HYPERTHERMIA
CLINICS INTERNATIONAL

Hyperthermia Treatment for Sarcoma

LEVEL 1B EVIDENCE

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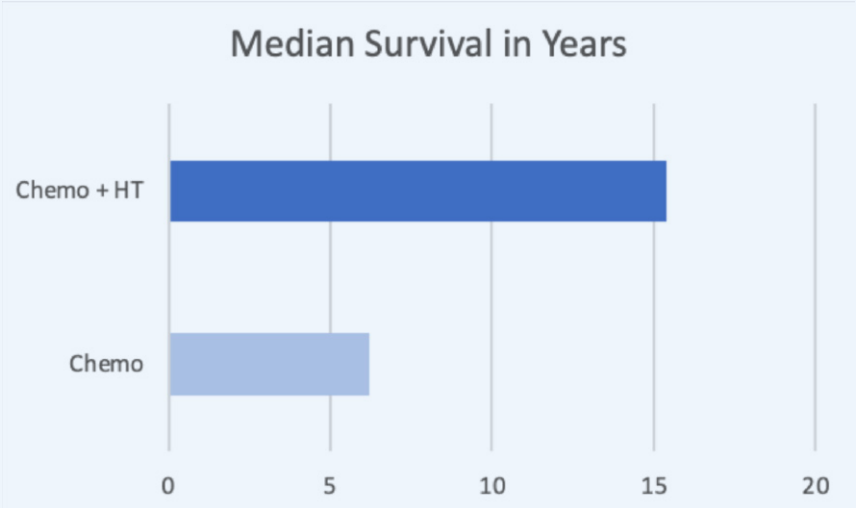
Summary of Clinical Evidence

Hyperthermia + Chemotherapy

Regional Hyperthermia added to Chemotherapy doubles the length of overall survival in patients with high-risk localised soft tissue sarcoma, and significantly improves the 9 year overall survival. (EORTC trial, ESMO 2015).

Overall survival (OS) results from a long-term follow-up of the randomised, multicentre, phase III EORTC trial (EORTC 62961/ESHO; registered: NCT00003052) of neoadjuvant chemotherapy alone or combined with regional hyperthermia in patients with localised high-risk soft tissue sarcoma, showed a median OS of 15.4 years for patients receiving neoadjuvant chemotherapy plus regional hyperthermia compared to 6.2 years for patients receiving only neoadjuvant chemotherapy.

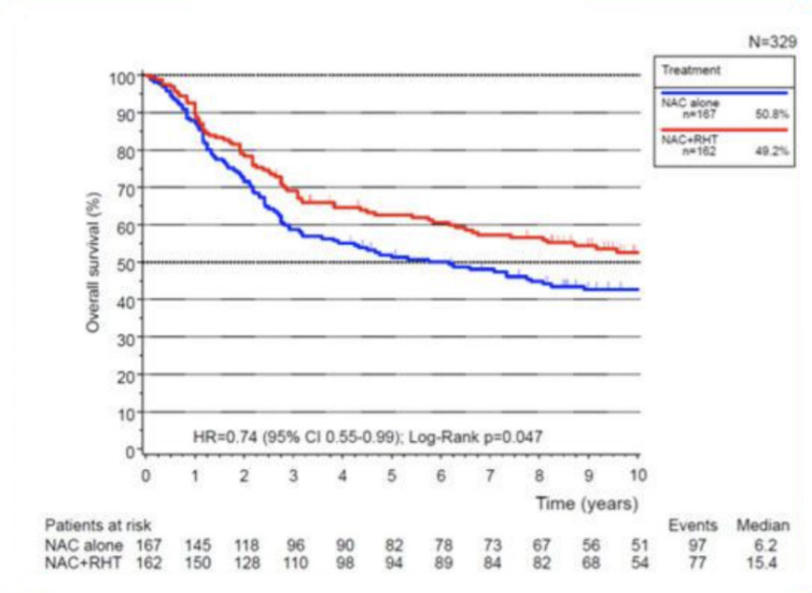
Overall Survival Rates Comparision



An intervention that can be shown to increase the five year overall survival by more than 10% for a specified cancer should be considered under prescribed minimum benefit (PBM) cover. (Medical Schemes Act No 131 of 1998).

Previously reported findings (Issels et al. Lancet Oncol 2010) demonstrated that the addition of regional hyperthermia to neoadjuvant chemotherapy significantly improved local progression-free survival (LPFS) and disease-free survival (DFS) in patients with localised high-risk, soft tissue sarcoma, according to Rolf Issels, Klinikum der Univers. München-Großhadern Klinikum Grosshadern, Medical Clinic III, Munich, Germany.

Results of Phase 3 Study (n=329 pts)



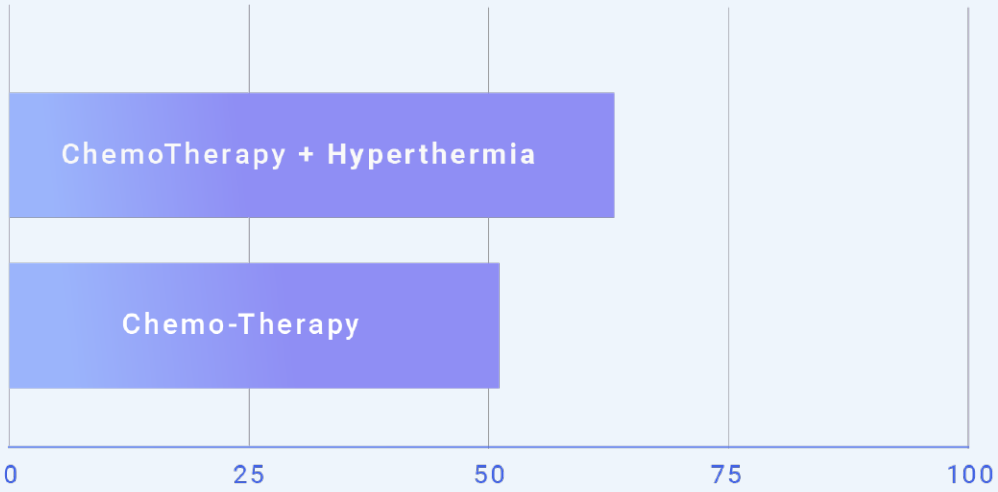
Source link:
https://www.esmo.org/meetings/past-meetings/european-cancer-congress-2015/News/Regional-Hyperthermia-Added-to-Neoadjuvant-Chemotherapy-Doubles-Length-of-Overall-Survival-in-Patients-With-Localised-High-Risk-Soft-Tissue-Sarcoma

https://www.esmo.org/var/esmo/storage/images/esmo/esmo-staff/ecc-news-press-prep-folder/media/ecc2015-13lba-3study/1237784-1-eng-GB/ECC2015-13LBA-3study_i1200.jpg

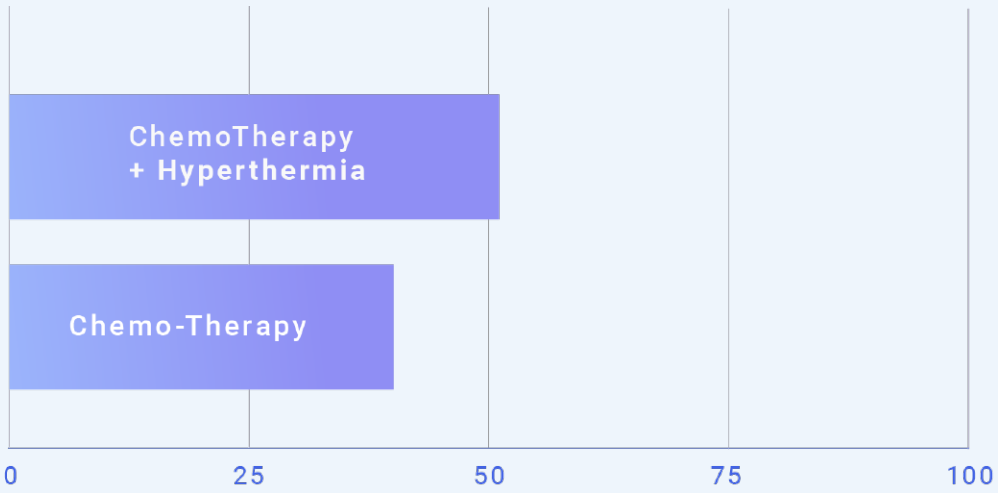
The 5 year overall survival in patients receiving dual hyperthermia and chemotherapy was **63% versus 51%** in those receiving chemotherapy without hyperthermia.

Similarly local progression free survival rates for **51% Vs 40%**, and Disease Free Survival was **42% versus 34%** (HR 0.72; 95% CI 0.55, 0.94 (log rank p = 0.016).

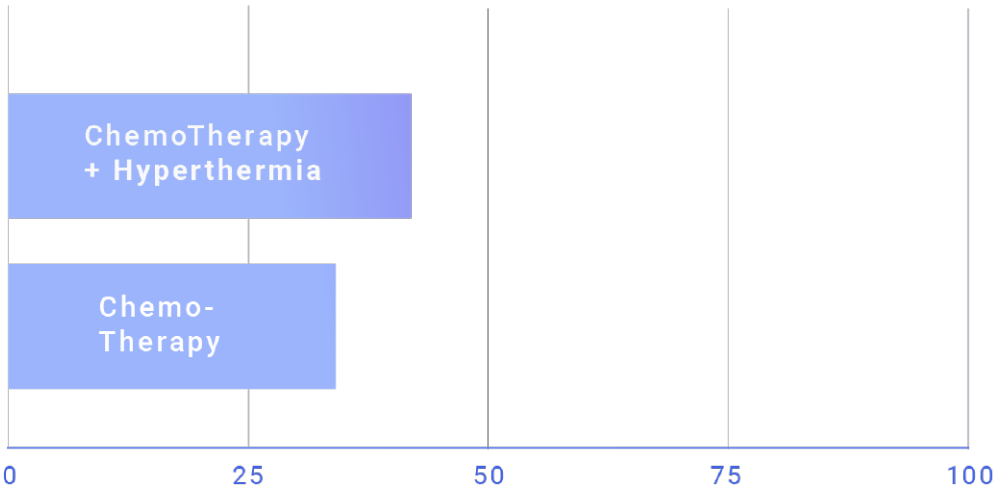
5 Year Overall Survival %



Local Progression Free Survival Rates



Disease Free Survival %



It was also shown to significantly improve the 9-year overall survival with no change in short term or long term toxicity between the two groups. In other clinical trials, regional hyperthermia when combined with chemotherapy, improved quality of life and survival statistics, and has scored well on several cost effective analysis.

“These findings strongly support adding regional hyperthermia to standard neoadjuvant chemotherapy in patients with localised high-risk soft tissue sarcoma. Induction with hyperthermia resulted in significantly increased Overall Survival (OS), Disease Free Progression (DFS), and Local Progression Free Survival (LPFS).”

Hyperthermia Indication
Soft Tissue Sarcoma

Non-Resectable or Locally Advanced

Indications According to ESMO Clinical Practice Guidelines:

- **Irresectable, locally advanced high-risk soft tissue sarcomas (> or = 5 cm) grade 2 or 3, combined with radiotherapy or chemotherapy;**
- **OR combined with radiotherapy or chemotherapy for limb-preserving surgery;**
- **Metastatic or recurrent tumours that have been previously exposed to treatment and require re-treatment.**

As you well know, this form of cancer remains a stubborn and aggressive form of cancer with limited treatment options. We believe that a strong case is made for adjunctive loco-regional modulated electro-hyperthermia (mEHT).

*Casali P, Bbecassis N, Bauer S, et al. Soft tissue and visceral sarcomas : ESMO – EURACAN Clinical Practice Guidelines for diagnosis , treatment Clinical Practice Guidelines. ESMO Clinical Practice Guidelines. 2018;29

Schedule of Hyperthermia (HT):

- Within two hours of each intravenous dose of chemotherapy
- Three times per week if combined with external beam radiotherapy, within 1hr of treatment.

Hyperthermia Plus Chemotherapy for Soft Tissue Sarcomas

Study	Patients	Ht schedule	Control	Outcome	Results
Randomised controlled multicentre Phase III, multicentre	G2-G3, deep, >3cm STS	HT+ChT (EIA x 8 cycles, 3 wks apart): n=169, HT given on days 1 and 4 of each cycle, total 16 HT	ChT (EIA x 8 cycles 3 wks apart): n=172	Progression free at 2yr Median Progression free survival Median Disease free survival 5yr survival 10yr Survival Median time to local progression Median survival	HT+ChT: 30% ChT: 19%; p=0.035 HT+ChT: 120mnths ChT: 75mnths; p=0.003 HT+ChT: 18mnths ChT: 32mnths; p=0.011 HT+ChT: 63% ChT: 51%; p=0.04 HT+ChT: 53% ChT: 43%; HT+ChT: 67.3mnths ChT: 29.2mnths; p=0.002 HT+ChT: 15.4yrs ChT: 6.2yrs; p=0.04
Retrospective	RAS of the thorax; n=16	RT+HT: 1/wk with AMC and 2/wk with BVI	RT: AMC or BVI protocol	Mean survival Response rate	15.5 months 7 CR; 2 PR

Abbreviations: ChT: chemotherapy; CR: Complete Response; EIA: etoposide, ifosfamide, and doxorubicin; STS: Soft tissue sarcoma; RT: Radiotherapy; HT: Hyperthermia; RAS: Radiation Associated Sarcoma

[1] Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem B, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma : a randomised phase 3 multicentre study. Lancet Oncol [Internet]. 2010.11(6):561–70. Available from: http://dx.doi.org/10.1016/S1470-2045(10)70071-1

[2] Issels R, Lindner L, Verweji J, et al. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma. JAMA Oncology. 2018;4(4):483-492.

[3] de Jong MAA, Oldenborg S, Oei SB, et al. Reirradiation and Hyperthermia for Radiation-Associated Sarcoma. Cancer. 2012;118(1):180-187

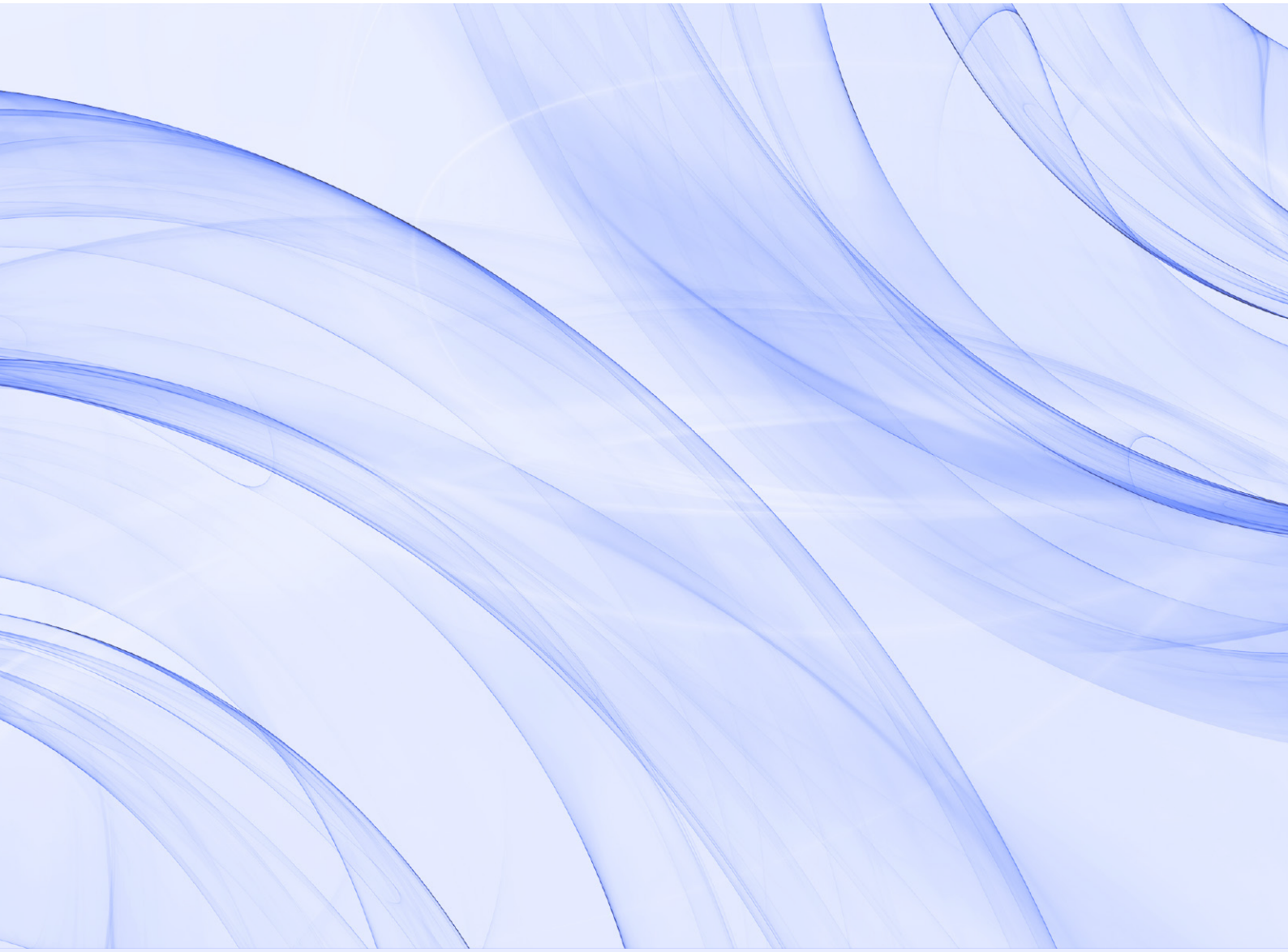
Safety & Cost Effective Analysis

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 [insert].

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, 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.

de Jong MAA, Oldenborg S, Oei SB, et al.
Reirradiation and Hyperthermia for Radiation-Associated Sarcoma.
Cancer. 2012;118(1):180-187

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.

Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem B, et al.
Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue Sarcoma: a randomised phase 3 multicentre study.
Lancet Oncol [Internet]. 2010.11(6):561–70.

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Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma.
JAMA Oncology. 2018;4(4):483-492

Minnaar,C.A.;Kotzen,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 and quality of life of HIV-positive cervical cancer patients.
Int. J. Hyperth. 2020,37,263–272, Cancers2022,14, 65620of 2029.

Szasz,A.M.; Minnaar,C.A.; Szentmártoni,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.

Medical Device Details

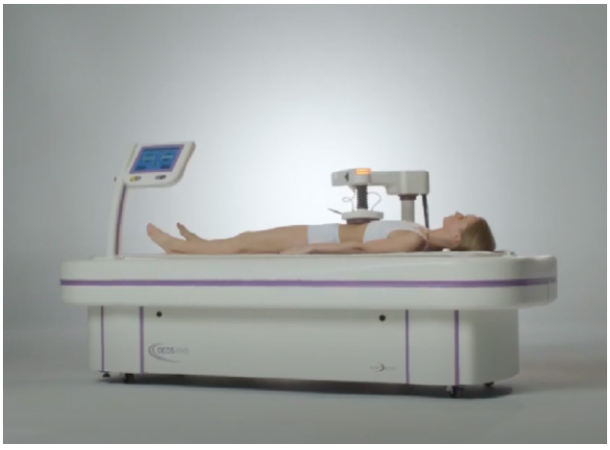
Oncotherm EHY2000 & EHY2030

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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PUBLISHED IN JANUARY 2023