HYPERTHERMIA
CLINICS INTERNATIONAL

Hyperthermia Treatment for Head & Neck Cancer

LEVEL 1A EVIDENCE

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- Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. (Datta 2015)
- Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial. (J Cancer Res Ther. 2010)

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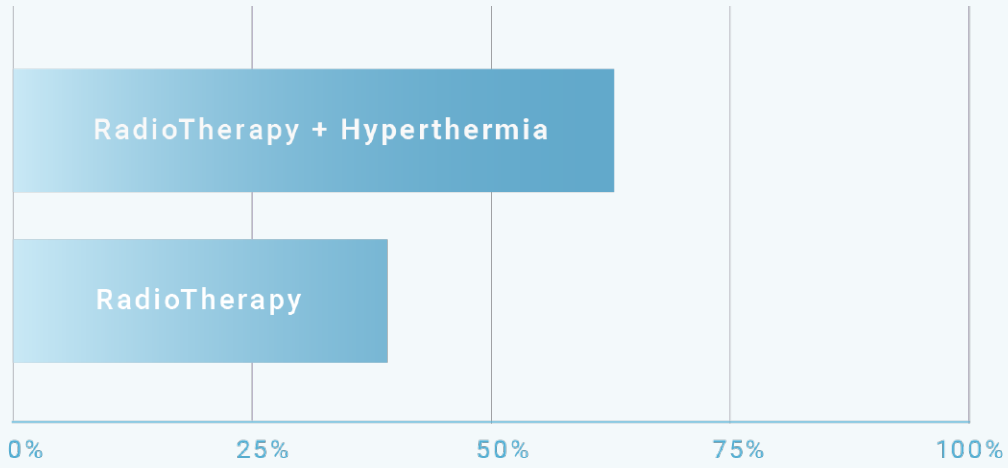
Summary of Research

In total 451 clinical cases from six studies were included in the meta-analysis. Five of six trials were randomised. The overall CR with radiotherapy alone was 39.6% (92/232) and varied between 31.3% and 46.9% across the six trials.

With thermoradiotherapy, the overall CR reported was 62.5% (137/219), (range 33.9-83.3%). The odds ratio was 2.92 (95% CI: 1.58-5.42, p = 0.001); the risk ratio was 1.61 (95% CI: 1.32-1.97, p < 0.0001) and the risk difference was 0.25 (95% CI: 0.12-0.39, p < 0.0001), all in favour of combined treatment with hyperthermia and radiotherapy over radiotherapy alone. Acute and late grade III/IV toxicities were reported to be similar in both the groups.

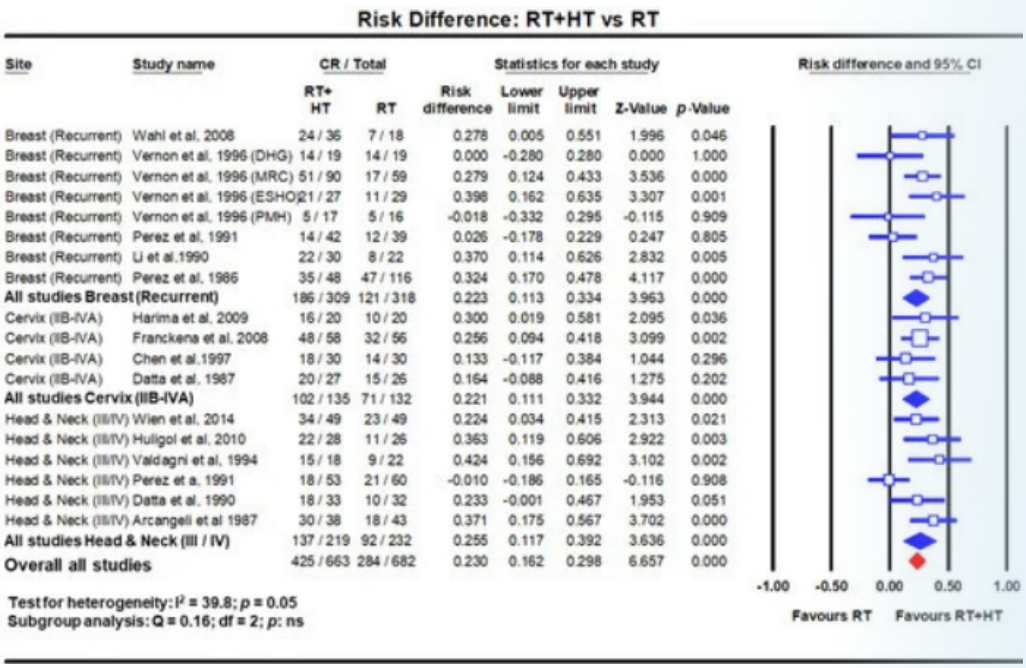
Overall Complete Response %



Conclusions

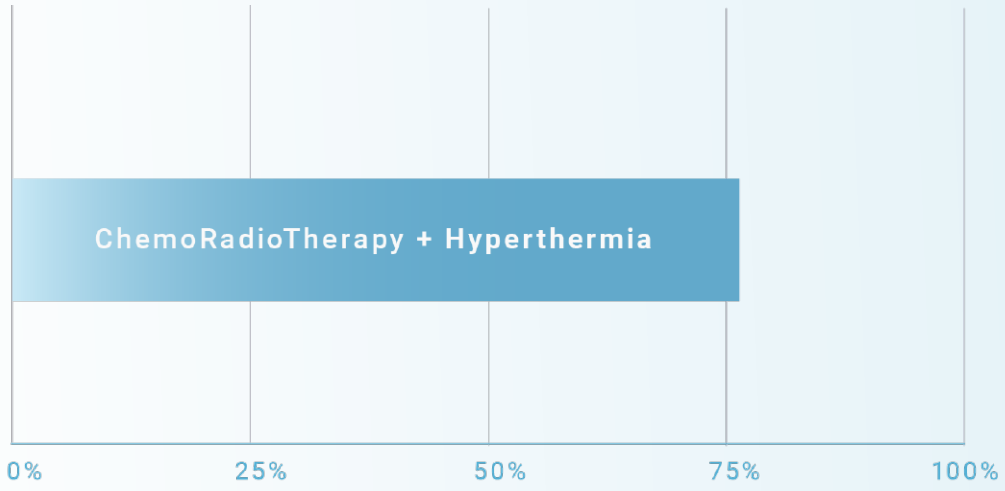
Hyperthermia along with radiotherapy enhances the likelihood of CR in HNCs by around 25% compared to radiotherapy alone with no significant additional acute and late morbidities. This level I evidence should justify the integration of hyperthermia into the multimodality therapy of HNCs.

Datta NR, Rogers S, Ordóñez SG, Puric E, Bodis S. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016;32(1):31-40. doi: 10.3109/02656736.2015.1099746. Epub 2015 Nov 16. PMID: 26928474

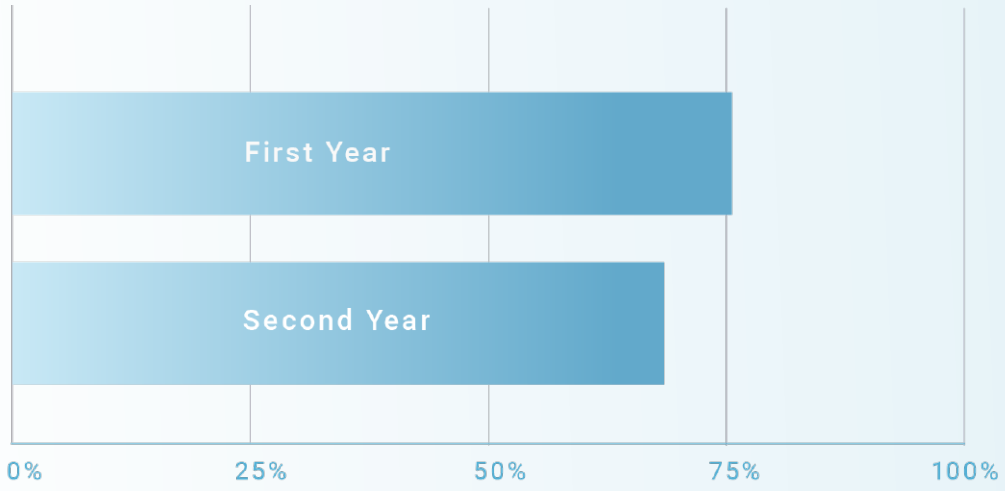


Between May 2004 and May 2008, 40 patients with advanced head and neck cancers were treated with HT and chemoradiotherapy (70 Gy in 7 weeks and weekly cisplatin 50 mg or paclitaxel 60 mg). Treatment toxicity was not increased and the complete response was 76.23%. Overall survival (Kaplan-Meir) was 75.69% at 1 year and 63.08% at 2 years.

Complete Response %

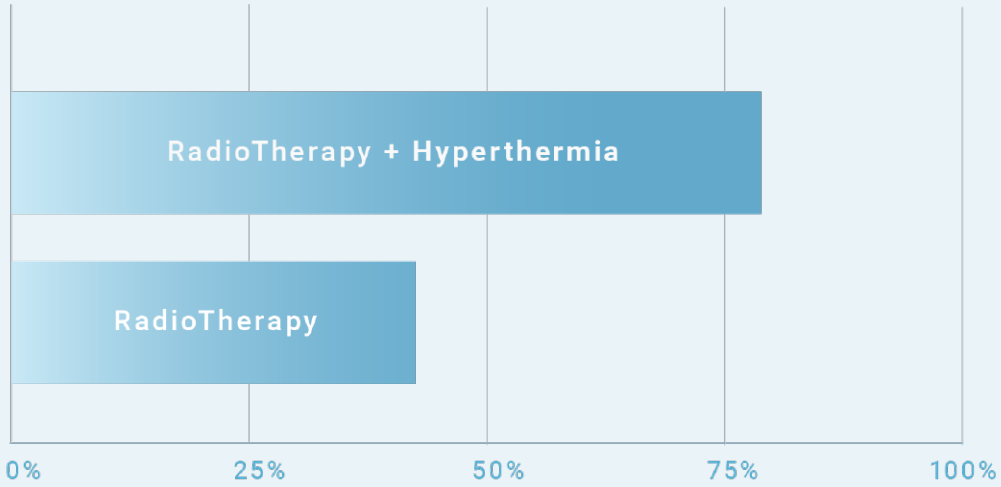


Overall survival %



Huilgol N.G. (2010b) administered RT to 26 patients and RT with HT (weekly) to 28 patients in a trial to evaluate the effects of HT on RT on head and neck tumours. All patients were matched according to age, sex, and stage of disease. All patients received 66-70 Gy in 6.5-7 weeks. The complete response in the RT group was 42.4% and in the RT plus HT group it was 78.6% ($p<0.05$). The increase in OS rates in the RT plus HT group was also significant (Kaplan-Meir analysis). No dose limiting thermal burns and treatment toxicity were recorded.

Complete Response %

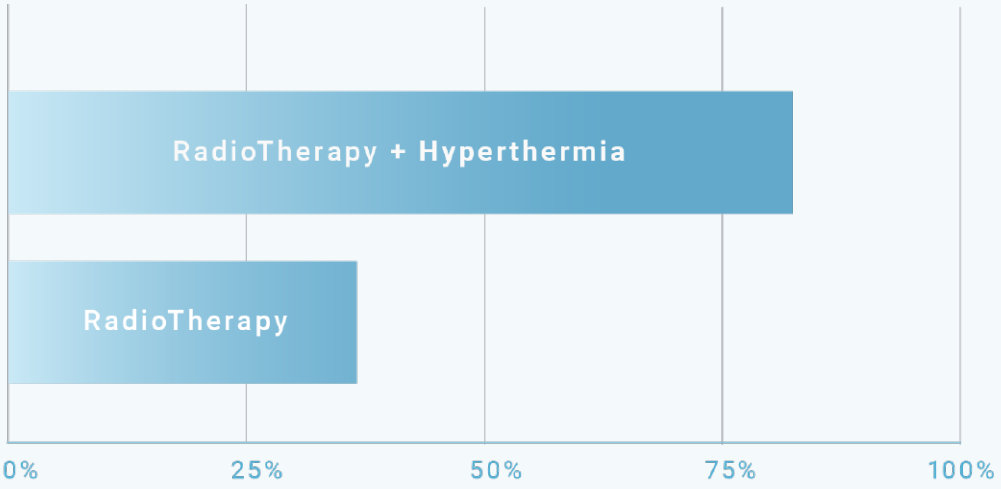


41 patients (44 nodes) with advanced Stage IV squamous cell cervical lymph nodes of the head and neck were randomised to receive treatment with RT alone or in combination with HT.

Both treatment response (82.3% in the HT group versus 36.8% in the group receiving RT alone) and increase in 5 year survival rates were significantly better in the combined group ($p=0.0164$ and $p=0.015$ respectively).

There was no increase in acute treatment toxicity in the HT group, however two patients developed bone necrosis later which may have been related to the combined treatment.

Treatment Response %



Ref	Patient characteristics	Treatment	CR / Total		Outcome	OR (95%CI)	p=
			No HT	HT			
[1]	NP (TNM II–IVA)	RT vs RT+ICHT	23/49	34/49	CR (radiologi-	2.56 (1.12, 5.86)	0.026
[6]	NP (TNM III–IV)	CRT vs CRT+ICHT	49/78	62/76	CR	2.62 (1.25, 5.49)	0.011
[5]	NP (TNM I–IV)	RT vs RT+ICHT	73/90	86/90	CR (radiologi-	5.01 (1.61, 15.55)	0.005
[2]	OC, OP, HP (TNM II–IV)	RT vs RT+HT	11/26	22/28	CR	5.00 (1.52, 16.46)	0.008
[7]	OP, HP	RT vs RT+HT	4/15	11/15	CR	7.56 (1.50, 38.15)	0.014
		Preop RT vs Preop RT+HT	4/24	10/18	CR (radiologi-	6.25 (1.51, 25.86)	0.011
[3]	Neck nodes	RT vs RT+HT	9/22	15/18	CR	7.22 (1.61, 32.46)	0.010
[8]	Recurrent laryngeal	CRT vs CRT+HT	0/28	8/26	CR	26.19 (1.42, 481.51)	0.028
[4]	OC, OP (I–IV)	RT vs RT+HT	10/32	18/33	CR	2.64 (0.96, 7.28)	0.061

Abbreviations: CR: Complete response; CRT: Chemoradiotherapy; ICHT: Intracavity Hyperthermia; HP: Hypxopharynx; NP: Nasopharyngeal; OC: Oral Cavity; OP: Oro-pharyngeal; OR: Odds Ratio; RT: Radiotherapy

Hyperthermia plus radiotherapy (with/without chemotherapy) head and neck tumours

Ref	Study	Patients	HT schedule	Control	Outcome	Results
[1]	Randomised	Nasopharyngeal; TNM	RT+HT: n=49 2/week, 60min, after EBRT (12	RT: n=49 2Gy/fraction (60-80Gy	PFS OS Local PFS	RT+HT: 100 months RT: 60 months; p=0.036 RT+HT: 86 months RT: 81 months; p=0.068 RT+HT: 111 months RT: 54 months; p=0.029
[2]	Randomised	Oral cavity, oropharyngeal, hypopharynx; Stages II-IVA	RT+HT: n=28 1/wk, 30min after RT	RT: n=26 2Gy/fraction (70Gy)	CR Median survival	RT+HT: 79% RT: 42%; p=0.036 RT+HT: 241 days RT: 145 days;
[3]	Randomised	Neck nodes	RT+HT: n=18 2/week (total 14) After RT	RT: n=22 70Gy 5yr OS	CR 5yr Local Response 5yr OS	RT+HT: 83% RT: 41%; p=0.0164 RT+HT: 67% RT: 24%; p=0.015 RT+HT: 53%
[4]	Randomised	Oral cavity and oropharyngeal; Stages I-IV (Cheek, tongue, hard palate, tonsil, alveolus, floor	RT+HT: n=33 Immediately before RT; 2/week, total	RT: n=32 2Gy/fraction Total 60Gy	CR* Disease free survival at 18 months	RT+HT: 55% RT: 31%; RT+HT: 33% RT: 19%; p=0.11 Stage III/IV only: RT+HT: 25% RT: 8%; p=0.03
[5]	Randomised Phase III	untreated Nasopharyngeal; TNM stage 1-IV	RT+HT: n=90 1/wk, before or after RT (total 7)	RT: n=90, 2Gy x 35 fractions; CDDP+ 5-FU every 3wks (4 cycles) if	CR 5yr LC 5yr PFS	RT+HT: 96% RT: 81%; p=0.003 RT+HT: 91% RT: 79%; p=0.022 RT+HT: 73% RT: 63%; p=0.039
[6]	Randomised	Nasopharyngeal N2/N3	RT+HT: n=76 2/week, total 14 treatments, before or	RT: n=78 78Gy, 39 fractions; CDDP 2x 80mg/m2,	CR 3 months 5yr Survival	RT+HT: 82% RT: 63%; p<0.05 RT+HT: 68% RT: 50%; p<0.05

Abbreviations: CDDP: Cisplatin; CR: Complete Response; EBRT: External Beam Radiation; HT: Hyperthermia; LC: Local Control; OS: Overall survival; PFS: Progression free survival; RT: Radiotherapy; TNM: Tumour Node Metastases;
*CR was significantly improved in stage III and IV

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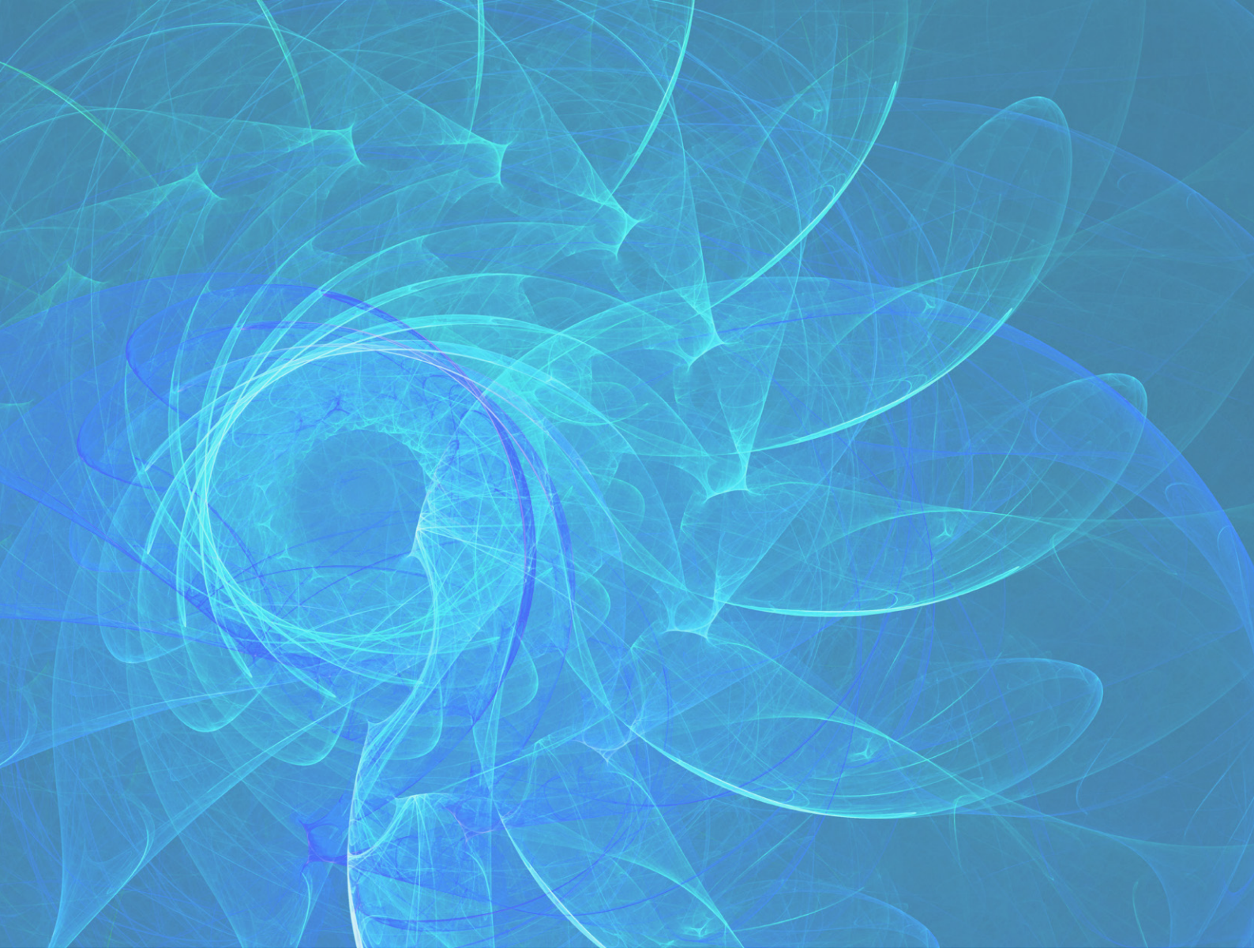


Why patients need this treatment

Head and neck tumours are associated with disfiguration and decreased quality of life. While early stage head and neck tumours respond well to radiotherapy, more advanced tumours have a poorer outcome.
Improving the outcomes for these patients offers the possibility of decreased morbidity and improved quality of life and survival.

Cost vs Clinical Efficacy

Modulated electro-hyperthermia is not an expensive modality in comparison to radiotherapy, chemotherapy and surgery and the additional cost of the treatment could prevent costs associated with residual disease post-treatment in the event of treatment failure.

Medical Device Details

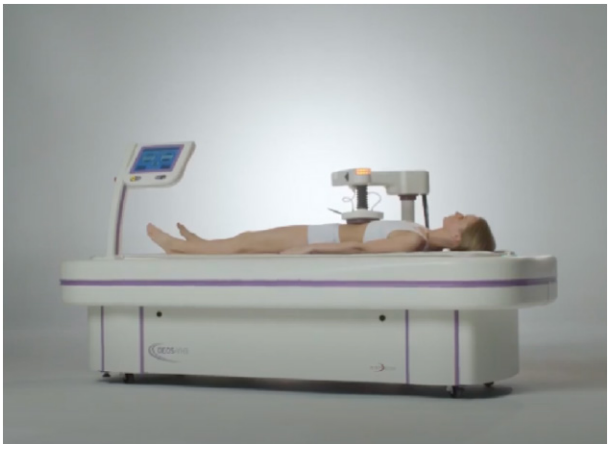
Oncotherm EHY2000 & EHY2030

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.

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