

# Modulated electro-hyperthermia added to chemoradiotherapy improves five-year survival: **final results** of a phase III randomised controlled trial

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35<sup>th</sup> Annual Meeting

European Society for  
Hyperthermic Oncology

# INTRODUCTION

## **Trial Protocols developed in 2013:**

### **Modulated electro-hyperthermia (mEHT):**

- **Mild**, capacitive-coupled heating technology
- **Amplitude modulation** enhance the cell-killing effects

**Simple to use and affordable**  
**Immune-modulating effects**

Ethics approval: M190295  
National Clinical Trials Register ID:3012  
ClinicalTrials.gov ID: NCT03332069

**Therefore used to investigate the radiosensitising effects in out **HIV-positive** and –negative patients in a **resource constricted environment****

# METHODOLOGY

- **210 participants** randomized to receive CRT +/- mEHT
  - Stratum: HIV status, stage and age
- **HIV-positive** participants (CD4>200 / on ART> 6 months)
- **FIGO Stage IIB-IIIB** (staged clinically)
- **PET/CT** pre- and 6/12 post-RT for disease response

CRT	mEHT
<ul style="list-style-type: none"><li>- 50Gy EBRT in 25#</li><li>- <b>3 x 8Gy HDR BT</b></li><li>- <b>80mg/m<sup>2</sup> Cisplatin 21 days apart</b></li></ul>	<ul style="list-style-type: none"><li>- 2/wk immediately before EBRT</li><li>- <b>60 minutes at 130W</b></li></ul>

# RESULTS

**Table 2.** Participant characteristics.

Participant Characteristic		mEHT		Control		p-Value
		106	(50.5%)	104	(49.5%)	
HIV Status	Positive	52	(49.1%)	55	(52.9%)	$p = 0.579$
	Negative	54	(50.9%)	49	(47.1%)	
Age Group	<50 years	52	(49.1%)	46	(44.2%)	$p = 0.483$
	≥50 years	54	(50.9%)	58	(55.8%)	
ECOG	0	3	(2.8%)	7	(6.7%)	$p = 0.184$
	1	103	(97.2%)	97	(93.3%)	
Race	African	98	(92.5%)	97	(93.3%)	$p = 0.335$
	Caucasian	4	(3.8%)	1	(1.0%)	
	Indian	0	(0.0%)	0	(0.0%)	
	Asian	0	(0.0%)	0	(0.0%)	
	Mixed Race	4	(3.8%)	6	(5.8%)	
Education	Primary	45	(43.3%)	50	(49.0%)	$p = 0.334$
	Secondary	55	(52.9%)	51	(50.0%)	
	Tertiary	4	(3.8%)	1	(1.0%)	
Employment	Unemployed	83	(78.3%)	82	(78.8%)	$p = 0.923$
	Employed	23	(21.7%)	22	(21.2%)	
FIGO Staging	IIB	40	(37.7%)	36	(34.6%)	$p = 0.895$
	IIIA	1	(0.9%)	1	(1.0%)	
	IIIB	65	(61.3%)	67	(64.4%)	
Histological Grade	1	7	(6.9%)	4	(4.1%)	$p = 0.759$
	2	70	(69.3%)	67	(69.1%)	
	3	24	(23.8%)	26	(26.8%)	
Tumour Dimensions (cm)	Median	7		7.1		$p = 0.1429$
	Min	2.7		1.8		
	Max	11.7		14.87		
Tumour SUV	Median	18.07		19.26		$p = 0.7769$
	Min	7.01		6.07		
	Max	63.25		97		
HB (g/dL)	Median	10.9		11		$p = 0.9424$
	Min	5.7		5.2		
	Max	16.2		16.2		
Age	Median	49.2		50.6		$p = 0.3665$
	Min	27.3		29.2		
	Max	70.8		74.8		
BMI	Median	27		26.5		$p = 0.3883$
	Min	15		15		
	Max	49		41.7		

Abbreviations: BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HB: Haemoglobin; HIV: Human Immunodeficiency Virus; mEHT: Modulated Electro-Hyperthermia; SUV: Standard Uptake Value.

**Table 3.** Treatment characteristics.

Treatment Characteristics		mEHT		Control		p-Value
		106	(50.5%)	104	(49.5%)	
No of HDR BT doses	0	0	(0.0%)	0	(0.0%)	$p = 0.223$
	1	0	(0.0%)	2	(2.0%)	
	2	3	(2.9%)	1	(1.0%)	
	3	101	(97.1%)	99	(97.1%)	
No of Cisplatin Doses	0	14	(13.6%)	11	(10.7%)	$p = 0.727$
	1	42	(40.8%)	47	(45.6%)	
	2	47	(45.6%)	45	(43.7%)	
	Median	74		74		
Total RT Dose	Min	20		2		$p = 0.6133$
	Max	74		74		
	Median	37		37		
Days between enrolment and Treatment	Min	18		21		$p = 0.2241$
	Max	79		104		
	Median	10				
No of mEHT doses	Min	1				
	Max	10				


Abbreviations: HDR BT: High Dose Rate Brachytherapy; HIV: Human Immunodeficiency Virus; mEHT: Modulated Electro-Hyperthermia; RT: Radiotherapy.

## PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

### The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial

Carrie Anne Minnaar, Jeffrey Allan Kotzen, Olusegun Akinwale Ayeni, Thanushree Naidoo, Mariza Tunmer, Vinay Sharma, Mboyo-Di-Tamba Vangu, Ans Baeyens 

Published: June 19, 2019 • <https://doi.org/10.1371/journal.pone.0217894>

# SAFETY AND TOXICITY

- No dose-limiting toxicities
- High Compliance (97% completed  $\geq 8$  of 10 treatments)
- No sig. differences in CRT-related toxicity between groups

## mEHT Toxicity:

grade 1–2 adipose burns: 9.5%

grade 1 surface burns: 2%

pain during mEHT: 8.6%

Significant improvement in  
QoL at 3 and 6 months post-  
RT in mEHT group

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2020, VOL. 37, NO. 1, 263–272  
<https://doi.org/10.1080/02656736.2020.1737253>



Taylor & Francis  
Taylor & Francis Group

OPEN ACCESS

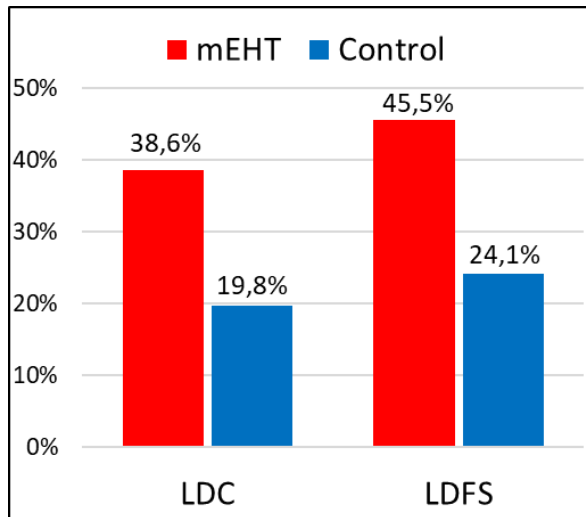


## Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients

Carrie Anne Minnaar<sup>a</sup>, Jeffrey Allan Kotzen<sup>b</sup>, Thanushree Naidoo<sup>c</sup>, Mariza Tunmer<sup>a,b</sup>, Vinay Sharma<sup>a,d</sup>,  
Mboy-Di-Tamba Vangu<sup>e,f</sup> and Ans Baeyens<sup>a,g</sup>

# 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%	$p = 0.003$



**PLOS ONE**

OPEN ACCESS PEER-REVIEWED  
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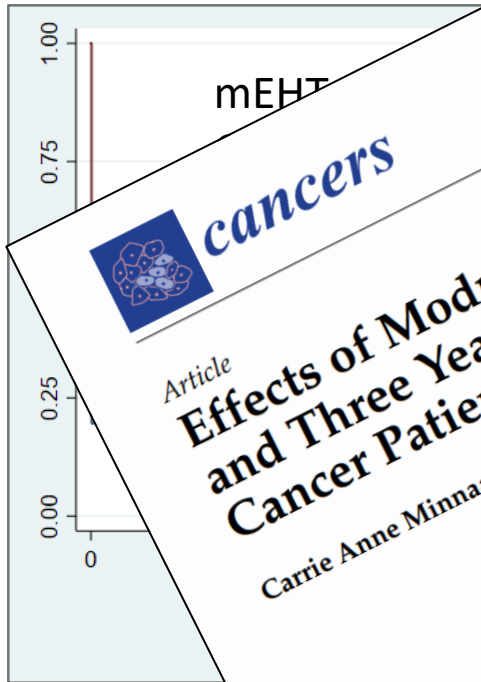
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Published: June 19, 2019 • <https://doi.org/10.1371/journal.pone.0217894>

# THREE YEAR SURVIVAL

Disease recurrence at 2  
**significantly reduced**

KM:3yr Disease Free S



 **cancers**

Article

## Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical

Carrie Anne Minnaar<sup>1,2</sup>, Innocent Maposa<sup>3</sup>, Jeffrey Allan Kotzen<sup>1,2</sup> and Ans Baeyens<sup>1,4,\*</sup>

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- \* Correspondence: ans.baeyens@ugent.be



OR: 3.4

HR:0.70,

**p=0.001**

**p=0.035**

no significant  
differences in late  
toxicity between the  
groups.

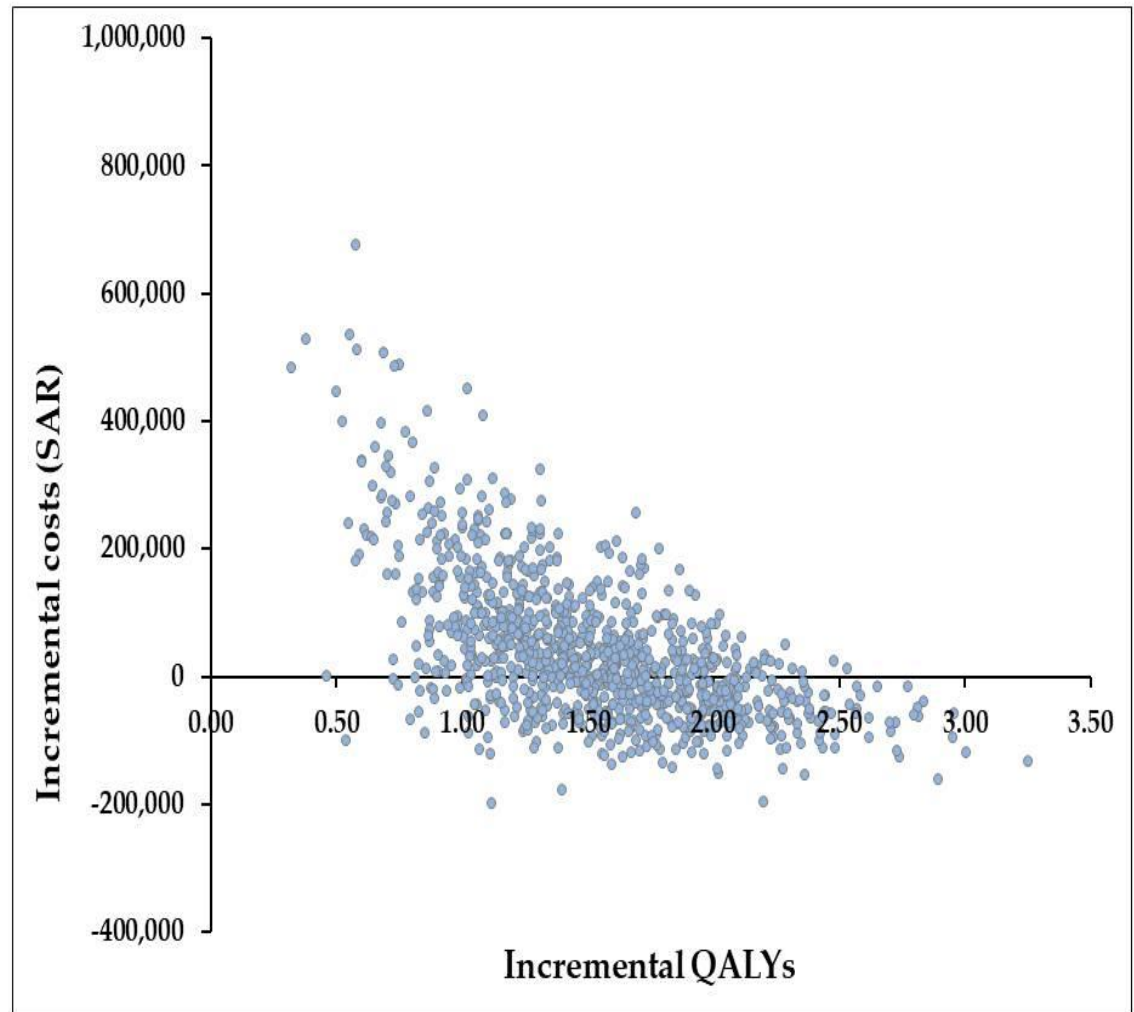


# COST EFFECTIVENESS ANALYSIS

**Clinical and Cost**  
benefit to the  
addition of mEHT  
to CRT

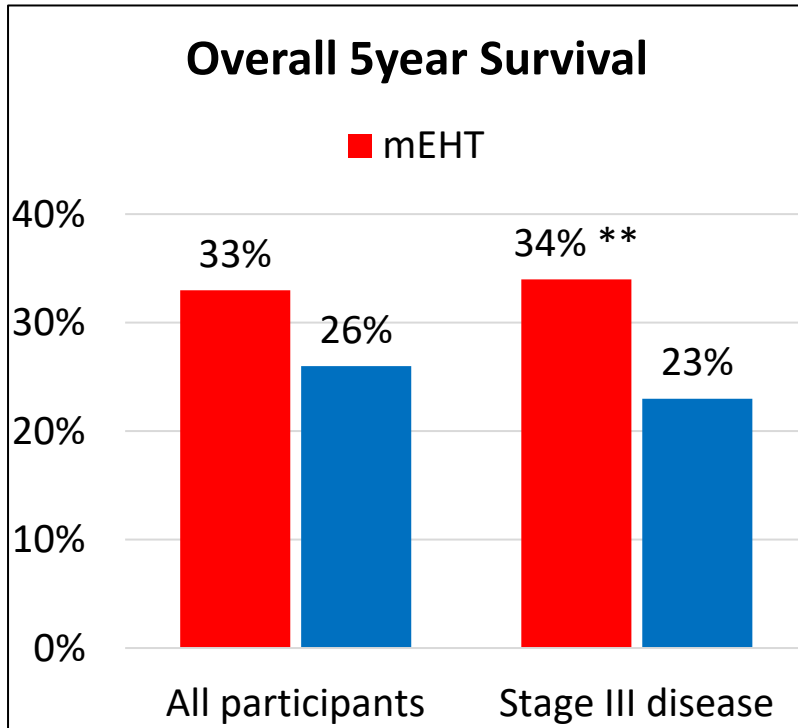
Probability of 78%  
and 82% in private  
and government  
facilities

**mEHT+CRT**  
**Dominated the**  
**Markov model**





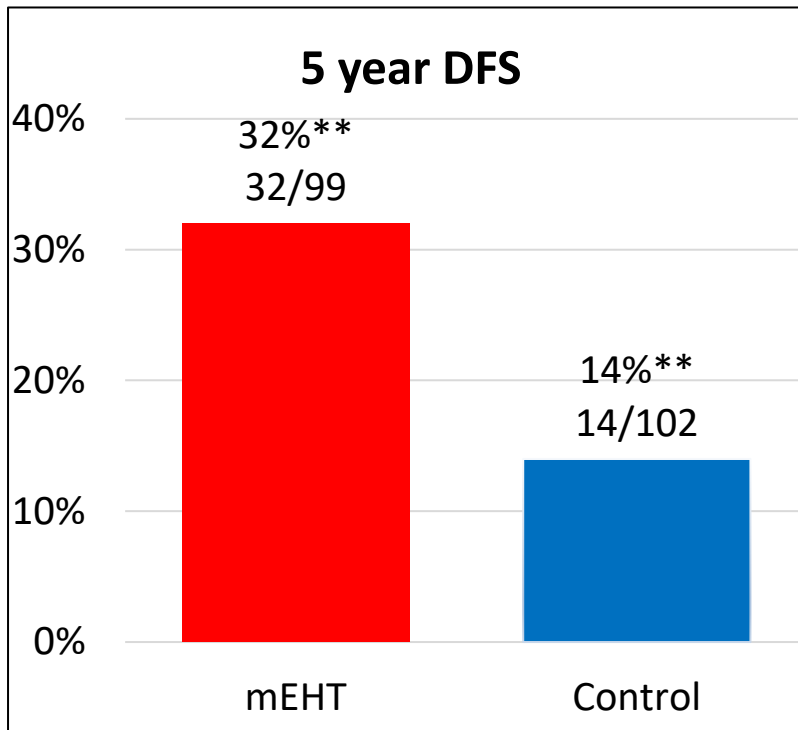
# FIVE YEAR SURVIVAL



HR:0.74;  
95%CI: 0.53-  
1.03; p=0.083

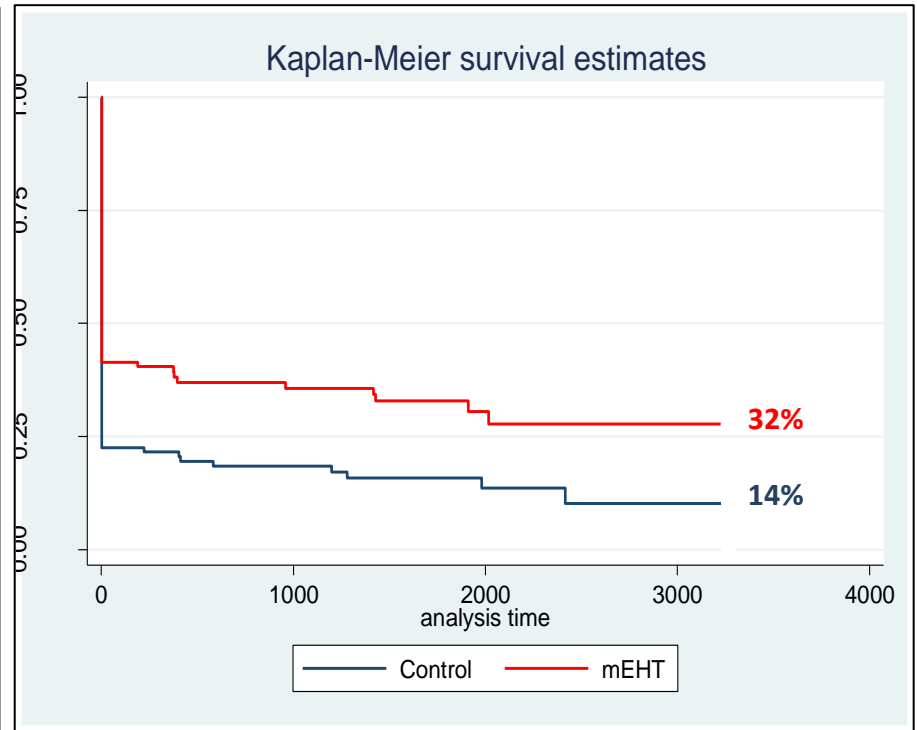
HR:0.65;  
95%CI: 0.43-  
0.99; **p=0.046**

# FIVE YEAR SURVIVAL



Chi-squared:  $p=0.002$

OR:3.00; 95%CI:1.49-6.07;  $p=0.002$



HR:0.73; 95%CI:0.53-1.00;  $p=0.049$

*There were no significant differences in late toxicity between the groups.*

# ABSCOPAL EFFECT

54 participants in each group  
disease pre-treatment

CMR of  
6 m  
m  
Con  
Chi-s



## Potential of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients

Carrie Anne Minnaar<sup>1</sup>, Jeffrey Allan Kotzen<sup>2</sup>, Olusegun Akinwale Ayeni<sup>3</sup>,  
Mboyo-Di-Tamba Vangu<sup>3</sup> and Ans Baeyens<sup>1,4\*</sup>

ORIGINAL RESEARCH  
published: 24 March 2020  
doi: 10.3389/fonc.2020.00376

All disease resolved

Residual disease

3\*



# ABSCOPAL EFFECT

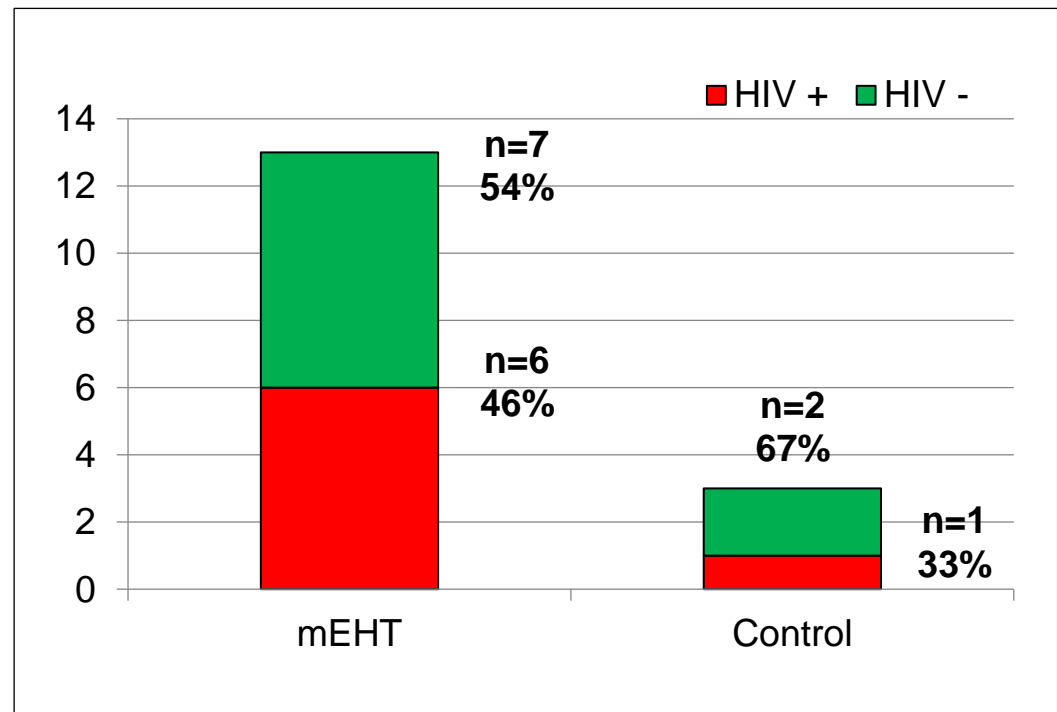
## Systemic Control – using the **ABSCOPAL** effect

The abscopal effect was not associated with:

- HIV status
- No. of cisplatin Doses
- Disease Stage
- Age

85% Remained alive and DF at 5 years  
2/13 died of non-disease related causes

**Abscopal effect and HIV status**

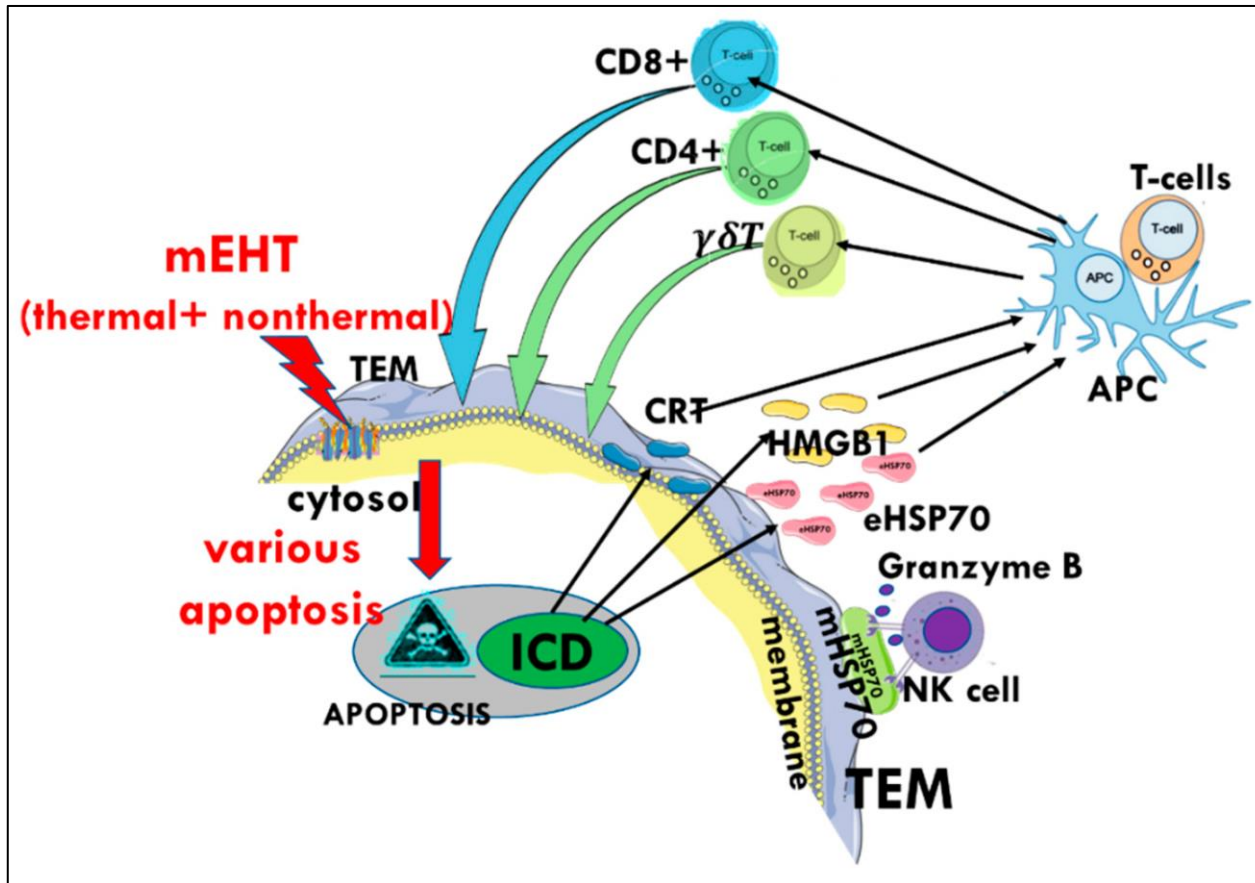


mEHT Group: 13 out of 54 [24.1%]

Control Group: 3 out of 54 [5.6%]

( $p=0.013$ )

# IMMUNE RESPONSE TRIGGERED BY MEHT



mEHT associated  
apoptosis = apoptotic  
bodies

→ release of mHSPs  
→ activate NK cells  
→ ICD and DAMP  
= maturation of DCs into  
APCs  
→ triggers T-cells

Potential for adaptive  
immune response

Potentiates the abscopal effect: Immune mediated response to RT resulting in resolution of lesions outside the treatment field

# CONCLUSION

## **mEHT + CRT for the management of LACC:**

- Safe

- Improves QoL

- Improves LDC

- mEHT improves 5 year DFS

- SYSTEMIC EFFECTS** – abscopal

- Lowers treatment costs, without increasing toxicity*  
in LACC patients, even in resource-constrained settings.

# FUTURE PERSPECTIVES



*Combining mEHT with immunotherapy*



*Phase I/II paediatric brainstem glioma study*



*A larger phase III trial on adult GBM  
tumours managed with radiotherapy  
combined with mEHT*



# ACKNOWLEDGMENTS



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# THANK YOU



Wits University  
Donald Gordon  
Medical Centre

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MEDICLINIC 



## 35<sup>th</sup> Annual Meeting

European Society for  
Hyperthermic Oncology