MAJOR SCIENTIFIC EVIDENCERS FROM RANDOMIZED TRIALS IN THE CLINICAL USE OF HYPERTHERMIA

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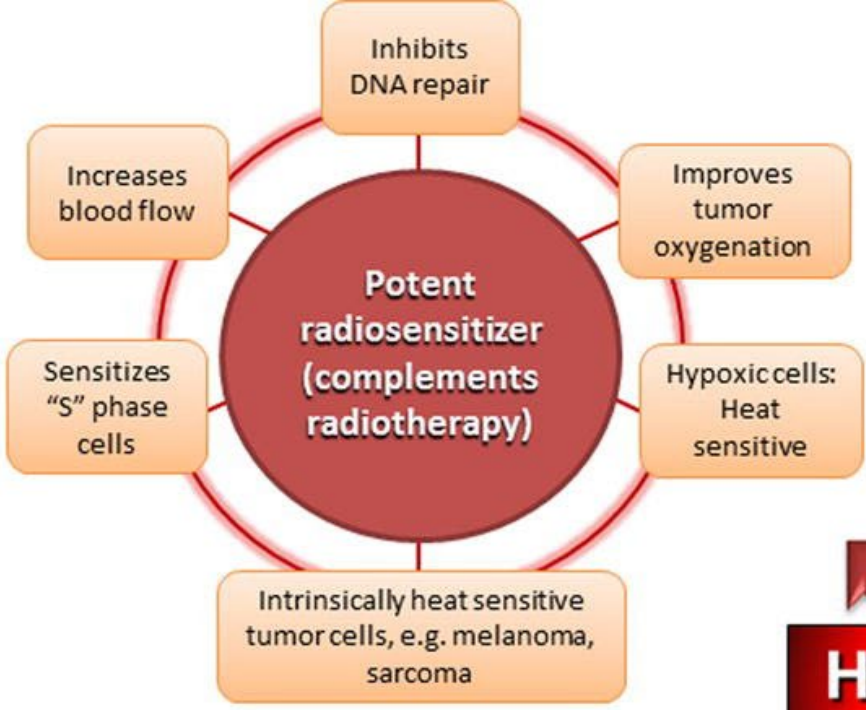
Coordinator of International Clinical Hyperthermia Society - Italian Network

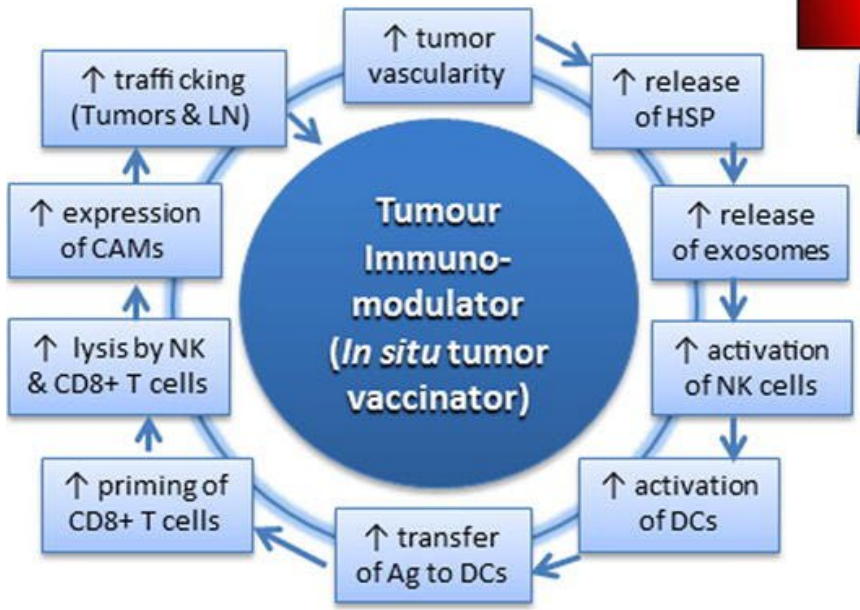
TARGET Project : Terapie Oncologiche Loco-Regionali Toscana

ISPRO
Istituto per lo studio, la prevenzione e la rete oncologica

WORSHOP SECOND WORD CONGRESS INTEGRATIVE MEDICINE AND HEALTH, ROMA
Sept 20th 2023



Hyperthermia
(39° - 45°C)



HSP: Heat shock proteins; NK: Natural killer; DC: Dendritic cells; Ag: Antigens; CAM: Cell adhesive molecule; LN: Lymph nodes

Interaction with Chemotherapeutic Agents

Independent:
5-Flurouracil, Methotrexate, Actinomycin D, Cytarabine, Taxanes,

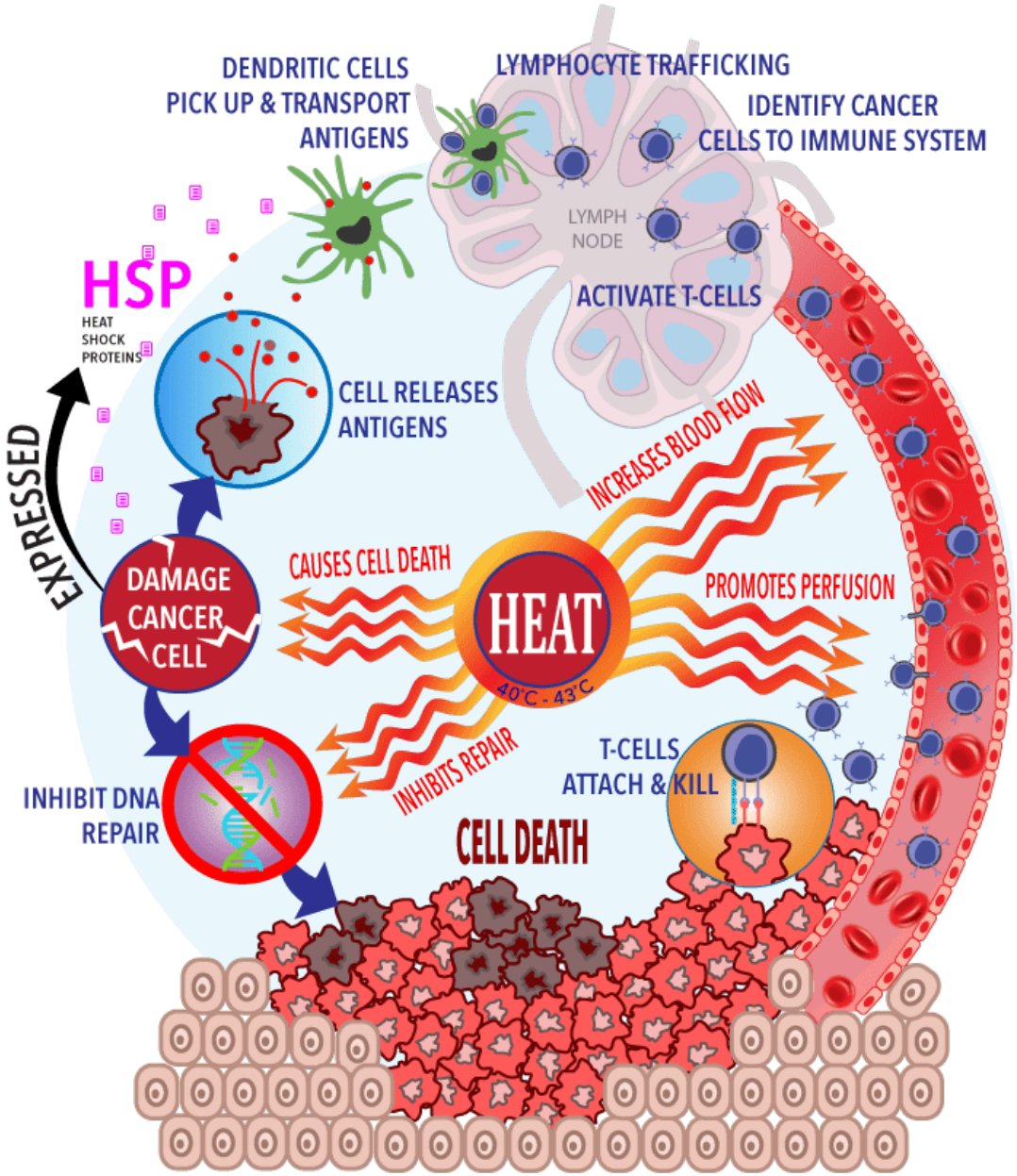
Additive:
Doxorubicin, Cyclophosphomide, Ifosphomaide, Gemcitabine

Synergistic:
Cisplatin, Carboplatin, Mitomycin C, Bleomycin

Nanoparticle based Hyperthermia

- Enhanced permeability & retention effect
- Closer proximity to tumor vasculature results in higher global parenchymal tumour temperature
- Heating " inside out" results in higher intratumoral temperature and reduced damage to normal tissue
- Sensitizes cancer stem cells
- Theranostics
- Could be designed to deliver targeted chemotherapeutic agents and radioactive tracers to tumors

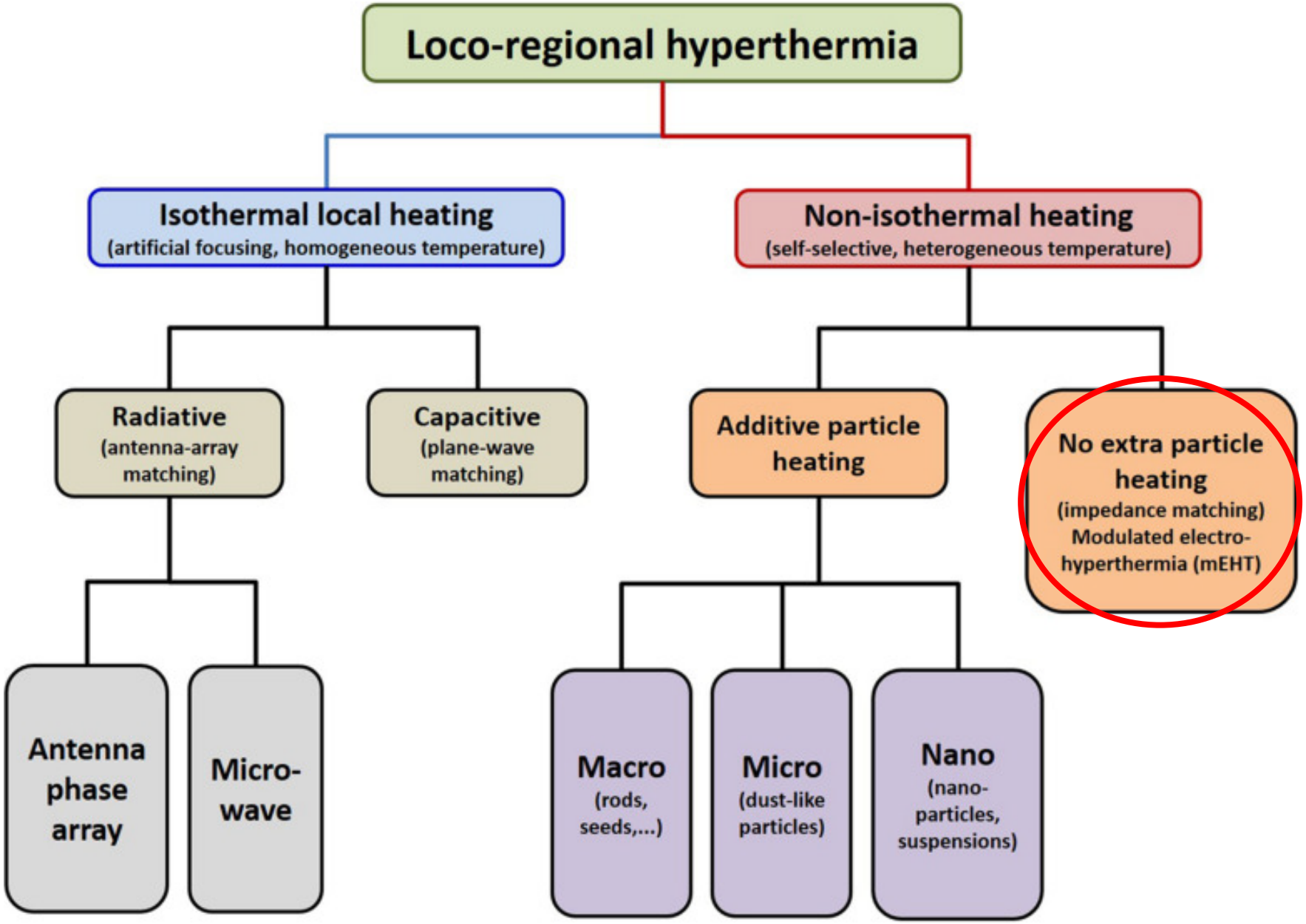
Immunomodulation Induced by Hyperthermia

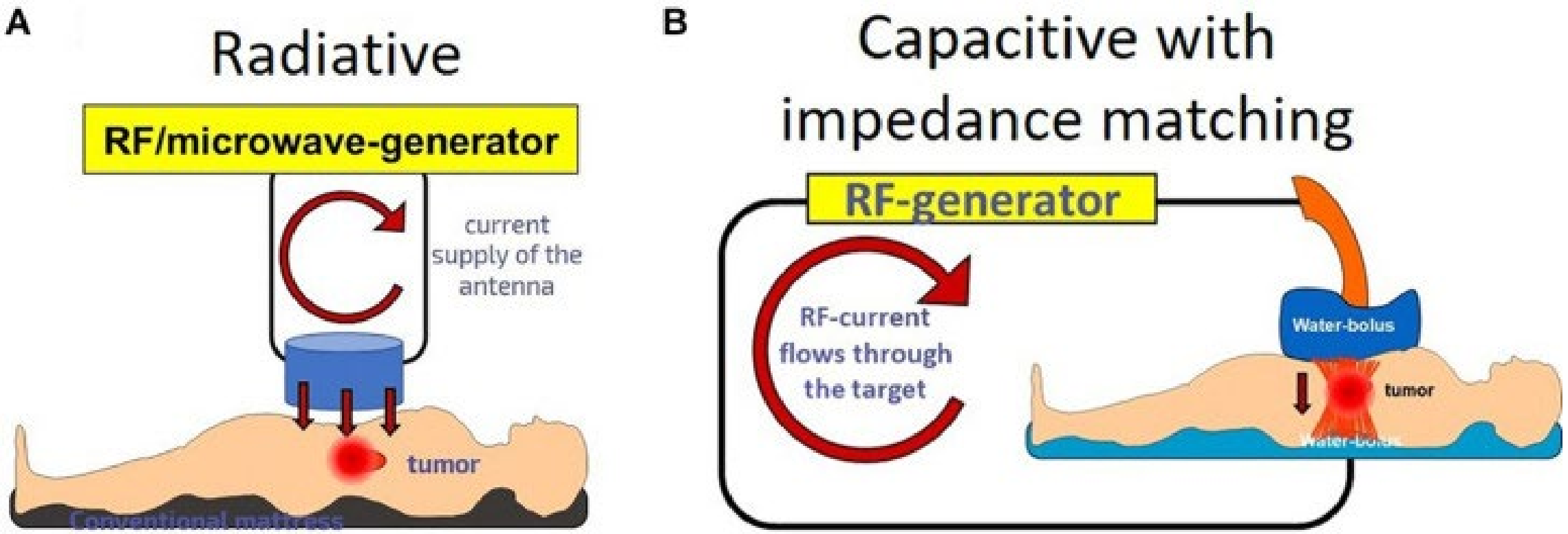


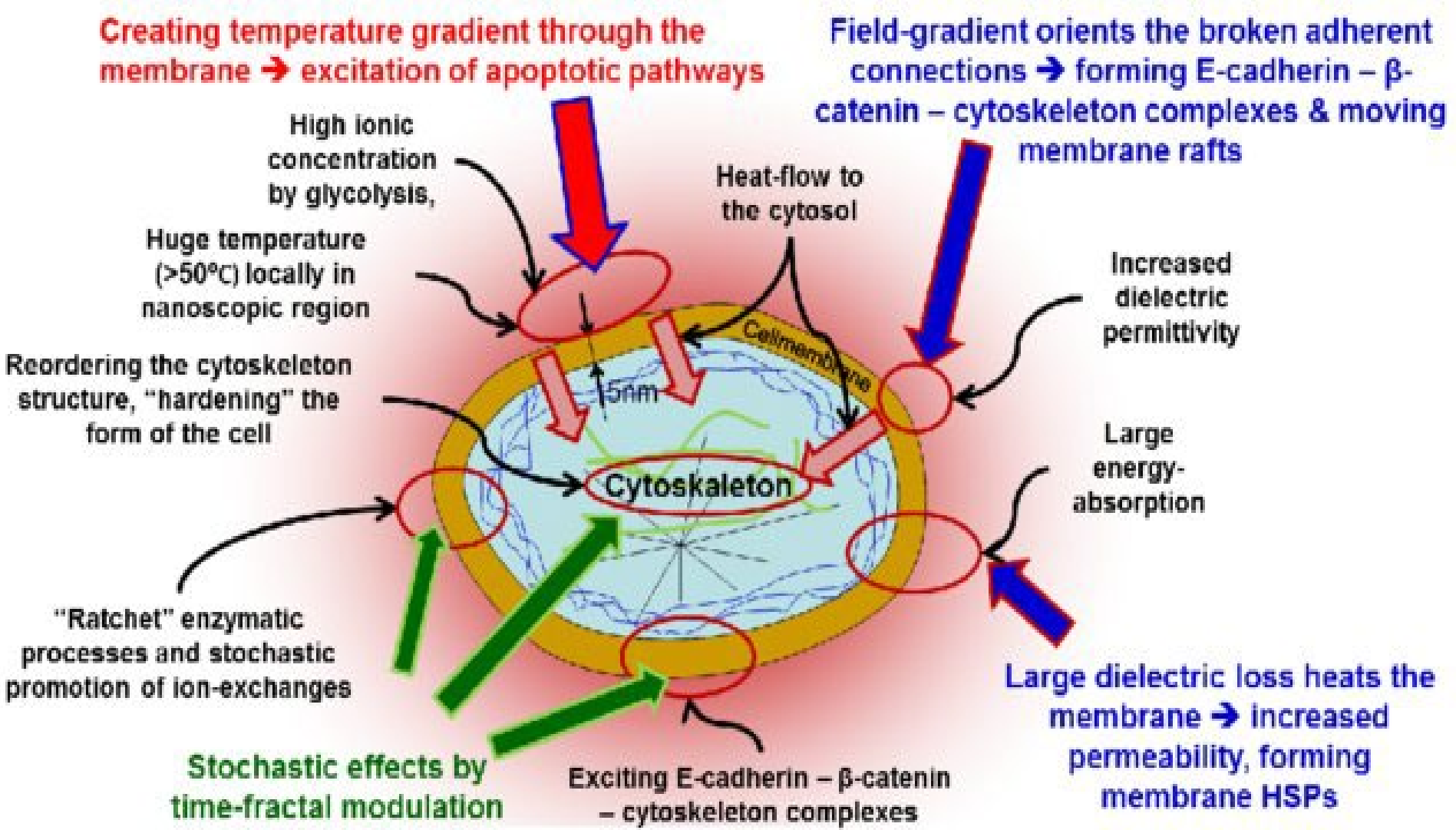
HYPERTHERMIA:

1. CAUSES CELL DEATH
2. INHIBITS DNA REPAIR
3. HEAT SHOCK PROTEINS
4. LYMPHOCYTE TRAFFICKING
5. INCREASED BLOOD FLOW
6. VESSEL PERFUSION

- Healthy Cell
- Cancer Cell
- Antigen
- Heat Shock Protein
- Dendritic Cell
- T-Cell
- Blood Cell
- RF Energy


Loco-regional hyperthermia
Isothermal local heating
(artificial focusing, homogeneous temperature)
Non-isothermal heating
(self-selective, heterogeneous temperature)
Radiative
(antenna-array matching)
Capacitive
(plane-wave matching)
Additive particle heating
No extra particle heating
(impedance matching)
Modulated electro-hyperthermia (mEHT)
Antenna phase array
Micro-wave
Macro
(rods, seeds,...)
Micro
(dust-like particles)
Nano
(nano-particles, suspensions)


A
Radiative
RF/microwave-generator
current
supply of the
antenna
tumor
B
Capacitive with
impedance matching
RF-generator
RF-current
flows through
the target
Water-bolus
tumor

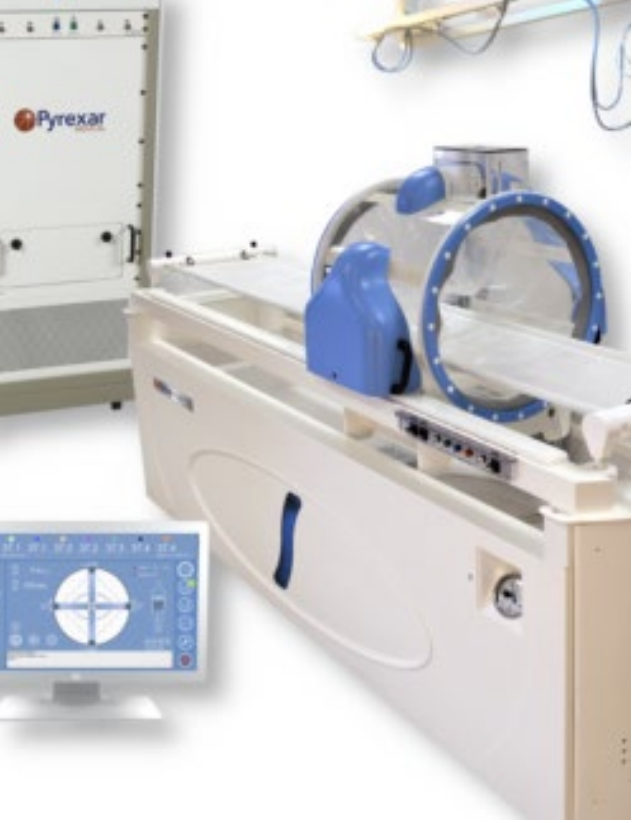


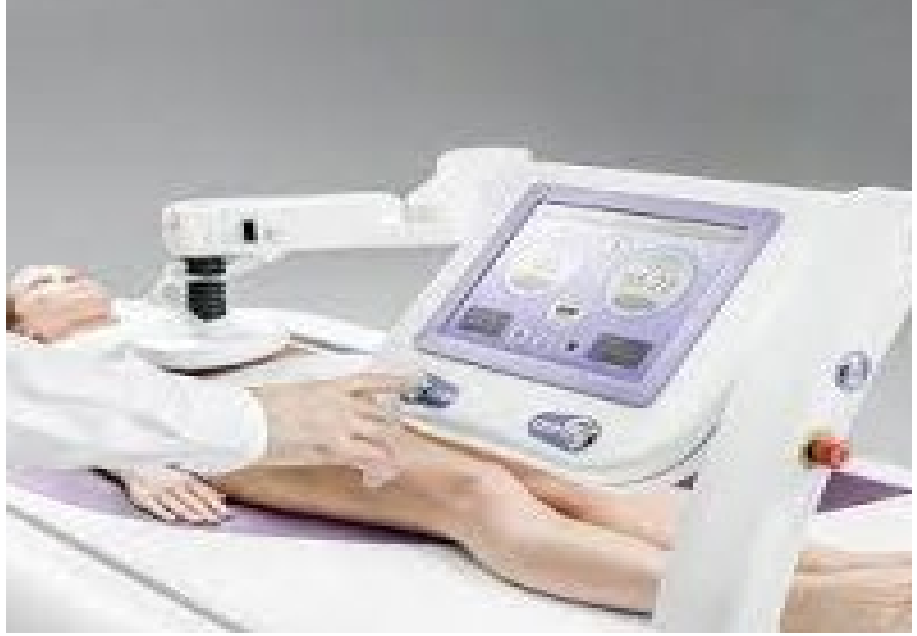
Main selection factors of modulated Electro-Hyperthermia

European Guide lines

Special Issues on: Hyperthermia cancer treatment and Heating technology

Journal	Year	Topic	Guest Editors	Link
Cancers IF: 6.126	2020	Hyperthermia-based Anticancer Treatments	Nicolaas A.P. Franken, Arlene L. Oei & Johannes Crezee	https://www.mdpi.com/journal/cancers/special_issues/HbAT
Cancers	2018	Magnetic Nanoparticles for Hyperthermia Applications	Riccardo Di Corato	https://www.mdpi.com/journal/applsci/special_issues/Magnetic_Nanoparticles_Hyperthermia
Sensors IF: 3.275	2020	Measurements Techniques of Biological Tissues Dielectric Properties, Updated Data and Current Applications	Marta Cavagnaro & Giuseppe Ruvio	https://www.mdpi.com/journal/sensors/special_issues/dielectric_measurements





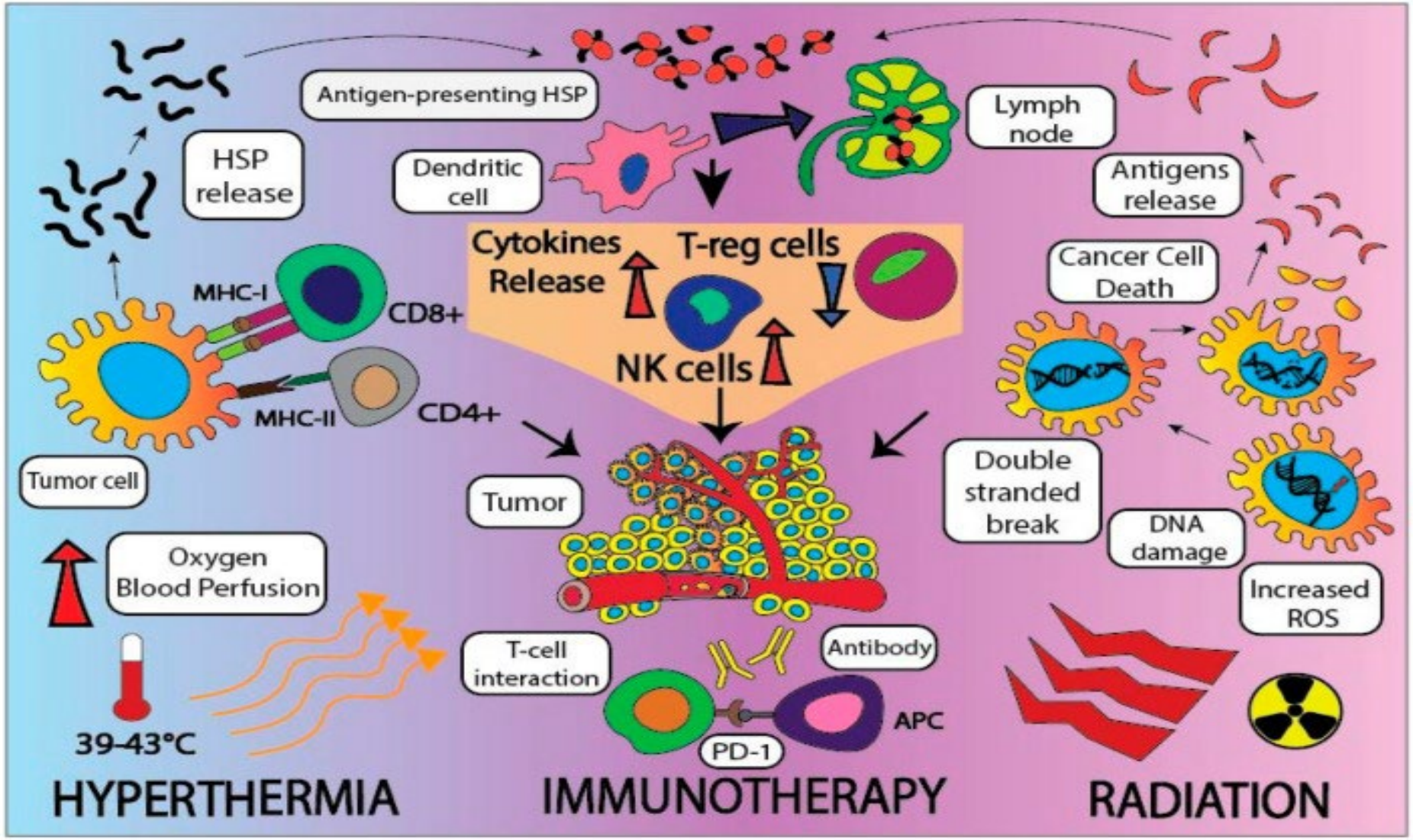
Latest generation (2023) capacitive external hyperthermia machines

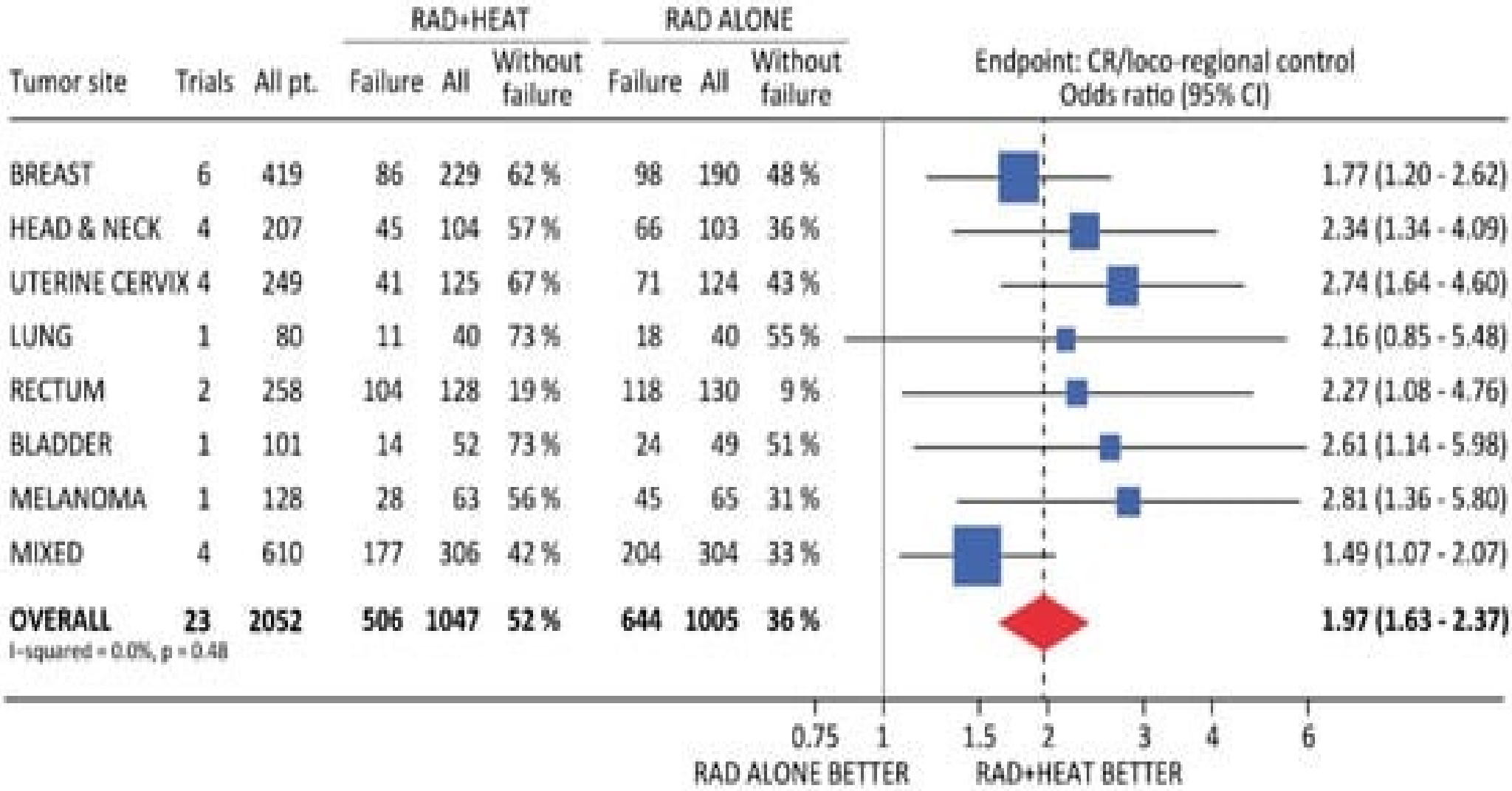
UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Zeljko Vujaskovic
Director of the Division of
Tranlational Radiation Sciences
in the Departement of Radiation
Oncology

The deep-tissue hyperthermia, which can be combined with standard radiation therapy as well as proton-beam therapy to enhance the cancer-killing effects of the radiation in pancreatic cancer

Mahmood J, Vujaskovic Z et Al. Immunotherapy, Radiotherapy, and Hyperthermia: A Combined Therapeutic Approach in Pancreatic Cancer Treatment. Cancer 2018 Dec; 10(12):469




RAD+HEAT
RAD ALONE
Tumor site
Trials
All pt.
Failure
All
Without failure
Failure
All
Without failure
Endpoint: CR/loco-regional control
Odds ratio (95% CI)
BREAST 6 419 86 229 62 % 98 190 48 % 1.77 (1.20 - 2.62)
HEAD & NECK 4 207 45 104 57 % 66 103 36 % 2.34 (1.34 - 4.09)
UTERINE CERVIX 4 249 41 125 67 % 71 124 43 % 2.74 (1.64 - 4.60)
LUNG 1 80 11 40 73 % 18 40 55 % 2.16 (0.85 - 5.48)
RECTUM 2 258 104 128 19 % 118 130 9 % 2.27 (1.08 - 4.76)
BLADDER 1 101 14 52 73 % 24 49 51 % 2.61 (1.14 - 5.98)
MELANOMA 1 128 28 63 56 % 45 65 31 % 2.81 (1.36 - 5.80)
MIXED 4 610 177 306 42 % 204 304 33 % 1.49 (1.07 - 2.07)
OVERALL 23 2052 506 1047 52 % 644 1005 36 % 1.97 (1.63 - 2.37)
I-squared = 0.0%, p = 0.48
0.75
1
1.5
2
3
4
6
RAD ALONE BETTER
RAD+HEAT BETTER

Up to date Indications for Hyperthermia

EVIDENCE 1 A: RANDOMIZED STUDIES (phase III)

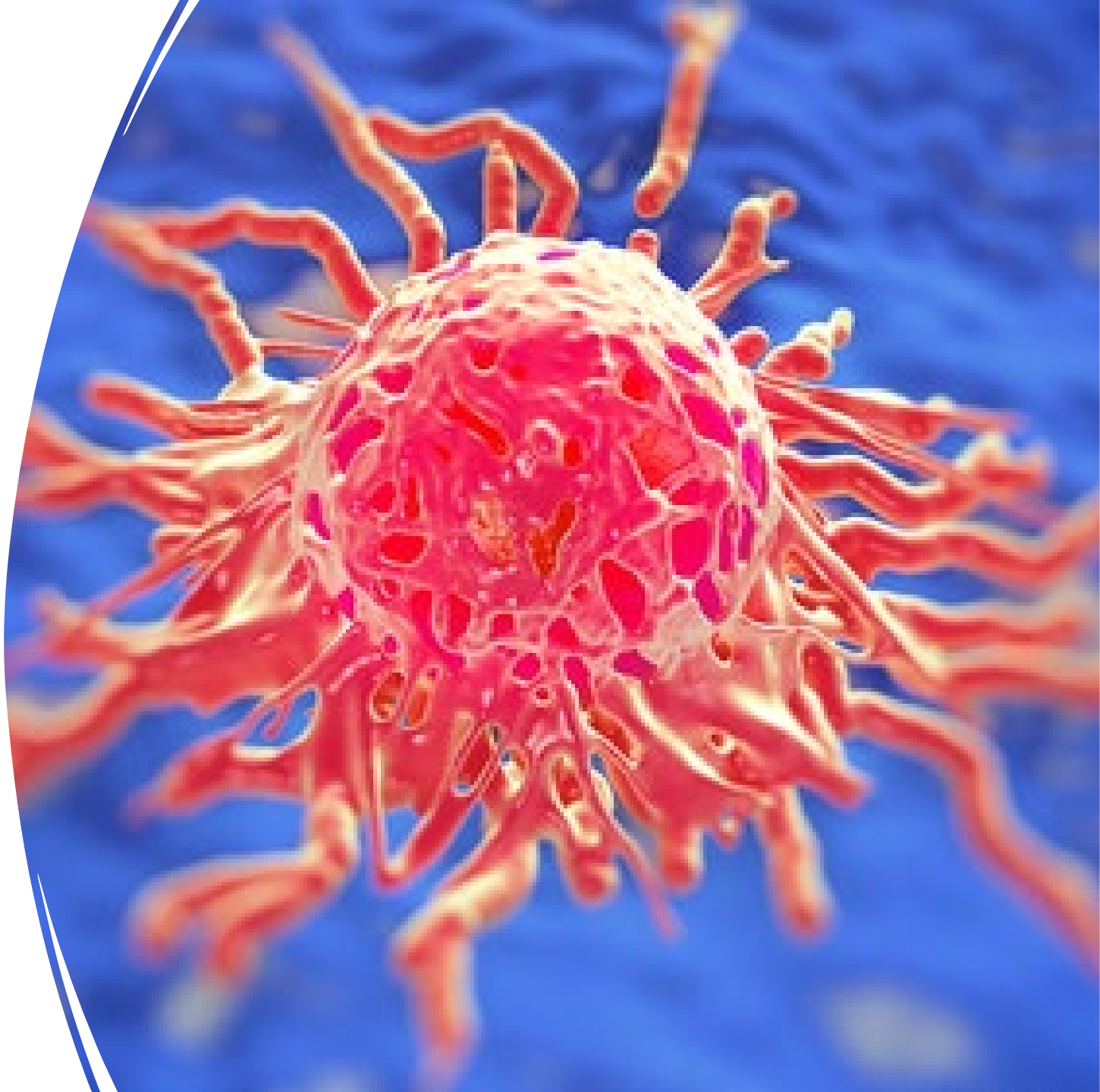
- Soft tissue sarcoma
- Cervical cancer
- bone metastases
- Melanoma
- Head and neck cancers
- Thoracic recurrence of breast cancer
- Rectal cancer and Anal cancer
- Gliomas

SHARED PALLIATIVE CLINICAL EVIDENCE (from phase II studies)

- **Pancreatic cancer**
- Locally advanced/relapsed cancers of the head and neck
- Locally advanced or recurring bladder cancer
- Locally advanced or recurrent rectal cancer
- Already irradiated bone metastases
- Visceral stenosis and compression already irradiated
- Palliative containing analgesic therapy

Class I	Evidence and/or general agreement that a given treatment or procedure is **beneficial, useful, effective.**	Is recommended or is indicated
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.	

Soft tissue sarcoma



JAMA Oncology | Original Investigation

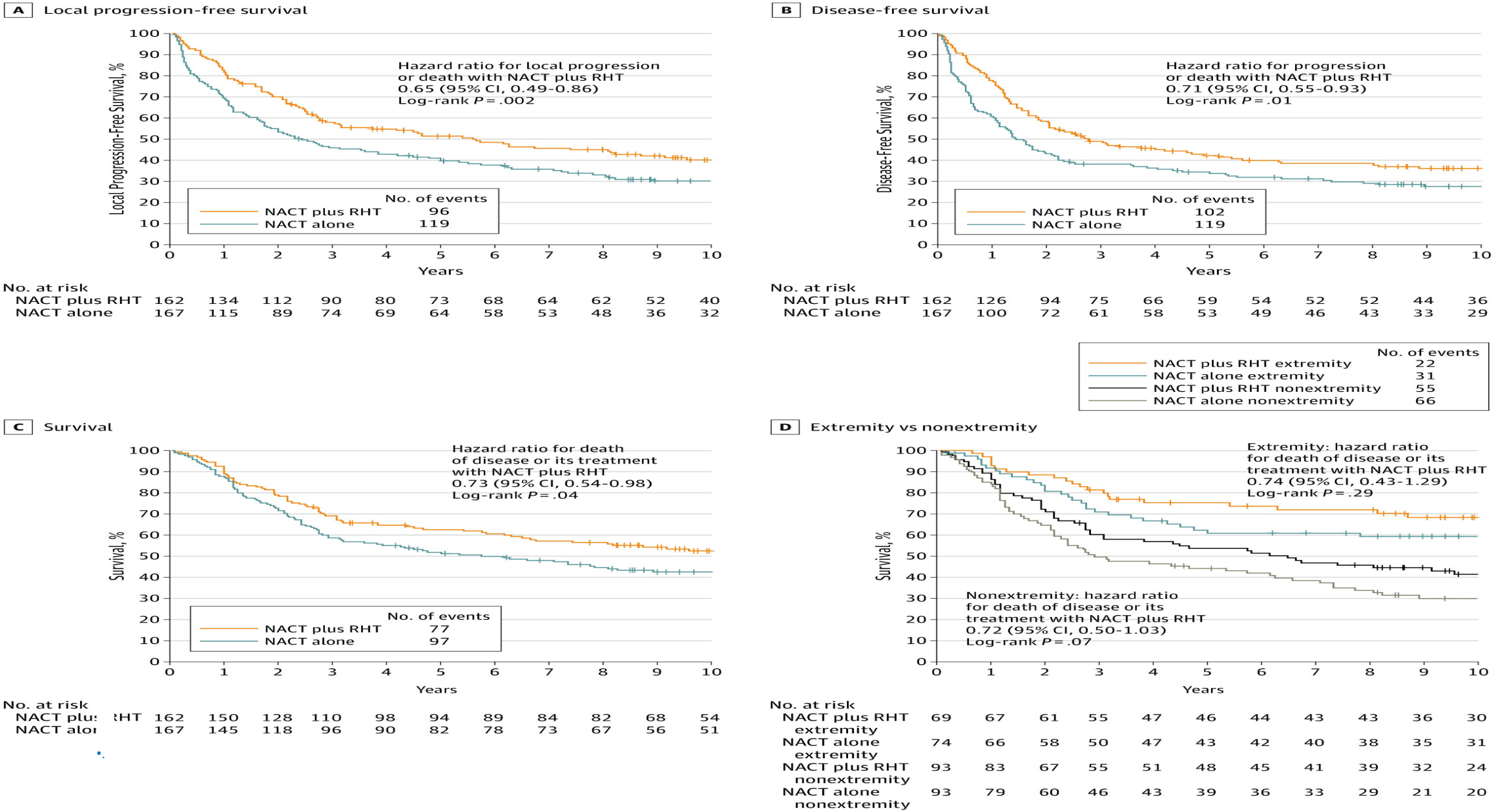
Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

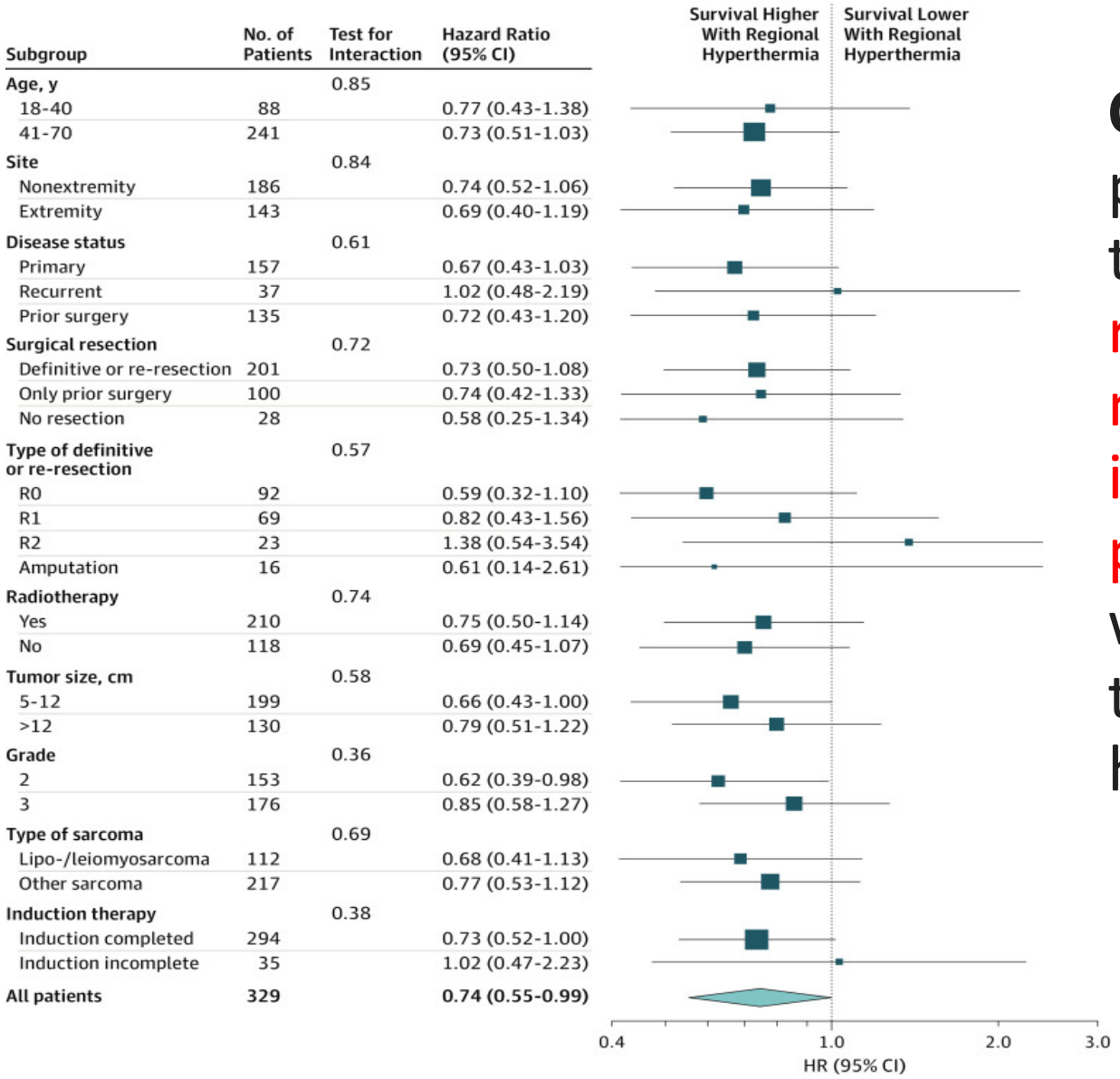
Rolf D. Issels, MD, PhD; Lars H. Lindner, MD; Jaap Verweij, MD; Rüdiger Wessalowski, MD; Peter Reichardt, MD; Peter Wust, MD; Pirus Ghadjar, MD; Peter Hohenberger, MD; Martin Angele, MD; Christoph Salat, MD; Zeljko Vujaskovic, MD; Soeren Daugaard, MD; Olav Mella, MD; Ulrich Mansmann, MD; Hans Roland Dürr, MD; Thomas Knösel, MD; Sultan Abdel-Rahman, PhSc; Michael Schmidt, MD; Wolfgang Hiddemann, MD; Karl-Walter Jauch, MD; Claus Belka, MD; Alessandro Gronchi, MD; for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

2018

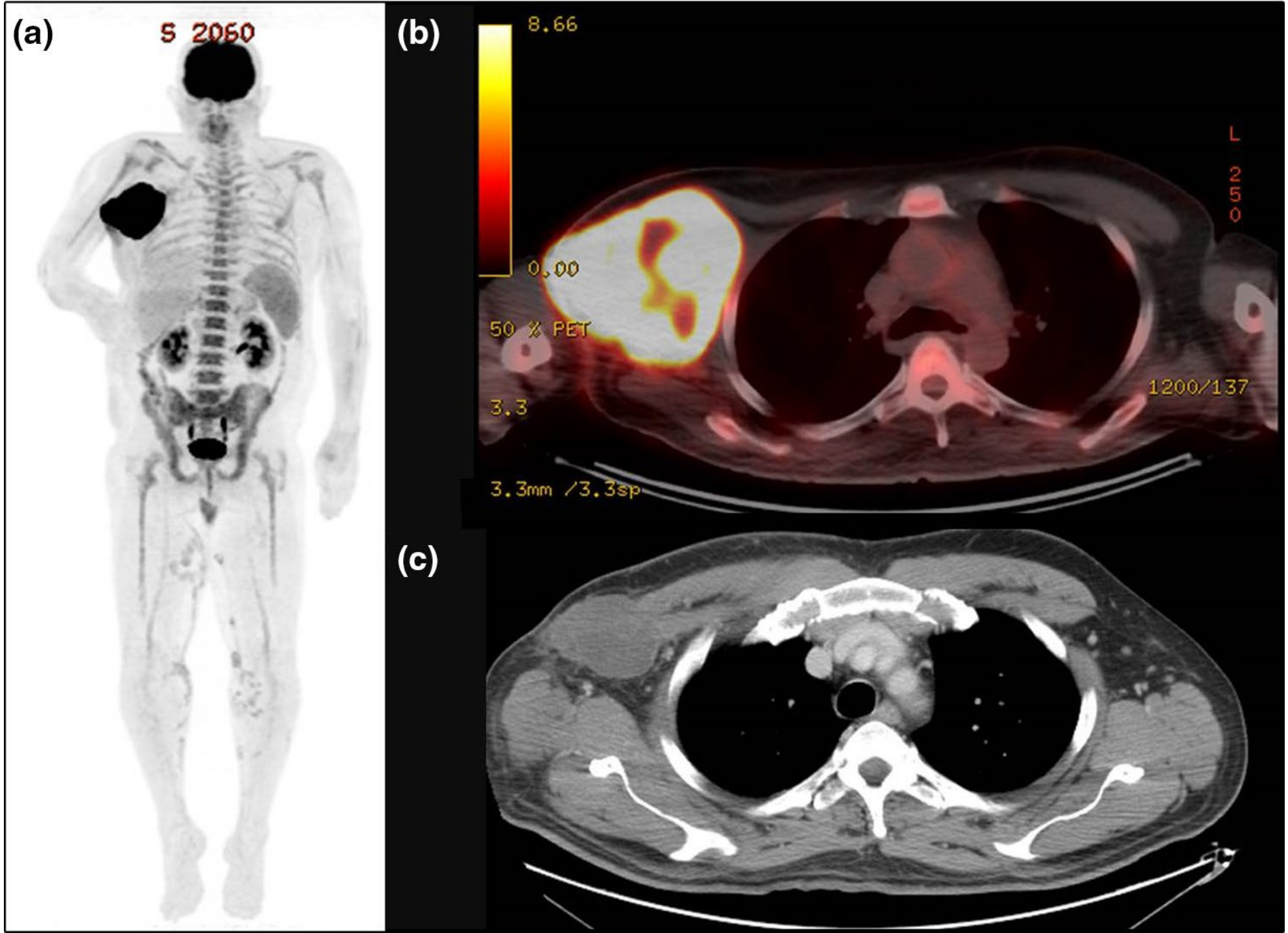
Chemotherapy Plus Hyperthermia for Patients With High-Risk Soft Tissue Sarcoma



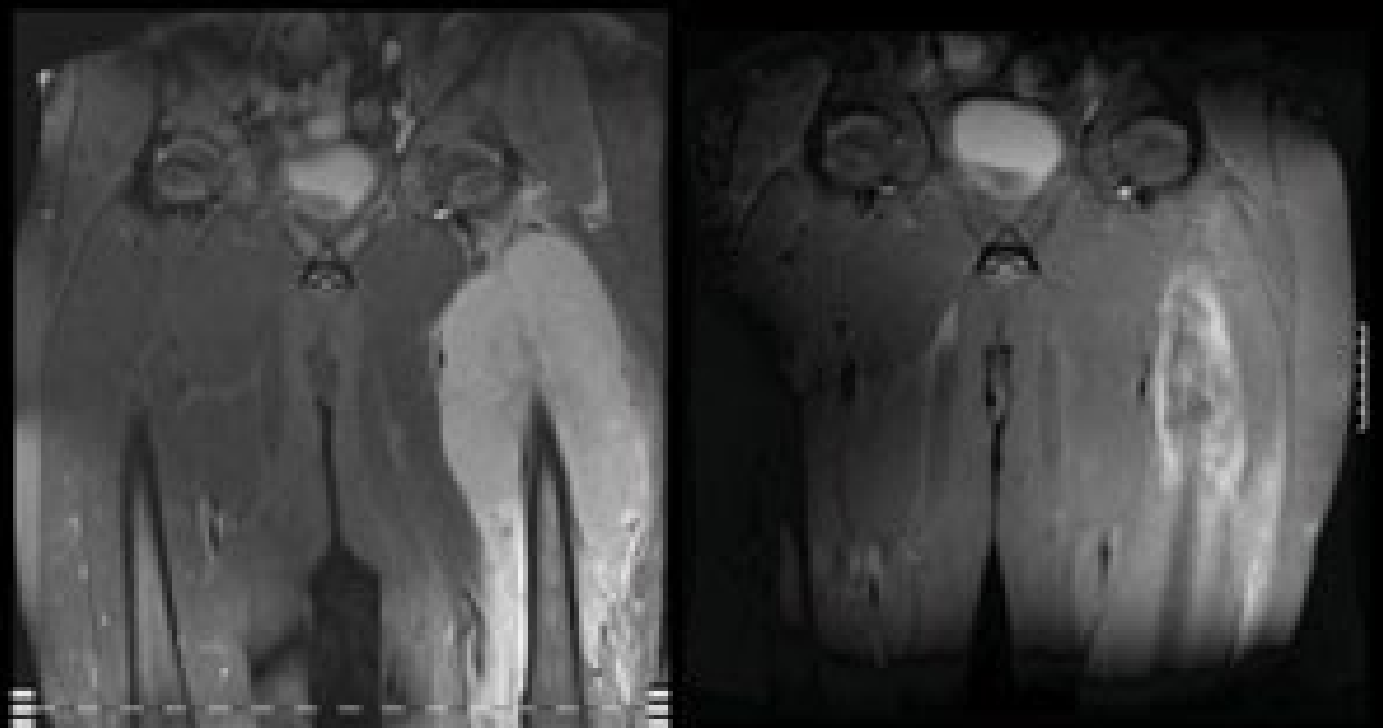
Chemotherapy Plus Hyperthermia for Patients With High-Risk Soft Tissue Sarcoma



Conclusions and relevance: Among patients with localized high-risk soft tissue sarcoma the addition of regional hyperthermia to neoadjuvant chemotherapy resulted in increased survival, as well as local progression-free survival. For patients who are candidates for neoadjuvant treatment, adding regional hyperthermia may be warranted


(a)
S 2060
(b)
8.66
0.00
50 % PET
3.3
3.3mm /3.3sp
L 250
1200/137
(c)

13-year-old boy, soft tissue sarcoma, left upper leg



a) Poor response

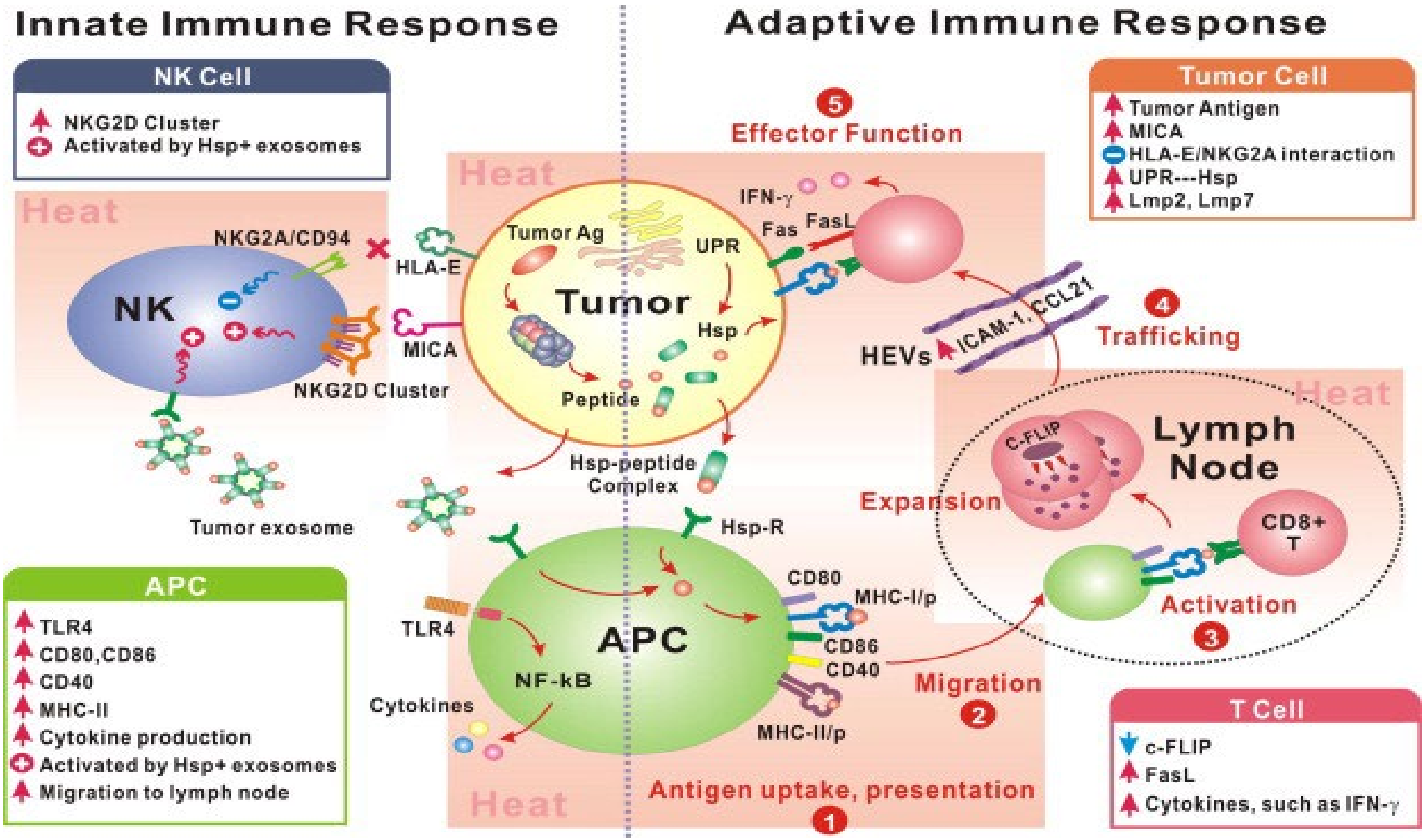
b) 4 x Hyper-PEI

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

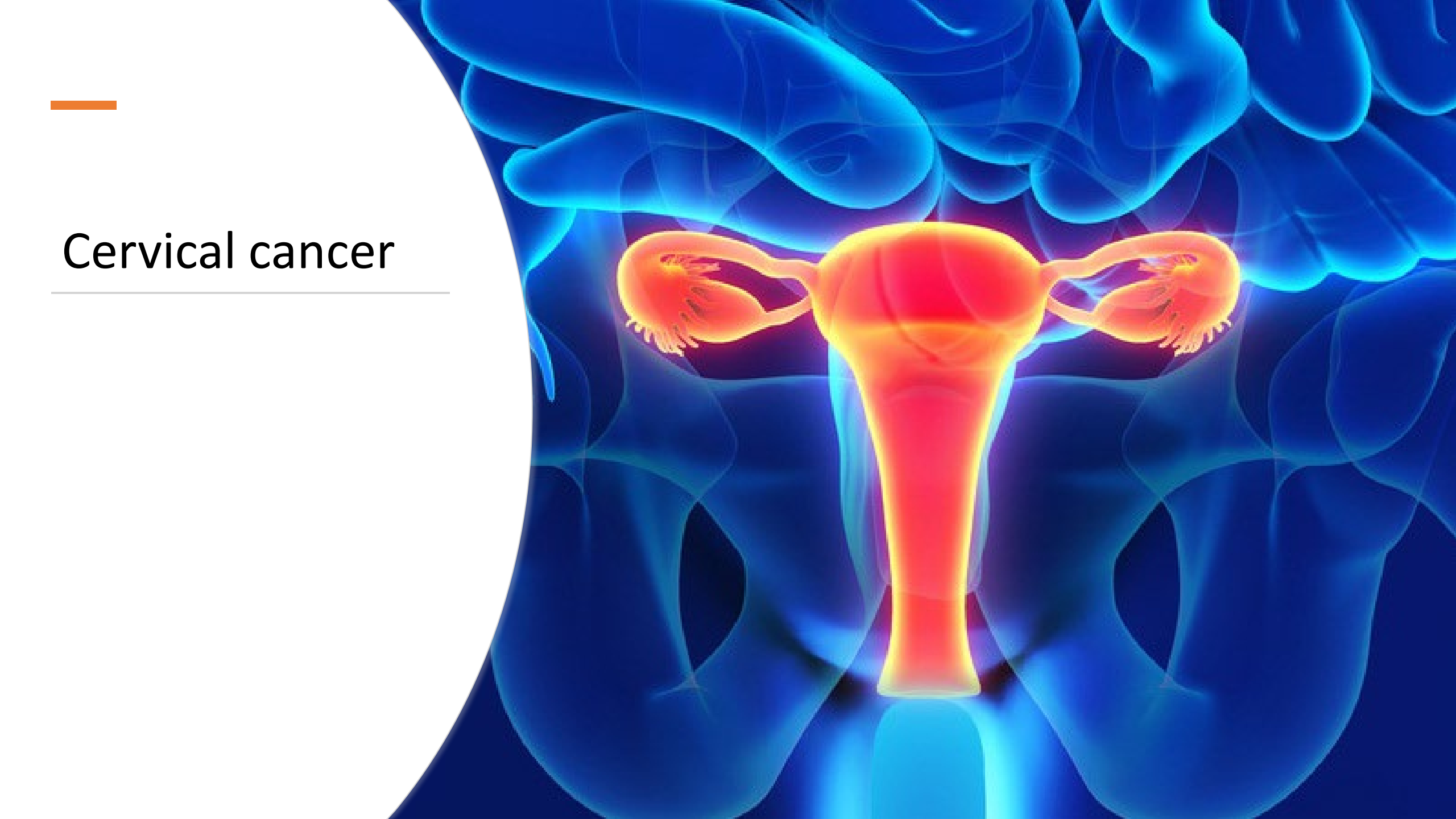
Rolf D. Issels [1] • Elfriede Noessner [1] • Lars H. Lindner • ... Ulrich Mansmann • Michael von Bergwelt-Baildon • Thomas Knoesel • Show all authors • Show footnotes

Published: October 16, 2021 • DOI: https://doi.org/10.1016/j.ejca.2021.09.015 •

- Conclusion of the study:
- Preoperative therapy re-programs a non-inflamed tumour at baseline into an inflamed tumour
- The post-treatment immune infiltrate became predictive for clinical outcomes
- The combination with regional hyperthermia primes the tumour microenvironment, enabling enhanced anti-tumour immune activity in high-risk soft tissue sarcomas


Innate Immune Response
Adaptive Immune Response
NK Cell
NKG2D Cluster
Activated by Hsp+ exosomes
Tumor Cell
Tumor Antigen
MICA
HLA-E/NKG2A interaction
UPR---Hsp
Lmp2, Lmp7
5
Effector Function
Heat
IFN-γ
Fas
FasL
NKG2A/CD94
HLA-E
Tumor Ag
UPR
NK
Tumor
Hsp
MICA
NKG2D Cluster
Peptide
HEVs
ICAM-1, CCL21
4
Trafficking
Hsp-peptide Complex
Tumor exosome
Lymph Node
C-FLIP
Expansion
CD8+ T
Activation
3
Hsp-R
CD80
MHC-I/p
CD86
CD40
TLR4
APC
NF-kB
Cytokines
Migration
2
MHC-II/p
Antigen uptake, presentation
1
APC
TLR4
CD80,CD86
CD40
MHC-II
Cytokine production
Activated by Hsp+ exosomes
Migration to lymph node
T Cell
c-FLIP
FasL
Cytokines, such as IFN-γ

Cervical cancer

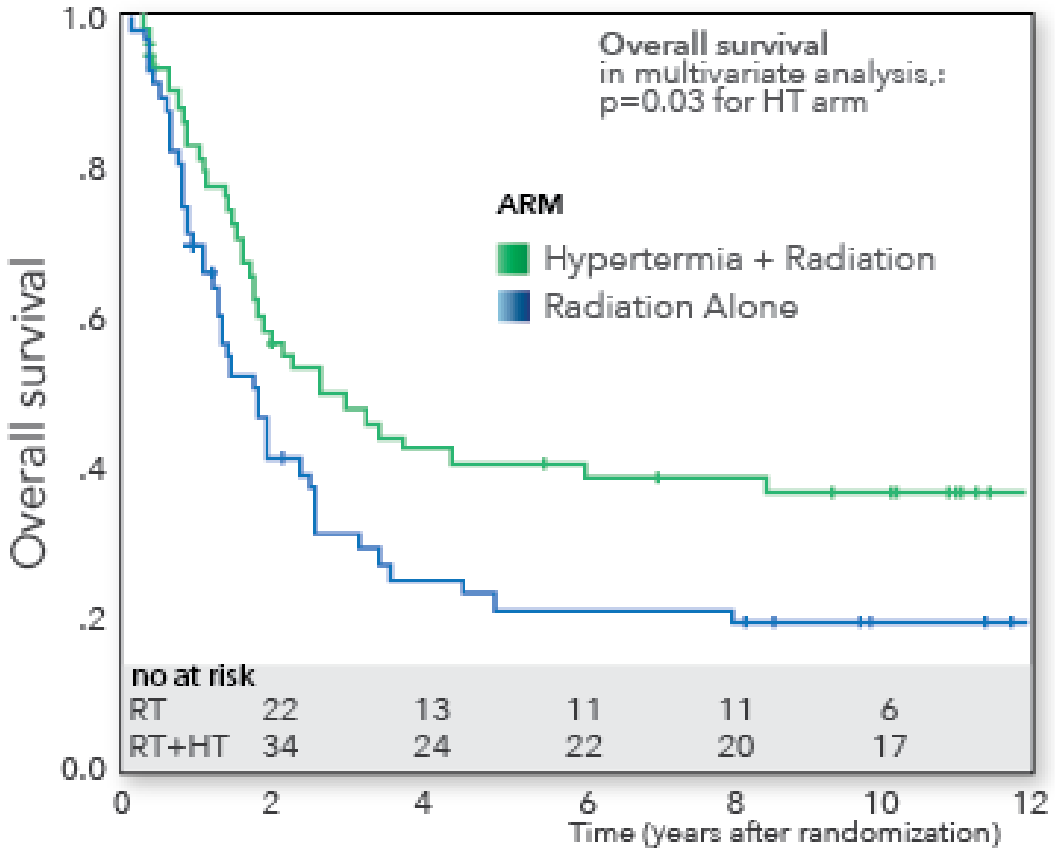


Combined use of hyperthermia and radiation therapy for treating locally advanced cervical carcinoma (Review)

Lutgens L, van der Zee J, Pijls-Johannesma M, De Haas-Kock DFM, Buijsen J, Mastrigt GAPGV, Lammering G, De Ruysscher DKM, Lambin P

2010

THE COCHRANE COLLABORATION®



The pooled data analysis yielded:

- a **significantly higher complete response rate** (relative risk (RR) 0.56; 95% confidence interval (CI) 0.39 to 0.79; p < 0.001)
- a **significantly reduced local recurrence rate** (hazard ratio (HR) 0.48; 95% CI 0.37 to 0.63; p < 0.001)
- a **significantly better overall survival (OS)** following the combined treatment with RHT(HR 0.67; 95% CI 0.45 to 0.99; p = 0.05).

Chemoradiotherapy with hyperthermia versus chemoradiotherapy alone in locally advanced cervical cancer: a systematic review and meta-analysis

INTERNATIONAL JOURNAL OF HYPERTHERMIA
2021, VOL. 38, NO. 1, 1333–1340
https://doi.org/10.1080/02656736.2021.1973584

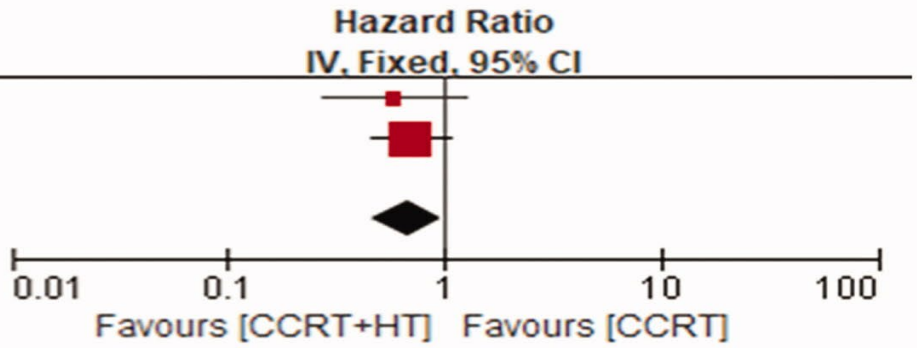
Ji Woon Yea, Jae Won Park, Se An Oh and Jaehyeon Park

Department of Radiation Oncology, Yeungnam University College of Medicine, Daegu, South Korea

(a)

Study or Subgroup	log[Hazard Ratio]	SE	CCRT+HT Total	CCRT Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Harima 2016	-0.55	0.39	51	50	22.5%	0.58 [0.27, 1.24]
Wang 2020	-0.36	0.21	217	218	77.5%	0.70 [0.46, 1.05]
Total (95% CI)			**268**	**268**	**100.0%**	**0.67 [0.47, 0.96]**

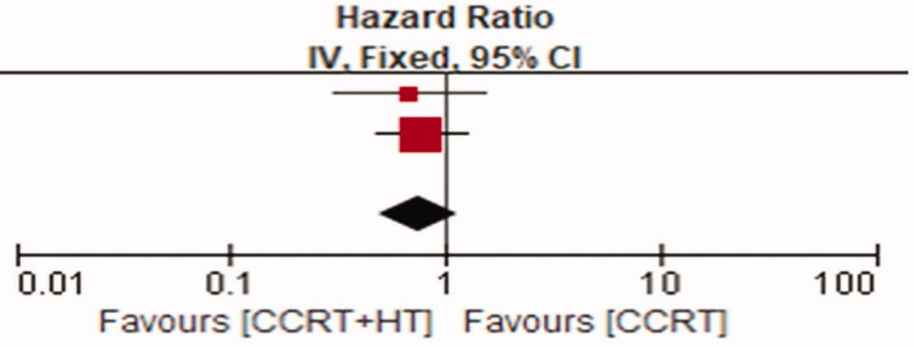
Heterogeneity: $Chi^2 = 0.18$, $df = 1$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 2.18$ ($P = 0.03$)



(b)

Study or Subgroup	log[Hazard Ratio]	SE	CCRT + HT Total	CCRT Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Harima 2016	-0.39	0.41	51	50	27.1%	0.68 [0.30, 1.51]
Wang 2020	-0.27	0.25	217	218	72.9%	0.76 [0.47, 1.25]
Total (95% CI)			**268**	**268**	**100.0%**	**0.74 [0.49, 1.12]**

Heterogeneity: $Chi^2 = 0.06$, $df = 1$ ($P = 0.80$); $I^2 = 0\%$
Test for overall effect: $Z = 1.42$ ($P = 0.16$)



Conclusion: This systematic review and meta-analysis showed that:

- **CCRT with HT** significantly **improved OS in LACC patients** **without increasing acute and chronic toxicity**.
- Therefore, tri-modality treatment could be a feasible approach for patients with LACC

2021

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[1], Jeffrey Allan Kotzen[2], Olusegun Akinwale Ayeni[3], Thanushree Naidoo[2], Mariza Tunmer[2,4], Vinay Sharma[4], Mboyo-Di-Tamba Vangu[3,5], Ans Baeyens[1,6]*

PLOS ONE 2019

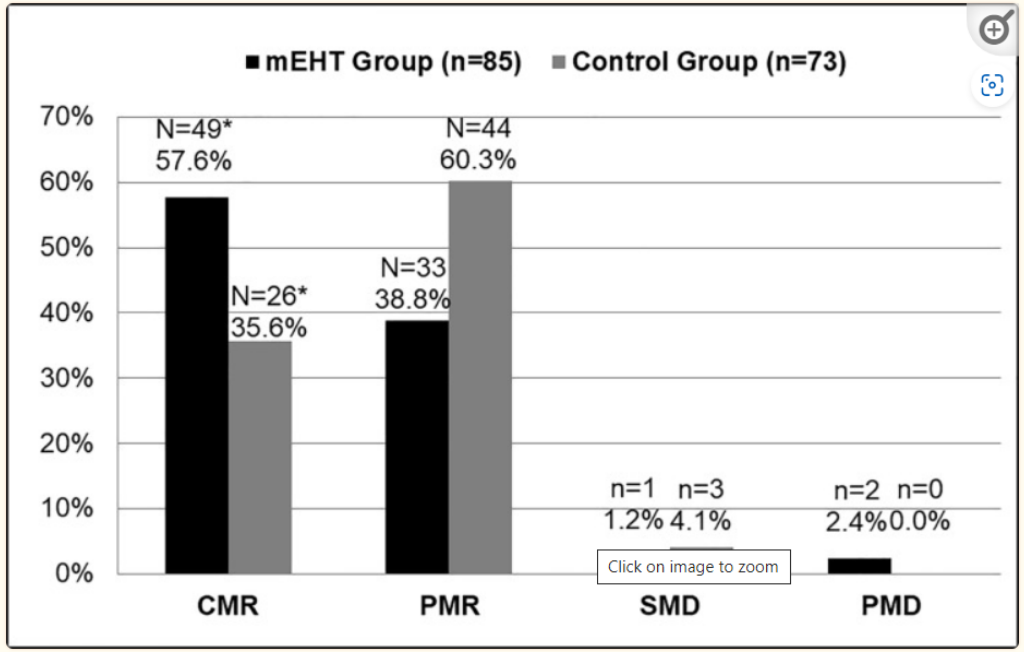


Fig 2

Tumour Response as Seen on ^{18}F-FDG PET/CT (PERCIST 1.0) by Treatment Group.

mEHT: Fischer's exact table of association between all four metabolic responses and mEHT: $p = 0.005$*.

Abbreviations: mEHT: Modulated electro-hyperthermia; CMR: Complete Metabolic Response; PMR: Partial Metabolic Response; SMD: Stable Metabolic Disease; PMD: Progressed Metabolic Disease.

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Carrie Anne Minnaar[1], Jeffrey Allan Kotzen[2], Olusegun Akinwale Ayeni[3], Thanushree Naidoo[2], Mariza Tunmer[2,4], Vinay Sharma[4], Mboyo-Di-Tamba Vangu[3,5], Ans Baeyens[1,6]*

PLOS ONE 2019

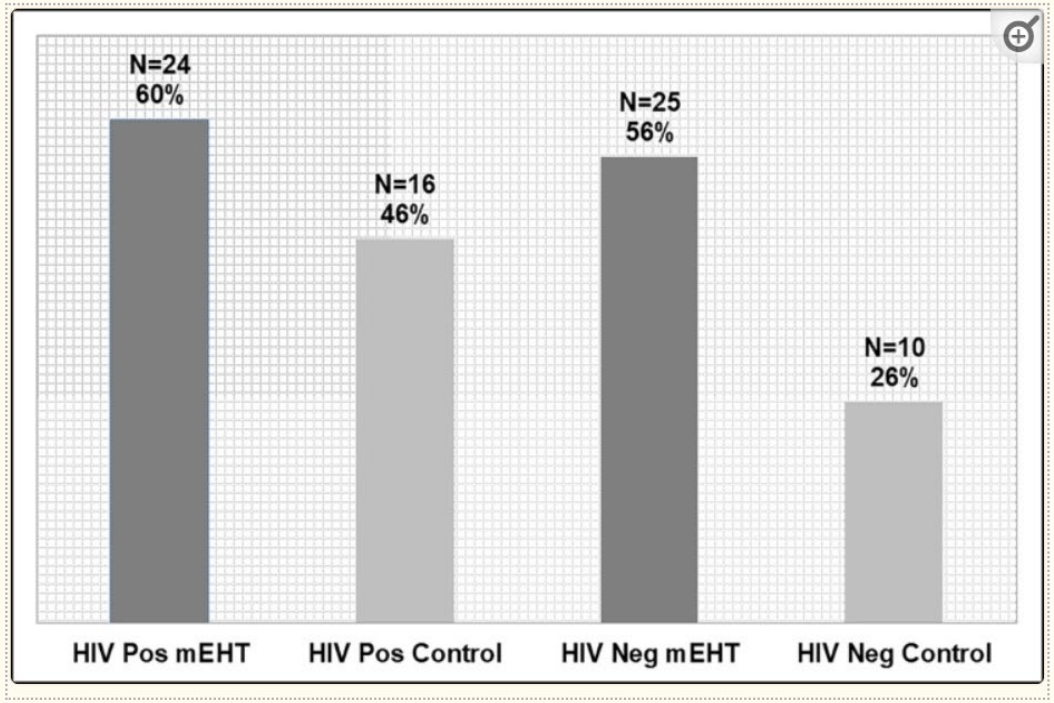


Fig 3

Tumour Response on ^{18}F-FDG PET/CT (PERCIST 1.0) by Treatment Group and HIV Status.

Total participants in each subgroup: HIV-Positive mEHT: n = 40; HIV-Positive Control: n = 35; HIV-Negative mEHT: n = 45; HIV-Negative Control: n = 38. Abbreviations: mEHT: Modulated electro-hyperthermia.

2022

cancers

MDPI

Article

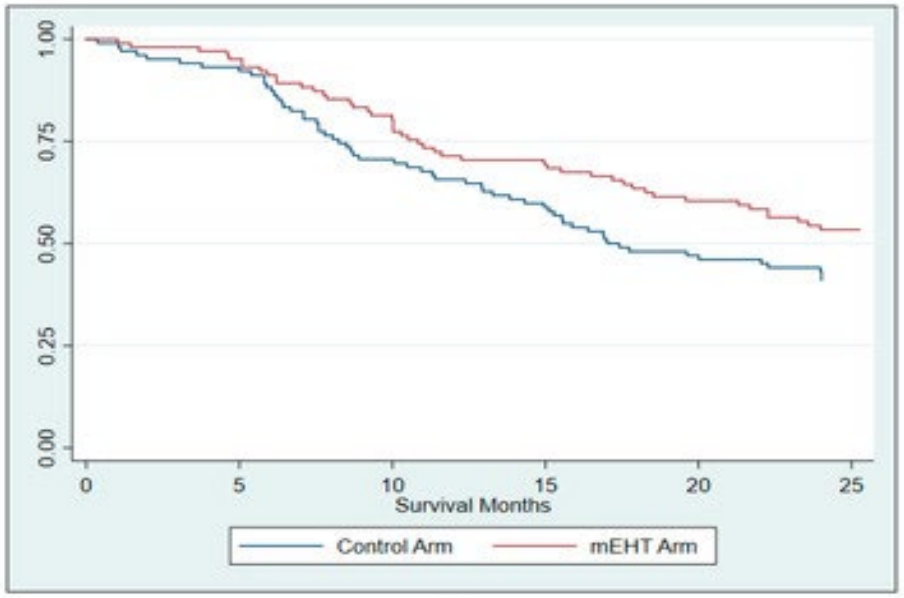
Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients

Carrie Anne Minnaar [1,2], Innocent Maposa [3], Jeffrey Allan Kotzen [1,2] and Ans Baeyens [1,4,*]

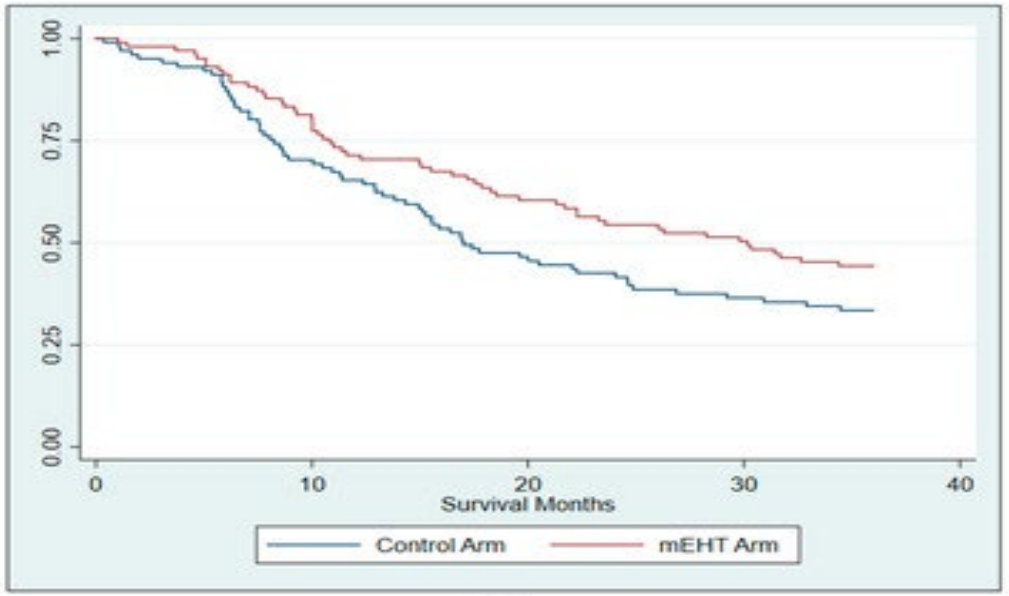
24 MESES

36 MESES

OS

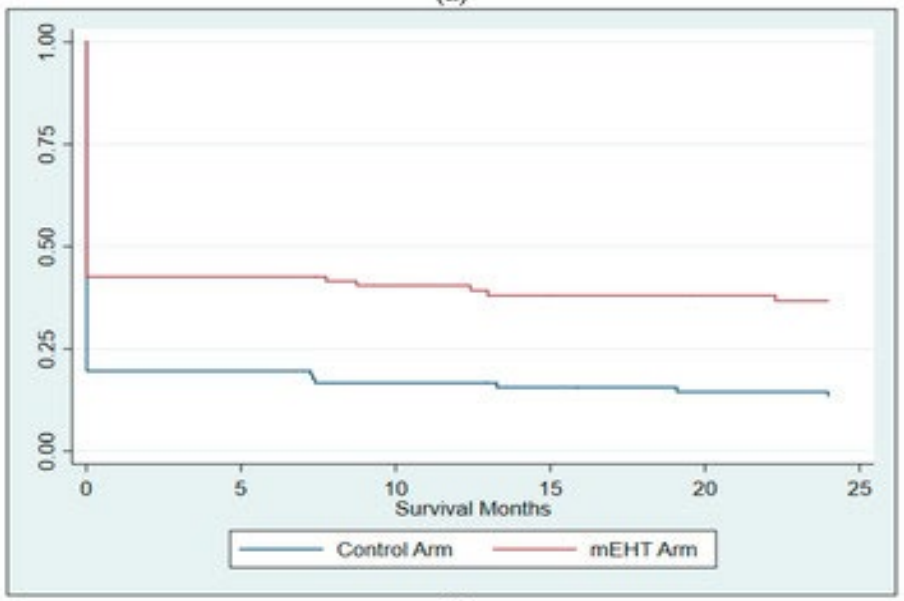


(a)

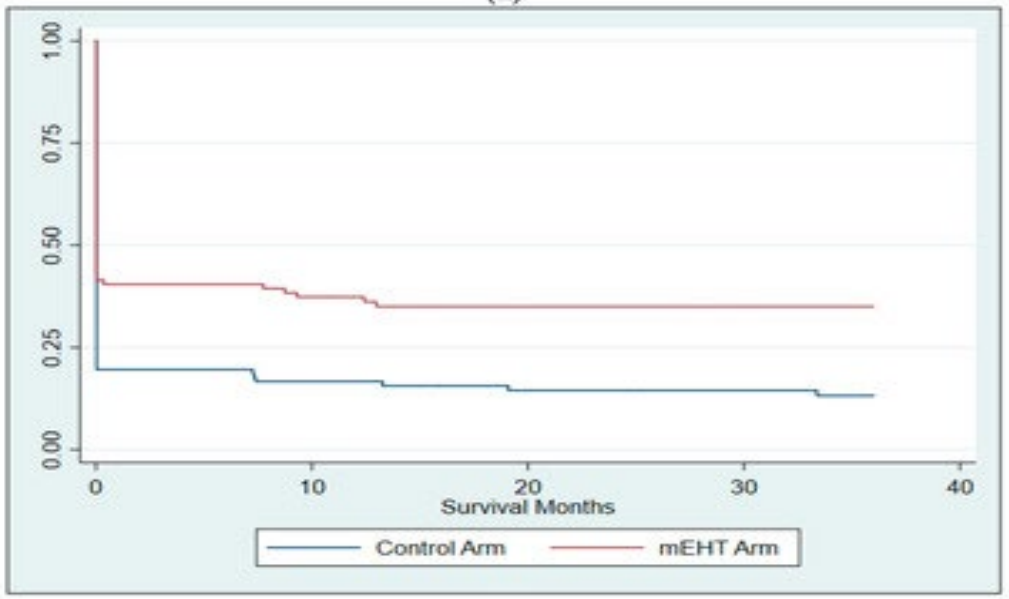


(a)

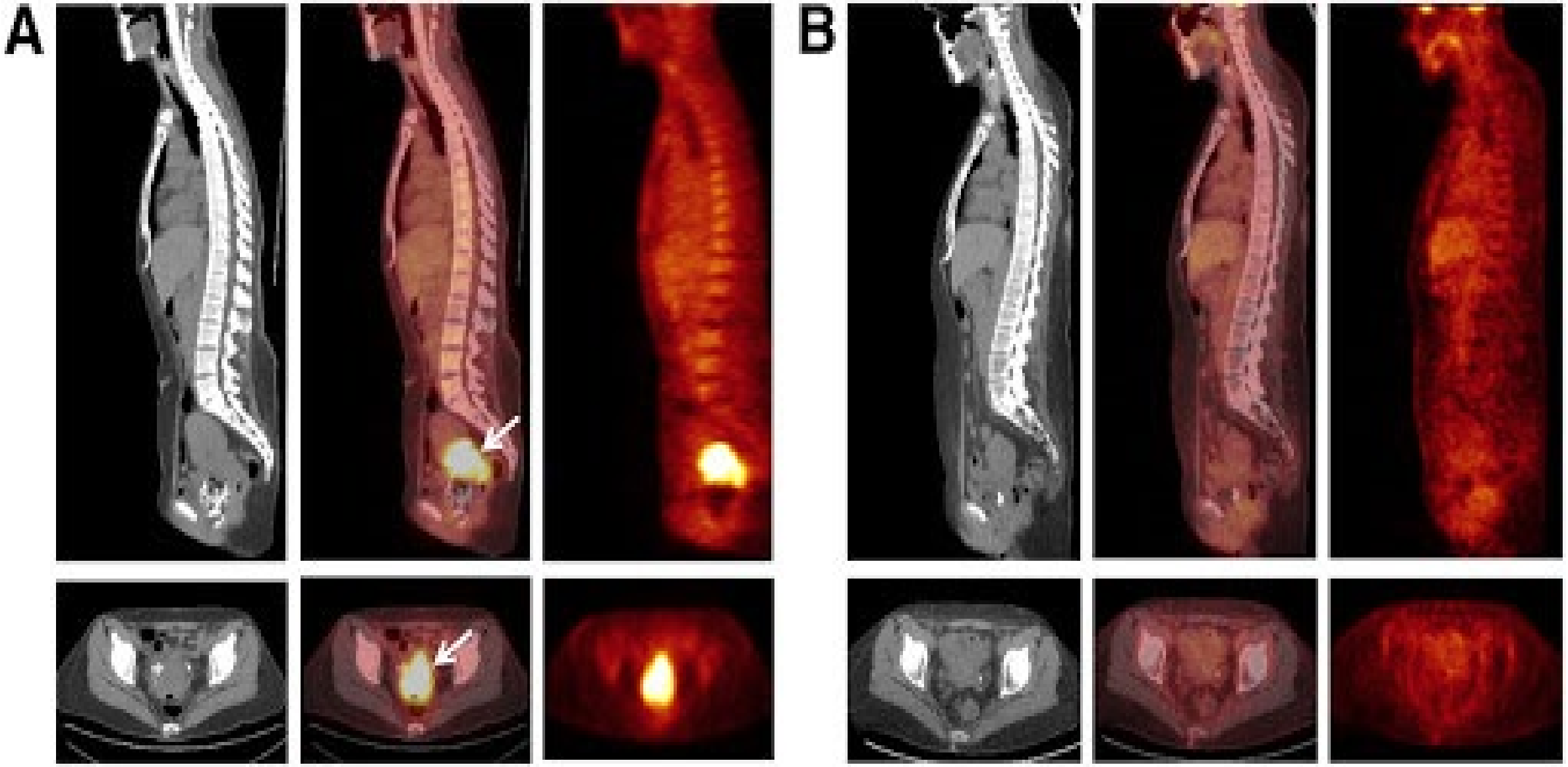
PFS



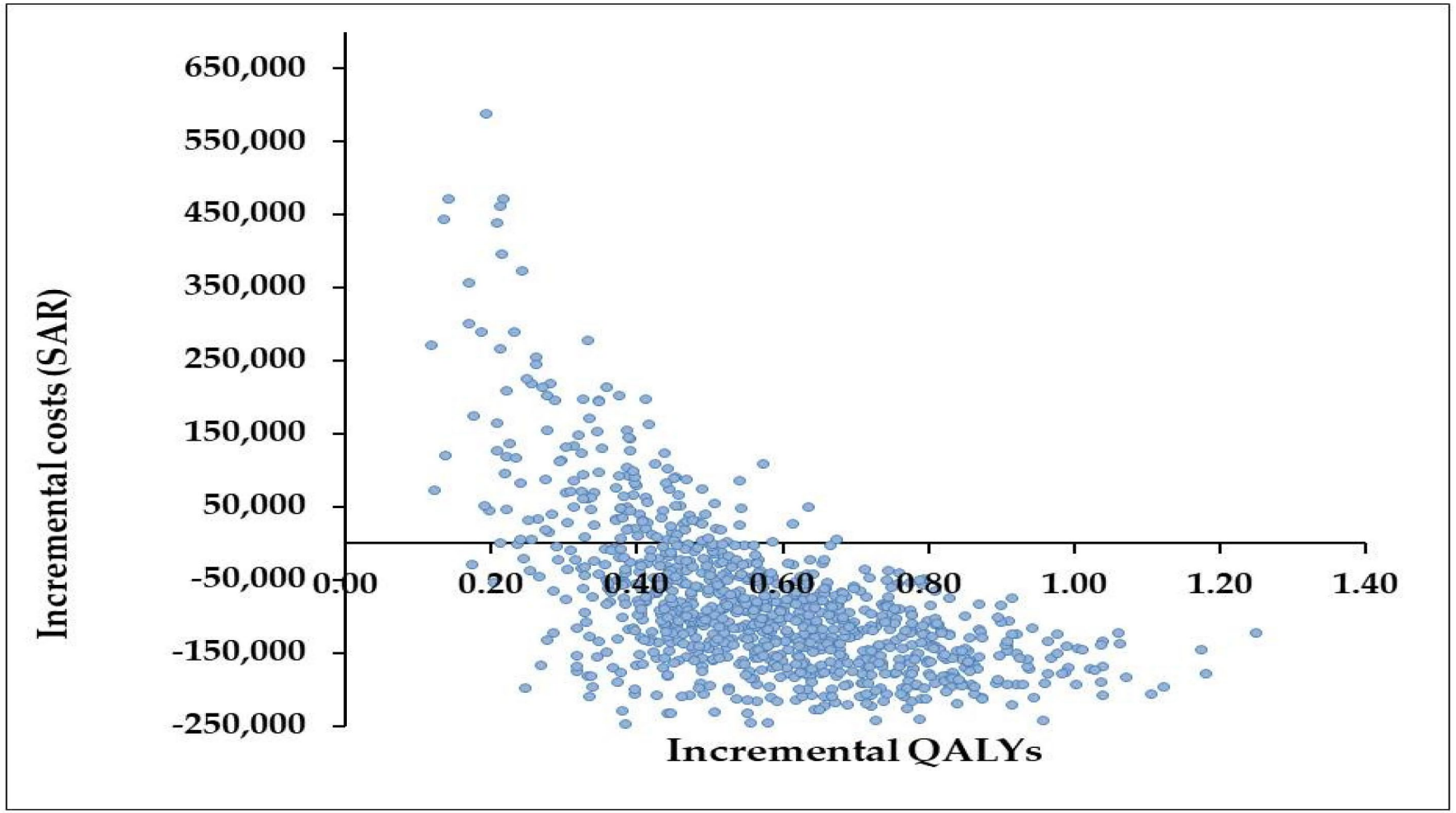
(b)



(b)


A
B

QALY (quality-adjusted life years) is a unit of measurement used in utility cost analysis that combines life span with quality → it proves **clinical benefit** with **high probability of cost savings** with the **addition of HT to chemo-radiotherapy.**



(a)

Bone metastases

International Journal of Radiation Oncology biology • physics

Clinical Investigation

Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial

Mau-Shin Chi, MD,*,† Kai-Lin Yang, MD,*,‡,§ Yue-Cune Chang, PhD,‖ Hui-Ling Ko, MD,* Yi-Hsien Lin, MD,¶,# Su-Chen Huang,* Yi-Ying Huang,* Kuang-Wen Liao, PhD,** Motoharu Kondo, MD, PhD,†† and Kwan-Hwa Chi, MD*,‡,¶

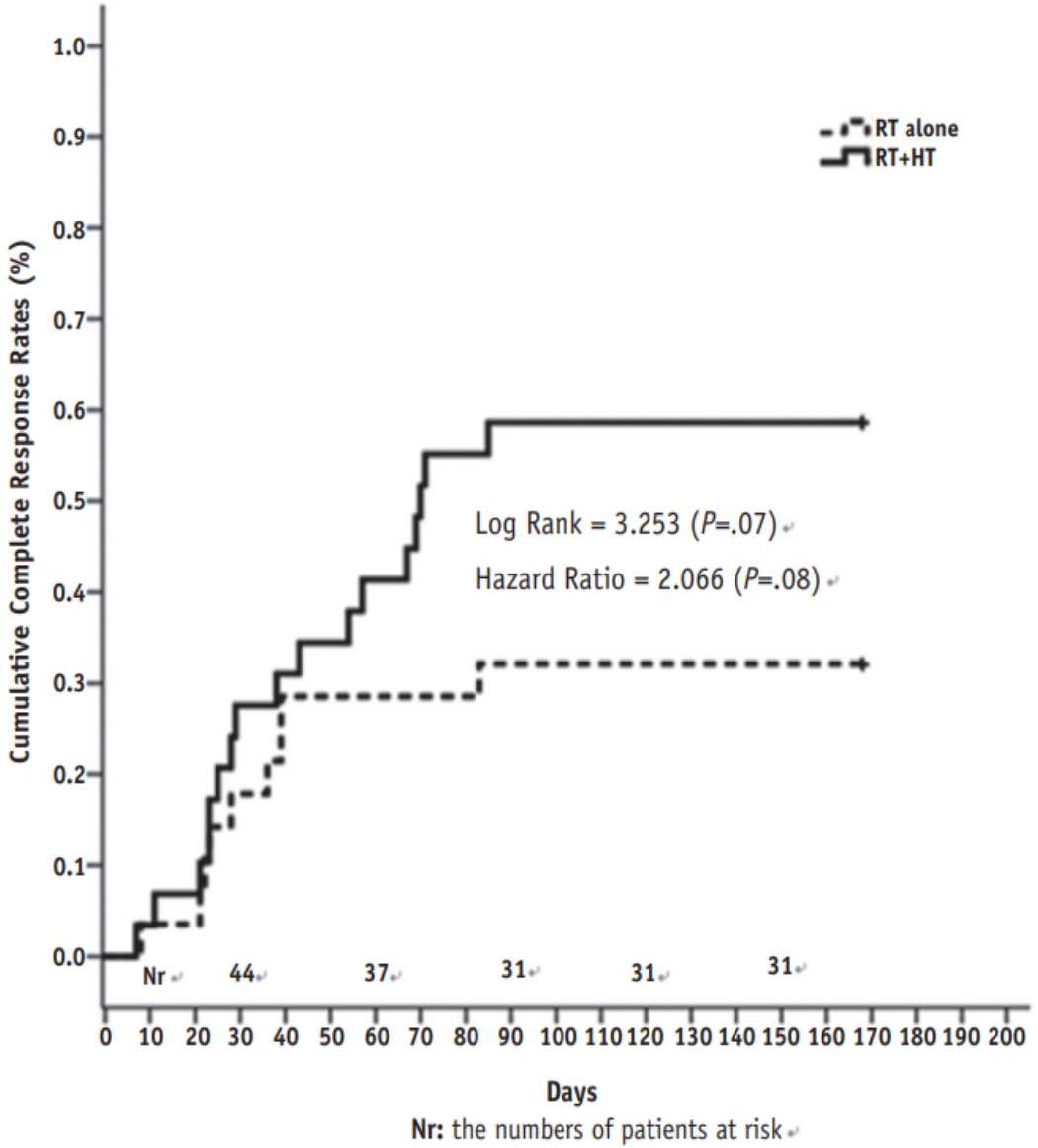


Fig. 2. Cumulative complete response rates in radiation therapy plus hyperthermia (RT + HT) and radiation therapy alone (RT-alone) group.

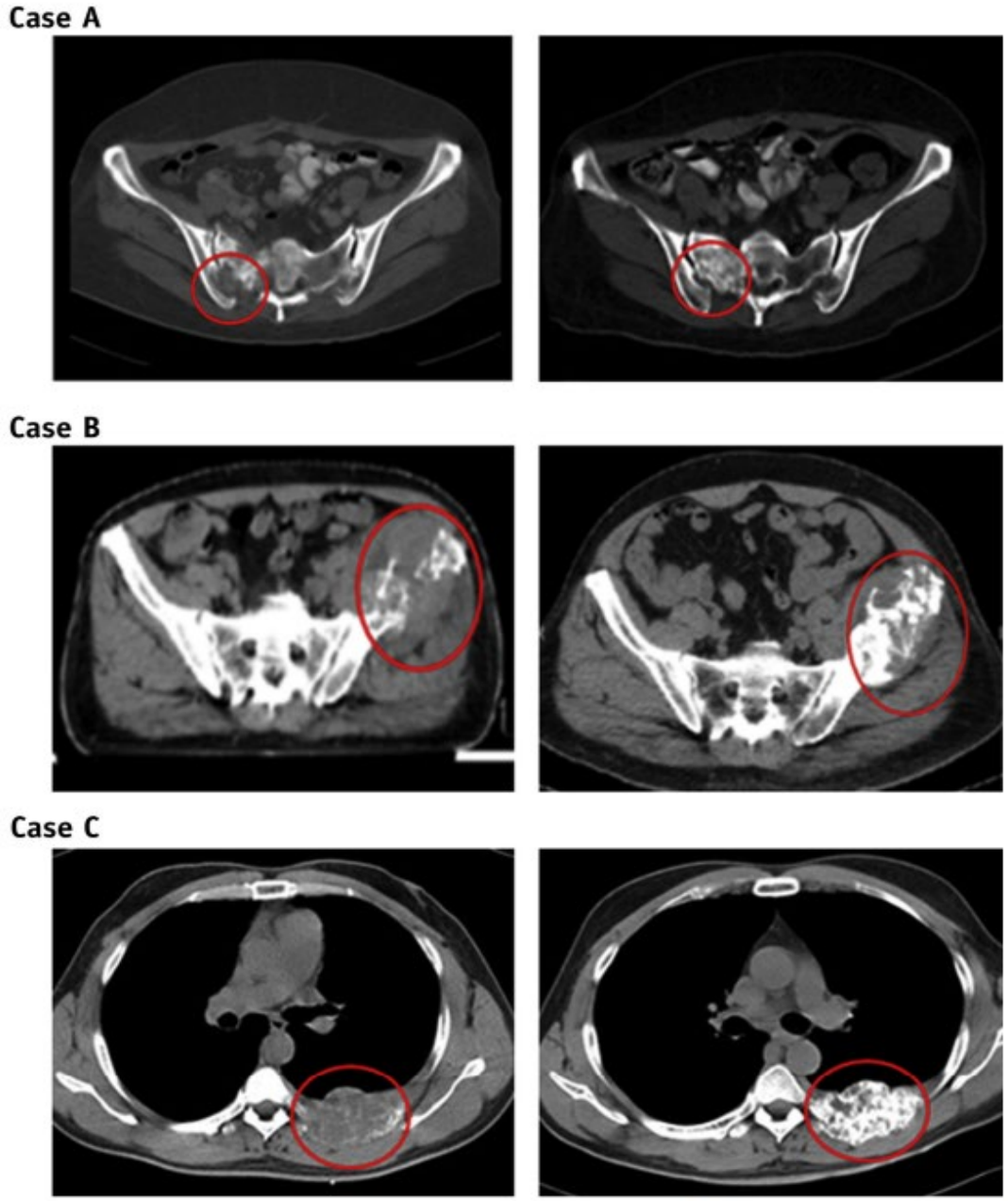


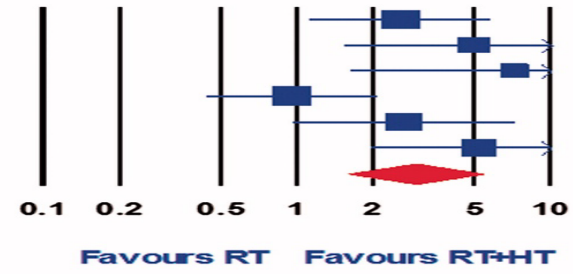
Fig. 4. Three cases of bone ossification of the osteolytic lesions after radiation therapy plus hyperthermia. Images presented were established within a 2-month period after treatment.

Head and neck cancers

(a) **Odds ratio (Radiotherapy + Hyperthermia vs. Radiotherapy alone)**

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Local CR / Total RT+HT	Local CR / Total RT alone	Weight (Random) Relative weight
Wen et al, 2014	2.56	1.12	5.86	0.026	34 / 49	23 / 49	19.89
Huilgol et al, 2010	5.00	1.52	16.46	0.008	22 / 28	11 / 26	14.36
Valdagni et al, 1994	7.22	1.61	32.46	0.010	15 / 18	9 / 22	10.90
Perez et al, 1991	0.96	0.44	2.08	0.908	18 / 53	21 / 60	20.75
Datta et al, 1990	2.64	0.96	7.28	0.061	18 / 33	10 / 32	16.85
Arcangeli et al, 1987	5.21	1.94	13.98	0.001	30 / 38	18 / 43	17.26
Overall effect	2.92	1.58	5.42	0.001	137 / 219	92 / 232	

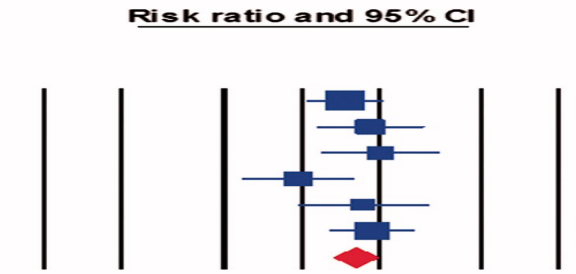
Test for heterogeneity, $I^2 = 55.38$, $p = 0.047$



(b) **Risk ratio (Radiotherapy + Hyperthermia vs. Radiotherapy alone)**

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Local CR / Total RT+HT	Local CR / Total RT alone	Weight (Random) Relative weight
Wen et al, 2014	1.48	1.04	2.10	0.029	34 / 49	23 / 49	26.11
Huilgol et al, 2010	1.86	1.14	3.03	0.013	22 / 28	11 / 26	15.00
Valdagni et al, 1994	2.04	1.18	3.51	0.010	15 / 18	9 / 22	12.44
Perez et al, 1991	0.97	0.58	1.62	0.908	18 / 53	21 / 60	13.93
Datta et al, 1990	1.75	0.96	3.18	0.069	18 / 33	10 / 32	10.35
Arcangeli et al, 1987	1.89	1.28	2.78	0.001	30 / 38	18 / 43	22.16
Overall effect	1.61	1.32	1.97	0.000	137 / 219	92 / 232	

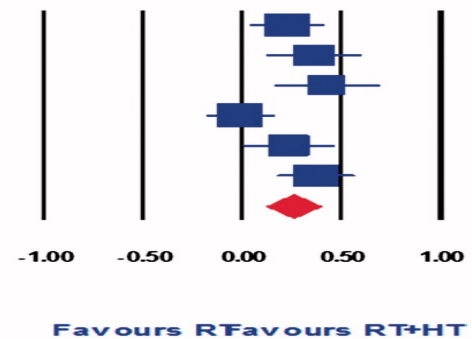
Test for heterogeneity, $I^2 = 13.37$, $p = 0.329$



(C) **Risk difference (Radiotherapy + Hyperthermia vs. Radiotherapy alone)**

Studyname	Risk difference	Standard error	Variance	Lower limit	Upper limit	p-Value	Local CR / Total RT+HT	Local CR / Total RT alone	Weight (Random) Relative weight	Relative weight
Wen et al, 2014	0.22	0.10	0.01	0.03	0.41	0.021	34 / 49	23 / 49	18.39	
Huilgol et al, 2010	0.36	0.12	0.02	0.12	0.61	0.003	22 / 28	11 / 26	15.02	
Valdagni et al, 1994	0.42	0.14	0.02	0.16	0.69	0.002	15 / 18	9 / 22	13.64	
Perez et al, 1991	-0.01	0.09	0.01	-0.19	0.17	0.908	18 / 53	21 / 60	19.40	
Datta et al, 1990	0.23	0.12	0.01	-0.00	0.47	0.051	18 / 33	10 / 32	15.58	
Arcangeli et al, 1987	0.37	0.10	0.01	0.17	0.57	0.000	30 / 38	18 / 43	17.97	
Overall effect	0.25	0.07	0.00	0.12	0.39	0.000	137 / 219	92 / 232		

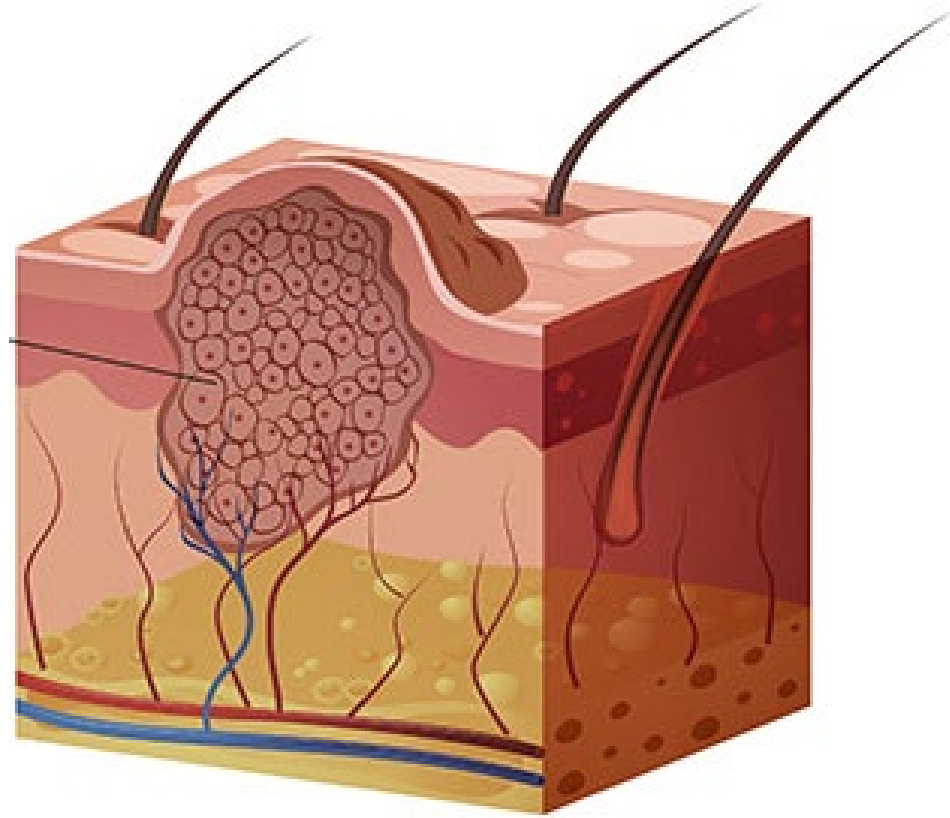
Test for heterogeneity, $I^2 = 59.44$, $p = 0.031$



Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT associated Adverse events
Zhao 2014	**Phase III randomized prospective**	Nasopharyngeal cancer	83	40 CRT 43 CRT+HT		**3 years** **OS = 53.5% (CRT) vs 73% (CRT+HT) p=0.041** **PFS= 37.5 (CRT) vs 48 (CRT+HT) months p=0.05**	
Kang 2013	**Phase III randomized prospective**	Nasopharyngeal cancer	154	78 CRT 76 CRT+HT	CR: 62.8% (CRT) vs 81.6% (CRT+HT)	**5 years** **DFS= 25.5% (CRT) vs 51.3% (CRT+HT) p<0.005** **OS = 50% (CRT) vs 68.4% (CRT+HT) p<0.005**	
Hua 2011	**Phase III randomized prospective**	Nasopharyngeal cancer	180	90 CRT 90 CRT+HT	CR: 81.1% (CRT) vs 95.6% (CRT+HT)	**5 years** **DFS= 63.1% (CRT) vs 72.7% (CRT+HT) p<0.005** **OS = 70.3% (CRT) vs 78.2% (CRT+HT) n.s.**	
Huilgol 2010	**Phase III randomized prospective**	Oral cavity Oropharynx Hypopharynx	324	CRT+HT CRT	CRT+HT: 86% vs CRT: 64%	**3 years** **OS = 49% (CRT) vs 70% (CRT+HT) p=0.040** **PFS= 30.5 (CRT) vs 50 (CRT+HT) months p=0.05**	

RT= radiotherapy, HT= hyperthermia, OS= overall survival, SR= survival rate, Clinical benefit= complete response+partial response+ stable disease, CHT= chemotherapy, DFS=Disease free survival, CRT= chemoradiotherapy, LRFS= local relapse-free survival, n.s.= not significant

Melanoma



Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma

Overgaardd et Al. The Lancet, 1995

Overgaard et al, 1995[31]	RCT	N= 70 (134 malignant lesions) **Melanoma -** recurrent or metastatic melanoma lesions	Radiation + HT 3 fractions of radiation over 8 days, followed by 1-hour HT at target temperature of 43°C	Radiation alone	CR (at 3 months) Persistent local control Safety	CR: 62% in Tx arm, 35% in Ctrl arm (p < 0.05) 2-yr local tumor control: 28% in radiation alone vs 46% in combined treatment (p = 0.008) Most important prognostic variables: hyperthermia (OR 2-yr local control: 1.73, 95% CI 1.07-2.78, p = 0.023), radiation dose, tumor size. Safety: Addition of heat did not increase acute or late effects of radiation.

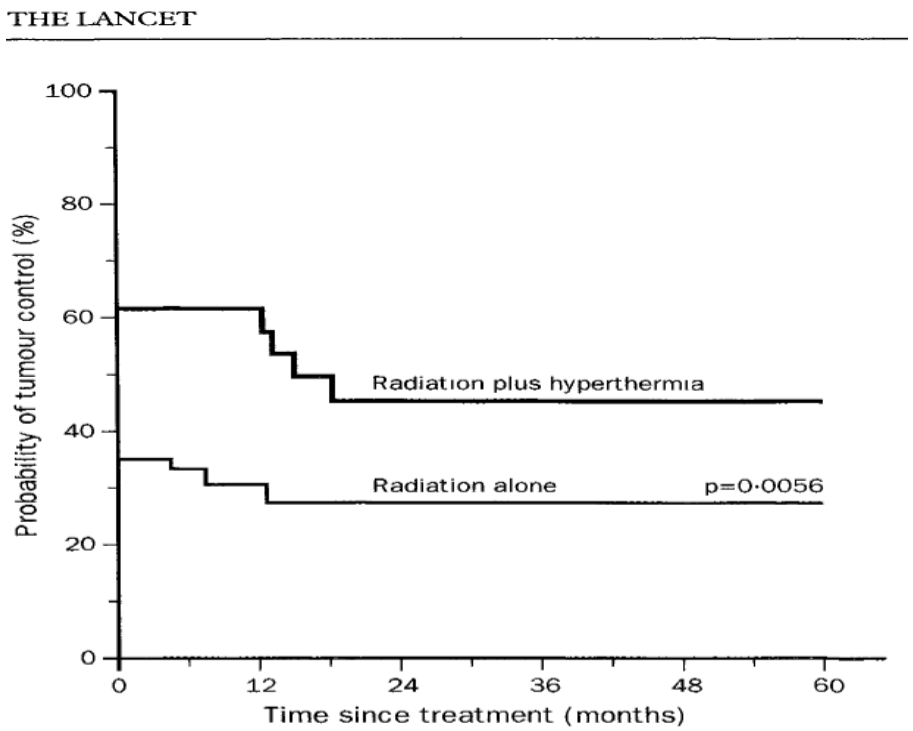


Figure: **Probability of tumour control after treatment with radiation alone or radiation plus hyperthermia**

THE LANCET

VOLUME 23 · NUMBER 13 · MAY 1 2005

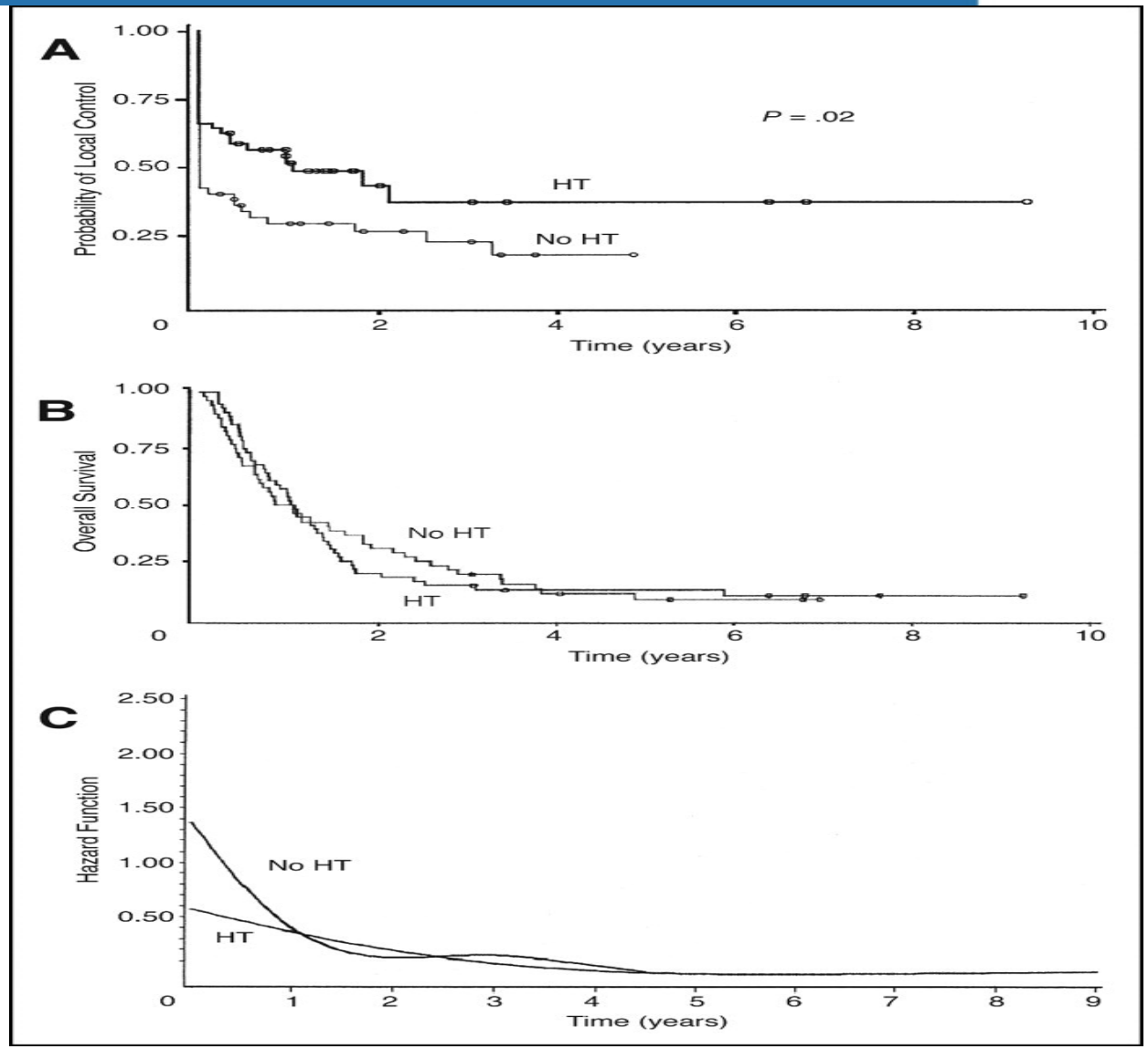
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

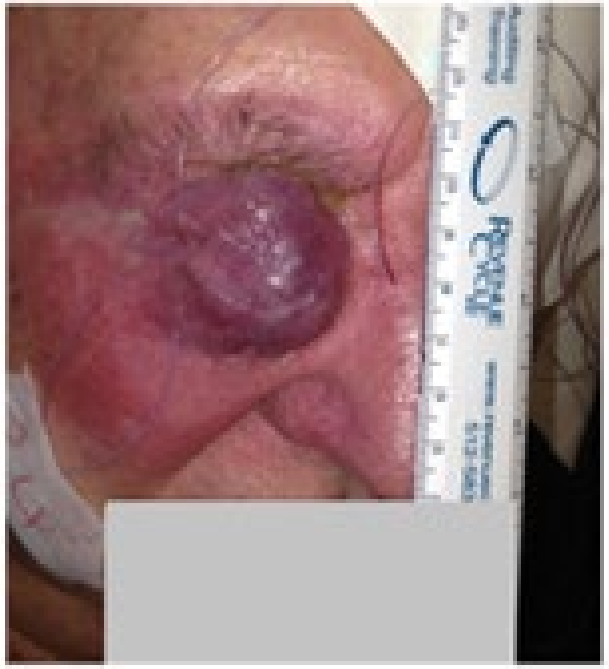
Randomized Trial of Hyperthermia and Radiation for Superficial Tumors

Ellen L. Jones, James R. Oleson, Leonard R. Prosnitz, Thaddeus V. Samulski, Zeljko Vujaskovic, Daohai Yu, Linda L. Sanders, and Mark W. Dewhirst

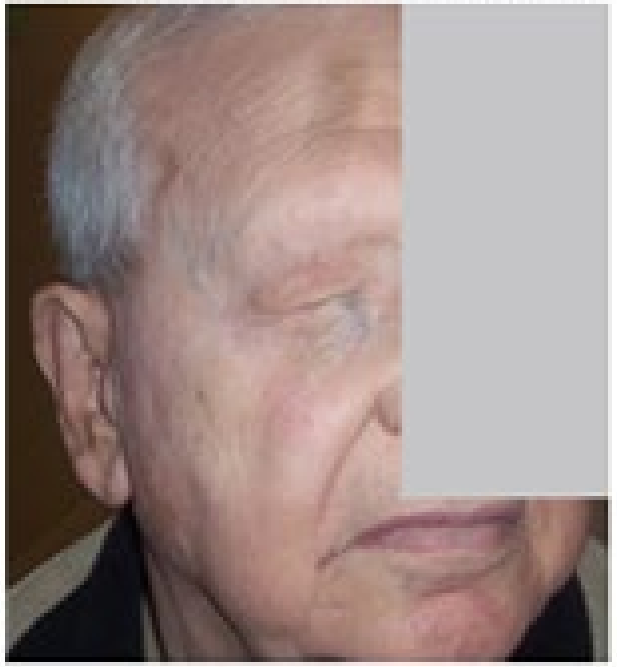
2005



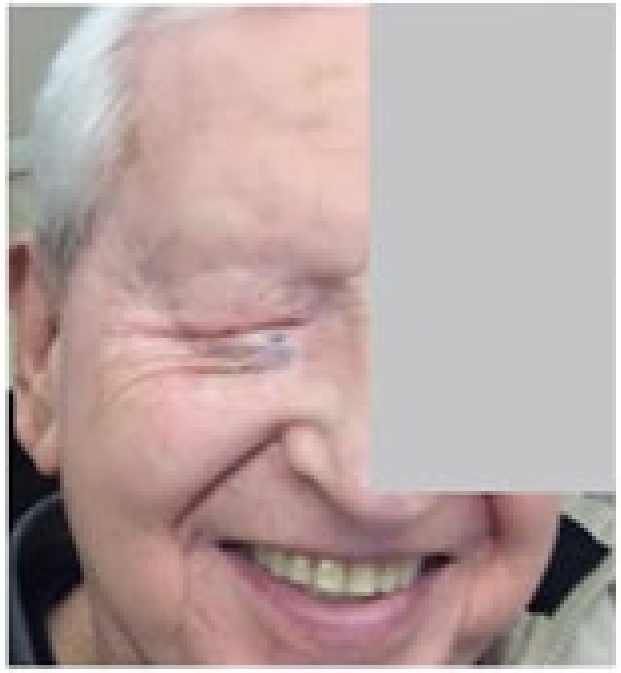
Before Treatment



3 Months After Treatment

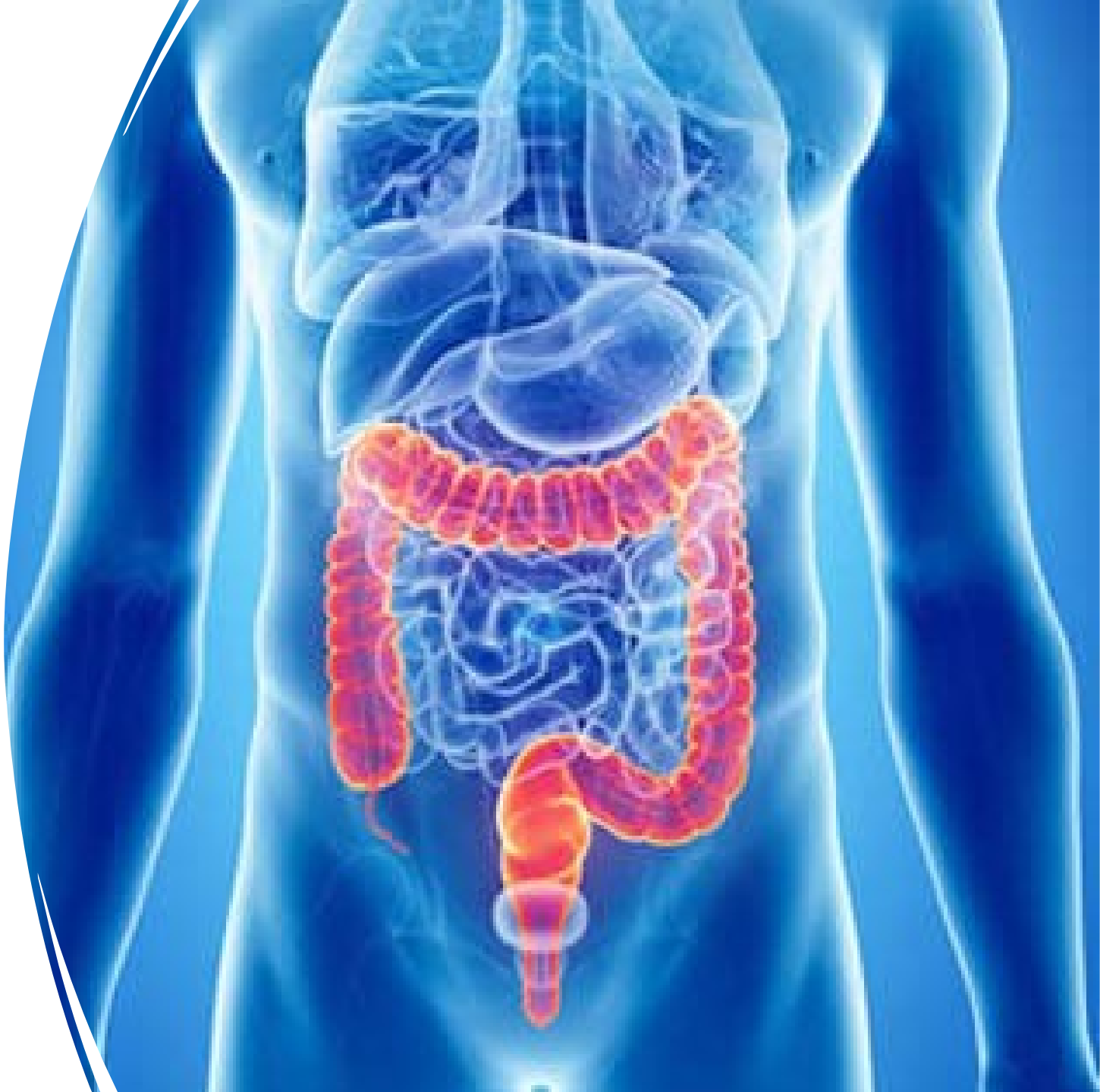


8 Months After Treatment



Eyelid melanoma after RT + Hyperthermia : complete response

Rectal -Anal cancer



Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT associated Adverse events
Ott 2019	**Randomised prospective study**	Squamous rectal cancer	112	CRT vs CRT + HT		**5 years follow-up, overall (95.8 vs. 74.5%, P = 0.045), disease-free (89.1 vs. 70.4%, P = 0.027),** local **recurrence-free (97.7 vs. 78.7%, P = 0.006), and colostomy-free survival rates (87.7 vs. 69.0%, P = 0.016)**	Comparable toxicity: skin reaction, diarrhea, stomatitis, and nausea/emesis were not increased with the additional use of hyperthermia.
Zwirner 2018	non-randomised prospective study	locally advanced rectal cancer	86	Preoperative CRT-HT		5-years OS =87.3% DFS =79.9 LRFS =95.8%	ND
Gani 2016	non-randomised retrospective study	adenocarcinoma of the middle or lower rectum	103	Neoadjuvant 43 CRT 60 CRT-HT		5-years CRT **OS= 76%** DFS= 73% LRFS =77% 5-years CRT-HT **OS= 88% p < 0.08** DFS= 78% LRFS =75%	ND
Shoji 2015	non-randomised prospective study	rectal cancer	49	Preoperative CRT-HT	CR+yCR=29%		One case of G3 perianal dermatitis

Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT associated Adverse events
Kato 2014	prospective study	locally advanced rectal cancer	48	Preoperative CRT-HT	pCR=69%		No hematological toxicity
Schroeder 2012	**Randomized prospective study**	locally advanced rectal cancer	106	Neoadjuvant 45 CRT vs. 61 CRT+HT	**pCR rate CRT = 16% CRT+HT =22.5% (p = 0.043)**	5-years **OS= 88% v 76%** DFS= 77% vs 73% (ns) LRFS =75% vs 77% (ns)	G0-2 local discomfort in 8%
Maluta 2010	prospective study	locally advanced adenocarcinoma of middle and lower rectum	76	Preoperative CRT – HT	CR=23,6% Disease control=94,8%	5-years OS= 86,5% DFS= 74,5% LRFS =73,2%	G0-2 general or local discomfort in 15%, no G3, G4 Subcutaneous burns in 5.2%

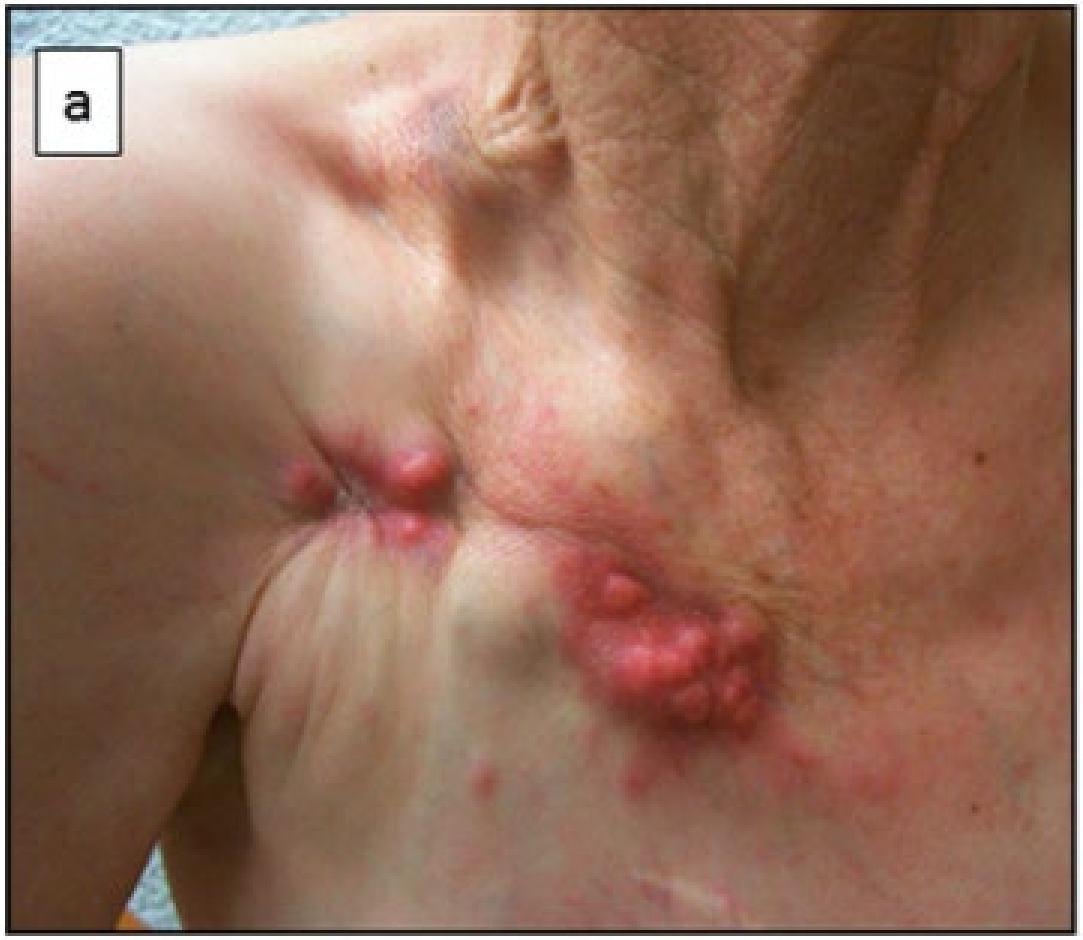
RT= radiotherapy, HT= hyperthermia, OS= overall survival, SR= survival rate, Clinical benefit= complete response+partial response+ stable disease, CHT= chemotherapy, DFS=Disease free survival, CRT= chemoradiotherapy, LRFS= local relapse-free survival, ND=not specified.

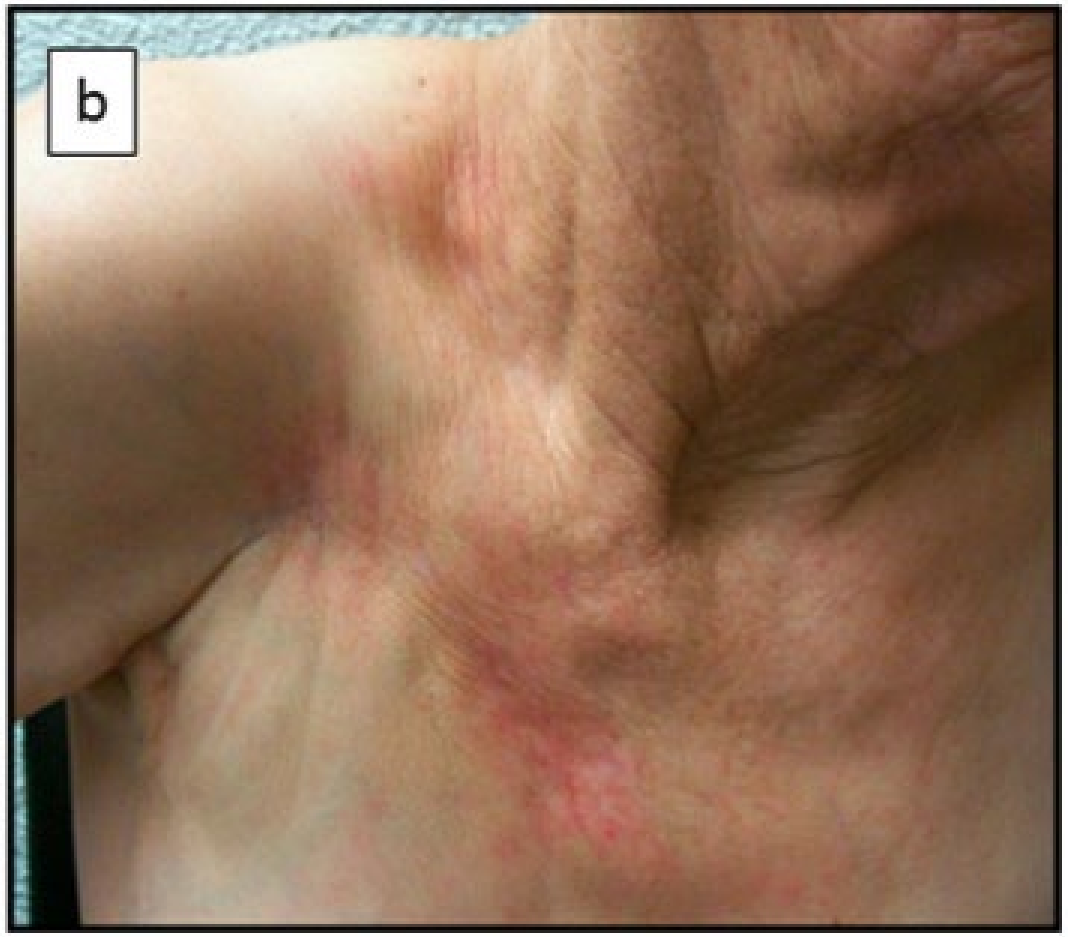
Thoracic recurrence of breast cancer

Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT associated Adverse events
Linthorst 2013	prospective	Recurrent Breast cancer	198	RT+ HT	CR= 40% Local control=76%	Median 82 months SR at 3, 5, 10 years= 75, 60, 36%	G3- 4 toxicity in 10%
Takeda 2013	prospective randomized	Recurrent or advanced breast cancer	172	Immunotherapy (dendritic cells) Immunotherapy +HT	CR=7.7% CR=26.0%		
Varma 2012	prospective	Advanced breast carcinoma	59	RT+ HT	Local control=70%		⩾G 3 toxicity in 14%
Oldenborg 2010	prospective	Recurrent breast cancer	78	RT+ HT	3, 5-year local control rates were 78% and 65%	3 year survival 66%.	G 3 toxicity in 32%

RT= radiotherapy, HT= hyperthermia, OS= overall survival, SR= survival rate, Clinical benefit= complete response+partial response+ stable disease, CHT= chemotherapy

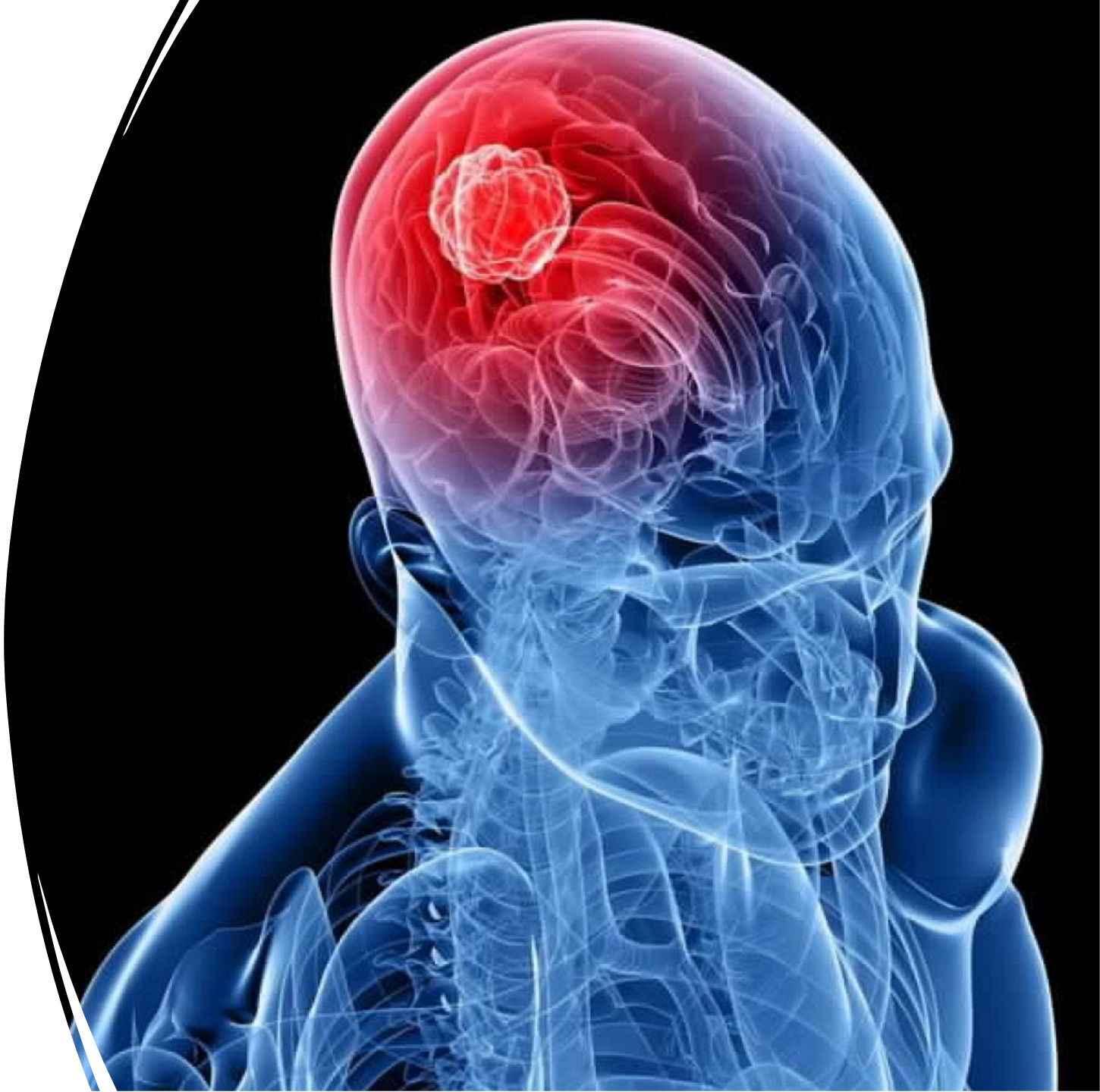
Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT associated Adverse events
De-Colle 2019	prospective observational study	recurrent breast cancer	20	RT+ HT	Clinical benefit 90%	2 years OS=90% DFS= 90% 5 year OS=50%	⩾G 3 toxicity in 15%
Klimanov 2018		Metastatic breast cancer	103	53 CHT+HT 50 CHT	Clinical benefit =76% (CHT+HT) vs 42% (CHT) p<0,05		
Linthorst 2015		Recurrent breast cancer	248	RT+ HT	CR rate 70% 1, 3, and 5 years Local Control was 53%, 40% and 39%	SR at 1, 3, and 5 years= 66%, 32%, and 18%	
Oldenborg 2015		Recurrent breast cancer	404	RT+ HT	CR=86% ORR was 86%. 3-year LC rate was 25%	Median 17 months and SR at 3 year = 37%	⩾G 3 toxicity in 24%
Refaat 2015		Recurrent or advanced breast cancer	127	RT+ HT	CR=52,7% Local control=55,1%	SR at 1, 3, and 5 years=58,3%, 29,5%, 22,5%	





COMPLETE RESPONSE OF CHEST RECURRENCE FROM BREAST CA

Gliomas



FIRST RANDOMIZED STUDY of HYPERTHERMIA with FDA APPROVAL 1998

● *Clinical Investigation*

SURVIVAL BENEFIT OF HYPERTHERMIA IN A PROSPECTIVE RANDOMIZED TRIAL OF BRACHYTHERAPY BOOST ± HYPERTHERMIA FOR GLIOBLASTOMA MULTIFORME

PENNY K. SNEED, M.D.,* PAUL R. STAUFFER, M.S.E.E.,* MICHAEL W. MCDERMOTT, M.D.,† CHRIS J. DIEDERICH, PH.D.,* KATHLEEN R. LAMBORN, PH.D.,† MICHAEL D. PRADOS, M.D.,‡ SUSAN CHANG, M.D.,‡ KEITH A. WEAVER, PH.D.,* LAURA SPRY, B.A.,‡ MARY K. MALEC, B.S.,‡ SHARON A. LAMB, R.N.,† BRIGID VOSS, R.N.,† RICHARD L. DAVIS, M.D.,§ WILLIAM M. WARA, M.D.,* DAVID A. LARSON, M.D., PH.D.,*† THEODORE L. PHILLIPS, M.D.,* AND PHILIP H. GUTIN, M.D.,†

Departments of *Radiation Oncology, †Neurological Surgery, ‡Neuro-Oncology Service of the Department of Neurological Surgery and §Department of Pathology, University of California, San Francisco, CA

Conclusion:

A multivariate analysis for these 68 patients adjusting for age and KPS showed that improved survival was significantly associated with randomization to "heat" ($p = 0.008$; hazard ratio 0.51)

Modality of hyperthermia : **interstitial**

Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT associated Adverse events
Roussakow 2017	Prospective cohort study	Recurrent GBM	54	TMZ+ mEHT		median OS= 10.10 months	no grade III–IV toxicity
Fiorentini 2019	retrospective observational two-arm comparative, multicentric study	recurrent GBM and AST	164 114 GBM 50 AST	mEHT 29 GBM 28 AST BST 85 GBM 32 AST	DC mEHT vs BSC at 3 months **GBM=62% vs 24%** **AST=77%vs 69%** **p<.05**	Median HT OS :GBM= 14 months AST= 16.5 months 1 year OS HT :AST=77.3% GBM=61% 2 year OS HT :AST=40.9% GBM=29% 5 year OS :HT vs BSC AST=83% vs 25% GBM= 3.5% vs 1.2%	no grade III–IV toxicity
Heo 2017	cohort study	Recurrent GBM	20	RT+HT		Median OS= 8.4 months 6 months OS= 67% 1 year OS= 30%, median PFS= 4.1 months	no grade III–IV toxicity
Hager 2008	retrospective observational single-arm comparative, multicentric study	Recurrent GBM 123 Recurrent Astro III&IV	179	mEHT	**DC at 3 months** **GBM=32%** **AST=57%**	From diagnosis From relapse Grade III Grade IV 37 months 19	no grade III–IV toxicity

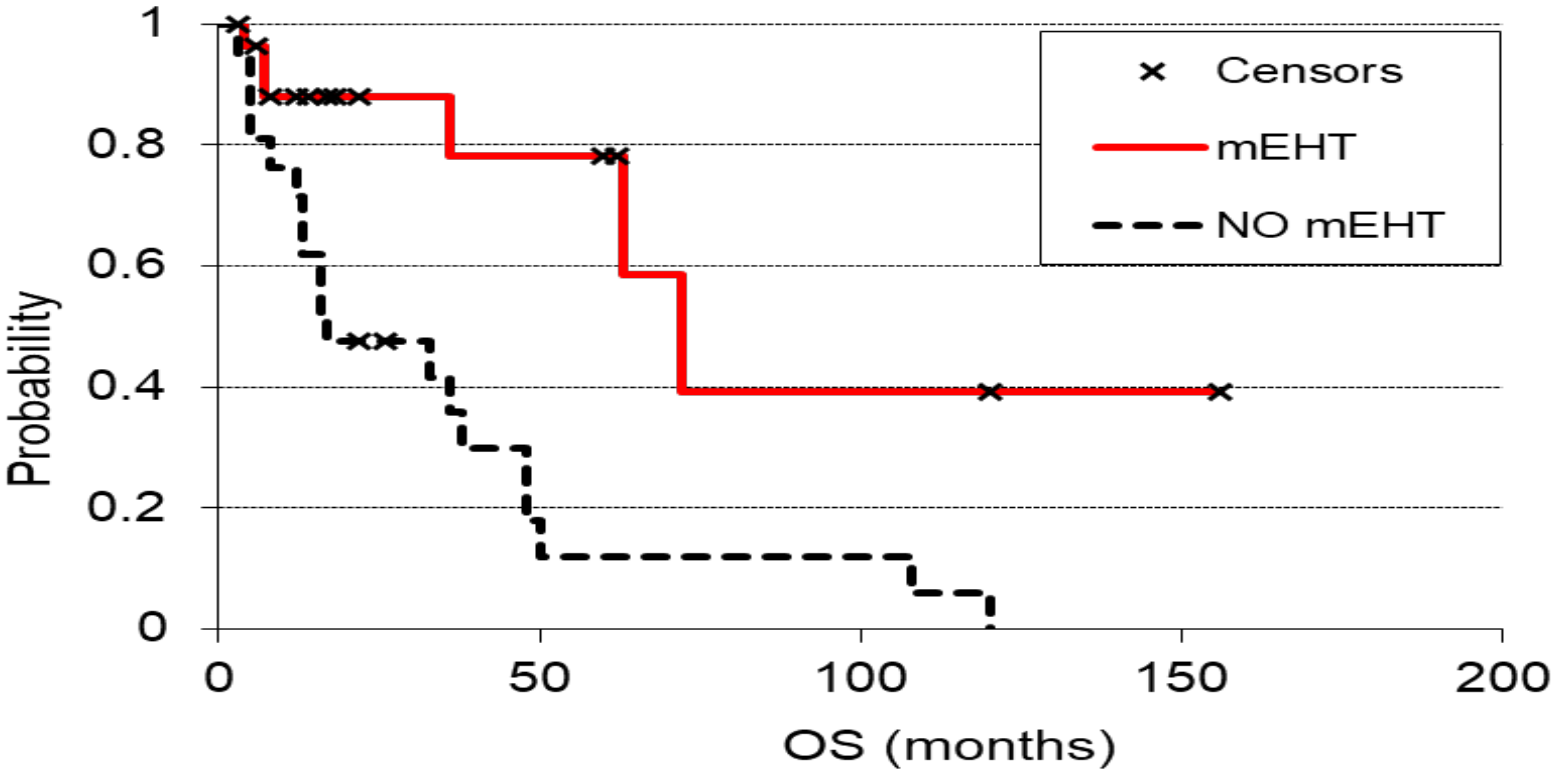
Integrative Cancer Therapies
1–11

DOI: 10.1177/1534735418812691
journals.sagepub.com/home/ict
SAGE

Modulated Electrohyperthermia in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: Retrospective Multicenter Controlled Study

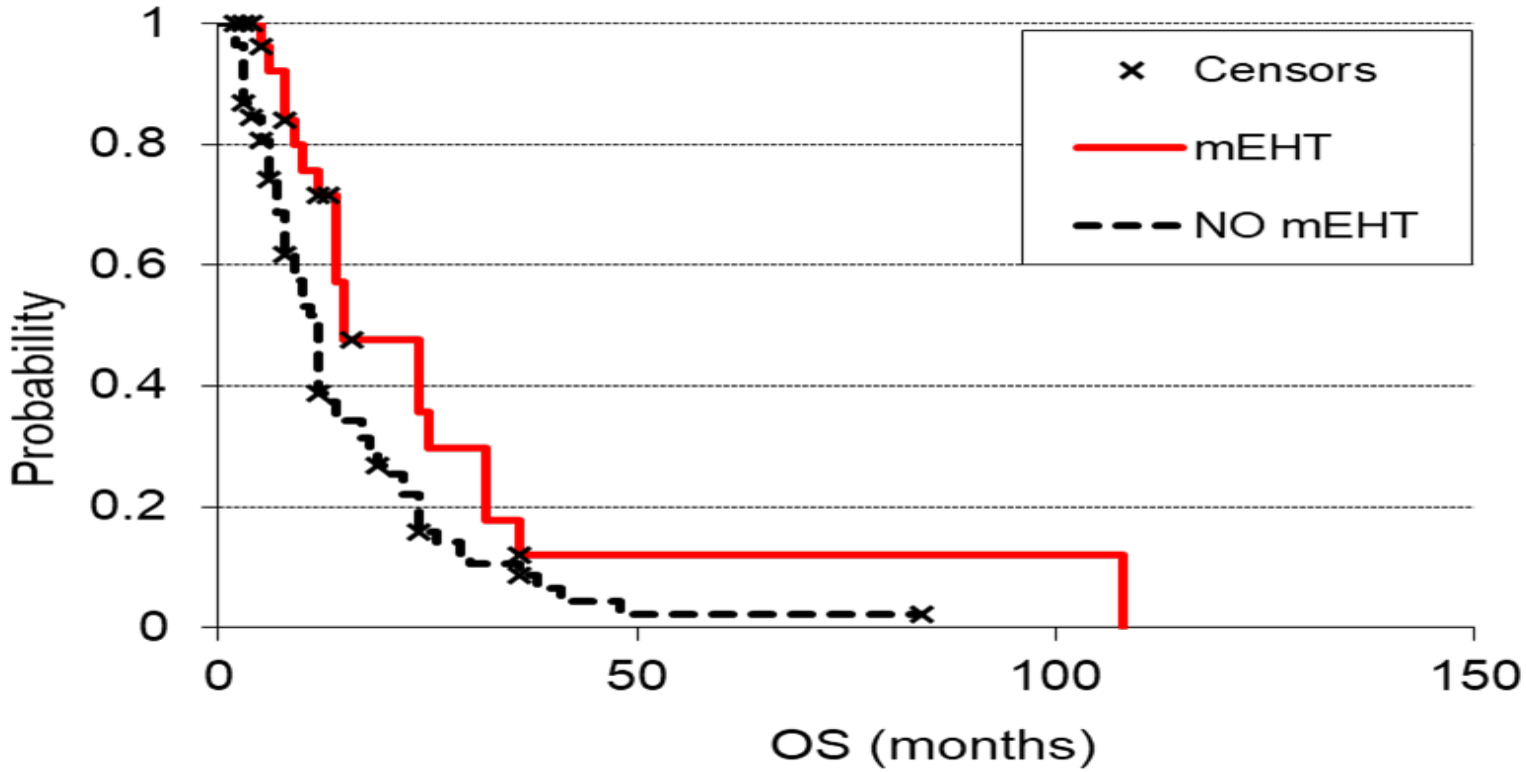
Giammaria Fiorentini, MD[1], Donatella Sarti, PhD[1], Carlo Milandri, MD[2], Patrizia Dentico, MD[2], Andrea Mambrini, MD[3], Caterina Fiorentini, MD[4], Gianmaria Mattioli, MD[1], Virginia Casadei, MD[1] and Stefano Guadagni, MD[5]

OS of the AST group



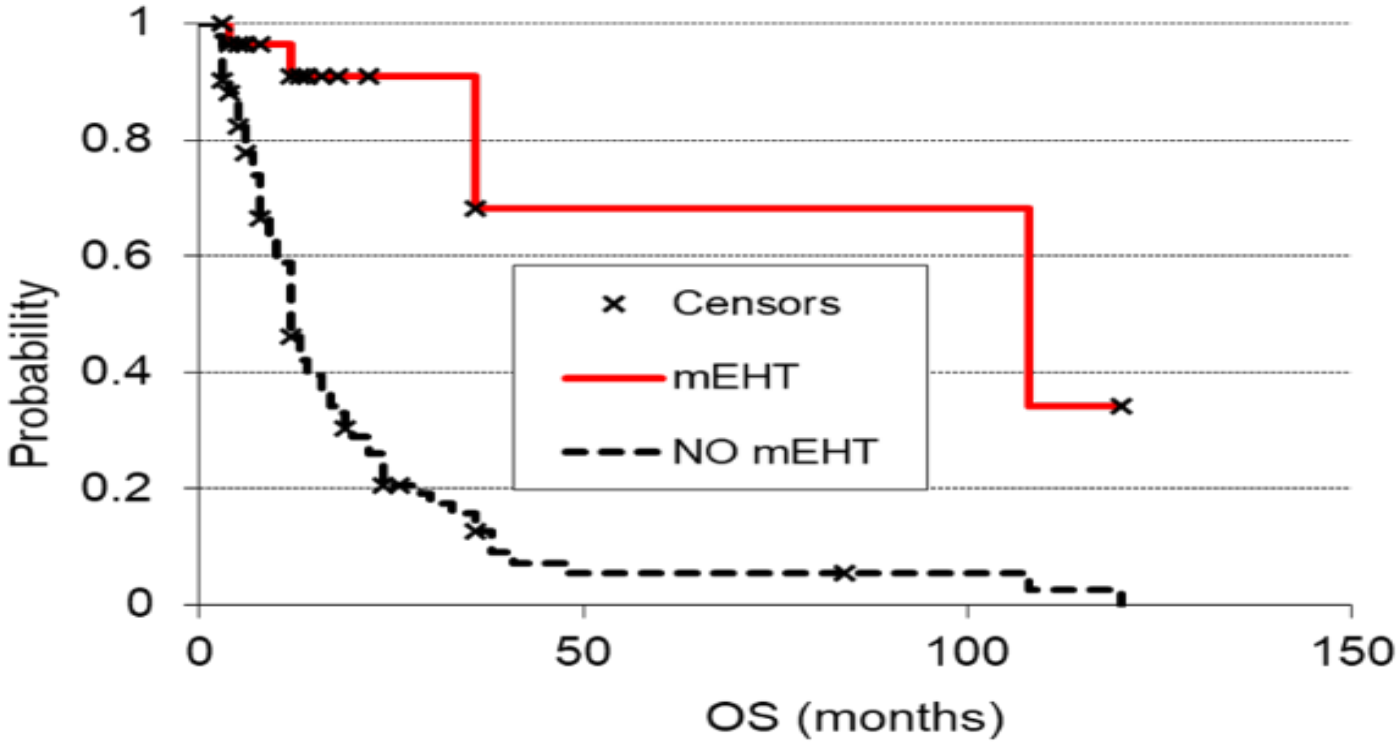
Median/Mean are 72/91.6 and 17/34 for with and without mEHT respectively. The results are statistically significant (p=0.0006). Events real/expected (Cox-mantel log-rank test) were 6/14.3 and 19/10.7 in groups with and without mEHT, respectively.

OS of GBM group



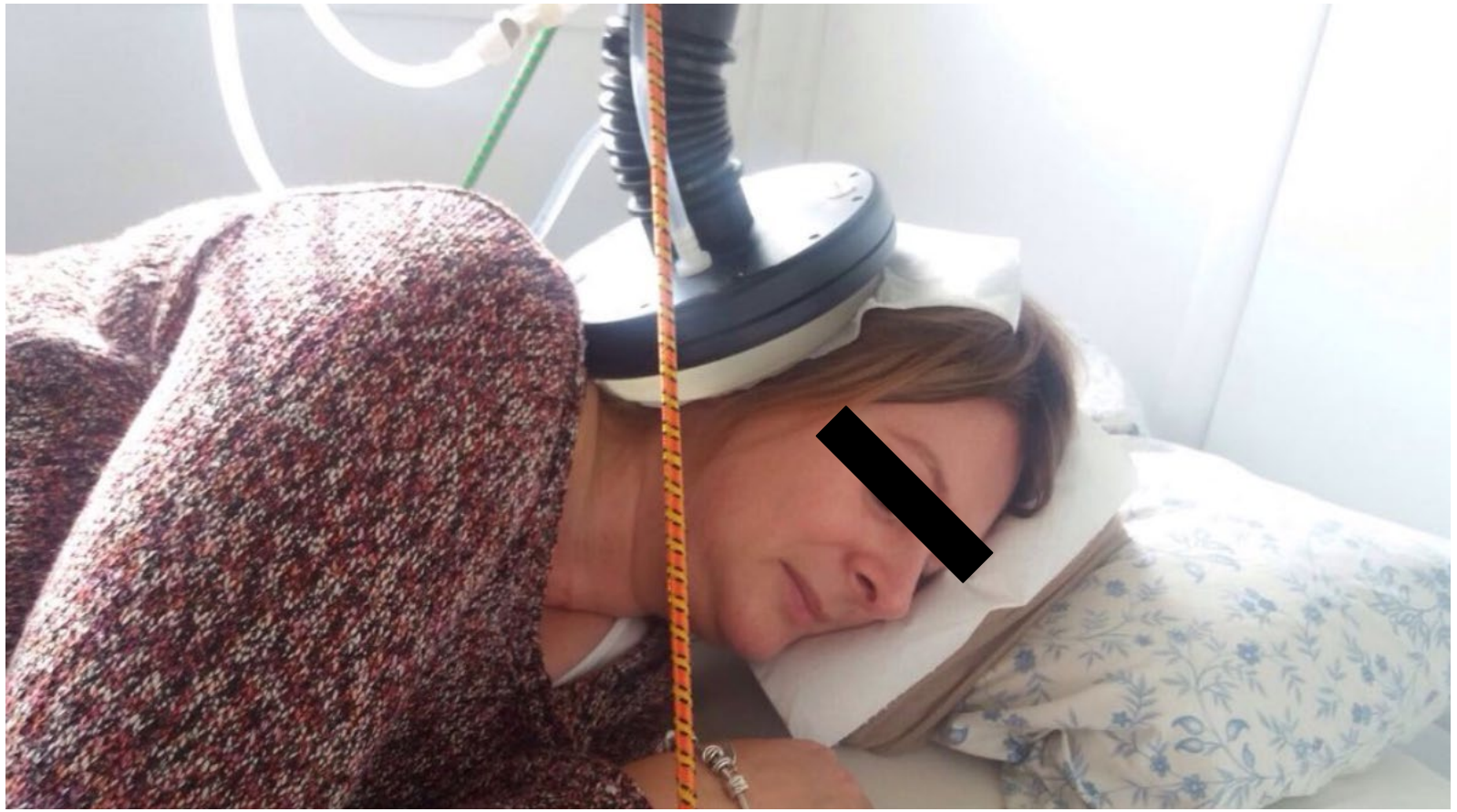
Median/Mean are 15/29 and 12/15.8 for with and without mEHT respectively. The results are statistically significant (p=0.026). Events real/expected (Cox-mantel log-rank test) were 19/28.2 and 68/58.8 in groups with and without mEHT, respectively.

Effect of temozolomide for GBM patients



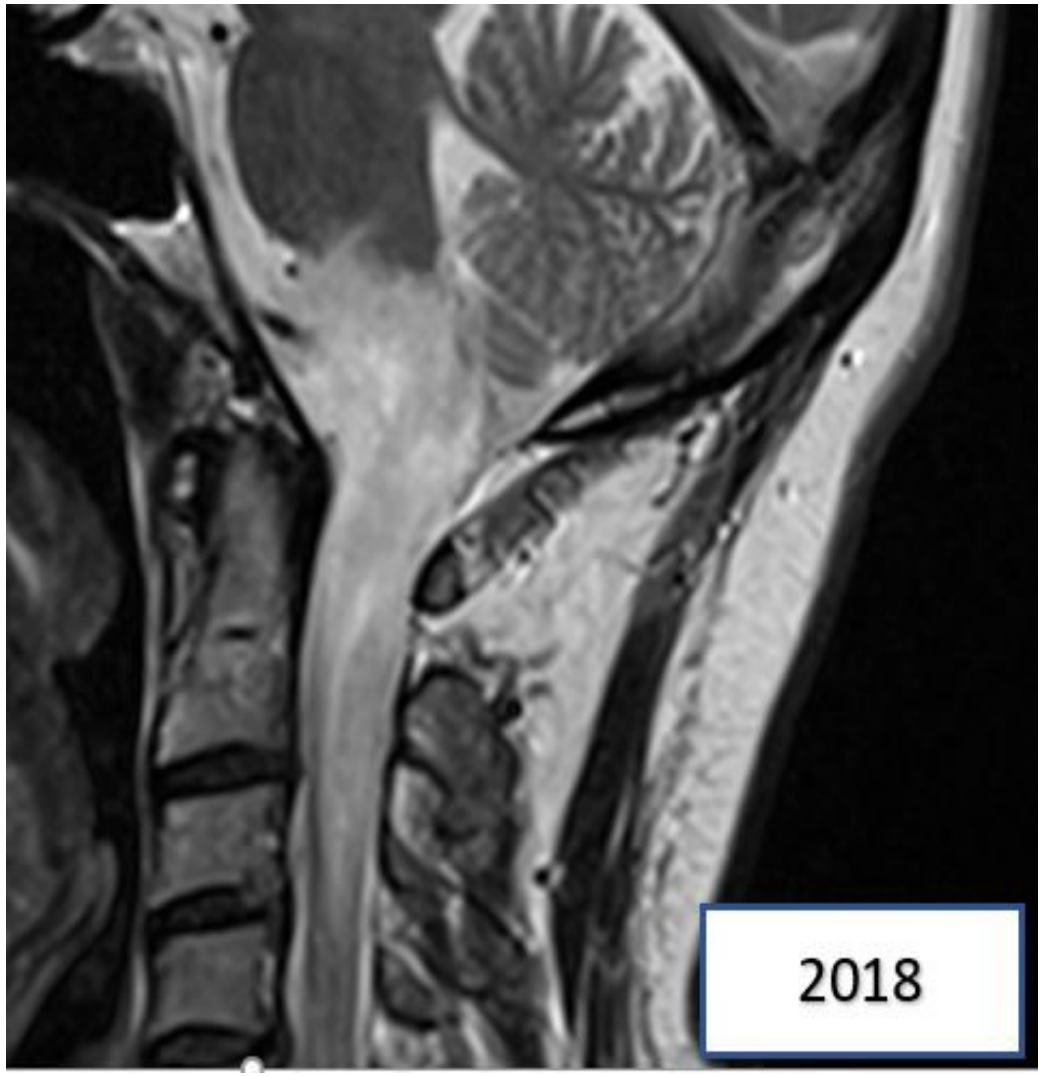
Complementary therapy contains TMZ. Median/Mean are 108/86.7 and 12/20.5 for with and without mEHT respectively. The results are statistically significant (p=0.00001). Events real/expected (Cox-mantel log-rank test) were 4/20.4 and 75/58.6 in groups with and without mEHT, respectively

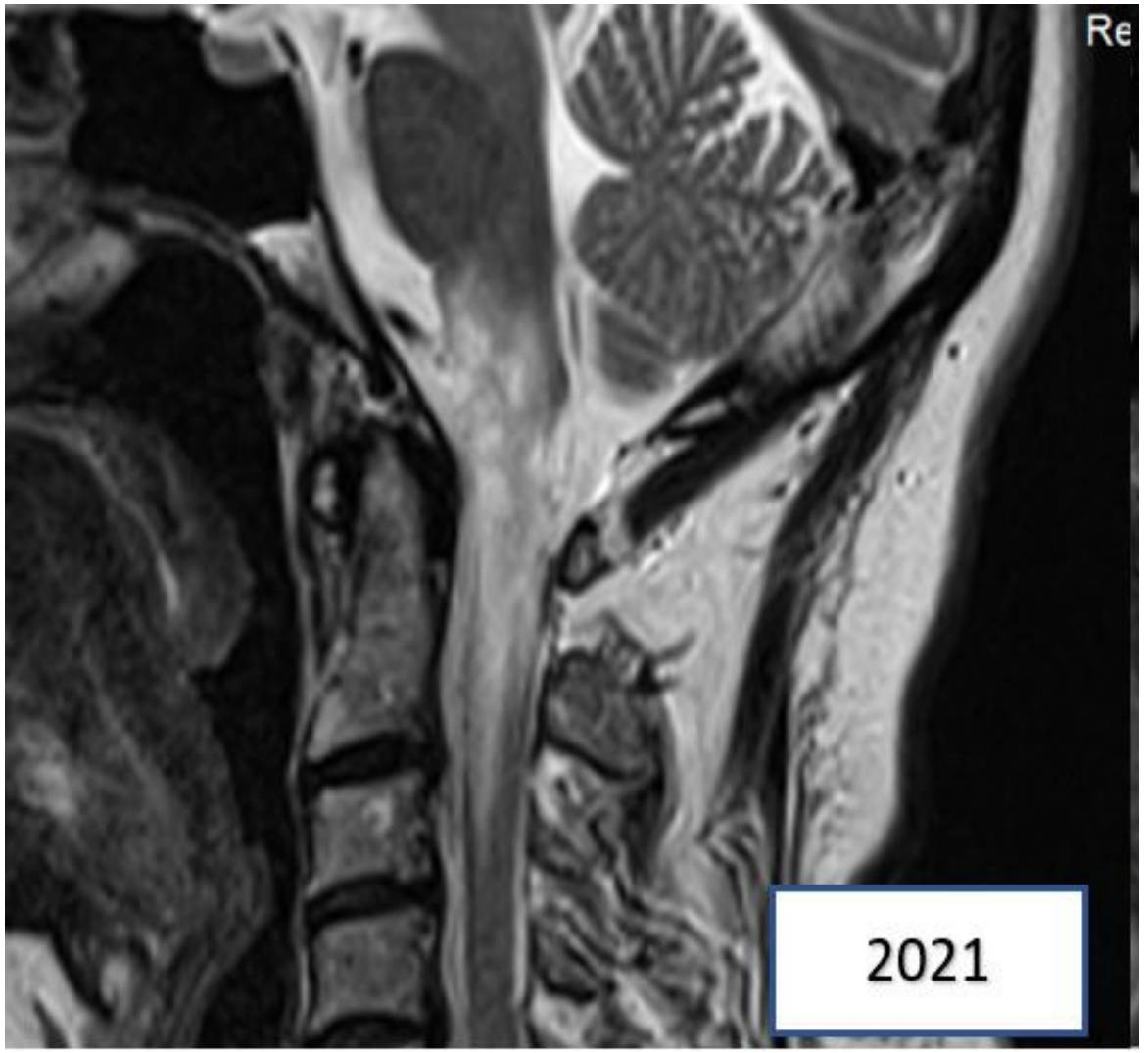
mEHT



Treating area: **Brain tumor (Pons site)**

Invasivity: **NON-INVASIVE**


2018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ASTROCYTOMA G II
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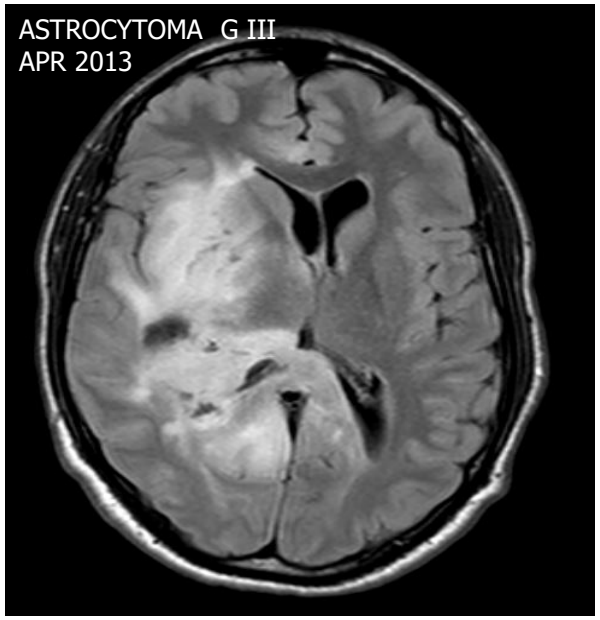
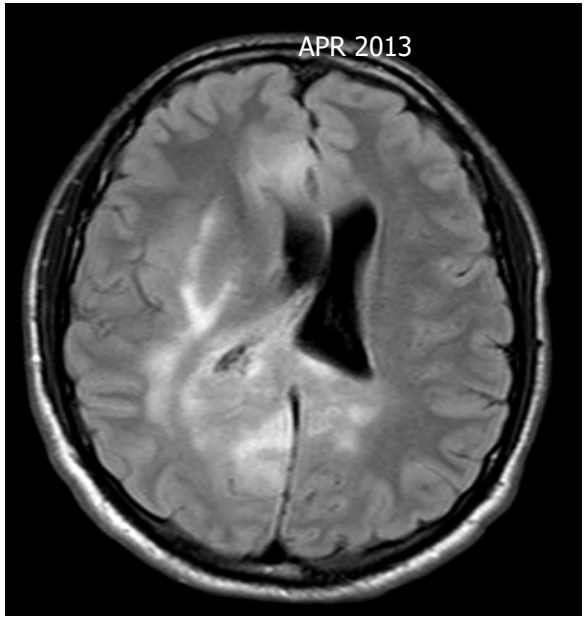
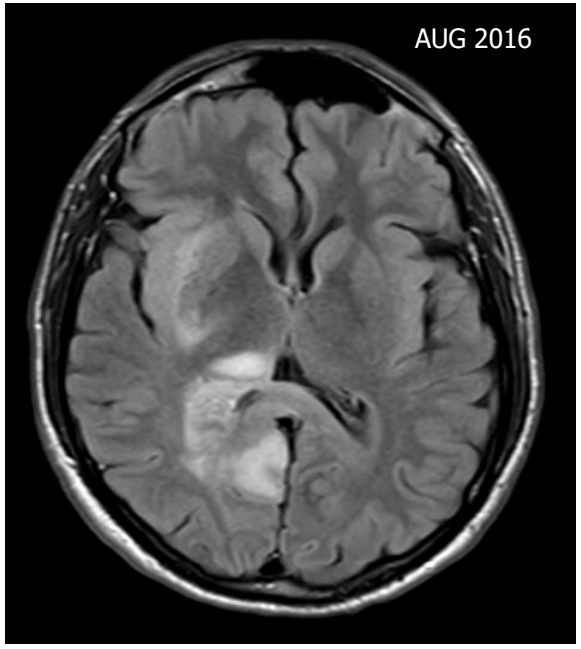
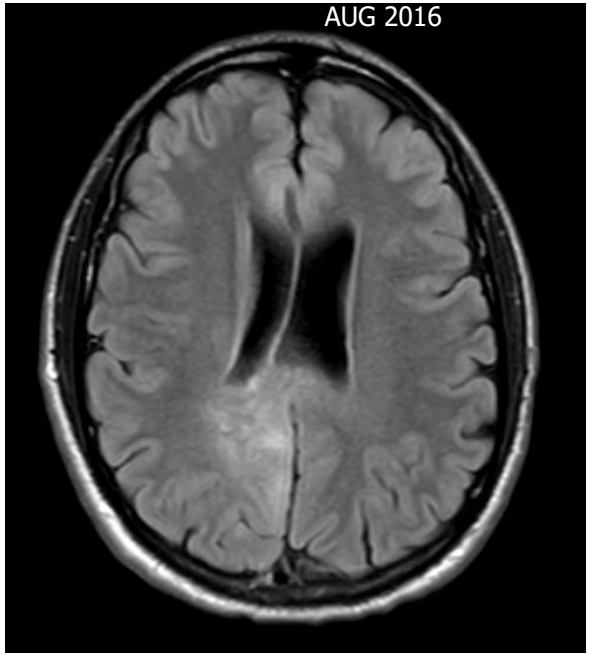
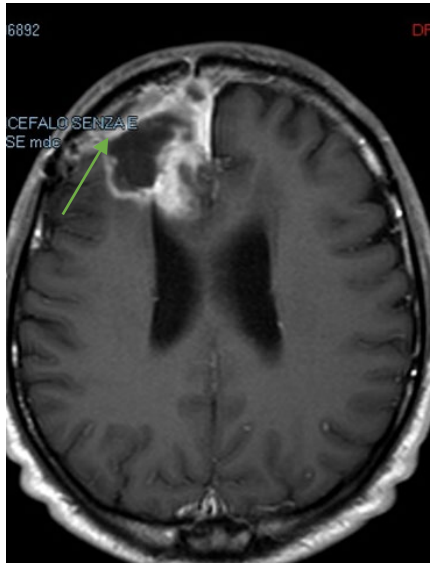

ASTROCYTOMA G III
APR 2013


APR 2013

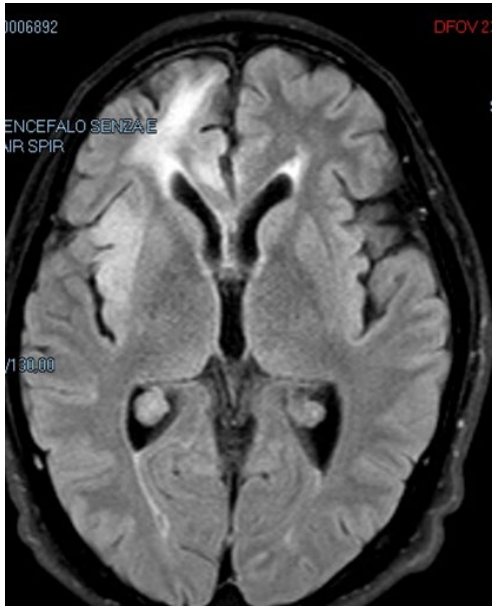

AUG 2016


AUG 2016

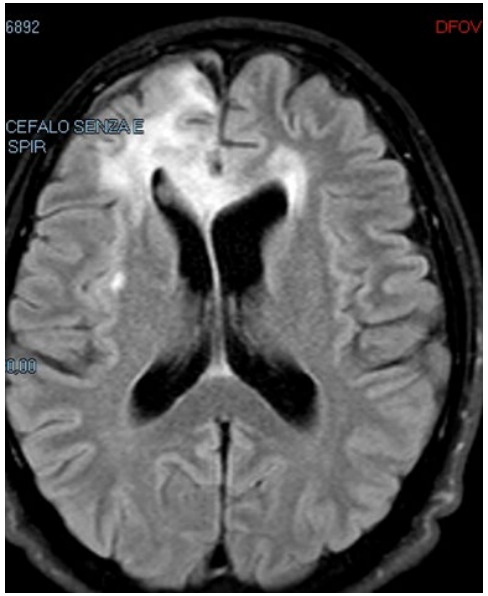
A) GBM Dec 2017



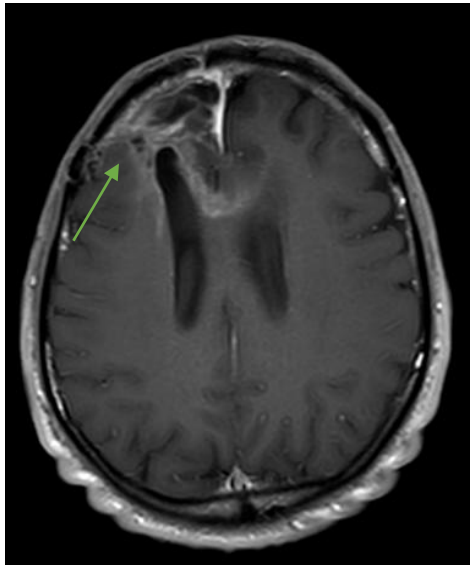
B)



C)



D) GBM Jan 2018



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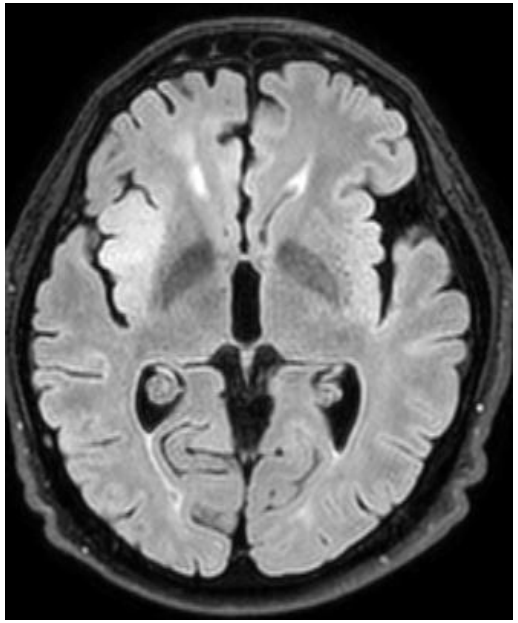
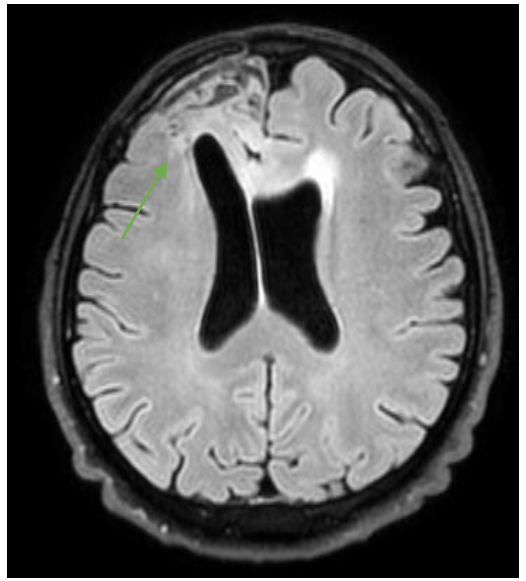
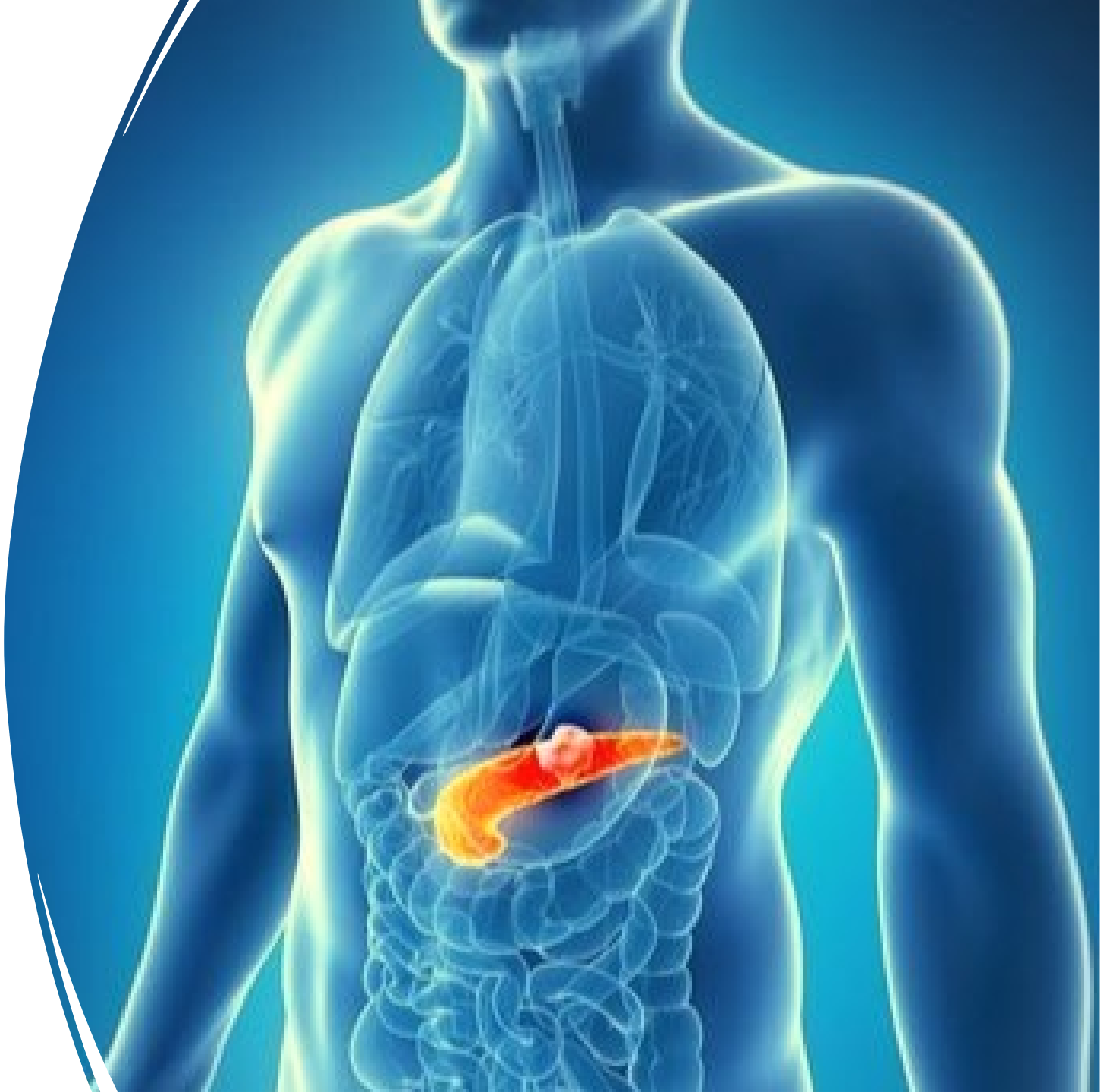
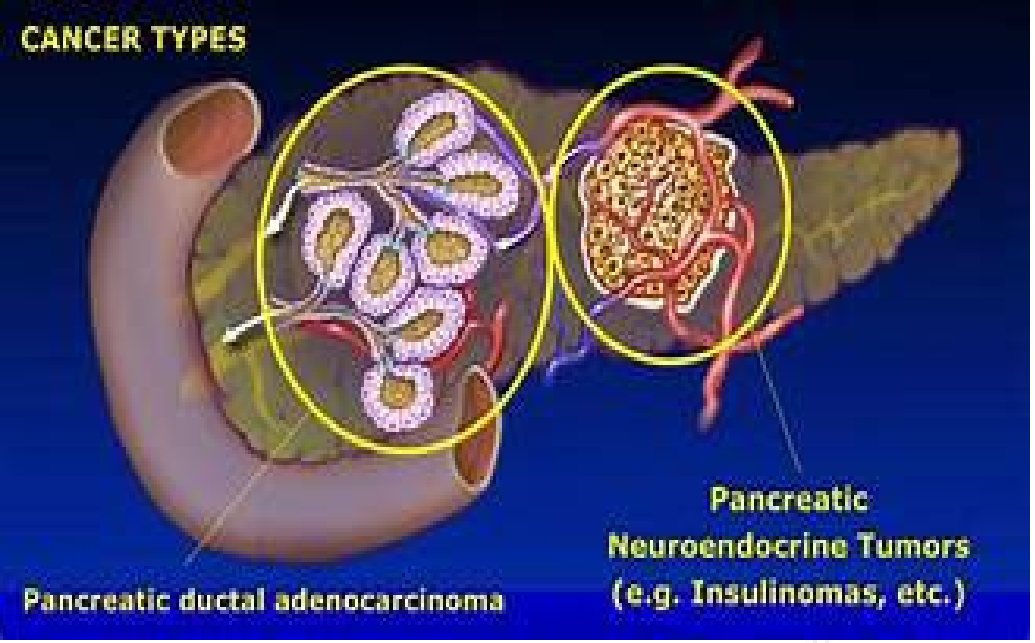


F)



Pancreatic Cancer





stage	TNM classification	clinical classification (in terms of treatment)	median survival (months)
0	Tis, N0, M0	resectable	
IA	T1, N0, M0	resectable	24.1
IB	T2, N0, M0	resectable	20.6
IIA	T3, N0, M0	resectable	15.4
IIB	T1/2/3, N1, M0	locally advanced potentially resectable	12.7
III	T4, N0/1, M0	locally advanced unresectable	10.6
IV	T1/2/3/4, N0/1, M1	metastatic	4.5

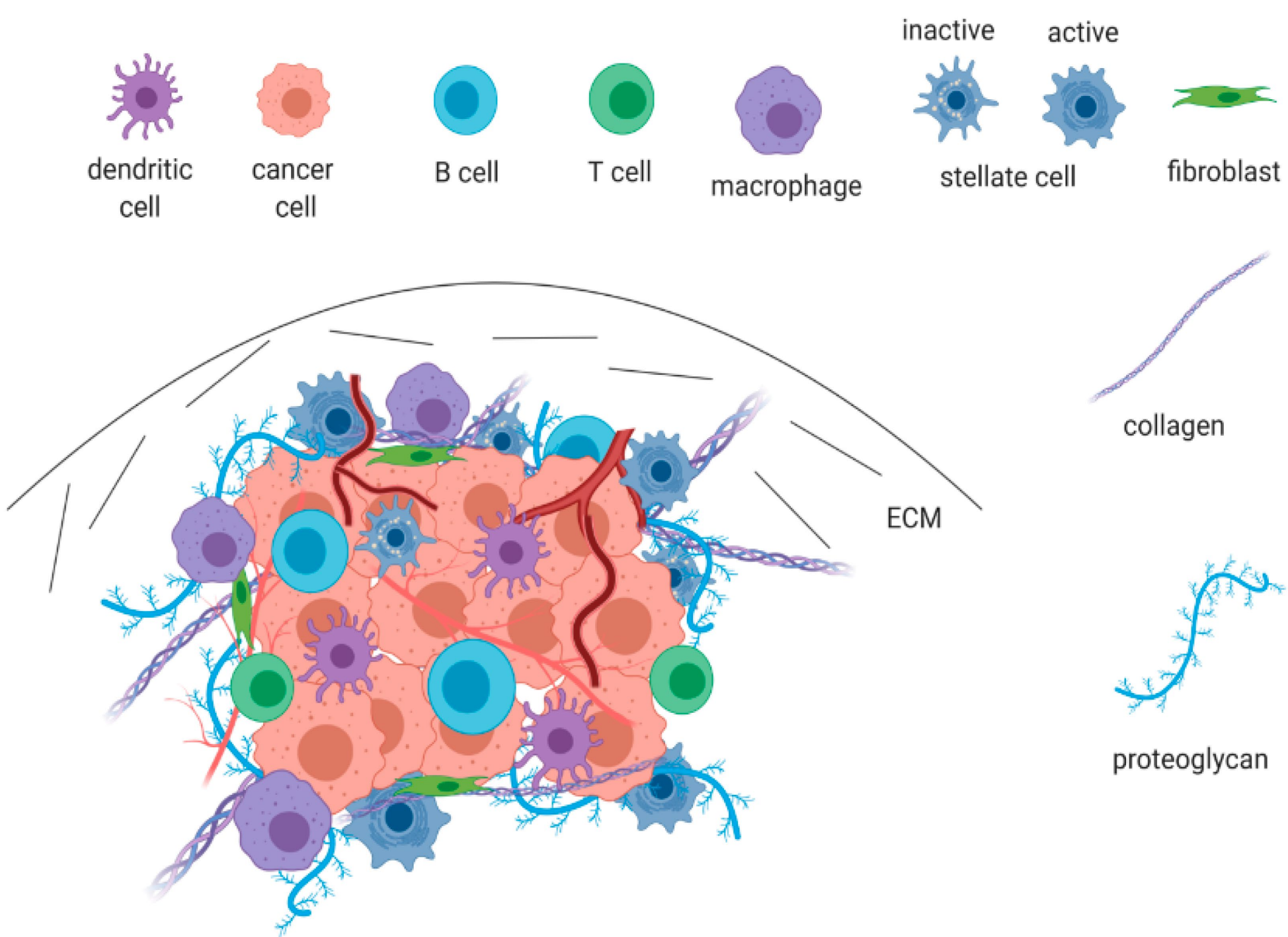
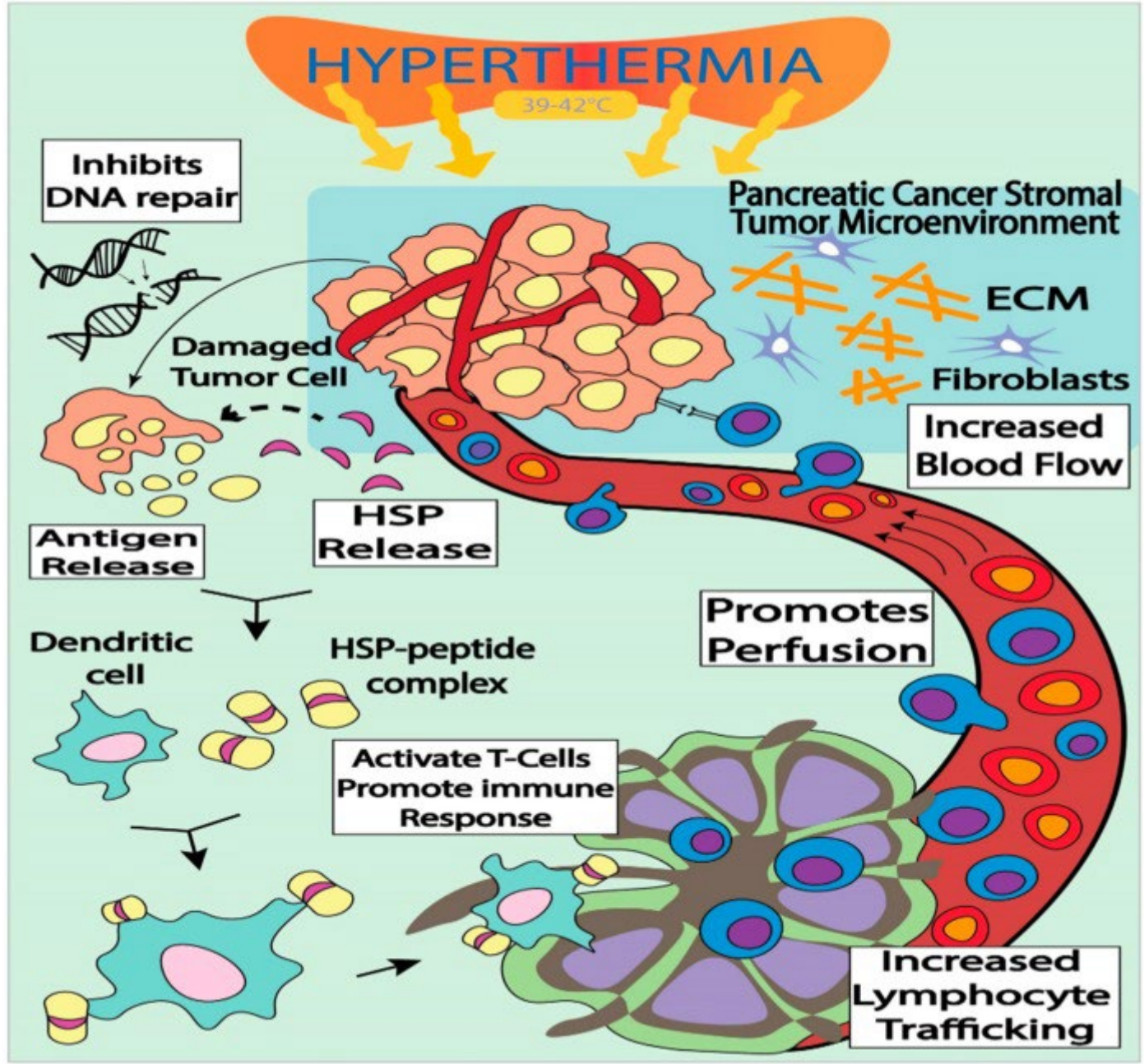

inactive
active
dendritic cell
cancer cell
B cell
T cell
macrophage
stellate cell
fibroblast
collagen
ECM
proteoglycan

Table 1 **Locoregional therapies and their main effects on the tumoral microenvironment of pancreatic ductal adenocarcinoma.**

	Vasculature	Stroma	Immune response
Hyperthermia	Increased blood flow and vascular permeability. Recruitment of bradykinin and histamin. Increased iNOS.	Destructuration of collagen fibers. Reduction of CAF. Reduction of tumor stiffness.	Promotes APC activation. Increased infiltrating CD8+. Increased pro-inflammatory cytokines. Abscopal effect (RFA).
Radiation therapy	Reduced blood perfusion. Destructuration of microvessels with thickening vessel walls. Platelet aggregation. Microthrombus formation. Increased HIF-1 and VEGF. Increased vascular permeability.	Accumulation of extracellular matrix proteins. Increased stromal cells (fibroblasts). Thickened and stiffened tissue. Loss of hyaluronic acid. Collagen remodeling. Modification of CAF population.	Release of tumor antigens (DAMPs) ≥ APC presentation and CD8+ activation. Increased peptide availability and T cell repertoire. Release of inflammatory cytokines, CD8+, and CD4+ cells. Increased adhesion molecules (VCAM-1, ICAM-1). T cells homing. Increased PDL-1.

iNOS: Inducible nitric oxide synthase; CAF: Carcinoma-associated fibroblasts; APC: Antigen presenting cell; RFA: Radiofrequency ablation; DAMPs: Damage-associated molecular patterns; HIFU: High-intensity focused ultrasound.


HYPERTHERMIA
39-42°C
Inhibits DNA repair
Pancreatic Cancer Stromal Tumor Microenvironment
ECM
Fibroblasts
Damaged Tumor Cell
Increased Blood Flow
HSP Release
Antigen Release
Promotes Perfusion
Dendritic cell
HSP-peptide complex
Activate T-Cells Promote immune Response
Increased Lymphocyte Trafficking

The clinical benefit of hyperthermia in pancreatic cancer: a systematic review

Astrid van der Horst, Eva Versteijne, Marc G. H. Besselink, Joost G. Daams, Esther B. Bulle, Maarten F. Bijlsma, Johanna W. Wilmink, Otto M. van Delden, Jeanin E. van Hooft, Nicolaas A. P. Franken, Hanneke W. M. van Laarhoven, Johannes Crezee & Geertjan van Tienhoven

Conclusions: Hyperthermia, when **added to chemotherapy and/or radiotherapy**, may positively affect treatment outcome for patients with pancreatic cancer. However, the quality of the reviewed studies was limited and future randomized controlled trials are needed to establish efficacy (2018).

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Locally advanced pancreatic cancer

Author	Year	Treatment	Hyperthermia protocol	No. of Pts. (n)	Survival	Tumor Response	RHT related toxicity
Sarti [61]	2020	mEHT+RT or CHT with gemcitabine regimen vs RT or CHT	mEHT with 13.56 MHz (EHY-2000) twice a week (8 times)	32	OS= 18 months (range 10.3-28.6) versus 10.97 months (range 4.00-22.16) PFS=12 months (range 3-28.6) versus 4.53 months (range 1.33-17.57) (p=0.003)	DCR= 85% vs 26% (p=0.0018).	3% of G1-G2 skin pain and burns
Fiorentini [26]	2019	mEHT+RT or CHT with gemcitabine regimen vs RT or CHT	mEHT with 13.56 MHz (EHY-2000) twice a week (8 times)	106	OS= 18.0 months vs 10.9 months (p<0.001)	3 months DCR= 92% vs 66%	no grade III–IV toxicity
Iyikesici [60]	2019	CHT with gemcitabine or FOLFIRINOX regimen +mEHT	mEHT with 13.56 MHz (EHY-3010) at 110-130W power for 60 minutes	25	OS=15.8 months (95% CI, 10.5–21.1) PFS=12.9 months (95% CI, 11.2–14.6)	3 months DCR=96%	None
Ono [56]	2019	CHT with FOLFIRINOX, Gemsitabin plus nab-Pacritaxel or S-1 +RHT	RHT with Thermotron RF-8, for 50 minutes after CHT once a week (5 times)	28	1 year OS=41% 2 years OS=15%	3 months DCR=57% 6 months DCR=45% 12 months DCR=12% 18 months DCR=6%	ND

World Journal of Clinical Oncology

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ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Observational Study

Hyperthermia combined with chemotherapy *vs* chemotherapy in patients with advanced pancreatic cancer: A multicenter retrospective observational comparative study

Giammaria Fiorentini, Donatella Sarti, Andrea Mambrini, Ivano Hammarberg Ferri, Massimo Bonucci, Paola Giordano Sciacca, Marco Ballerini, Salvatore Bonanno, Carlo Milandri, Roberto Nani, Stefano Guadagni, Patrizia Dentico, Caterina Fiorentini

METHODS

This was a **multicenter retrospective observational comparative study**; data were collected for **patients with stage III-IV pancreatic cancer** that were **treated with mEHT alone or** in **combination with CHT from 2003 to 2021**

→A total of 628 patients were treated in nine Italian Hospitals

→217 of them were included in this study

→89 (41%) of them received mEHT + CHT (mEHTgroup)

→128 (59%) with CHT (no-mEHT group)

CHT was mainly gemcitabine-based regimens in both study groups

mEHT protocol and device

→ was performed using the EHY-2000plus device (CE0123, Oncotherm, Torisdorf, Germany)

→ applying a radiofrequency current of 13.56 MHz as carrier frequency that was modulated by time-fractal fluctuation

→ The energy was transferred by capacitive coupling, with precise impedance matching

The hyperthermia protocol included

→ three mEHT treatments/week for 2 mo

→ starting at a 60 W power for 40 min

→ Following treatments were performed by increasing the power up to 150 W and the time up to 90 min in 2 wk.

mEHT was administered **after CHT or within 48 h**, in order to **couple the high drug blood concentration** with the **modulated electro hyperthermia** and **optimize their synergy**

Patients: sites of metastases

SITE	Total	mEHT 89		no-mEHT 128			P
LIVER	132	70	53%	63	51%		n.s.
Peritoneum	55	35	27%	20	%19		n.s.
Lymphnodes	37	22	17%	15	15%		n.s.
OTHER	10	5	4%	5	5%		n.s.

Patients: praevious treatments

Patients	Total 217	mEHT 89		no-mEHT 128			P
Metastatic	142	70	79%	72	56%		0.004
RT	10	1	1.1%	9	7%		n.s
CHT	136	68	76%	68	53%		0,005
Surgery	51	22	24%	31	24%		n.s.

RESULTS:

→ Overall survival and progression free survival

- Overall survival (20 mo, range 1,6-24 *vs* 9 mo, range 0,4-56.25, $P < 0.001$)
- progression-free survival (7 mo, range2-24 *vs* 5 mo, range 0.4-41, $P < 0.05$)
- OS and PFS were **better for the mEHT+CHT group** compared to the CHT group.

RESULTS: Tumor response and Safety

Tumor response at three month follow up was available for:

- 87(98%) of mEHT
- 111 (88%) patients for non-mEHT group

→ mEHT patients showed a higher number of PR (45% vs 24%, P= 0.0018) and a lower number of progressions (PD) (4% vs 31%, P <0.01) than no-mEHT group

→ SD had similar value in both groups: 51% for mEHT and 45% for no-mEHT

→ Median mEHT sessions was 16.8 (range 6-25), resulting 1495 mEHT delivered sessions.

Tumor response at 3 months

	mEHT	N=87	no-mEHT	N=111	
	n	%	n	%	p
PR	39	45	27	24	0,0018
SD	44	51	50	45	0,8430
PD	4	4	34	31	<0,001

Side effects and toxicity

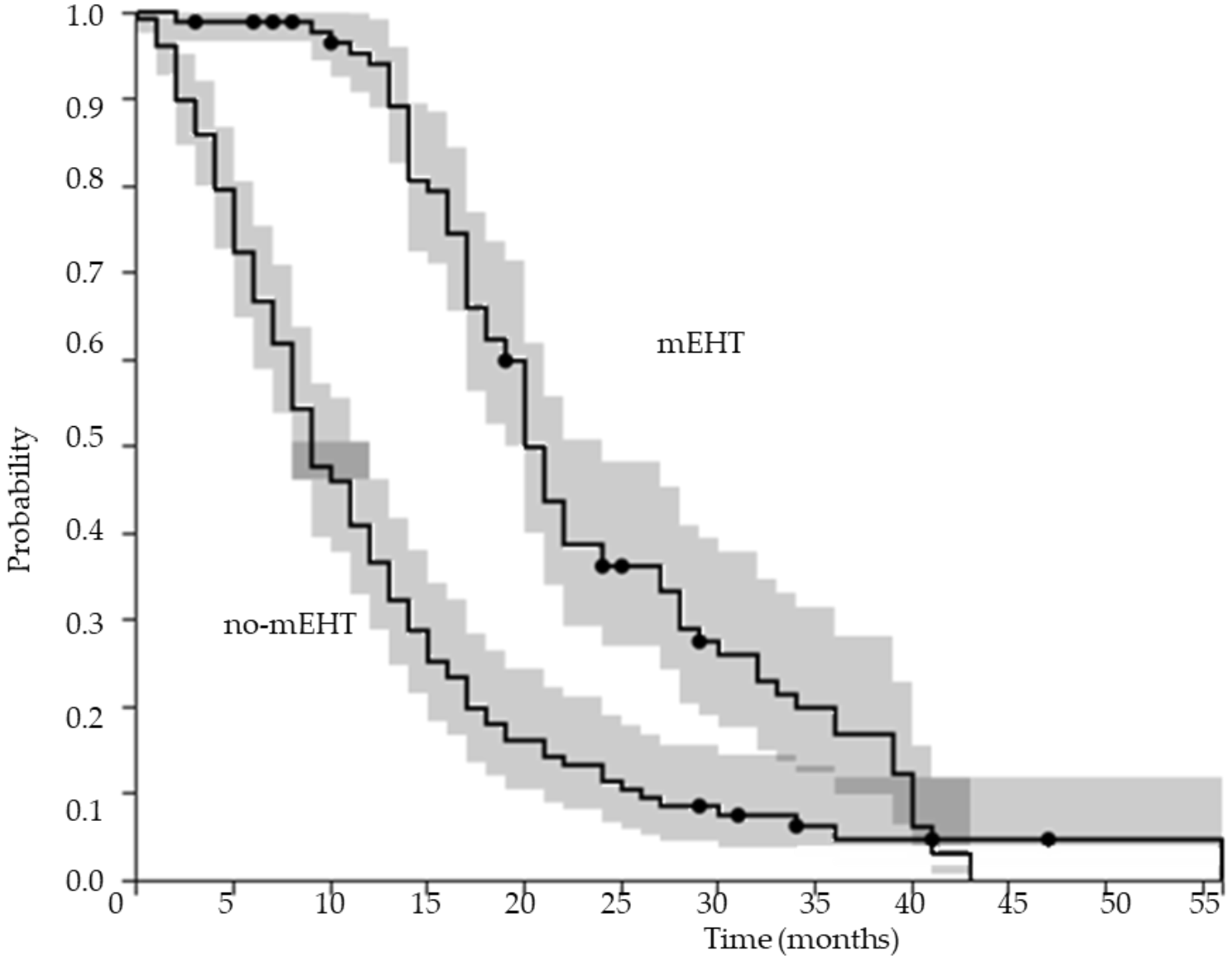
→Adverse events were reported in 2.6% of cases and included:

- G1 skin pain in 22 (1.5%) sessions
- G1-2 burns in 16 (1.1%) cases that resolved in few days

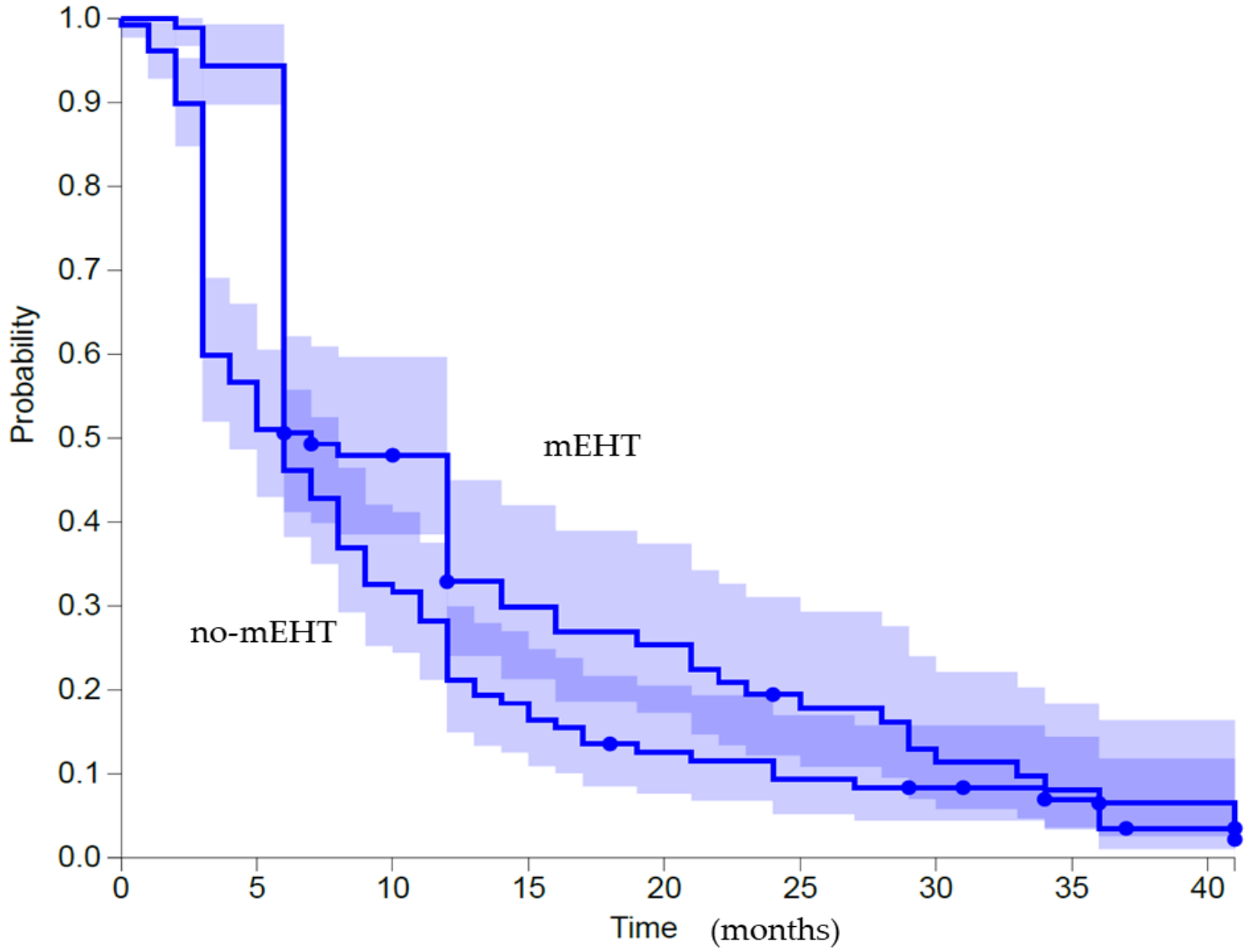
mEHT **did not increase** haematological, hepatic, pulmonary and metabolic toxicity due to CHT

Particularly no increased blood pressure or any other cardiac changes after adequate cardiological monitoring

OS of mEHT and no-mEHT groups. Dots represent censors, cloud area represent CI 95%.



PFS of mEHT and no-mEHT groups. Dots represent censors, cloud area represent CI 95%.



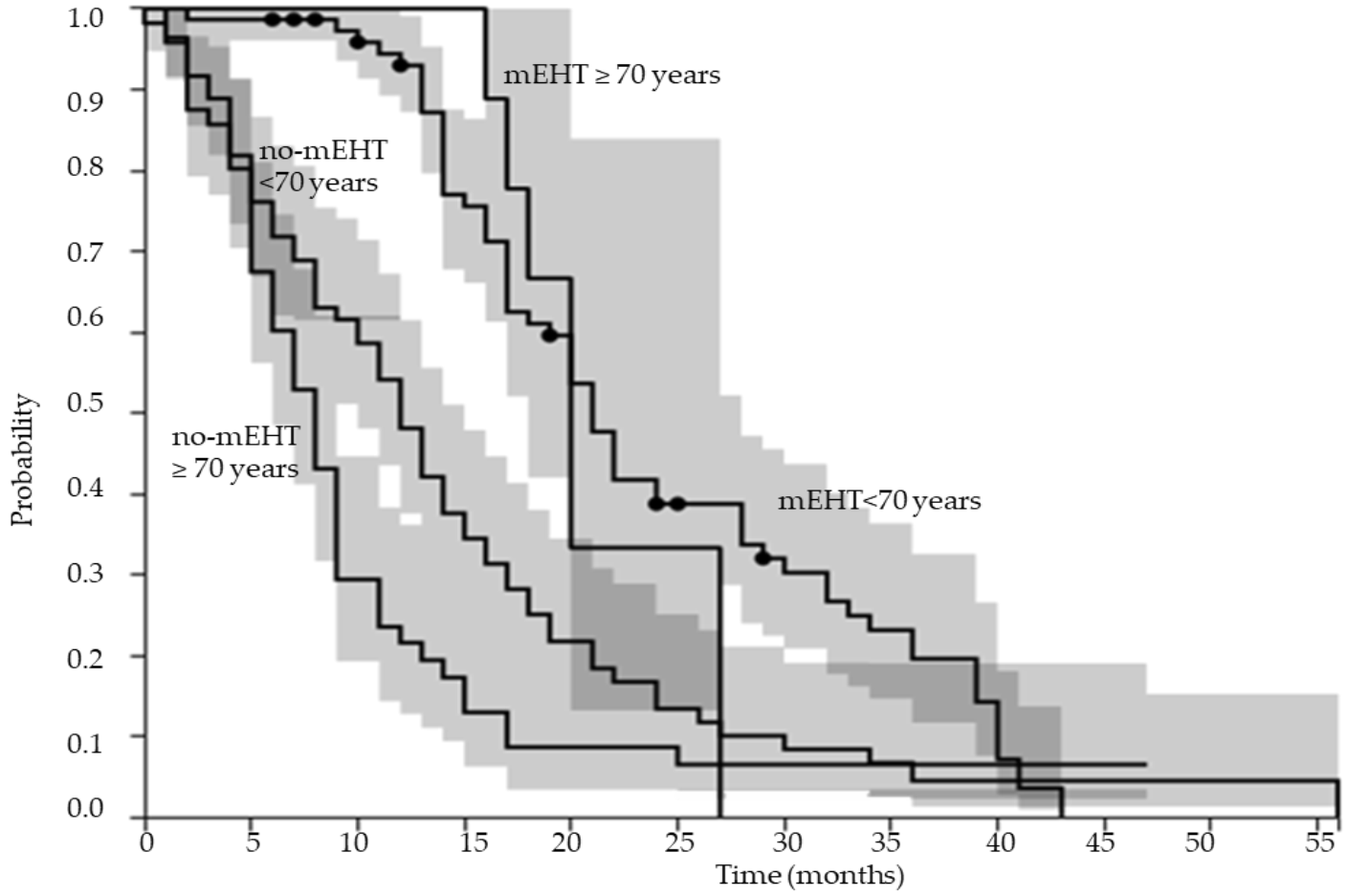
OS of mEHT and no-mEHT groups divided by age. Dots represent censors, cloud area represent CI 95%

The analysis of OS **by age less 70 years or more 70 years** showed that:

→ there was no difference in OS between mEHT less than 70 years (20 mo, range 2-43 m) and more 70years (20mo , range 3-27) P=0.235

→ whereas no-mEHT **patients with less than** 70 years had a higher OS than no-mEHT more than 70 years group (12 mo, range 1-56 vs 8 range 1-47, P= 0.01)

→ mEHT had a longer OS than no-mEHT group both among less than 70 years (20 mo range 3-27 vs 8 mo range 1-47, p <0.01) and more than 70 years (20 mo range 2-43 vs 12 mo range 1-56, P<0.01).



Clinical Case: Locally advanced PC with lymph node metastases (BRCA mutated)

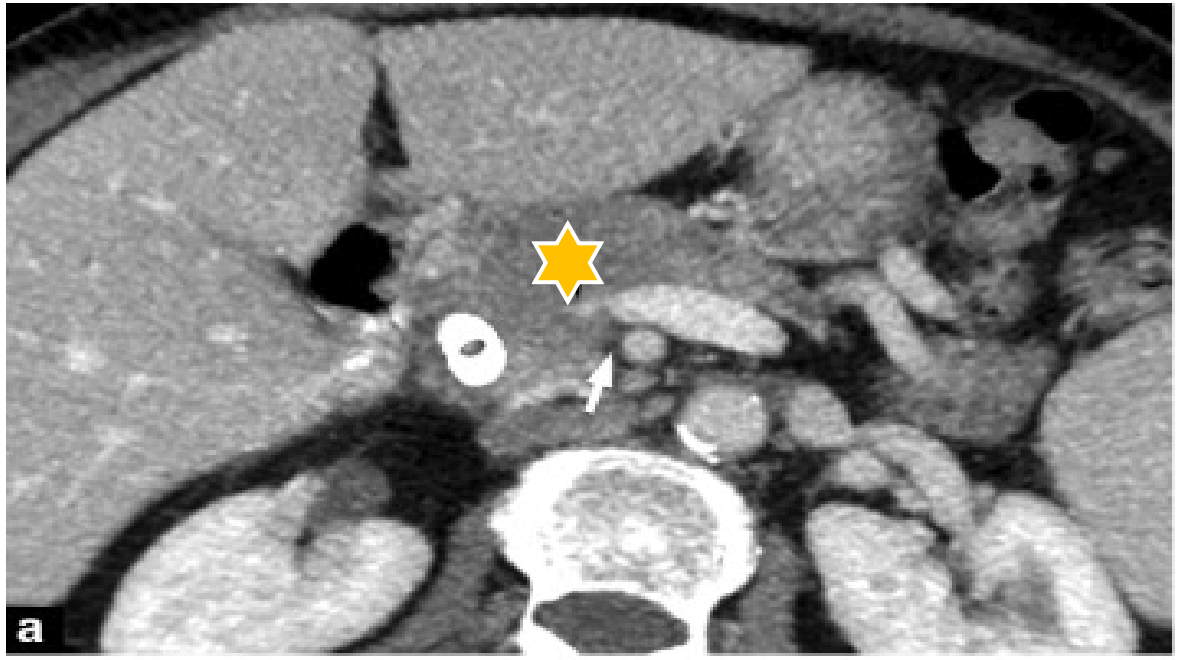
(Male 58 yrs, Stage T3N2M0)

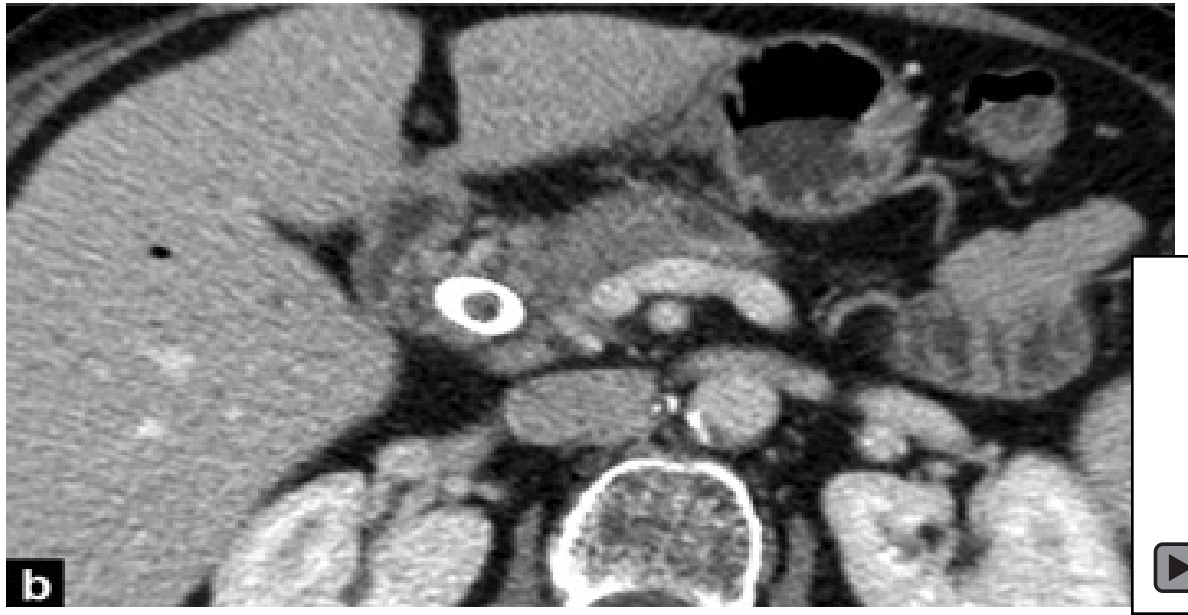
Modulated Electro Hyperthermia

→ three times a week PWR 140 W for 60 minutes + Capecitabine

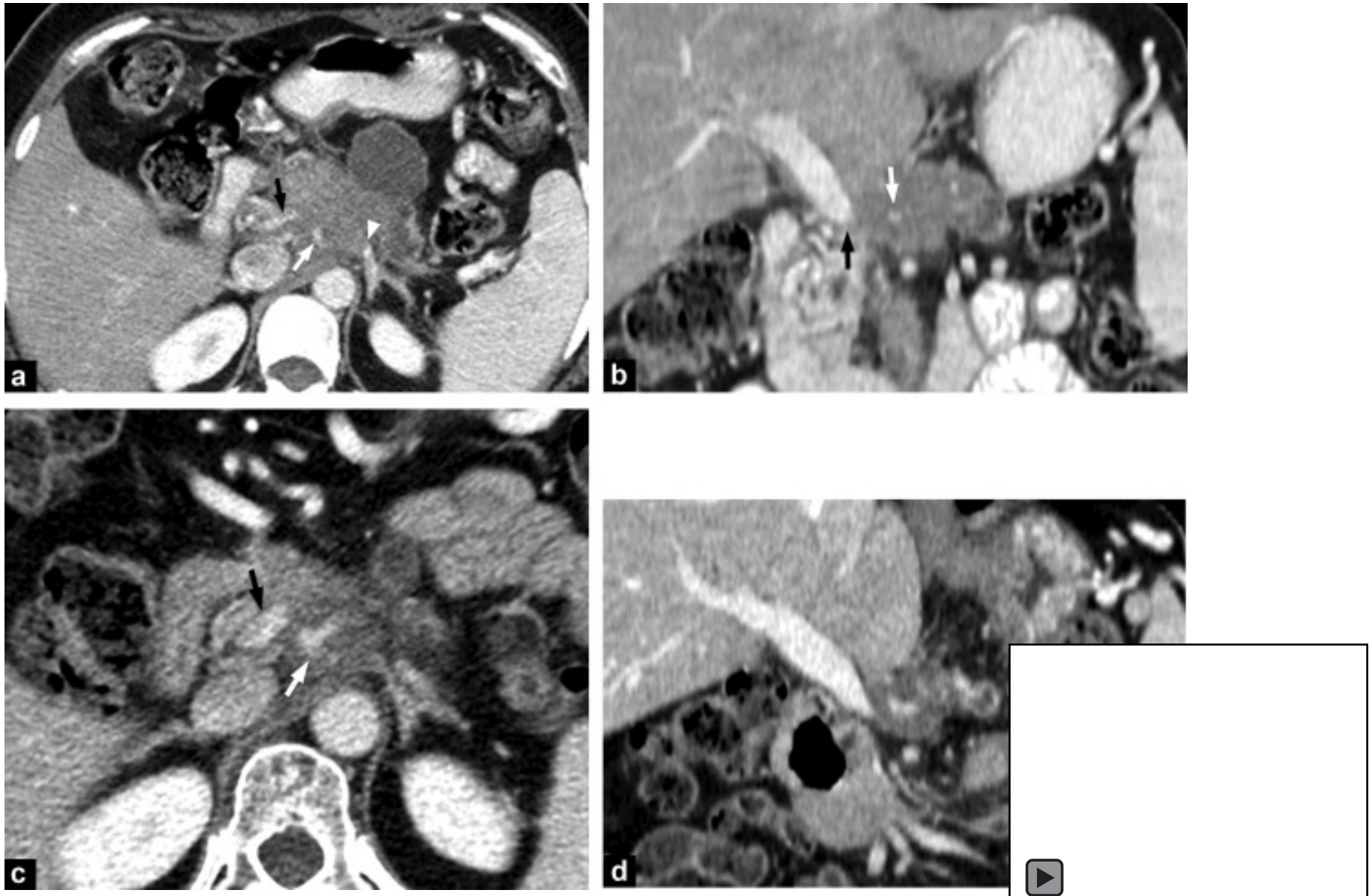
→ Treatment given as second line after GEM-ABRA progression

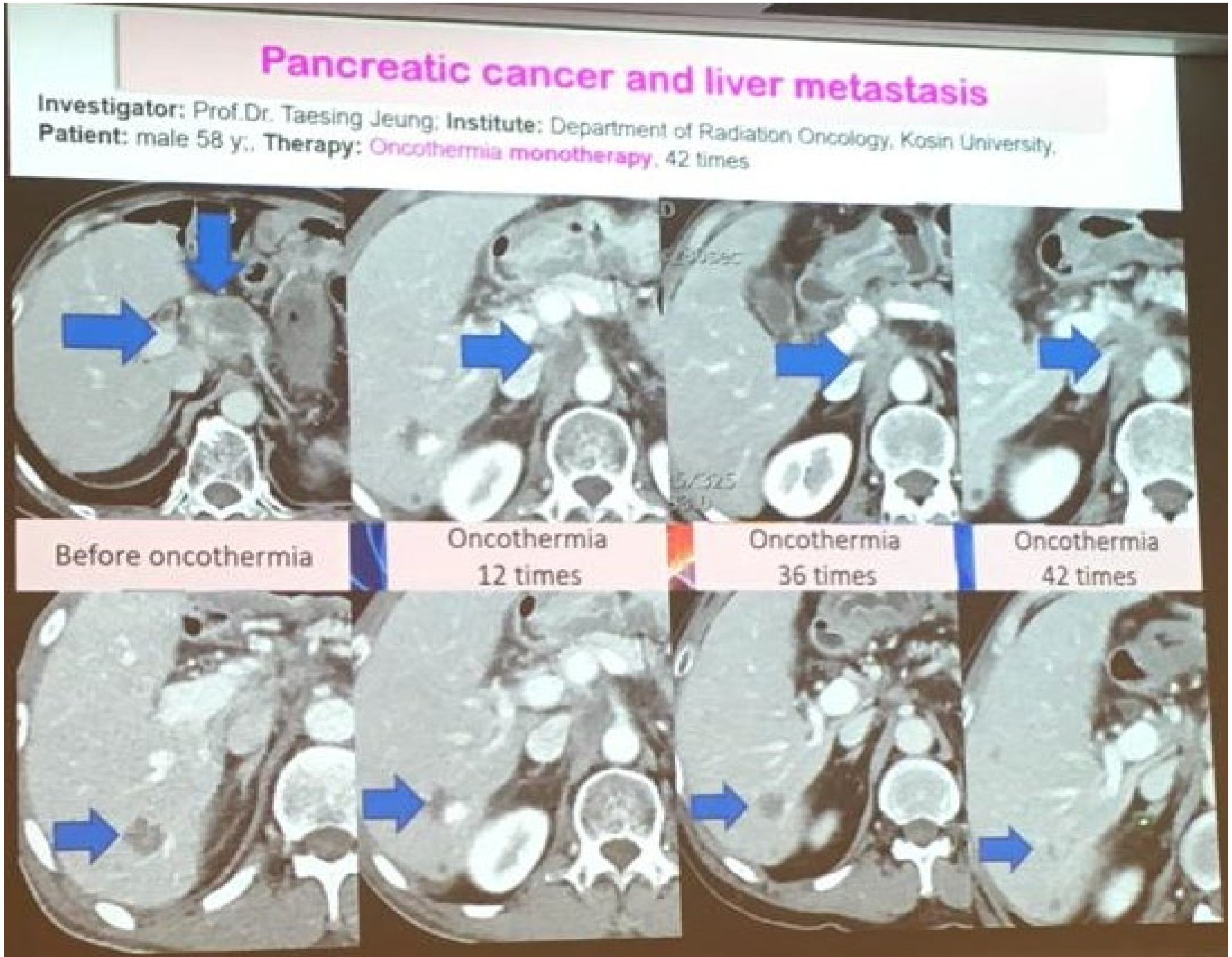
PT 33-PANCREATIC CANCER (HEAD) AFTER DRAINAGE RECEIVED MEHT (28 SESSIONS) PLUS GEM 9 C. SEE EVIDENCE OF RESPONSE





PT 26 - PANCREATIC CANCER (BODY) PROGRESSED AFTER 6 C. OF GEMOX, RESPONSE AFTER MEHT+ GEM (32 MEHT SESSIONS AND 8 C. OF GEM)




Pancreatic cancer and liver metastasis
Investigator: Prof.Dr. Taesing Jeung; Institute: Department of Radiation Oncology, Kosin University,
Patient: male 58 y;, Therapy: Oncothermia monotherapy, 42 times
Before oncothermia
Oncothermia
12 times
Oncothermia
36 times
Oncothermia
42 times

Take Home Massage

→ The addition of mEHT to systemic CHT **improved overall and progression-free survival** and **local tumor control** with comparable toxicity

→ On the basis of this study and the other numerous studies in the literature, it **now seems time** to **organize an international randomized trial to evaluate the utility of electro-hyperthermia in this serious disease**

LOCOREGIONAL HYPERTHERMIA: SOME of ONGOING STUDIES IN PANCREATIC CANCER

1. **NCT01077427: Hyperthermia European Adjuvant Trial (HEAT) in pancreatic cancer University Munich (Germany)**
2. **NCT02862015: Multicenter RCT of the Clinical Effectiveness of Oncothermia With Chemotherapy in Metastatic Pancreatic Cancer Patients. University Seul (S. Korea)**
3. **NCT02150135: Effect of Oncothermia on Improvement of Quality of Life in Unresectable Pancreatic Cancer Patients. University Seul (S. Korea)**
4. NCT00178763 **Hyperthermia With Chemotherapy for Locally Advanced or Metastatic Pancreas Cancer (Texas)**
5. NCT02439593 **Concurrent Hyperthermia and Chemoradiotherapy in LAPC: Phase II Study (HEATPAC; Zúrich, Suiza)**
6. NCT04889742 **Hyperthermia Enhanced Re-irradiation of Loco-regional Recurrent Tumors (HETERERO) Berlin, Alemania**

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ISPRO
Istituto per lo studio, la prevenzione e la rete oncologica

SST Servizio Sanitario della Toscana

Regione Toscana