Modulated electro-hyperthermia more than doubles five year disease free survival rates in advanced cervical cancer patients in South Africa

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

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Citation

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Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/qXK_iHG37nk,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 100-112.
https://oncotherm.com/MinnarCA_2024_mEHT-more-than-doubles-5-year-disease-free-survival_20240601

Modulated electro-hyperthermia more than doubles five-year disease-free survival rates in advanced cervical cancer patients in South Africa

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Oncotherm

Wits University Donald Gordon Medical Centre
Patient-centred. Independent. Academic.

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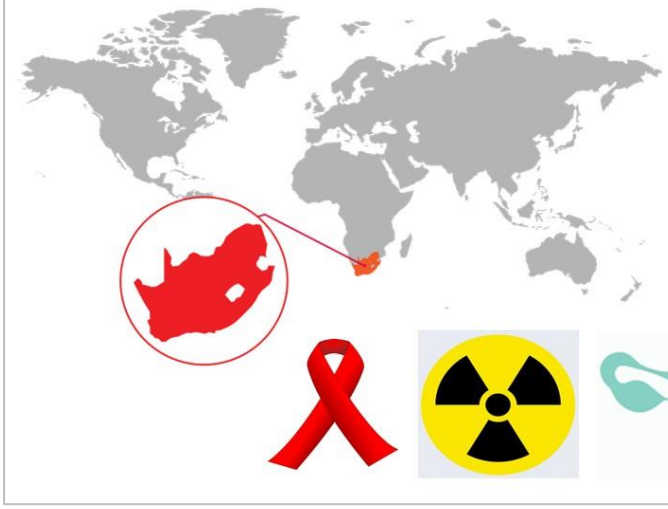
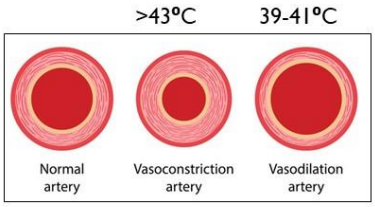
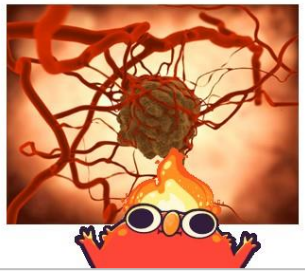
Outline:

- ✓ Introduction
- ✓ Methodology
- ✓ Safety
- ✓ Local Disease Control
- ✓ Long Term Control
- ✓ Systemic Control
- ✓ Future Perspectives

Introduction: Heat as a radio-sensitiser







Introduction: Heat as a radio-sensitiser

39-41°C = vasodilation

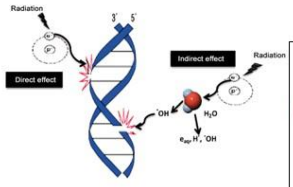
↑↑↑ Blood =

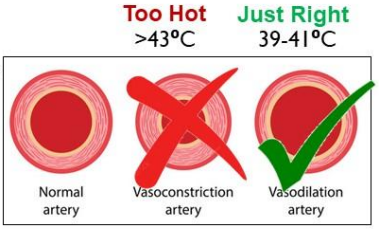
↑↑↑ Oxygen:

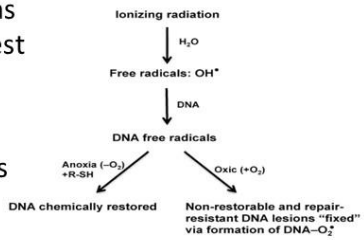
✓ increases ROS formation

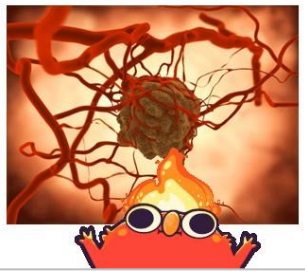
✓ inhibits repair from DSBs as the repair processes work best in an anoxic environment

✓ Heat slows down protein function, which further slows repair processes



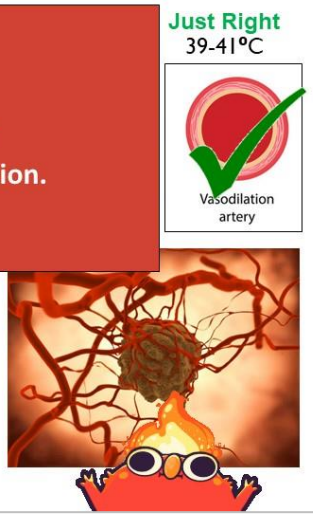






Introduction: Heat as a radio-sensitiser

Mild Heat = excellent radiosensitiser:
increasing the indirect cell kill effect for RT
and inhibiting the repair processes post irradiation.



Introduction: Heat as a radio-sensitiser

20 patients with cervical cancer were treated with mEHT

Measurements

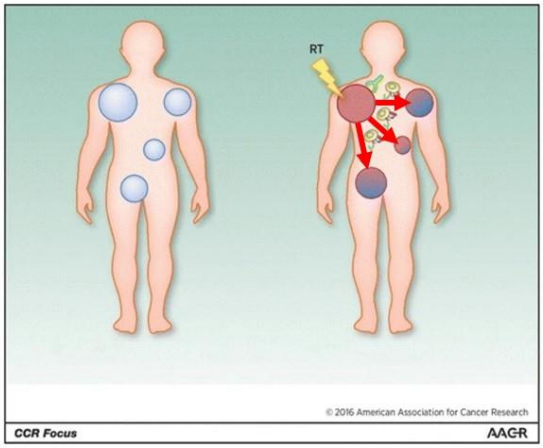
- **Temp**: Peri-tumour using an internal organ temperature probe
- **Blood flow**: 3D colour Doppler ultrasound used to determine peak systolic velocity end diastolic velocity ratio *(SID* ratio) and the resistance index (RI) within blood vessels.

Results:

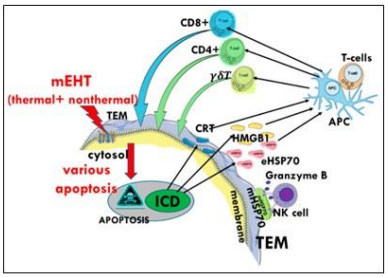
- **Temp:** mean peri-tumour temperature
  - Baseline: 36.7 ± 0.2 °C
  - 30 minutes: 37.5 ± 0.5 °C
  - 60 minutes: 38.5 ± 0.8 °C
- **Blood flow**:
  - *mEHT = significant increase in tumour blood flow*

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.

Introduction: Immuno-modulation



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



Introduction: Immuno-modulation

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

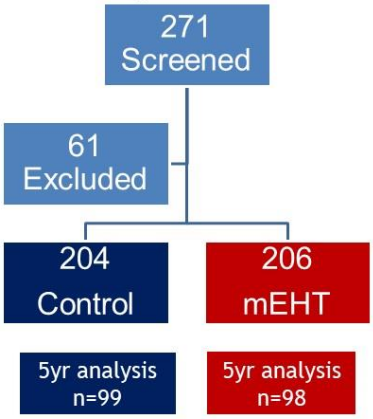
Potentially = adaptive immune response

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;

Methodology:

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



Methodology:

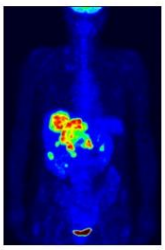
Sample:
Stage IIB-IIIB
Staged clinically: exam, chest x-ray; abdominal/pelvic ultrasound.

Control Group
50Gy EBRT
3x8Gy HDR
BT, 80mg/m^2
cisplatin

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

Intervention Group
50Gy EBRT
3x8Gy HDR
BT, 80mg/m^2
cisplatin
+ mEHT

HIV-positive participants were included provided their CD4 count was >200cells/mm^3 /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 bean RT

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 Control

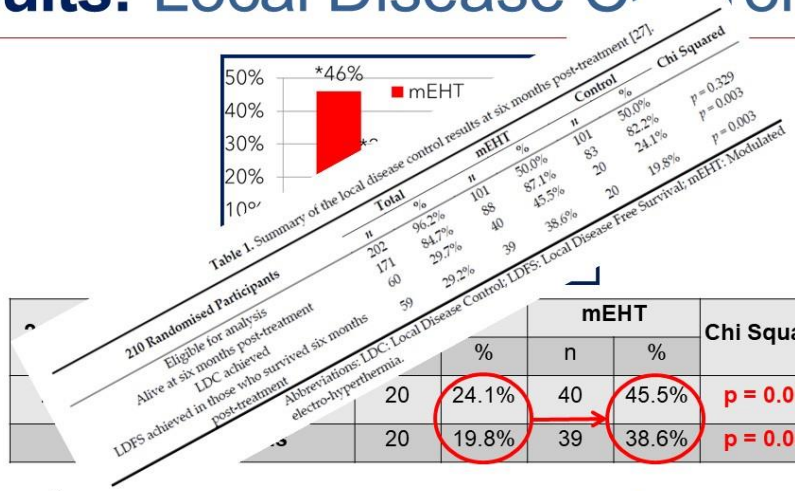

Table 1. Summary of the local disease control results at six months post-treatment [27].

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

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

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

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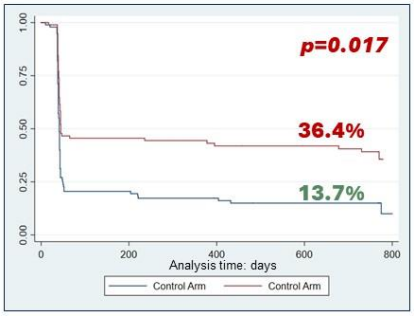
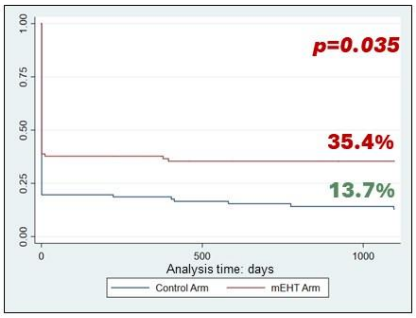
Results: Three-year Survival

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

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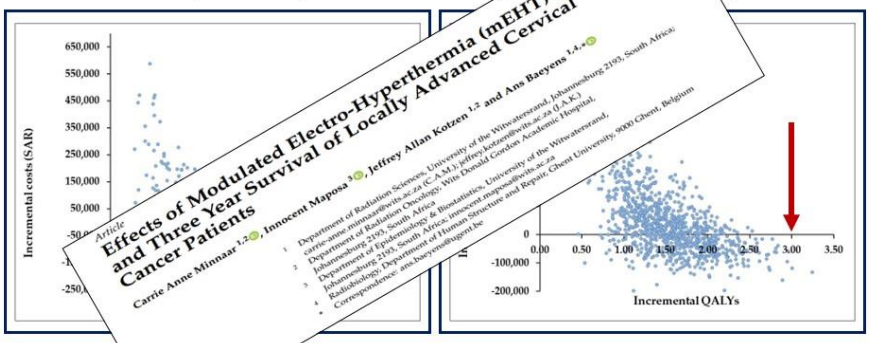
Results: Cost Effectiveness Analysis

Government model
82.2% probability



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,*]

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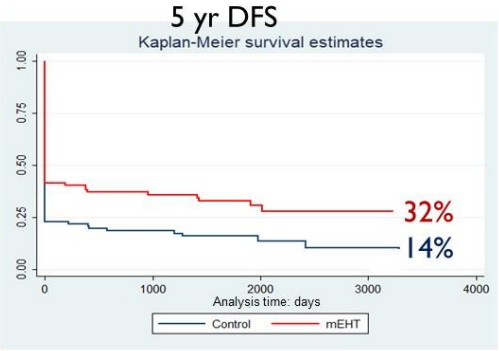
2 Department of Radiation Oncology, Wits Donald Gordon Academic Hospital, Johannesburg 2193, South Africa
3 Department of Epidemiology & Biostatistics, University of the Witwatersrand, Johannesburg 2193, South Africa; innocent.maposa@wits.ac.za
4 Radiobiology, Department of Human Structure and Repair, Ghent University, 9000 Ghent, Belgium
* Correspondence: ans.baeyens@ugent.be

- mEHT + [illegible]nated the model
- mEHT + CRT **less costly and more effective**

cancers

Results: Five-year 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



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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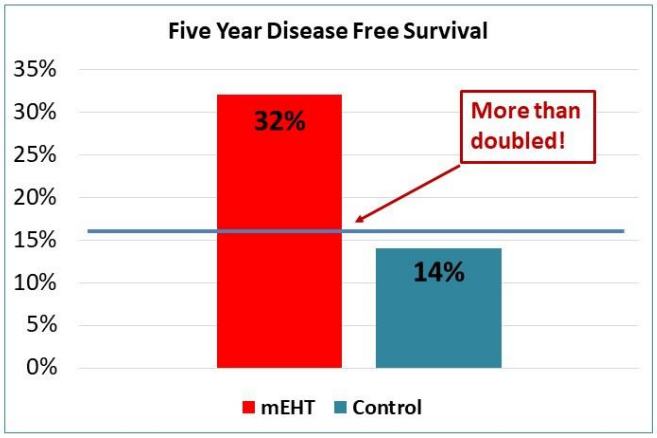
Results: Five-year Survival



32%[32/99] of hyperthermia participants

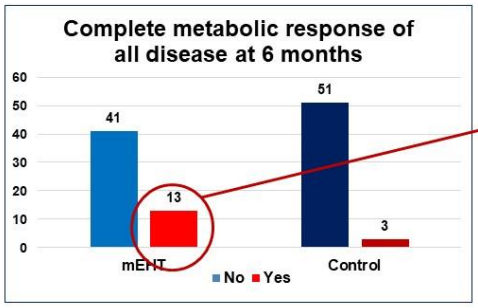
14%[14/102] of control participants

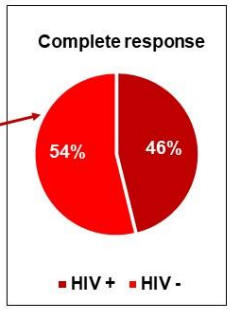
Achieved 5 years DFS

Odds were increased by 3x!

Results: Abscopal Response

- 108 Participants had extra pelvic disease on the pre-treatment PET/CT
- 54 participants in each group





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

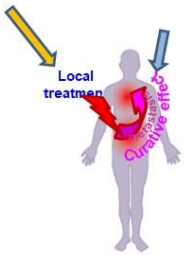
In a univariate analysis, CD4 count was also not predictive of an abscopal effect

frontiers in Medicine

Results: Systemic Immune Response

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



Ladies with stage IV disease outside the pelvis were cured with the addition of a simple local treatment!

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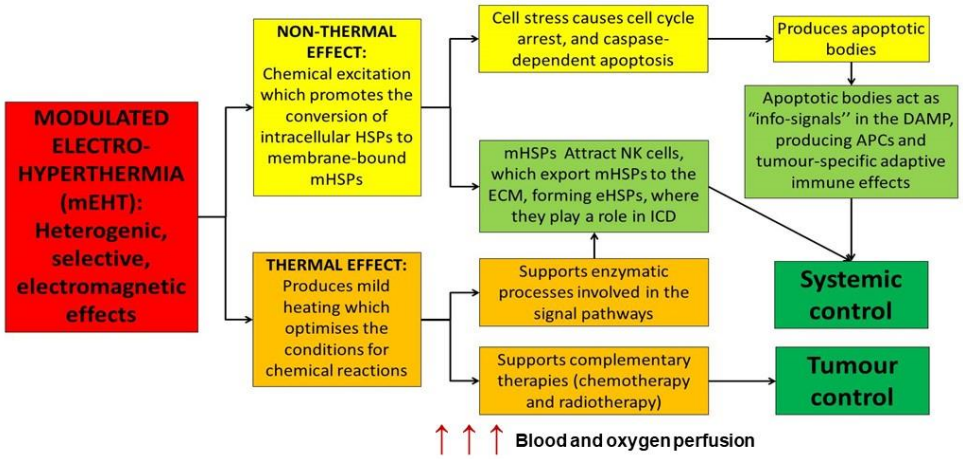
Results: Immunogenic Response



Minnaar CA, Szasz A. Forcing the Antitumor Effects of HSPs Using a Modulated Electric Field. *Cells*. 2022 Jun 4;11(11):1838

Conclusion:

Oncothermia added to CRT for LACC

- ✓ Significantly increases 5y DFS rates,
- ✓ Safely,
- ✓ While lowering treatment costs,
- ✓ And improving Quality of Life.

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

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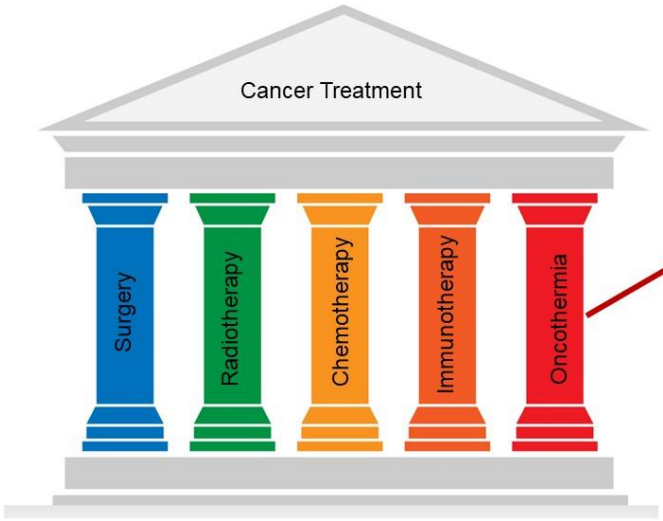
Future Perspectives:



ONCOTHERMIA: Synergistically working with available treatments to promote an immune-mediated, sustained response to cancer.

Thank you

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