Final 5 year results from the randomised controlled trial on modulated electro-hyperthermia added to chemotherapy for the management of locally advanced cervical cancer

Presentation from "Oncotherm in Italy" conference 2025.04.02.

Dr. Carrie Anne Minnaar

University of Witwatersrand, South Africa

Citation

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https://www.youtube.com/watch?v=Br4kmGCCJQU&list=PLEaAiXVgvMsGMMHSufONT8E7zYBSSDNO4

Oncothermia Journal 37, September 2025., 46-58.
https://oncotherm.com/MinnaarCA_2025_Oncotherm_in_Italy_20250402

Final 5 year results from the randomised controlled trial on modulated electro-hyperthermia added to chemoradiotherapy for the management of locally advanced cervical cancer

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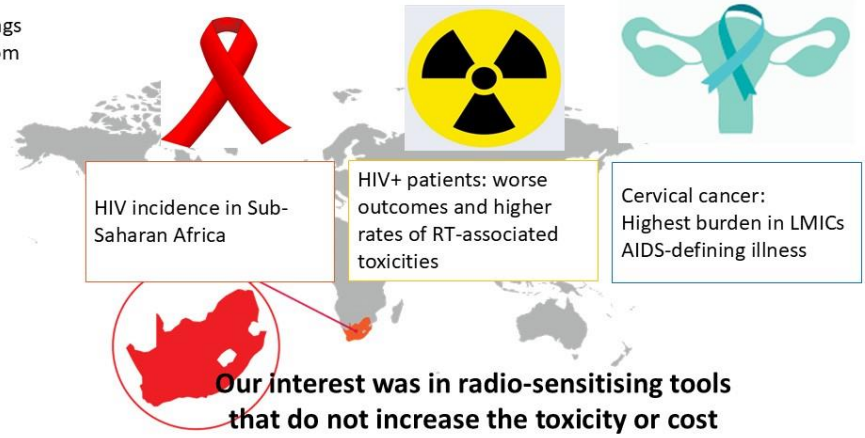
Background

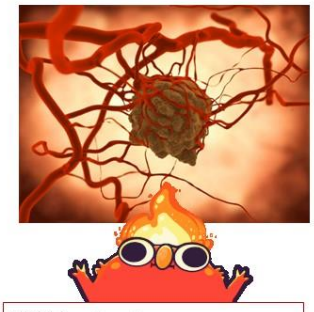
Resource constrained settings report poorer outcomes from cancer treatment:

- Inadequate access to treatment
- Sub-optimal treatment
- Co-morbidities
- Poverty

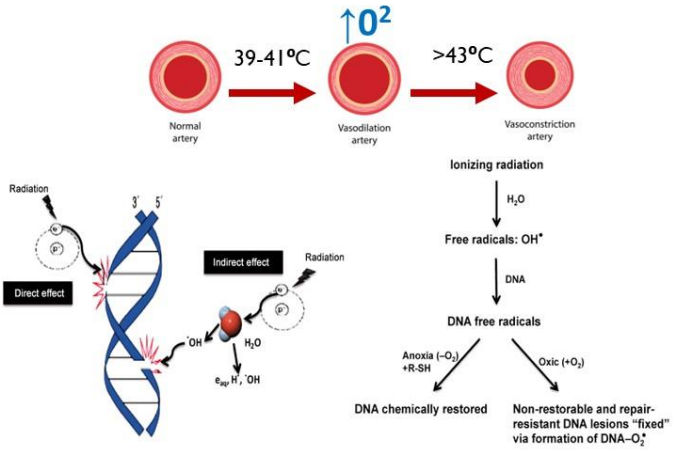


Our interest was in radio-sensitising tools that do not increase the toxicity or cost profile in resource constrained settings

Background



Mild heating increases oxygen perfusion, enhancing the damage done by ROS and inhibiting the repair processes



Methodology

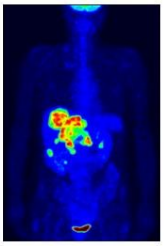
Sample:
Stage IIB-IIIB
Staged clinically: exam, chest x-ray; abdominal/pelvic ultrasound.

Control Group
50Gy EBRT
3x8Gy HDR
BT, 80mg/m²
cisplatin

Randomised using an online tool (RedCap)
Stratum: HIV status

Intervention Group
50Gy EBRT
3x8Gy HDR
BT, 80mg/m²
cisplatin
+ mEHT

HIV-positive participants were included provided their CD4 count was >200cells/mm³ /they had been on ART for >6m.



LDC:
PET/CT pre-treatment & 6m post-treatment.

Survival:
Last known disease status used for LTFU

QoL:
EORTC CX24 forms

Statistics:
Kaplan-Meier charts; Log rank tests; frequency tables; Markov model

Clinicians conducting follow ups were blinded to the group

Methodology:

mEHT

- 2 x per week
- Immediately before external beam RT
- Max 30 minutes between HT and RT
- Treated for 60 minutes and
- Aimed for at least 130W

Results

PLOS ONE

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frontiers in Medicine

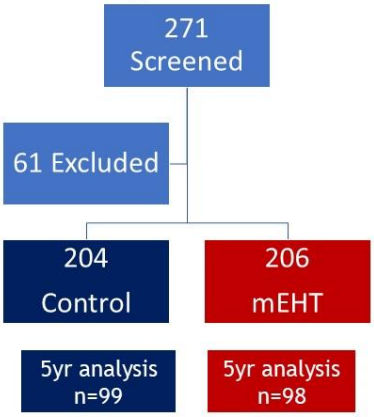
cancers

ICHS 38.
38th Conference of the International Clinical Hyperthermia Society

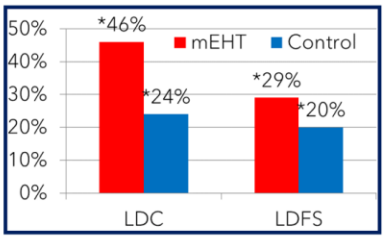
ESHO2019
13TH ANNUAL MEETING OF THE EUROPEAN SOCIETY FOR HYPERTHERMIC ONCOLOGY

ESTRO 2021

Phase III RCT 2014-2023
HR Ethics Committee : M1704133
ClincialTrials.gov ID: NCT03332069



Results: Local Disease Control



210 Randomised Participants	Control		mEHT		Chi Squared
	n	%	n	%	
LDC achieved at 6 months	20	24.1%	40	45.5%	*p = 0.003*
LDFS at six months	20	19.8%	39	38.6%	*p = 0.003*

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Results: Safety

6 months post treatment

- No dose-limiting toxicities
- High Compliance (97% completed ≥8 treatments)
- No significant differences in CRT-related toxicity between treatment groups
- Toxicity:
  - grade 1–2 adipose burns: 9.5%
  - grade 1 surface burns: 2%
  - pain during mEHT: 8.6%

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Late Toxicity

At three years still no difference in late toxicities between the groups

cancers

No effect on late toxicity at 5 years

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Results: Local Disease Contr

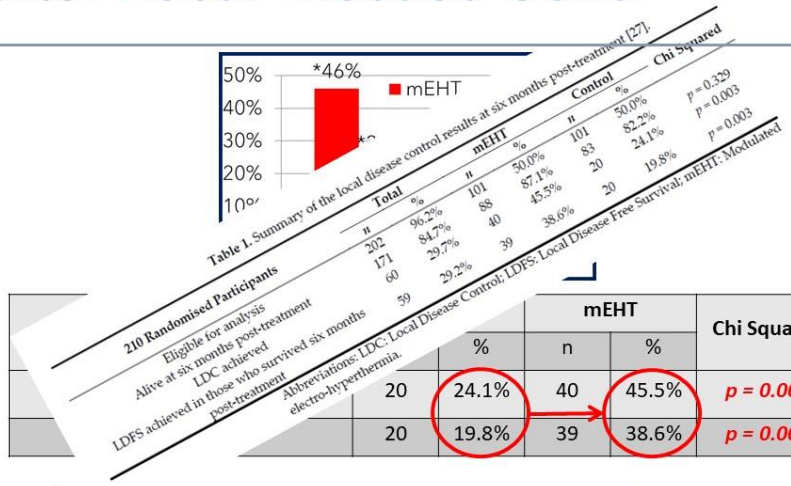

Table 1. Summary of the local disease control results at six months post-treatment [27].

	Total		mEHT		Control		Chi Squared
	n	%	n	%	n	%	
210 Randomised Participants	202	96.2%	101	50.0%	101	50.0%	$p = 0.329$
Eligible for analysis	171	84.7%	88	87.1%	83	82.2%	$p = 0.003$
Alive at six months post-treatment	60	29.7%	40	45.5%	20	24.1%	$p = 0.003$
LDC achieved	59	29.2%	39	38.6%	20	19.8%	
LDFS achieved in those who survived six months post-treatment							

Abbreviations: LDC: Local Disease Control; LDFS: Local Disease Free Survival; mEHT: Modulated electro-hyperthermia.

		mEHT		Chi Squared
	%	n	%	
20	24.1%	40	45.5%	*p = 0.003*
20	19.8%	39	38.6%	*p = 0.003*

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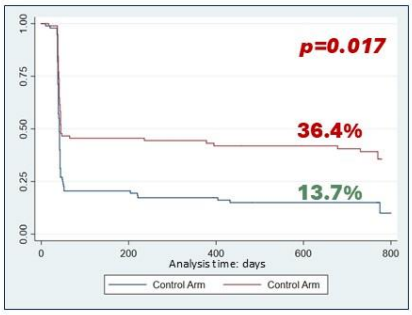
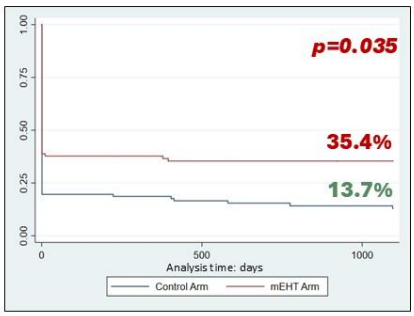
Results: 3 year Disease Free Survival

2 Year Disease Free



3 Year Disease Free



	OR	p=value	[95%CI]
2 year	3.59	*0.001*	1.79-7.21
3 year	3.4	*0.001*	1.71-6.91

cancers

Results: Quality of Life

Table 9. Mean change in scores from baseline to 24 months in the mEHT and Control Group.

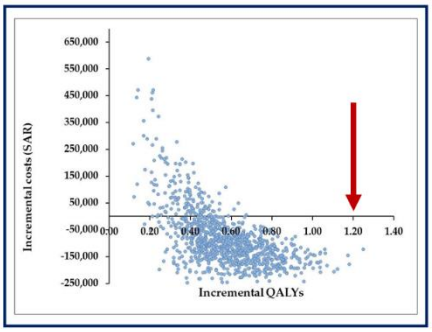
	mEHT				Control			
	Mean	SD	95%CI	*p*-Value	Mean	SD	95%CI	*p*-Value
Visual Analogue	25.1	21.5	16.6 to 33.6	$p < 0.0001$	15.6	31.9	2.9 to 28.2	$p = 0.0176$
Global Health	23.2	31.7	11.7 to 35.6	$p = 0.0002$	17.3	29.1	6.0 to 28.6	$p = 0.0041$
Financial Burden	−26.1	60.9	−48.0 to 4.1	$p = 0.0216$	−16.7	46.7	−34.8 to 1.4	$p = 0.0698$
Symptom Scales								
Pain Reduction	−34.4	32.8	−46.2 to −22.6	$p = 0.0001$	−15.5	35.7	−29.3 to −16	$p = 0.0298$
Nausea/Vomiting	−13.0	27.7	−23.0 to −3.0	$p = 0.0122$	−1.2	18.7	−8.4 to 6.1	$p = 0.7383$
Fatigue reduction	−18.4	27.9	−28.5 to −8.4	$p = 0.0008$	−10.7	34.0	−23.9 to 2.4	$p = 0.1071$
Functional Scales								
Social	12.0	31.2	0.7 to 23.2	$p = 0.0375$	17.3	41.7	1.1 to 33.4	$p = 0.0373$
Cognitive	19.8	33.2	7.8 to 31.6	$p = 0.0020$	−4.2	28.9	−15.4 to 7.0	$p = 0.4523$
Emotional	27.3	30.3	16.4 to 38.3	$p < 0.0001$	17.9	34.2	4.6 to 31.1	$p = 0.0101$
Role Function	9.4	35.1	−3.3 to 22.1	$p = 0.1415$	7.1	35.0	6.4 to 20.7	$p = 0.2893$
Physical	11.7	21.2	4.0 to `9.3	$p = 0.0040$	2.6	27.2	−7.9 to 13.2	$p = 0.6150$

Abbreviations: FIGO: CI: Confidence Interval; mEHT: Modulated Electro-Hyperthermia; SD: Standard Deviation.

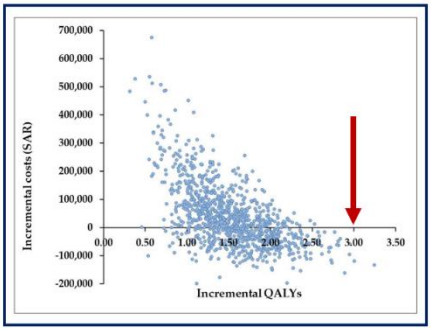
Overall significant improvement in 10 out of 11 scores in the mEHT group at 2 years

Results: Cost Effectiveness Analysis

Government model
82.2% probability



Private model
77.7% probability



- mEHT + CRT dominated the model
- mEHT + CRT **less costly and more effective**

Results: Cost Effectiveness Analysis

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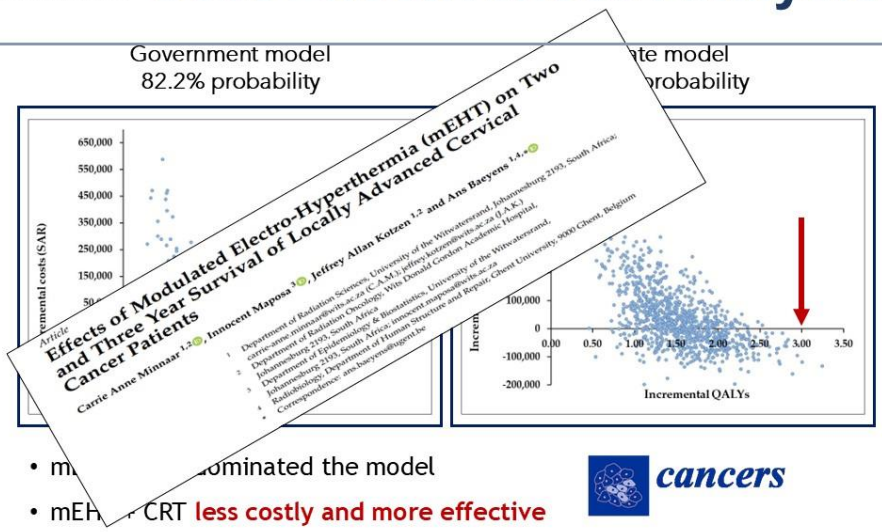


Article
Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients
Carrie Anne Minnaar 1,2, Innocent Maposa 3, Jeffrey Allan Kotzen 1,2 and Ans Baeyens 1,4,*

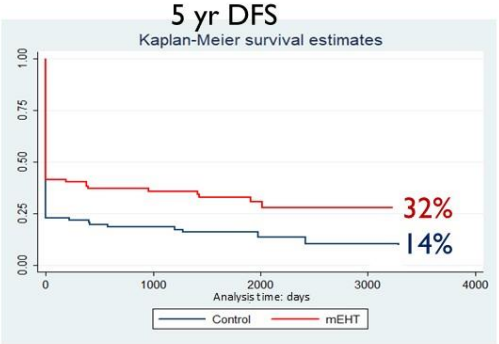
- m… dominated the model
- mEH… CRT **less costly and more effective**

cancers

Results: 5 year Disease Free Survival

5yr OS	mEHT	Control	
All	33% [33/99]	26% [25/98]	HR:0.74; 95%CI:0.53-1.03; p=0.083
Stage III	**34% [21/61]**	**23% [15/65]**	HR:0.65; 95%CI:0.43-0.99; p=0.046

5 yr DFS



OR:3.00; 95%CI:1.49-6.07; ***p=0.002;***
HR:0.73; 95%CI:0.53-1.00; ***p=0.049;***
Chi2: ***p=0.002***

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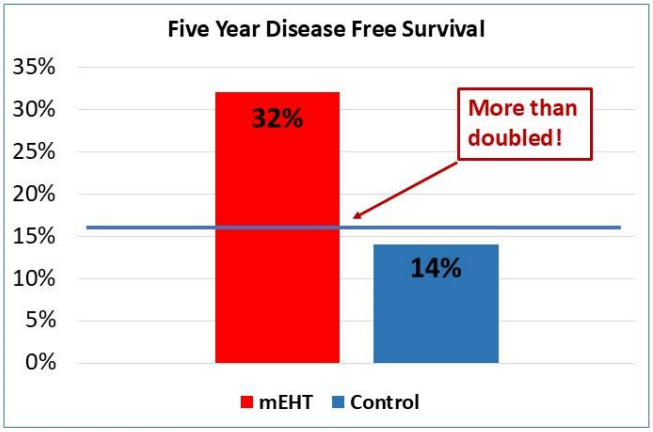
Results: 5 year Disease Free Survival



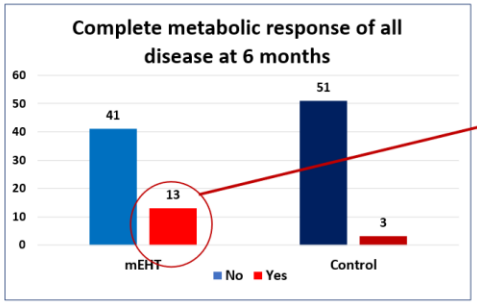
32%[32/99] of hyperthermia participants

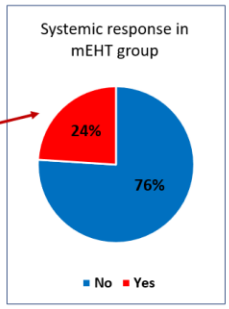
14%[14/102] of control participants

Achieved 5 years DFS

Odds were increased by 3x!

Results: Abscopal Response





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

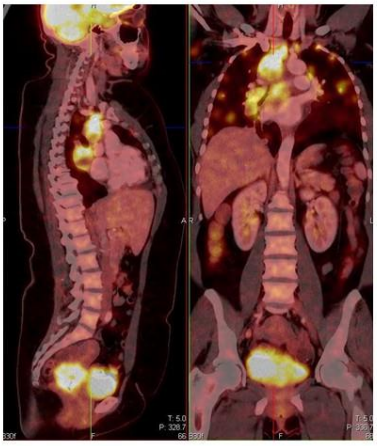
In a univariate analysis, CD4 count was also not predictive of an abscopal effect

Results: Abscopal Response

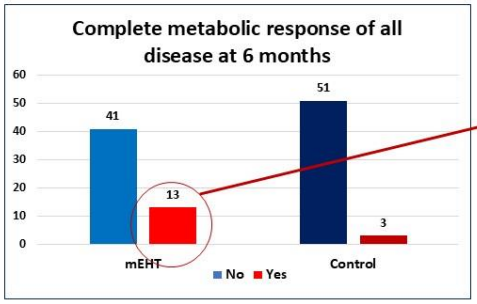
Pre-treatment PET/CT studies showed:

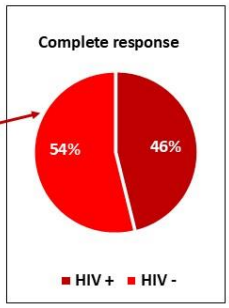
- **108 Participants had extra pelvic disease**
- **54 participants in each group**

!!!!!



Results: Abscopal Response





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Potentiation of the abscopal response by mEHT?!

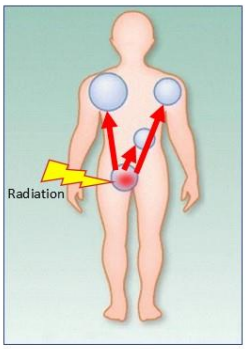
frontiers in Medicine

Results: Abscopal Response

SUSTAINED SYSTEMIC RESPONSE

- Participants with stage IVB disease outside the pelvis,
- who showed an abscopal response at 6 months,
- remained disease free at 5 years
- With the exception of 2 participants who died of non-cancer related causes

24 % of participants with stage IV disease outside the pelvis achieved 5yr disease free survival with addition of mEHT to RT



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Abscopal Response

mEHT damages cell membranes

Promotes ICD and DAMP

= apoptosis and release of apoptotic bodies

= release of mHSPs into the extra cellular matrix

→ transport intracellular antigenic peptides to DCs

= maturation of DCs into APCs

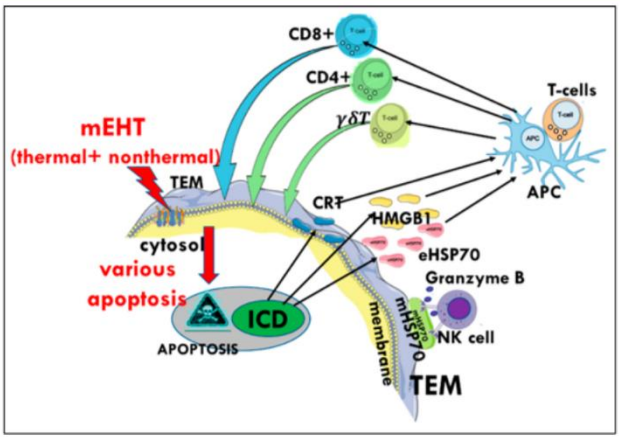
→ produce antigen-specific cytotoxic T-lymphocytes and activated NK cells

Potentially = adaptive immune response

Immunogenic Hyperthermia = mild heat + immune-modulation

Minnaar CA, Szasz A. Forcing the Antitumor Effects of HSPs Using a Modulated Electric Field. Cells. 2022 Jun 4;11(11):1838. doi: 10.3390/cells11111838. PMID: 35681533;

Abscopal Response



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Conclusion:

Modulated electro-hyperthermia added to CRT for the management of cervical cancer:

- ✓ **Significantly increases local disease control**
- ✓ **Significantly increased 5y DFS rates,**
- ✓ **Does not alter the toxicity profile**
- ✓ **Has potential to lower treatment costs**
- ✓ **Improves Quality of Life.**

- ✓ **Promotes a sustained long-term, immune-mediated, systemic response to the disease.**

Acknowledgements

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Department of Nuclear Medicine

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Thank you

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