HYPERTHERMIA
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Hyperthermia Treatment for Bone Metastases

LEVEL 1B EVIDENCE

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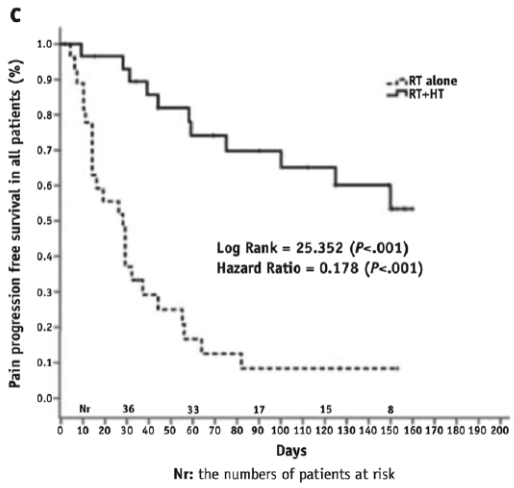
Summary of Clinical Evidence

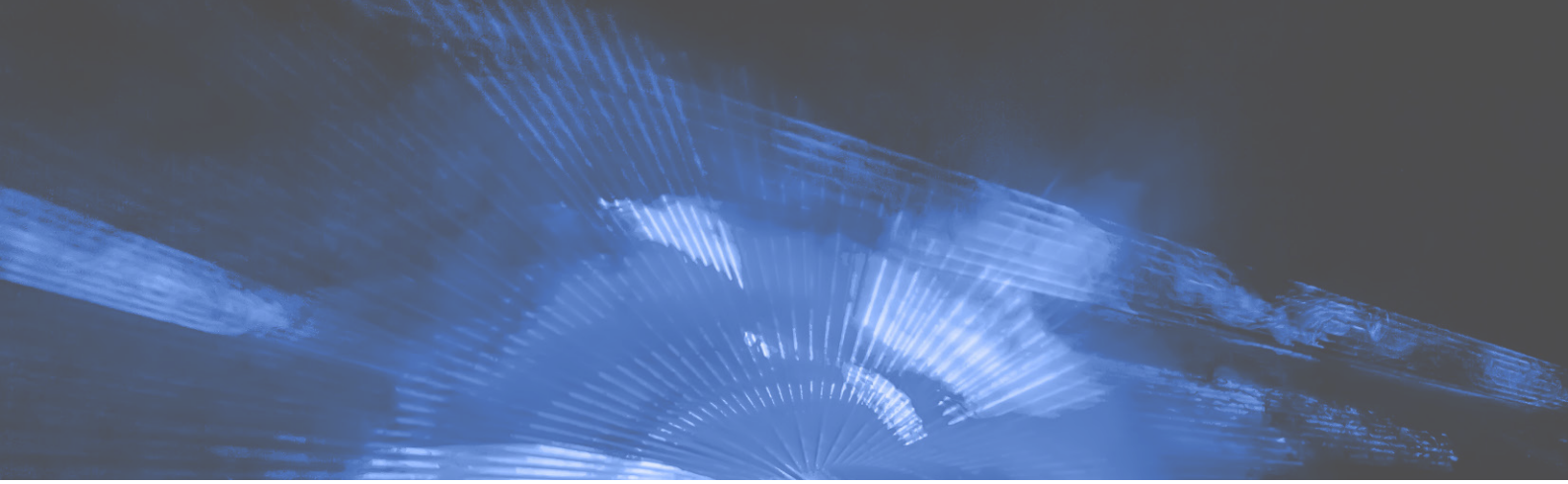
Loco-regional modulated electro-hyperthermia (mEHT) in combination with palliative radiotherapy for superior pain relief and increased radiological response.

Evidence: Level 1b

Hyperthermia (HT) significantly improves relief of painful bone metastases when combined with Radiotherapy (RT), increasing the 3 month complete response from 7.1% in RT alone, to 37.9% in the Hyperthermia combination group; and almost double the amount of patients achieved a zero pain score (BIP) in the HT + RT group; with pain relief lasting 3 x longer, viz. 7.9 weeks VS 24 weeks and beyond trial follow up.



Nr: the numbers of patients at risk



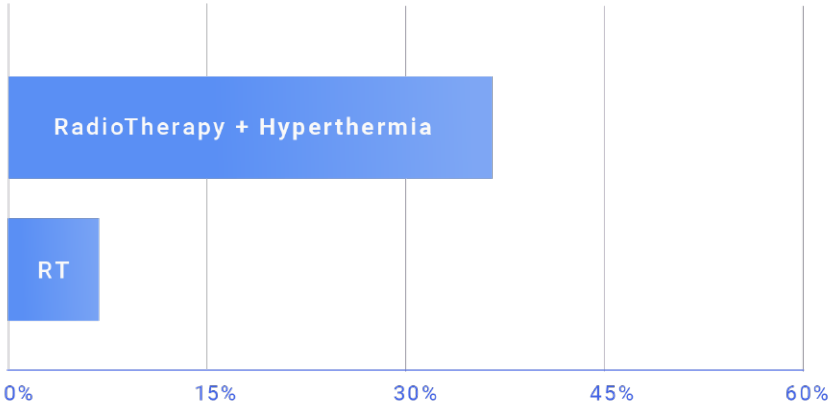
Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases

A Phase 3 Prospective, Randomized, Controlled Trial

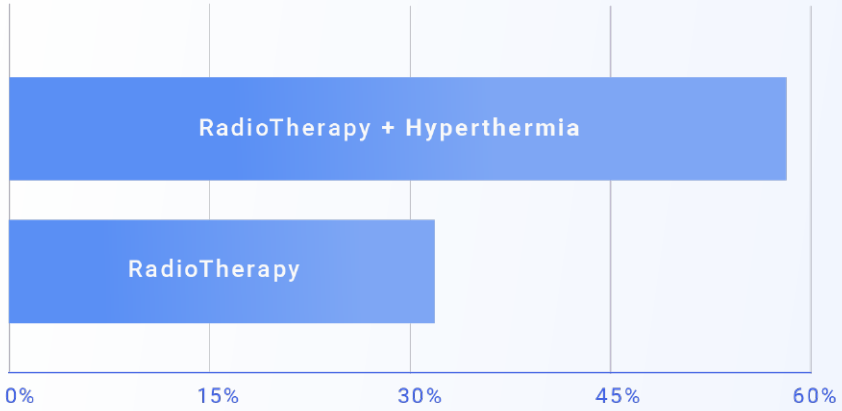
Patients were randomized to RT-alone (n=28) and RT + HT (n=29). At 3 months after treatment the RT + HT patient group showed a significant higher complete response (CR) than the RT-alone group, i.e., 37.9% vs. 7.1% [P=0.006; CR defined as a zero score on the Brief Pain Inventory (BPI)]. Also, the accumulated CR at the third month after treatment was higher for the RT+HT group, i.e., 58.6% vs. 32.1% respectively (P=0.045).

https://youtu.be/8KupZxYUNfY

3 Months Complete Response %

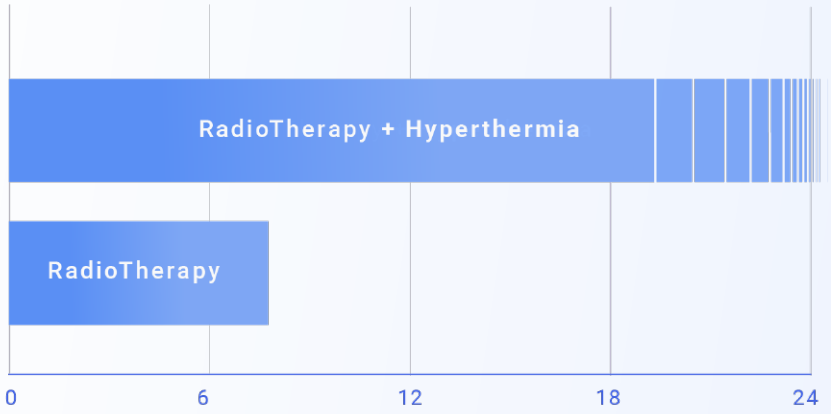


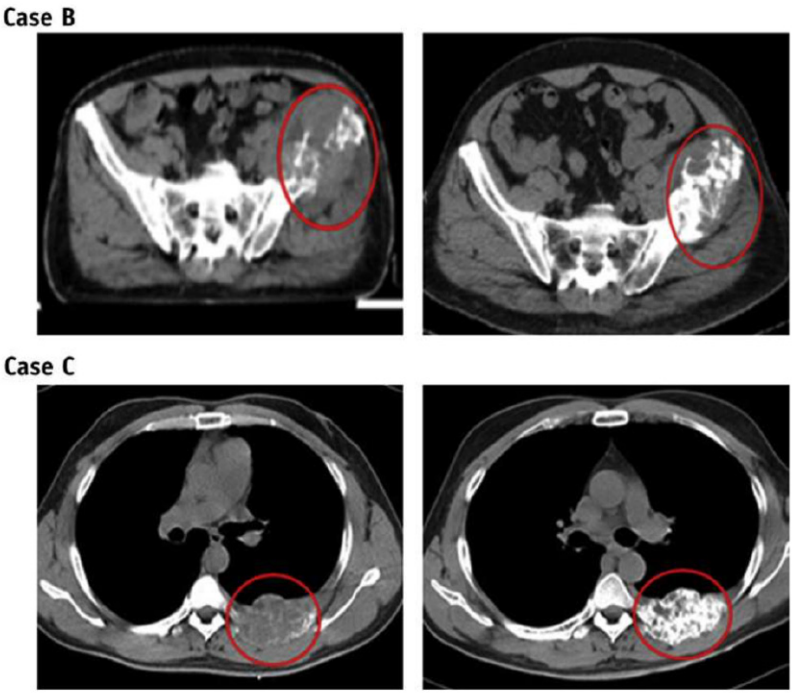
3 Months Accumulated CR %



Besides an improved CR-rate the study also reports a statistically significant prolongation of duration of pain relief: median time to pain progression was 7.9 weeks for the RT-alone group, while for the RT + HT group median time to progression was not reached after the 24 weeks of observation.
In the group of patients with radiologic response evaluation a higher response for the combined treatment arm at week 12 was noted: complete plus partial radiological response for RT+HT was 11/15 vs. RT-alone 3/12”

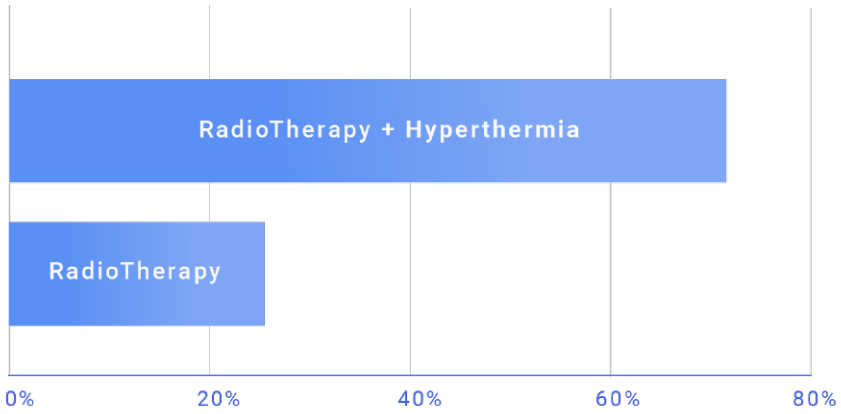
Time to Pain Progression





Three cases of bone ossification of the osteolytic lesions after radiation therapy plus hyperthermia. Image presented were established whitin a 2-month period after treatment

Complete + Partial Radiological Response %



Radiotherapy plus hyperthermia shows effectiveness in painful bony metastases

Indicated only for selected patients with extended live expectancy and radiotherapy resistant tumor!

"Most recently, the first randomized controlled trial to investigate the benefit of external beam radiotherapy combined with hyperthermia vs. external beam radiotherapy in the treatment of patient with painful bony metastases was published."

"The results reported in the randomized trial of Chi et al. (4) for palliative treatment of painful bony metastases with radiotherapy and hyperthermia, again confirm the great potential of hyperthermia to sensitize the tumor to radiotherapy"

"...the indication for combined radiotherapy plus hyperthermia appears to be best suited for patients with a good condition and extended life expectancy under treatment, but where we expect that RT-alone will result in an insufficient response."

van Rhoon GC, van Holthe JML. Radiotherapy plus hyperthermia shows effectiveness in painful bony metastases—indicated only for selected patients with extended live expectancy and radiotherapy resistant tumor! Ther Radiol Oncol 2018;2:38.

Source link:
https://tro.amegroups.com/article/view/4538/5315
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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)

Modulated electro-hyperthermia is a relatively inexpensive modality in comparison to radiotherapy, chemotherapy and surgery and the additional costs of mEHT treatment has been shown to prevent costs associated with residual disease post-treatment. A budget impact analysis by Roussakow et al 2017 revealed significant cost saving below the standard cost-effective thresholds and greater than 30 quality adjusted life year (QALY) gained per 1000 relapsed high grade glioma patients with the addition of mEHT to their treatment protocol; as an example. C Mienaar et al 2022 has proven that less money was spent per patient receiving mEHT + chemo-radiation (CRT) Vs CRT alone for cervical cancer over a 3 year period; despite the additional cost of 2 months of mEHT treatment.

Using the principles Evidence Based Medicine:

- **The statistically relevant benefits of loco-regional modulated electro hyperthermia improving patient outcomes, relevant to this case, clearly exceed the non-invasive low risk profile of the treatment;**
- **Application is considered both clinically and socio-economically suitable to this patient, and is considered cost-effective;**
- **The therapy has been prescribed by a qualified practitioner with substantial experience in using this modality to treat cancer and with a comprehensive understanding of this 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 for Painful Bone Metastases.

We find no substantive reason why mEHT treatment should not be clinically indicated in combination with Radiotherapy.

References

Chi M-S, Yang K-L, Chang Y-C, Ko H-L, Lin Y-H, Huang S-C, Huang Y-Y, Liao K-W, Kondo M, Chi K-H. **Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia versus External Beam Radiation Alone in Treating Patients with Painful Bony Metastases: a Phase III Prospective Randomized Control Trial.** International Journal of Radiation Oncology • Biology • Physics (2017). doi: 10.1016/j.ijrobp.2017.09.030

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.

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 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.

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.

Minnaar,C.A.; Kotzen,J.A.; ,O.A.; Vangu,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.; 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.

van Rhoon GC, van Holthe JML. **Radiotherapy plus hyperthermia shows effectiveness in painful bony metastases—indicated only for selected patients with extended live expectancy and radiotherapy resistant tumor!** Ther Radiol Oncol 2018;2:38.

Medical Device Details

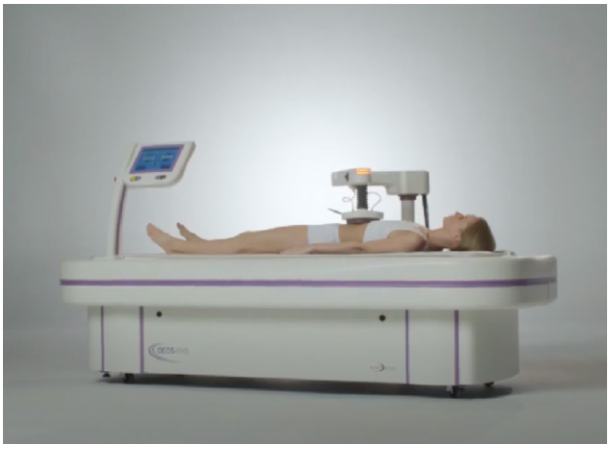
Oncotherm EHY2000 & EHY2030

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

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