Modulated electro-hyperthermia added to chemoradiotherapy improves five-year survival: final results of a phase III randomised controlled trial - ESHO 2023 presentation

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Citation

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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
ClincialTrials.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
- 50Gy EBRT in 25# **- 3 x 8Gy** HDR BT **- 80mg/m^2 Cisplatin 21 days apart**	- 2/wk immediately before EBRT **- 60 minutes at 130W**

RESULTS

Table 2. Participant characteristics.

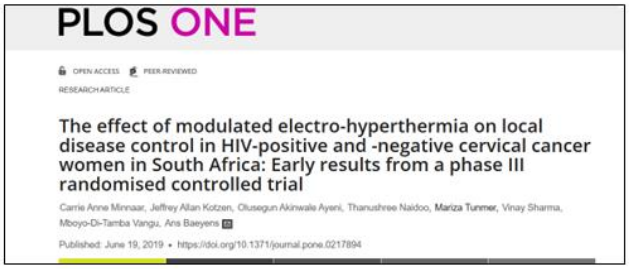
Participant Characteristic		mEHT 106	(50.5%)	Control 104	(49.5%)	*p*-Value
HIV Status	Positive	52	(49.1%)	55	(52.9%)	$p = 0.579$
	Negative	54	(50.9%)	49	(47.1%)	
Age Group	<50 years	52	(49.1%)	46	(44.2%)	$p = 0.483$
	≥50 years	54	(50.9%)	58	(55.8%)	
ECOG	0	3	(2.8%)	7	(6.7%)	$p = 0.184$
	1	103	(97.2%)	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 106	(50.5%)	Control 104	(49.5%)	*p*-Value
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%)	
Total RT Dose	Median	74		74		$p = 0.6133$
	Min	20		2		
	Max	74		74		
Days between enrolment and Treatment	Median	37		37		$p = 0.2241$
	Min	18		21		
	Max	79		104		
No of mEHT doses	Median	10				
	Min	1				
	Max	10				

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


PLOS ONE

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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 ≥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

INTERNATIONAL JOURNAL OF HYPERTHERMIA
2020, VOL. 37, NO. 1, 263–272
https://doi.org/10.1080/02656736.2020.1737253

Taylor & Francis
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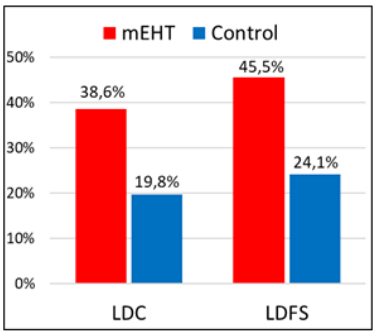
OPEN ACCESS Check for updates

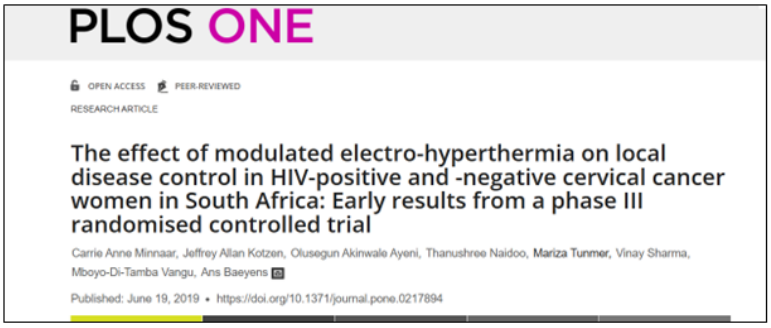
Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients

Carrie Anne Minnaar[a], Jeffrey Allan Kotzen[b], Thanushree Naidoo[c], Mariza Tunmer[a,b], Vinay Sharma[a,d], Mboyo-Di-Tamba Vangu[e,f] and Ans Baeyens[a,g]

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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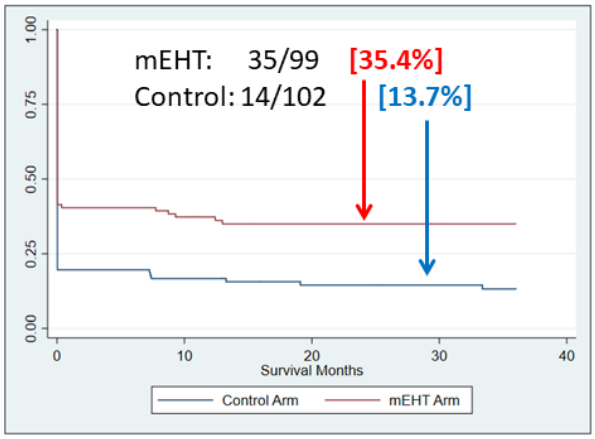
THREE YEAR SURVIVAL

Disease recurrence at 2 and 3 years was
significantly reduced by 25% with mEHT

KM:3yr Disease Free Survival

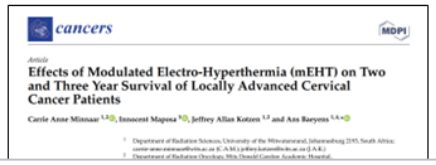


OR: 3.4, 95%CI:1.71–6.91, ***p=0.001***
HR:0.70, 95%CI:0.51–0.98, ***p=0.035***

3yr DFS doubled by mEHT

QoL at 2 yrs significantly higher in mEHT group

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

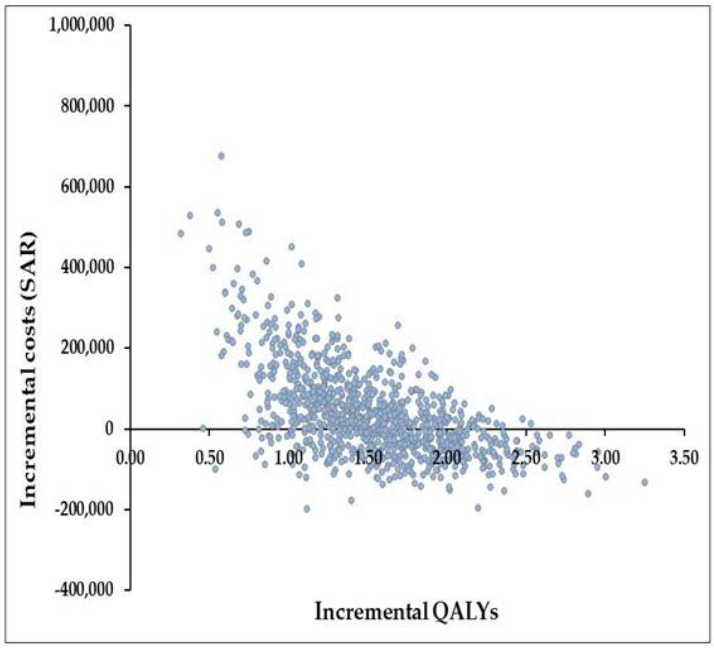

cancers
MDPI
Article
Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients

COST EFFECTIVENESS ANALYSIS

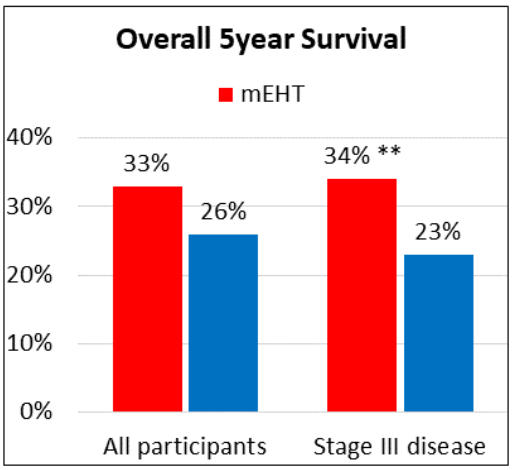
Clinical and Cost benefit to the addition of mEHT to CRT

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

mEHT+CRT Dominated the Markov model



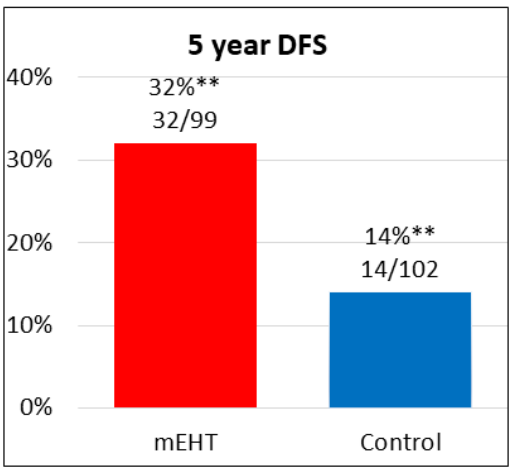
FIVE YEAR SURVIVAL



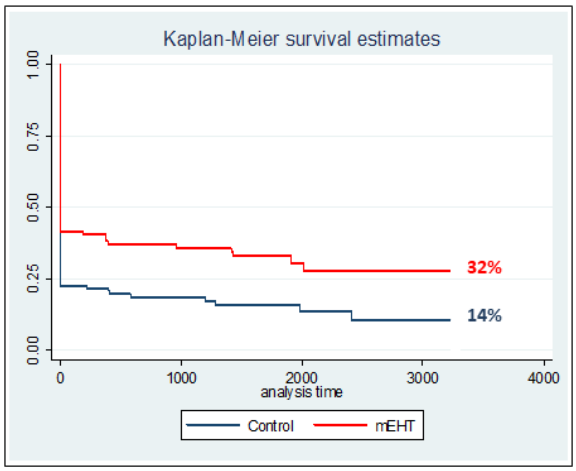
HR:0.74; 95%CI: 0.53-1.03; p=0.083

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*



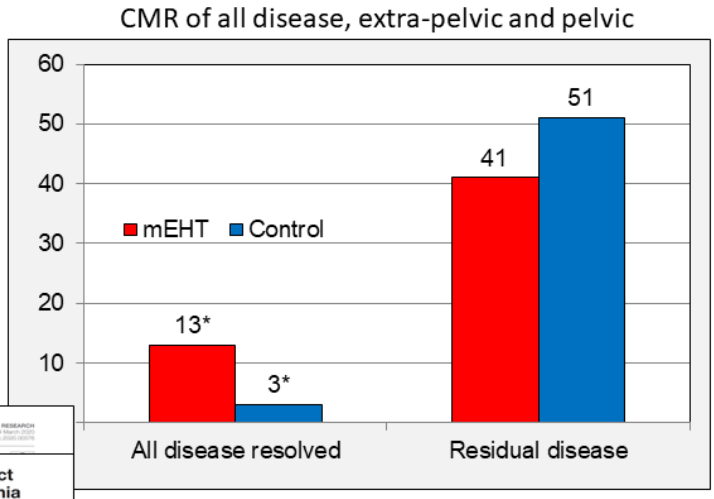
HR:0.73; 95%CI:0.53-1.00; *p=0.049*

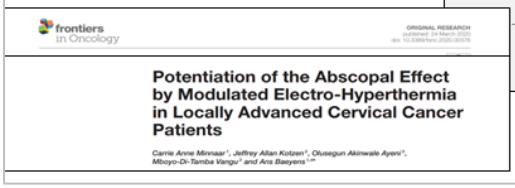
There were no significant differences in late toxicity between the groups.

ABSCOPAL EFFECT

54 participants in each group had extra-pelvic disease pre-treatment

CMR of all disease at 6 months:
mEHT: 24.1%
Control: 5.6%
Chi-squared *p=0.013*




frontiers in Oncology

ORIGINAL RESEARCH

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

ABSCOPAL EFFECT

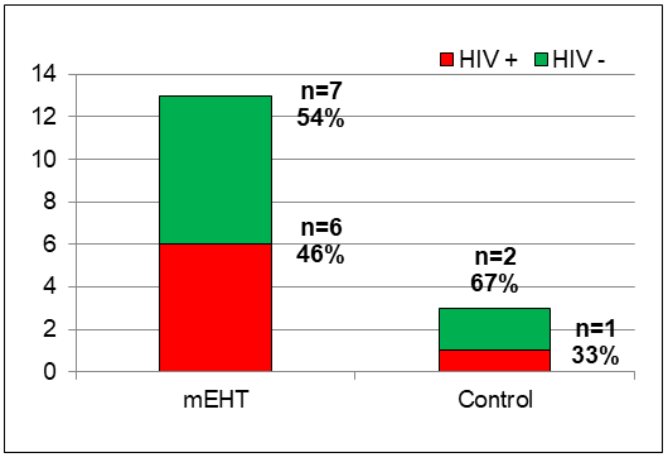
Systemic Control – using the ABSCOPAL effect

The abscopal effect was not associated with:

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

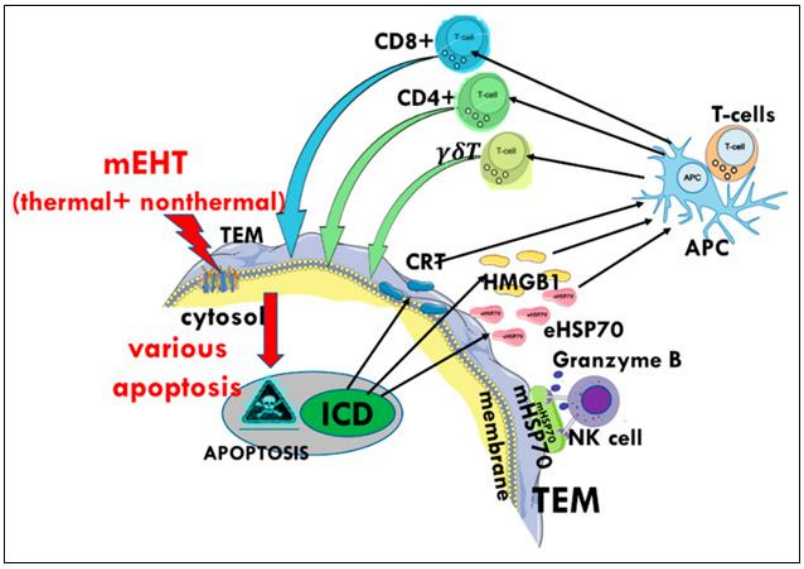
85% Remained alive and DF at 5 years
2/13 died of non-disease related causes

Abscopal effect and HIV s tatus



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

Minnaar CA, Szasz A.. Cells. 2022 Jun 4;11(11):1838. doi: 10.3390/cells11111838. PMID: 35681533;

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

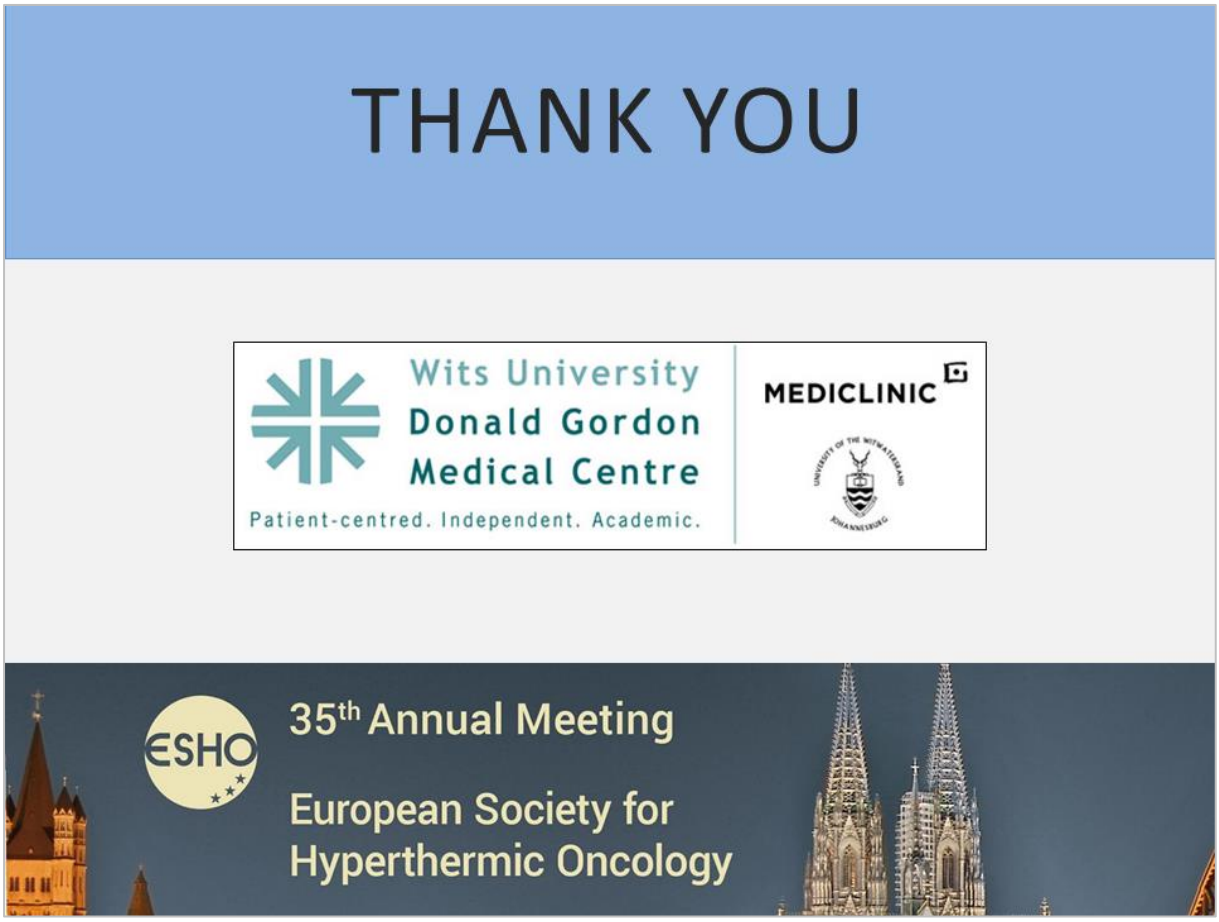
Phase I/II paediatric brainstem glioma study

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

ACKNOWLEDGMENTS

Thank you to all the participants who showed grace, strength, courage, and hope in the face of extreme adversity.

Thank you to the staff at the Department of Nuclear medicine, Medical Physics, Radiobiology, Medical oncology, and Radiology and Radiation Oncology at the Charlotte Maxeke Johannesburg Academic Hospital and the university of the Witwatersrand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