An overview of Oncothermia as a treatment modality for cervical cancer

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The authors do not have any conflicts of interest to declare.

Introduction:

Modulated electro-hyperthermia (mEHT); Oncothermia™

- **Mild** heating
- **Capacitive-coupled** set-up
- **Amplitude modulated** 13.56MHz radiofrequency waves

- **Cervical cancer** and the **treatments:**
- Significant morbidity and
- Negatively impacts the Quality of Life (QoL) of patients

Introduction:

1. We **summarise the literature** on mEHT for the management of cervical cancer
2. Describe a **cost effectiveness analysis** (CEA) on mEHT for the management of locally advanced cervical cancer (LACC),
3. Report **preliminary three year survival data** from the ongoing randomised controlled Phase III trial on mEHT plus chemoradiotherapy (CRT) in South Africa (SA).

Methodology:

Review:

- A literature search for "hyperthermia", "modulated electro-hyperthermia", and "Oncothermia" in "oncology", and "cervical cancer" was conducted.
- Studies that did not utilise mEHT were excluded. All papers on mEHT used for the management of cervical cancer were included.

Three Year Survival:

- Data from the ongoing LACC SA trial were used to evaluated three year survival for patients treated with mEHT plus CRT.

Methodology:

CEA:

- Cost analysis for **RT** with/without mEHT for LACC
- Report from **2012**
- Time horizon: **3 years**
- Perspective: **3rd party payer**
- **Markov** model, with **6 months cycle** length
- Data: 3 year data from the **Dutch Deep HT trial** [1], extrapolated into the South African setting, using mEHT costs.
- Costs are reported in SA Rands.
- Considered direct medical costs only
- Primary outcome: Cost per Quality Adjusted Life Year (**QALY**).

Methodology:

CEA:

- Cost analysis for **CRT** with/without mEHT for LACC
- Preliminary 2021 results
- Time horizon: **3 years**
- Perspective: **Private Healthcare** and **Public Healthcare**
- **Markov** model, with **6 months cycle** length
- Data: 3 year data from the **mEHT LACC SA** study
- Costs are reported in SA Rands.
- Considered direct medical costs only
- Primary outcome: Cost per Quality Adjusted Life Year (**QALY**).

Results: mEHT- Temp&Blood flow

20 patients with cervical cancer were treated with mEHT

Measurements

- **Temp**: Peri-tumour using an internal organ temperature probe
- **Blood flow**: 3D colour Doppler ultrasound used to determine peak systolic velocity end diastolic velocity ratio *(SID* ratio) and the resistance index (RI) within blood vessels.

Results:

- **Temp:** mean peri-tumour temperature
  - Baseline: 36.7 ± 0.2 °C
  - 30 minutes: 37.5 ± 0.5 °C
  - 60 minutes: 38.5 ± 0.8 °C
- **Blood flow**,
  - *mEHT = significant increase in tumour blood flow*

Lee S-Y, *et al,* **The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma**. *International Journal of Hyperthermia*. 2018;34(7):953-960.

Results: mEHT + Chemotherapy

- 2017 Lee *et al.(2017)*
- Randomised trial: mEHT+ChT vs ChT alone for **previously irradiated residual/locally recurrent cervical cancer**
- Incl. loco-regional metastases
- mEHT: **3/wk** →**36** treatments, Power: 80→**150**W, **60** minutes
- ChT: platinum based

Group	TP (cycle)	TC (cycle)	FP (cycle)	Cisplatin (cycle)
Cht (n=20)	8 (5-7)	6 (6-9)	6 (4-6)	0
ChT+mEHT (n=18)	6 (5-6)	4 (6)	6 (4-6)	2 (5-6)

TP, paclitaxel+cisplatin; TC, paclitaxel+carboplatin; FP, cisplatin+5-fluorouracil.

Results: mEHT + Chemotherapy

- **Overall response significantly better in mEHT group**
- mEHT did not result in any differences in treatment toxicity

Clinical response following completion of treatment.

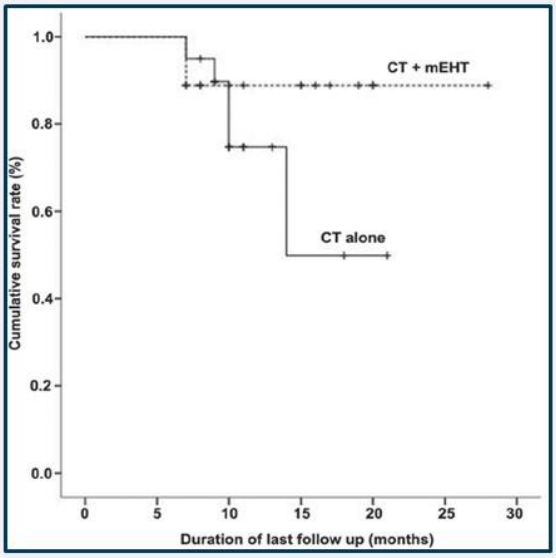
Group	CR	PR	SD	PD	P value
Cht (n=20)	4	3	1	12	*p= 0.0461*
ChT+ mEHT (n=18)	9	2	2	5	

Clinical response at last follow up

Group	CR	PR	SD	PD	P value
Cht (n=20)	4	3	1	12	*p= 0.0218*
ChT+ mEHT (n=18)	9	2	2	5	

Results: mEHT + Chemotherapy

- No significant difference in survival



Overall survival.
ChT +mEHT did not significantly increase the overall survival rate (p=0.235).

Lee S, *et al* **Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation.** *Oncology Letters*. 2017;14(1):73-78.

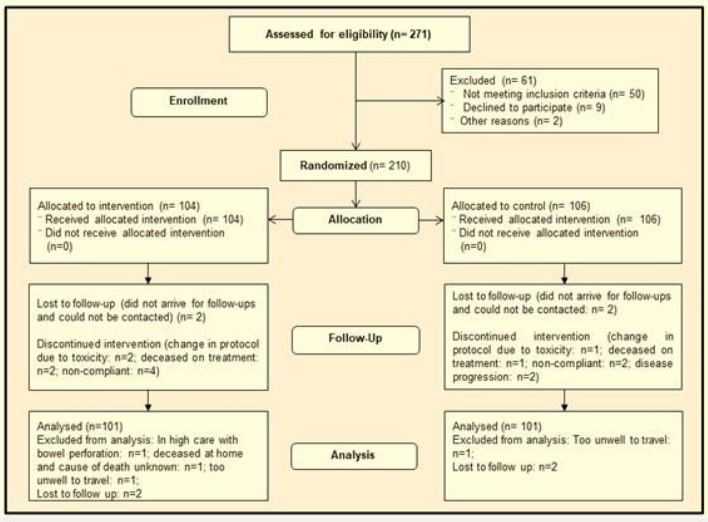
Results: mEHT + Chemoradiotherapy

mEHT LACC SA trial:

- FIGO stage IIB-IIIB;
- HIV +/-;
- CRT with radical intent;
- Signed informed consent

Protocol:

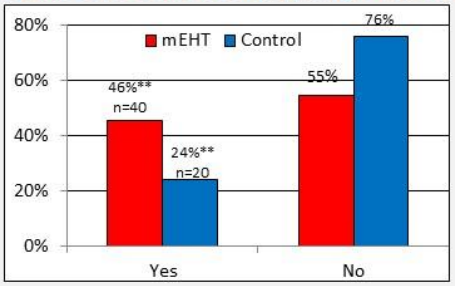
- mEHT:
  - 2/wk, total 10
  - immediately before EBRT
  - 55 minutes,
  - starting at 60W →130W
- Radiation:
  - 50Gy EBRT in 25#
  - 3x 8Gy HDR Brachytherapy
- Chemotherapy:
  - 2x Cisplatin: 80mg/m2



Results: mEHT + Chemoradiotherapy

- Improved LDC with the addition of mEHT to CRT [4]
- Without any significant effect on early toxicity [5].
- With a quality of life (QoL) benefit [5]

LDC at 6 months in Surviving Patients



mEHT Group:
n=88
[87% survival]
46% LDC

Control Group:
n=83
[82% survival];
24% LDC

Chi2: ***p=0.003***

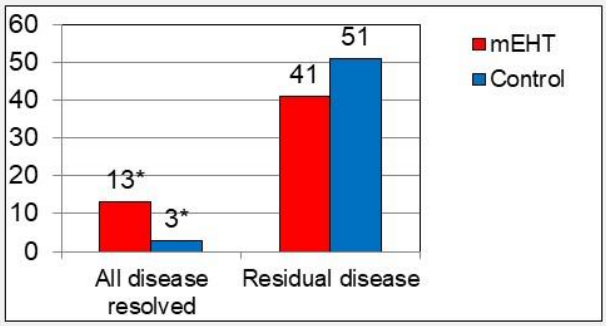
Pain, emotional well-being, and physical function, were significantly higher in mEHT group (EORTC)

	LDFS 6 months	LDC 6 months	CMR
mEHT	n=39/101 [39%]	n=40/88 [46%]	n=49/85 [59%]
Control	n=20/101 [20%]	n=20/83 [24%]	n=26/73 [36%]
p	OR: 0.36, 95% CI: 0.19-0.69; *p=0.002*	OR: 0.39, 95% CI: 0.20-0.77; *p=0.006*	Fischer's exact *p=0.005*

Results: mEHT + Chemoradiotherapy

Abscopal effect: in participants in whom extra-pelvic nodal disease was visualized on the pre-treatment ^{18}F-FDG PET/CT studies [6]

Confirming the immune-modulating effects of mEHT described in pre-clinical studies.



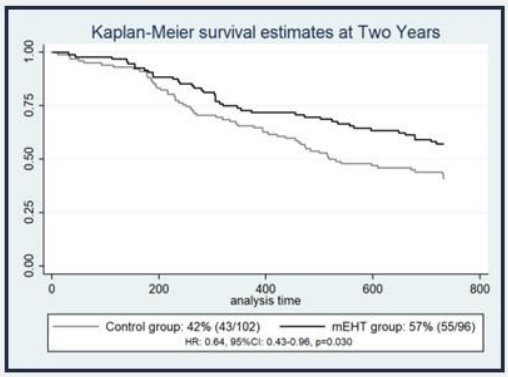
In a multivariate analysis, Age, Number of cisplatin doses, Total RT dose, Days between last RT and PET/CT, **were not associated with an abscopal effect.** In a univariate analysis, CD4 count was also not predictive of an abscopal effect.

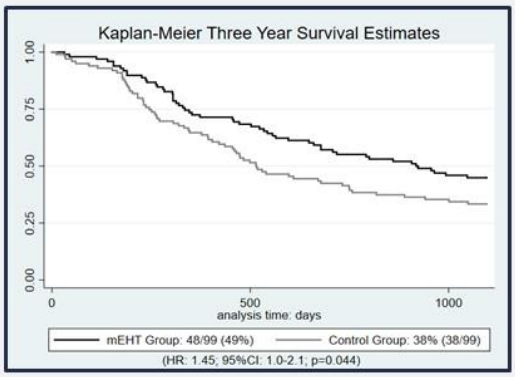
Results: mEHT + Chemoradiotherapy

Three Year Results:

3yr all mortality survival and DFS is significantly more likely in the mEHT group
mEHT did not result in any significant changes in late toxicity

	2YR OS	3YRS OS	DF at 3YRS
mEHT	n=55/96 [57%]	n=48/98 [49%]	n=33/98 [34%]
Control	n=43/102 [42%]	n=38/99 [38%]	n=14/99 [14%]
P value	HR: 0.64, 95% CI: 0.43-0.96, *p=0.030*	HR: 1.45; 95% CI: 1.0-2.1; *p=0.044*	OR:2.4; 95% CI: 1.3-4.4; *p=0.003*





Results: CEA

mEHT + RT

- **Addition of mEHT to RT dominated treatment by RT alone**
- The **addition of mEHT** was **less costly** and **more effective**.
- Driven by the difference in progression free survival (high costs of progressive disease)
- ***There is a 100% probability that the cost of combination treatment is less than that of radiation* therapy.**

Results: CEA

mEHT + CRT

- Markov Cost Effectiveness model assumes that patients start progression free and then enter the model. Once in the model, there are three different mutually exclusive states into which patients will move:
  - Progression free survival
  - Progression
  - Death
- Patients incur treatment costs during the first cycle and the other costs as they progress.

Results: CEA

mEHT + CRT

Public Healthcare Perspective:

- mEHT+CRT **DOMINATES** the CRT
- More health benefits at lower costs
- The probability that mEHT+CRT is cost-effective compared with CRT only treatment is about 82.2% at No additional cost

Results: CEA

mEHT + CRT

Private Healthcare Perspective:

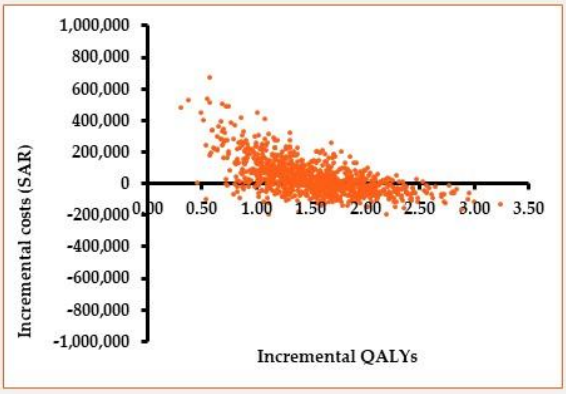
- mEHT+CRT **DOMINATES** the CRT
- More health benefits at lower costs
- The probability that mEHT+CRT is cost-effective compared with CRT only treatment is about 77.7% at No additional cost

Results: CEA

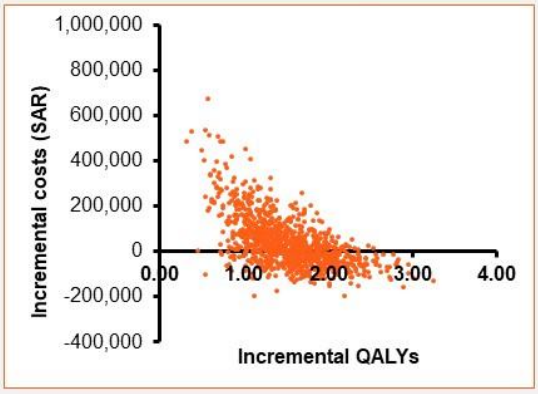
mEHT + CRT

ICER planes show mEHT+CRT = more health effects at a less cost over 3-years (mEHT dominant)

Public Healthcare Perspective:



Private Healthcare Perspective:



Conclusion:

- mEHT combined +ChT for the management of residual or recurrent disease significantly improves local disease response in these patients.
- mEHT +CRT significantly improves:
  - LDC, 3 year survival, 3 year DFS
  - without increasing the toxicity profile

Addition of mEHT to CRT for LACC is more effective and less costly

Future Perspective:

- Following the review, we recommend mEHT be included in the guidelines for the management of LACC and recurrent/residual cervical cancer.
- Consideration should be given to developing studies on **mEHT + immunotherapy**
- A **CEA analysis** of mEHT plus CRT using the new three year survival data is underway.

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Results: mEHT

- The following parameters were documented for the
- tumour area:
  - The ratio of peak systolic velocity to end-diastolic velocity
  - *(SID* ratio) of intra-tumoural vessels
  - The resistance index (RI) of intra-tumoural vessels
  - The RI in tumour-supplying vessels
  - The RI was calculated according to the following equation: RI= (peak systolic velocity - end-diastolic velocity)/peak systolic velocity

SID and RI significantly increased post treatment.