJ, Steen-banasik EM Van Der, Creutzberg CL, Berg HA Van Den, et al.
Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial.
Radiother Oncol. 2016.120(3):378–82

Minnaar,C.A.; Kotzen,J.A.; Ayeni,O.A.; Naidoo,T.; Tunmer,M.; Sharma,V.; Van-gu,M.D.T.; Baeyens,A.
The effect of modulated electro-hyperthermia on local disease control in HIV-positive and-negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial.
PLoS ONE2019,14,e0217894.

Minnaar,C.A.; Kotzen,J.A.; ,O.A.; Van-gu,M.; Baeyens, A.
Potentiation of the Abscopal Effect by Modulated Electro Hyperthermia in Locally Advanced Cervical Cancer Patients.
Front. Oncolgy2020,10,Article376

Szasz,A.M.; Minnaar,C.A.; Szentmár-toni,G.; Szigeti,G.P.; Dank,M.
Review of the Clinical Evidences of Modulated ElectroHyperthermia (mEHT) Method: An Update for the Practicing Oncologist.
Front. Oncol. 2019,9,Article1012

Westermann AM, Jones EL, Schem B, Steen-banasik EM Van Der, Koper P, Mella O, et al.
First Results of Triple-Modality Treatment Combining Radiotherapy, Chemotherapy, and Hyperthermia for the Treatment of Patients with Stage IIB, III, and IVA Cervical Carcinoma Cancer.
2005.104(4):763–70

Medical Device Details

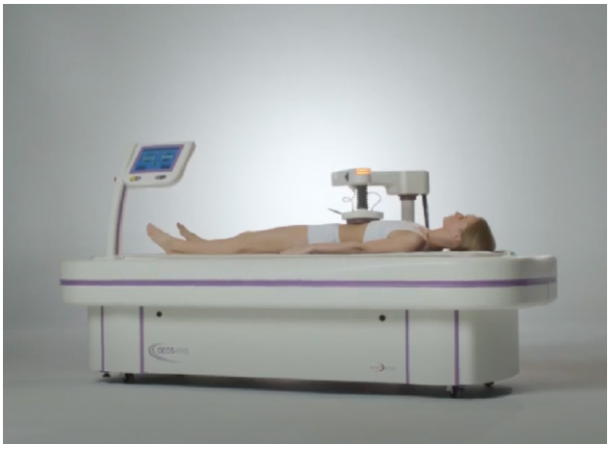
Oncotherm EHY2000 & EHY2030

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.

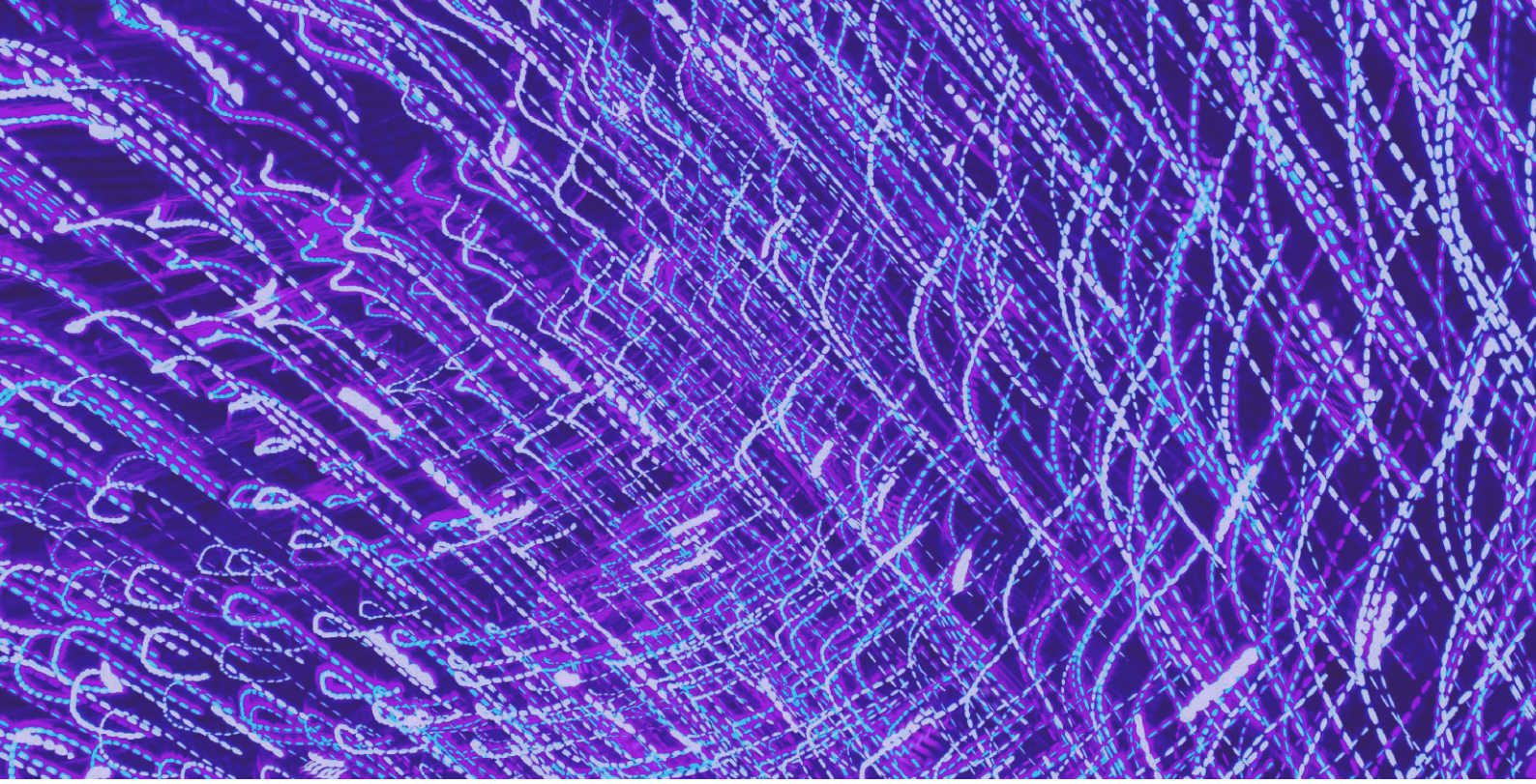


Accepted Hyperthermia Protocols

- 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
- When combined with chemotherapy, hyperthermia is administered on the same day and within 1hr of the chemotherapy continued at 2-3 sessions per week at 48hrly intervals apart until the following cycle of chemotherapy
- When combined with radiotherapy: one modulated electro-hyperthermia session administered after each fraction of radiation in the case of Stereotactic body-irradiation, or 2-3 times per week during normal fractionated external beam irradiation or until completion of RT

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.



Summary of PMB Motivation

Level 1 Evidence:

Modulated electro-hyperthermia (mEHT) for locally advanced cervical cancer as adjunctive to standard of care chemoradiation, with level 1 evidence demonstrating significantly improvement in 5 year overall survival.

Modulated Electrohyperthermia should be considered a PMB for the primary management of locally advanced cervical cancer combined with standard of care chemoradiation.
Any intervention that can be shown to increase the five year overall survival by more than 10% for a specified cancer enables the condition to be defined as treatable, and should thus should fall under prescribed minimum benefit (PBM) cover. (Medical Schemes Act No 131 of 1998).

Franckena and Van der Zee have published 12 year follow up data showing improved survival for locally advanced cervical cancer patients treated with radiotherapy plus hyperthermia, compared to radiotherapy alone: 20% (RT) vs 37% (RT+HT), (p=0.03). C Mienaaar et al has completed a phase 3 clinical trial chemoradiotherapy plus hyperthermia, with data showing that the disease free survival was more than doubled with the addition of modulated electro-hyperthermia (mEHT).

The addition of hyperthermia to radiotherapy protocols improved the risk difference for achieving CR and LRC by 22% (p<.001) and 23% (p<.001), respectively.9 The addition of hyperthermia improves local control (24% compared to 46%; p=0.003) and survival when added to chemoradiotherapy protocols for patients who are eligible for chemotherapy.

In the South African setting, mEHT was proven successful 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. (mEHT group: n=36[36%]; Control: n=16[16%]; HR:0.65; [95%CI]:0.45-0.96; p=0.029), with an OR of 3.1 of achieving disease free survival status at 4yrs with the addition of modulated electro-hyperthermia ([95%CI]:0.1.59-6.12; p=0.001).) (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 within the South African context.

A cost effectiveness analysis was performed using a Markov model, the results of which showed that CRT combined with mEHT dominated over CRT alone 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 system anti-cancer immune response (abscopal effect). (C Mienaar, et al. 2022)

Clinical Indications: Hyperthermia for Cervical Cancer

- Hyperthermia is indicated as first line treatment for FIGO stages IIB to IVA for histology subtypes: Squamous cell; Adenocarcinoma; Squamous-adenocarcinoma
- Hyperthermia must be administered with chemotherapy, concurrent or within 1hr of chemotherapy, or without chemotherapy but within 1hr of radiotherapy, and depending on the patient's fitness and ability to receive chemotherapy or radiotherapy (e.g. good renal function and performance status).
- Previous treatment with cisplatin/platinum-based chemotherapy does not influence patient outcomes when combined with radiotherapy or repeat chemotherapy.
- Hyperthermia is indicated with or without para-aortic nodal involvement. # Hyperthermia is supported by level 1 evidence for FIGO stages IIB to IIIB in combination with chemoradiation.
- Hyperthermia is clinical proven to improve patient outcomes in FIGO Stage IVA

Evidence Based Medicine

Using the principles Evidence Based Medicine: A) The statistically relevant benefits of loco-regional modulated electro-hyperthermia improving patient outcomes, relevant to the case, clearly exceed the non-invasive low risk profile of the treatment; and are stratified at the highest level of evidence, level 1, including a meta-analysis and a recent phase 3 randomised control trial;
B) Application is considered both clinically and socio-economically suitable to most patients, and is considered cost-effective;
C) The therapy must be prescribed by a qualified practitioner with substantial experience in using this modality to treat cancer and with a comprehensive understanding of the particular case.

The Declaration of Helsinki states "In the treatment of the sick person, the physician must be free to use a new diagnostic or therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering."

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.

We find no substantive reason why mEHT treatment should not be indicated in this clinical setting as a treatable condition and fall under Prescribed Minimum Benefits.

Given the clinical evidence above and that the impact on the 5yr Overall Survival is greater than 10%; we are hopeful for medical aid assistance.

HYPERTHERMIA
CLINICS INTERNATIONAL

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