

Vascular disrupting agents: a new avenue of research

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Acknowledgements

- **Scientific:**

- DECO
- Jens Overgaard
- Rumi Murata
- Thomas Wittenborn
- Morten Busk
- Ane Iversen
- Thomas Nielsen
- Univ. Florida
- Dietmar Siemann
- Oxigene
- David Chaplin

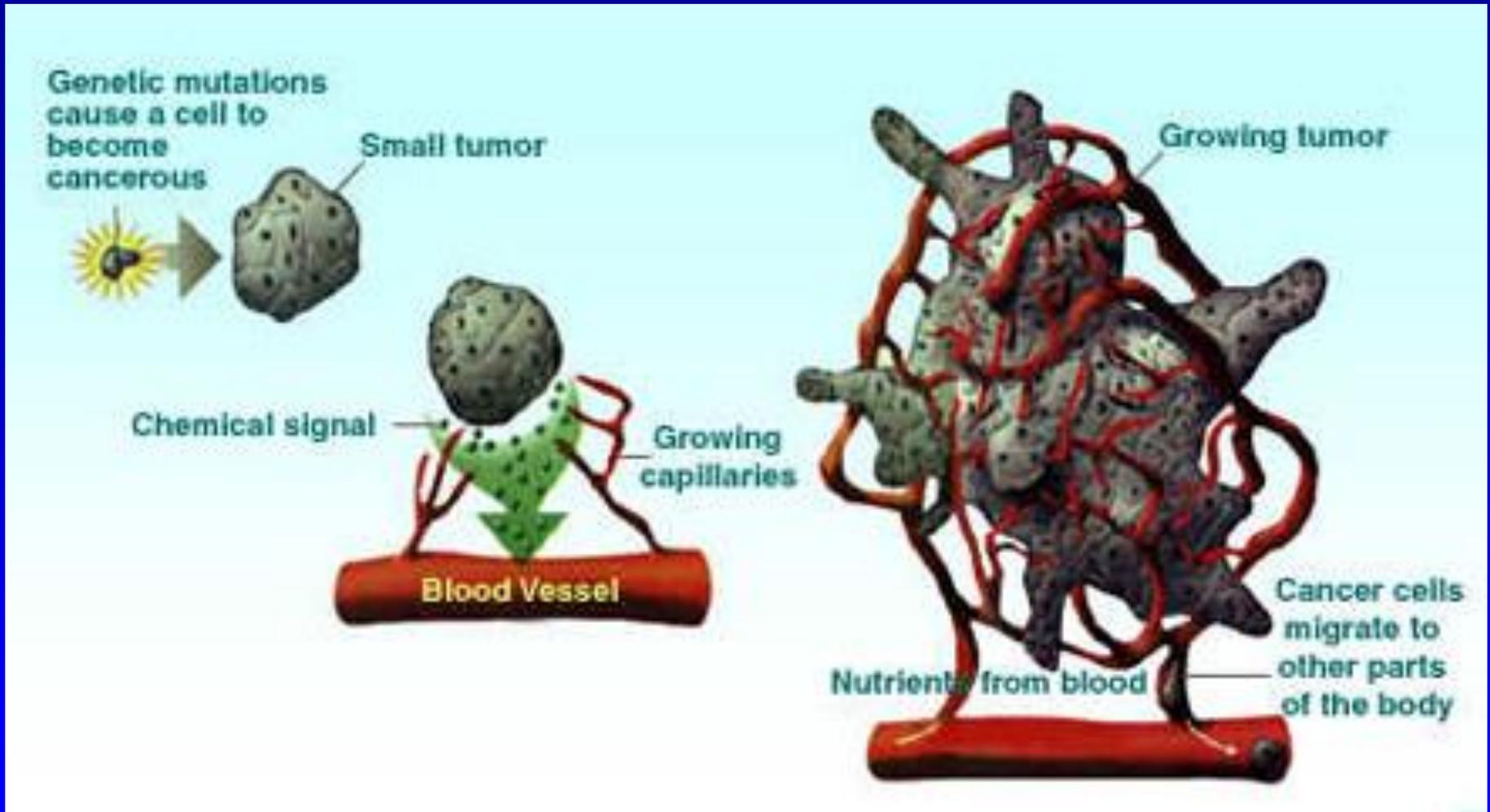
- **Technical:**

- Dorte Grand
- Inger Marie Horsman
- Pia Schjerbeck
- Marianne Verner Bjerre
- Marianne Kristiansen

- **Financial:**

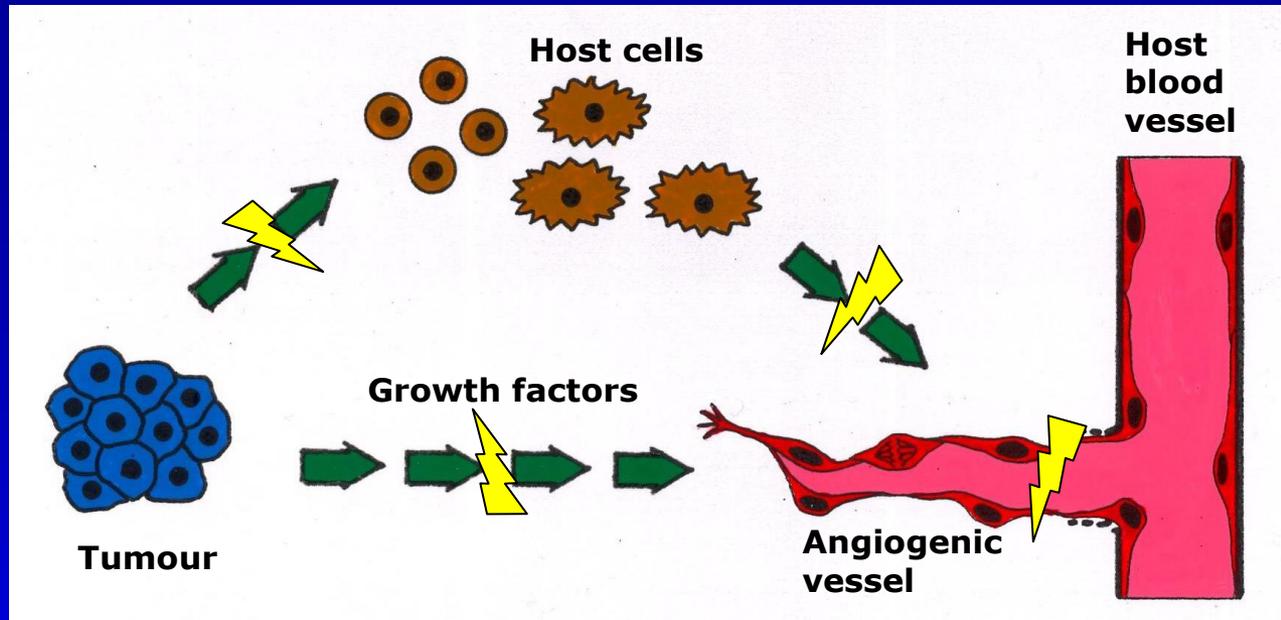
- Danish Cancer Society
- Danish Council for Independent Research: Medical Sciences
- The Danish Hyperthermia Fund
- Corporate (Oxigene)





Lertola (1998) Time Magazine 151 (20):40-46

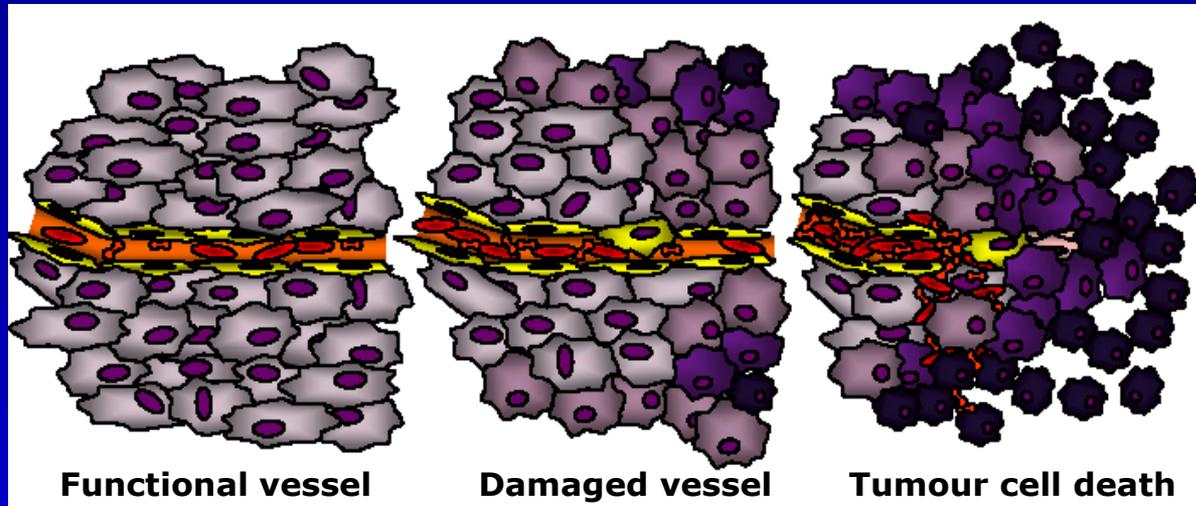
Angiogenesis inhibitors (AIs)



- **TIMP**
- **Thalidomide**
- **Suramin and analogues**
- **Fumagillin and TNP470**
- **Endostatin**
- **Angiostatin**
- **Anti-VEGF(R) Ab**
- **SU5416**
- **SU6668**
- **Sunitinib (SU11248)**
- **PTK787/ZK222 584**
- **Vandetanib (ZD6474)**
- **Sorafenib (Bay 43-9006)**
- **Cytokines**
- **CAI**
- **Arginine Deiminase**
- **Anginex**
- **AG-013736**
- **Pazopanib**
- **Nelfinavir**
- **Thrombospondin**
- **Nicotinamide**
- **Heparin**
- **EGFR inhibitors**
- **COX-2 inhibitors**
- **Chemotherapy**

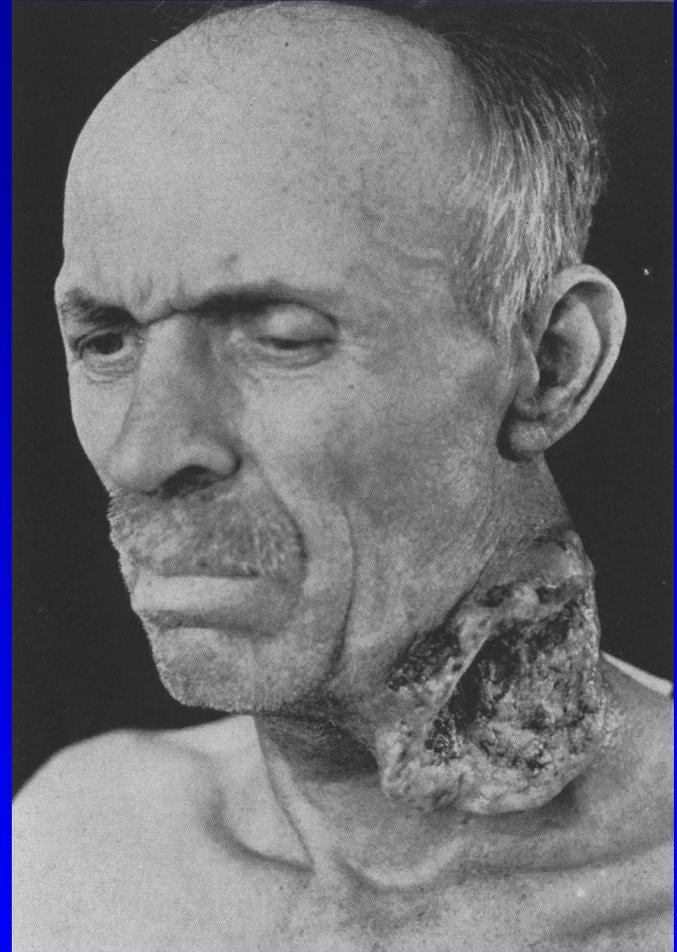
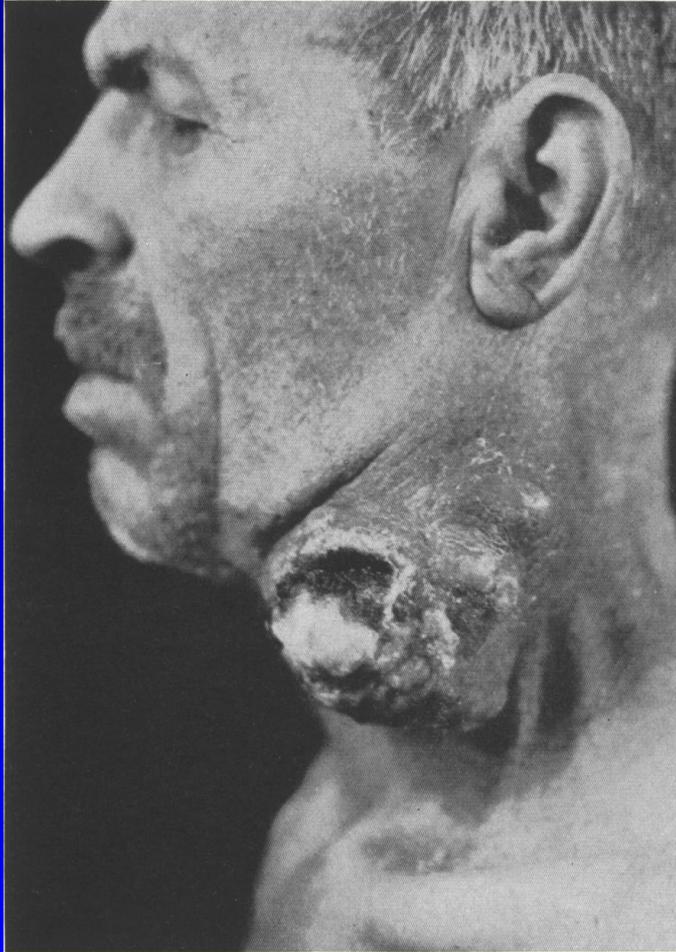


Vascular disrupting agents (VDAs)



- Hyperthermia
- Photodynamic therapy
- LAK cell therapy
- Tumour necrosis factor
- Interleukins
- Interferon-gamma
- Vinka alkaloids
- Colchicine
- Arsenic trioxides
- Dolastatins
- TZT-1027
- Flavone Acetic Acid (FAA)
- DMXAA (ASA404/Vadimezan)
- CYT997
- CA4P (Fosbretabulin/Zybrestat)
- AVE8062
- ZD6126 (ANG453)
- OXi-4503
- MN-029
- NPI-2358
- BNC105
- 2-methoxyestradiol
- ENMD-1198
- EPC2407 (MX116407)
- ABT-751
- Ligand-based approaches (Ab, peptides, growth factors)
- Radiation





Seed et al. Surgery 1940;7:696-709



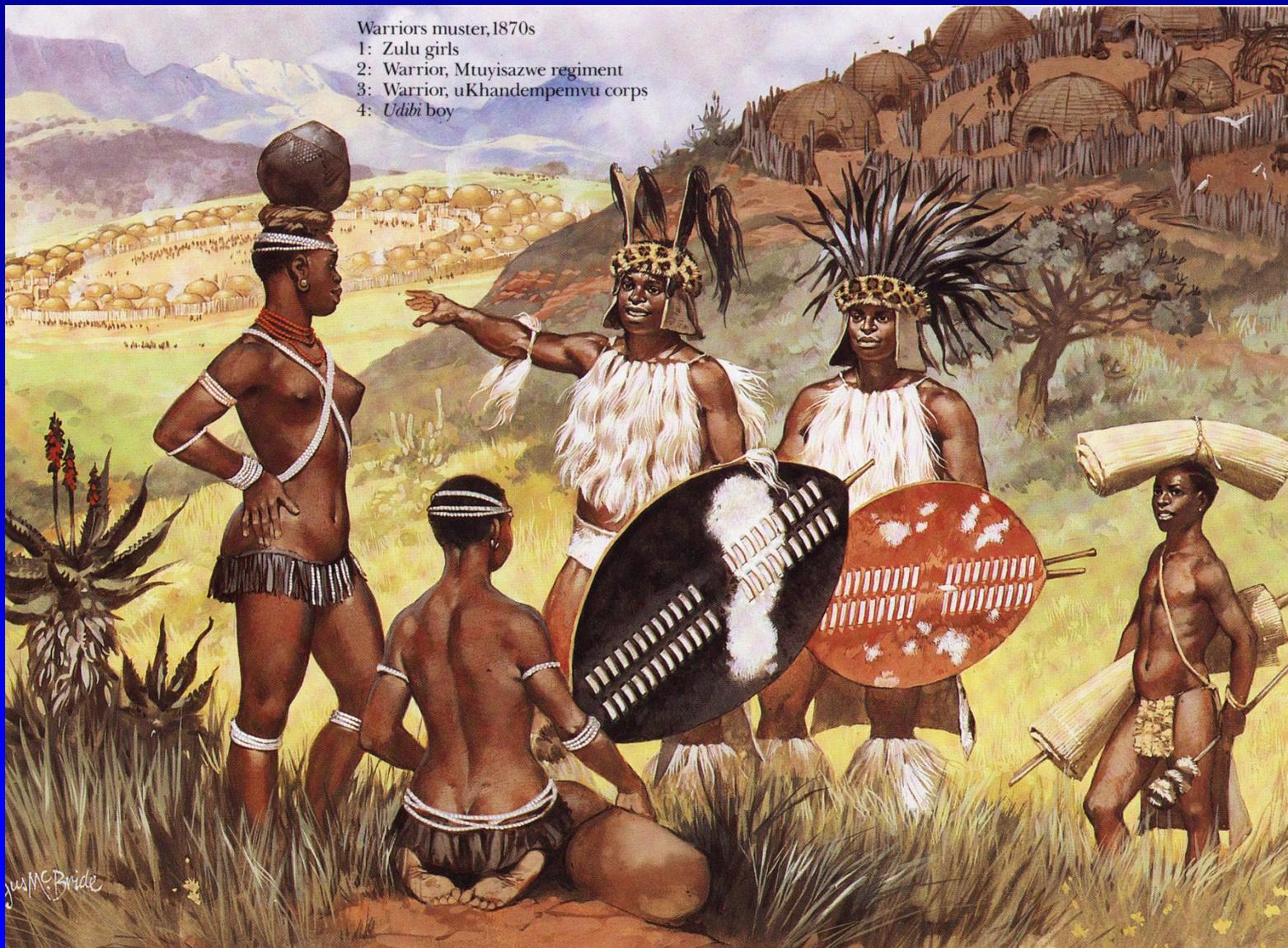
Warriors muster, 1870s

1: Zulu girls

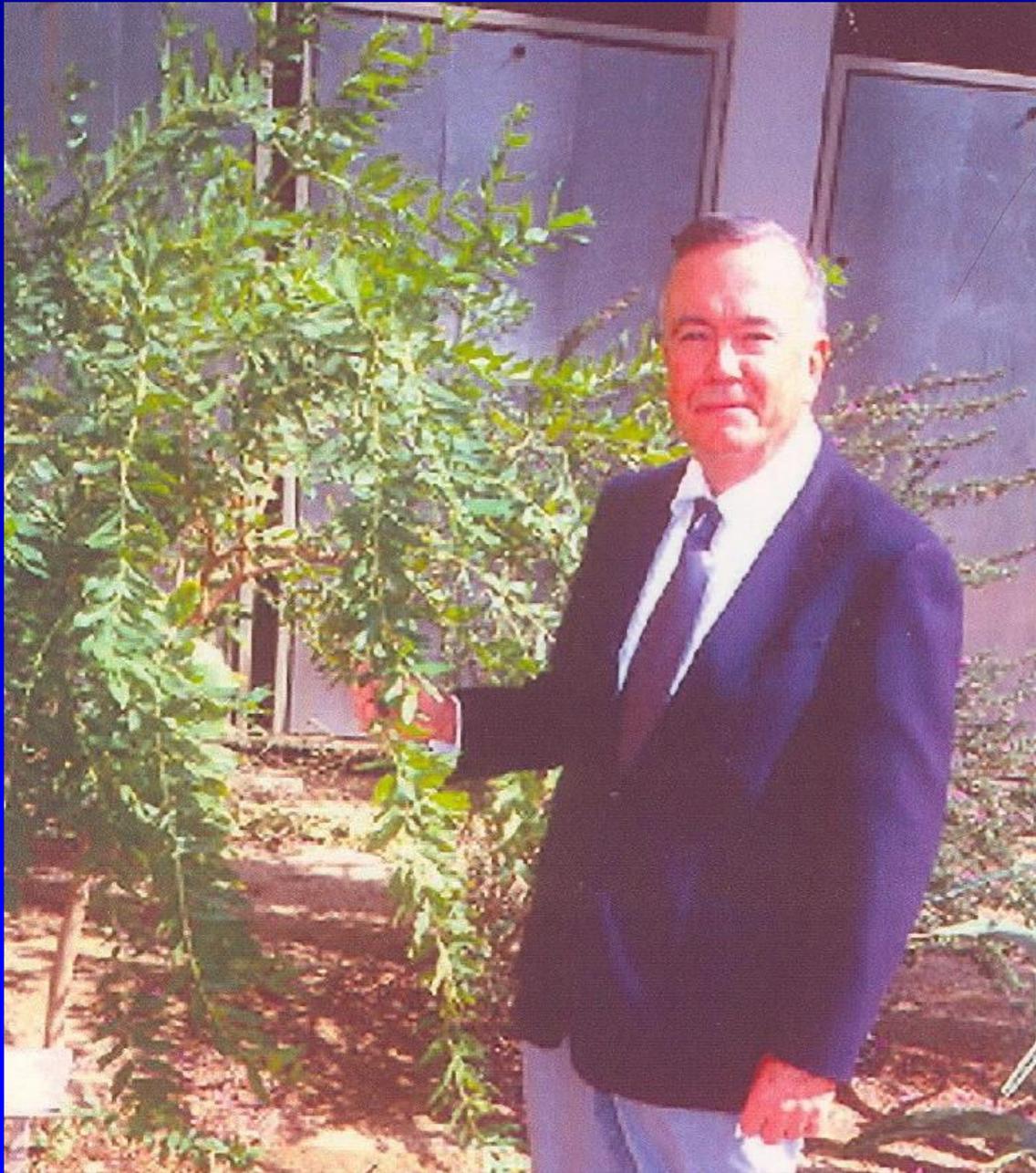
2: Warrior, Mtuyisazwe regiment

3: Warrior, uKhandempemvu corps

4: *Udibi* boy

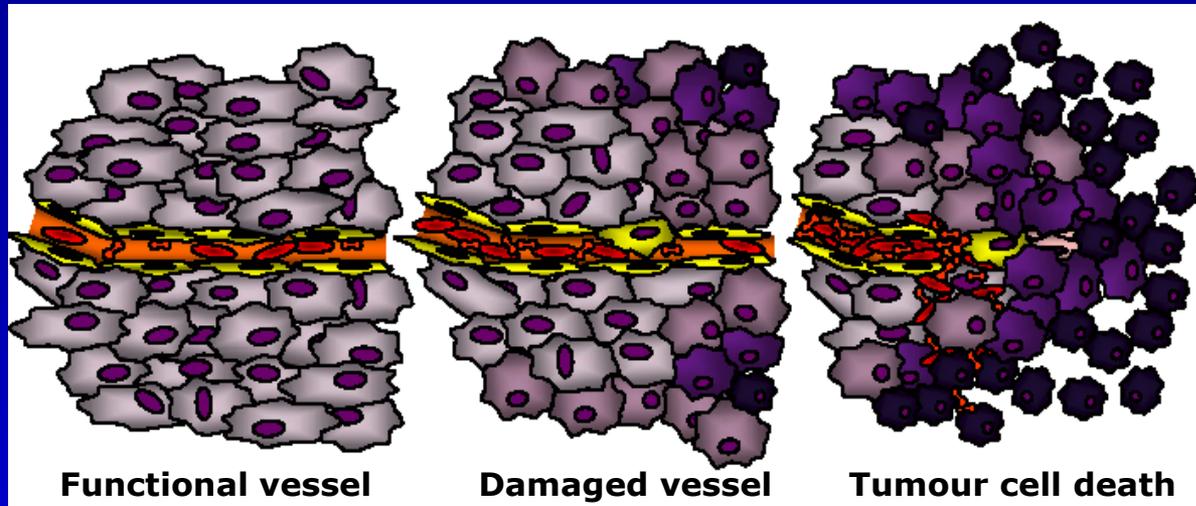


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Vascular disrupting agents (VDAs)



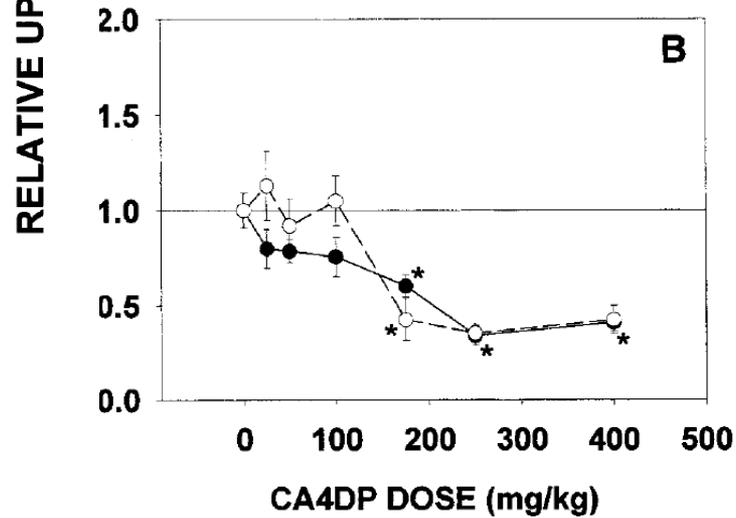
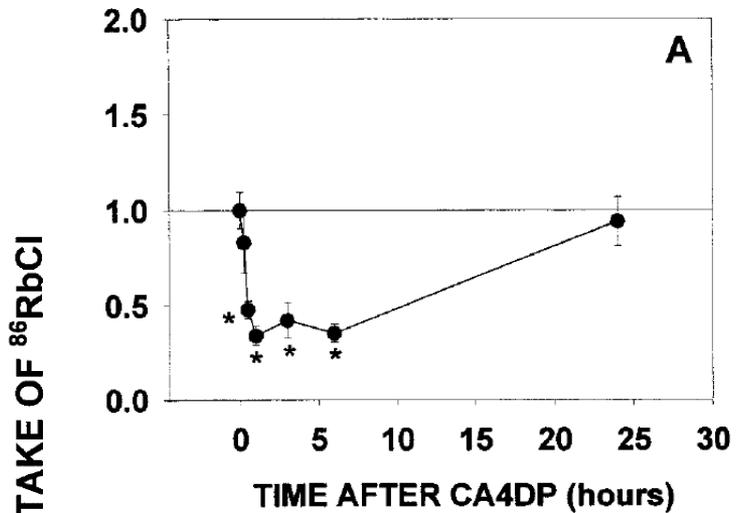
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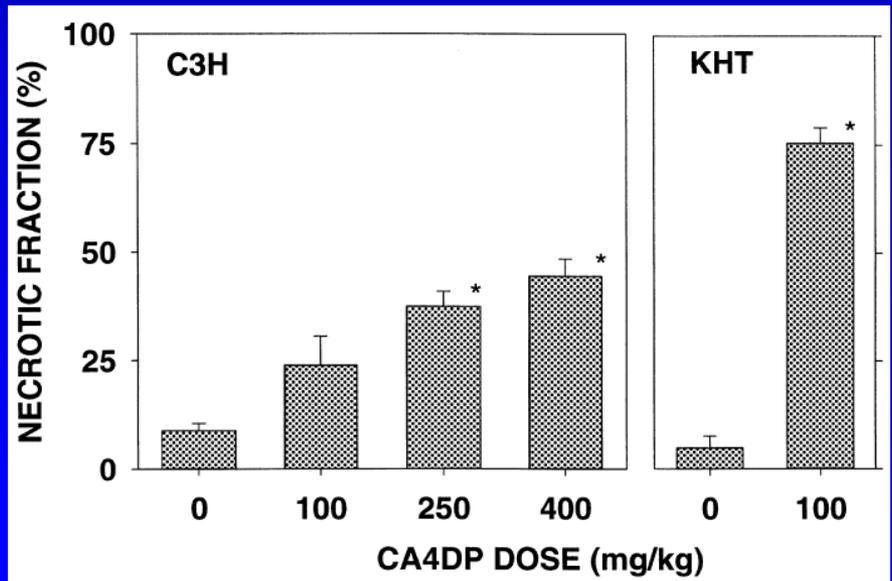
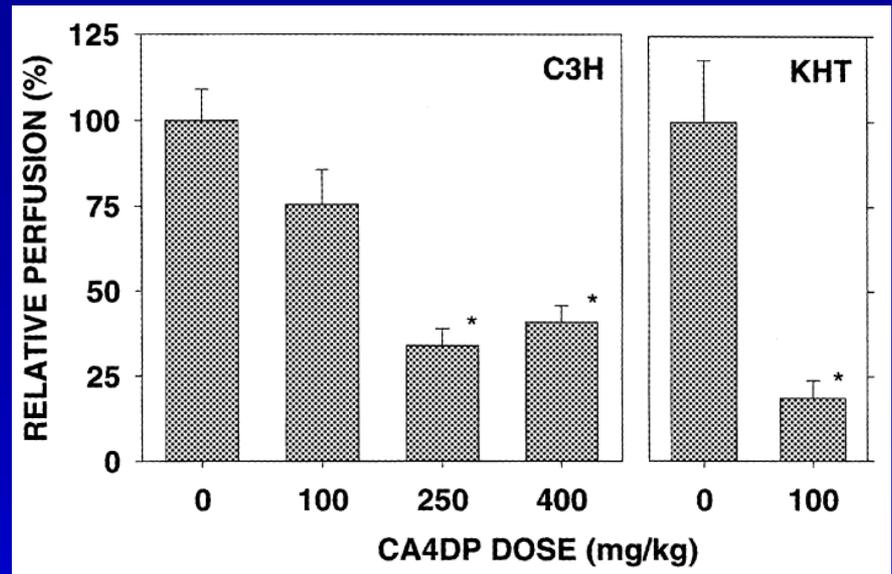
Reported side effects with VDAs

- **Cardiovascular**
 - Myocardial infarction/ischemia
 - Chest pain
 - Hypertension
 - Hypotension
 - QTc elongation
 - Increased troponin levels
- **Neurological**
 - Ataxia
 - Paresthesia
 - Apnoea
 - Brain ischemia
 - Visual disturbances
 - Extremity tingling
 - Tremor
 - Slurred speech
 - Headache
 - Dizziness
 - Anxiety
- **Pain**
 - Tumour
- **Gastrointestinal**
 - Abdominal pain/discomfort
 - Gut ischemia
 - Nausea
 - Vomiting
 - Diarrhoea
 - Constipation
- **Respiratory**
 - Dyspnoea
 - Hypoxia
- **Genitourinary**
 - Urinary incontinence
- **Musculoskeletal**
 - Arthralgia
 - Leg weakness
- **Haematological**
 - Thrombocytopenia
 - Neutropenia
- **Constitutional**
 - Fatigue
 - Fever



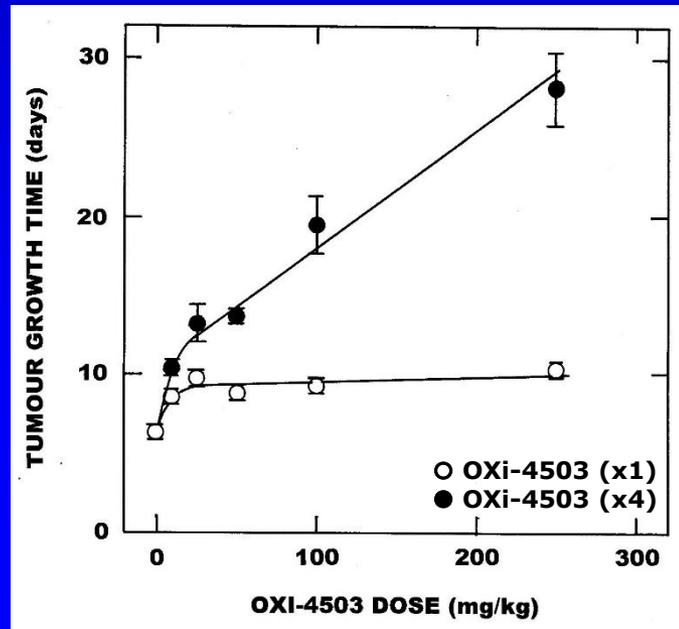
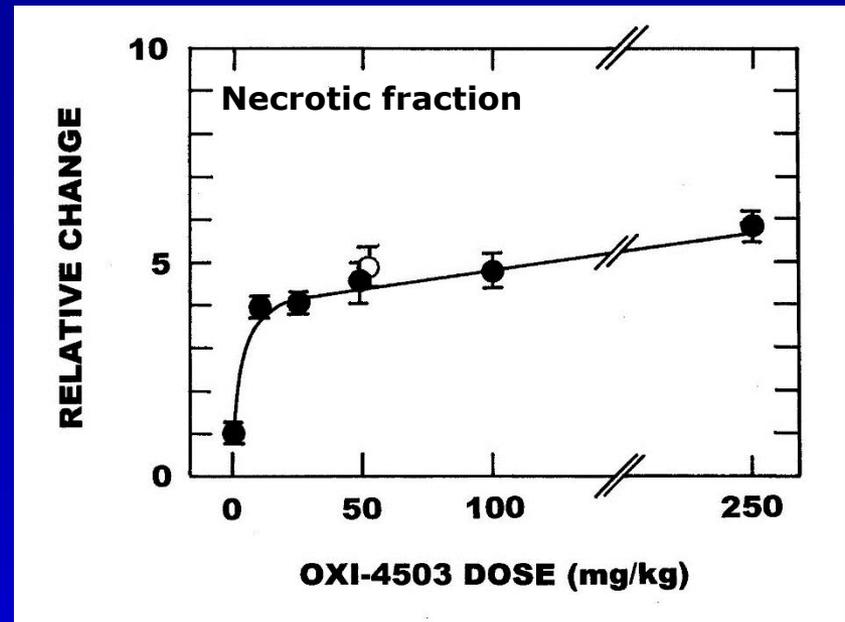
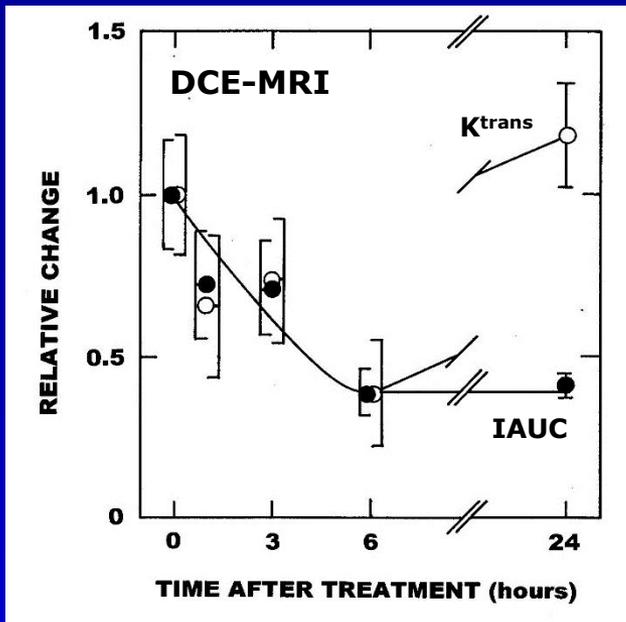


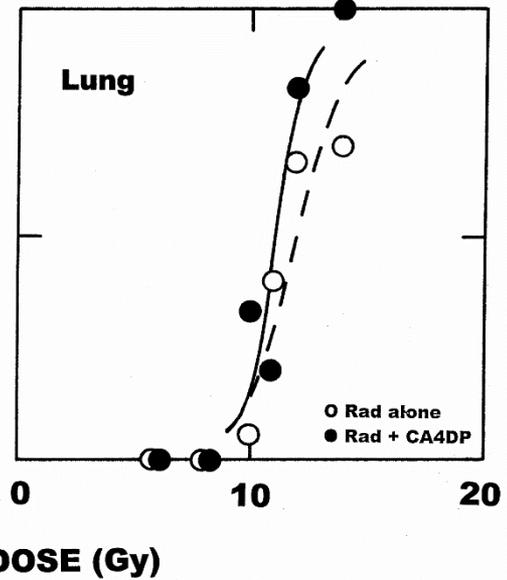
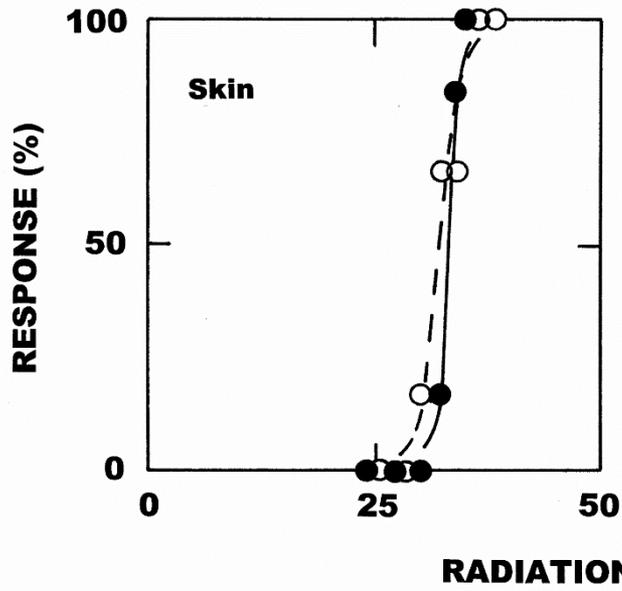
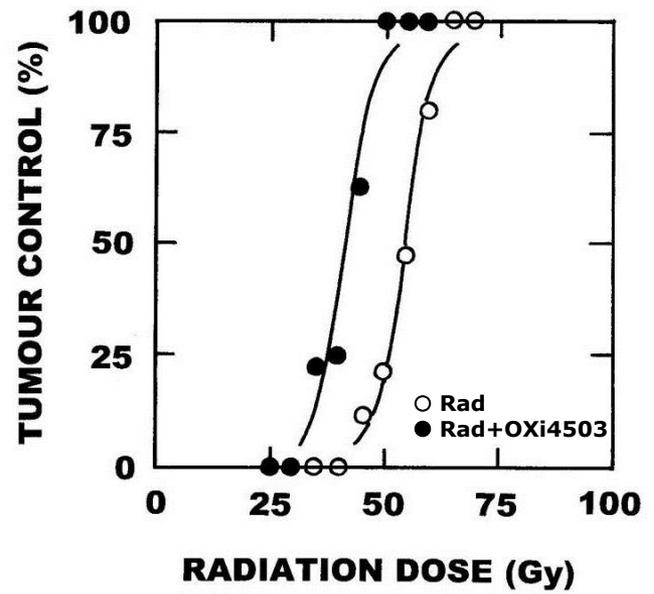
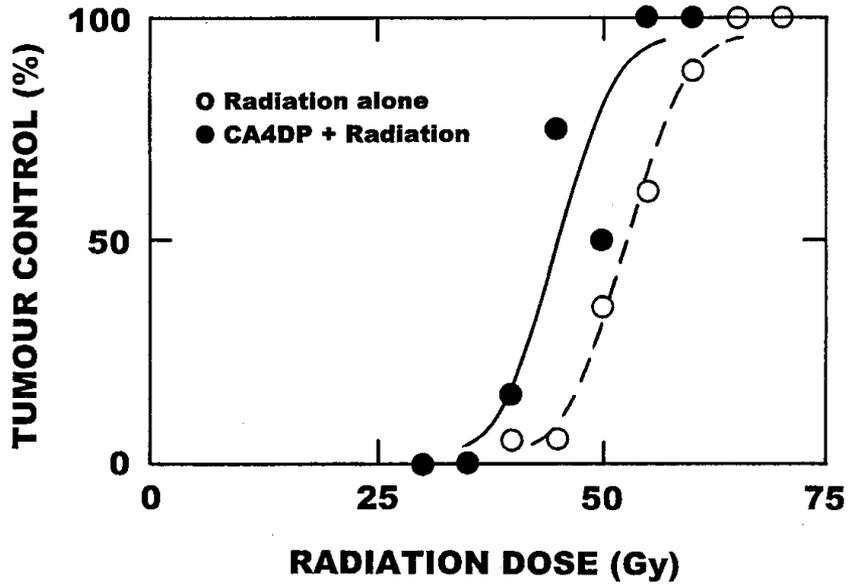
Murata et al. (2001)
IJRB 77:195-204



Murata et al. (2001)
R&O 60:155-161

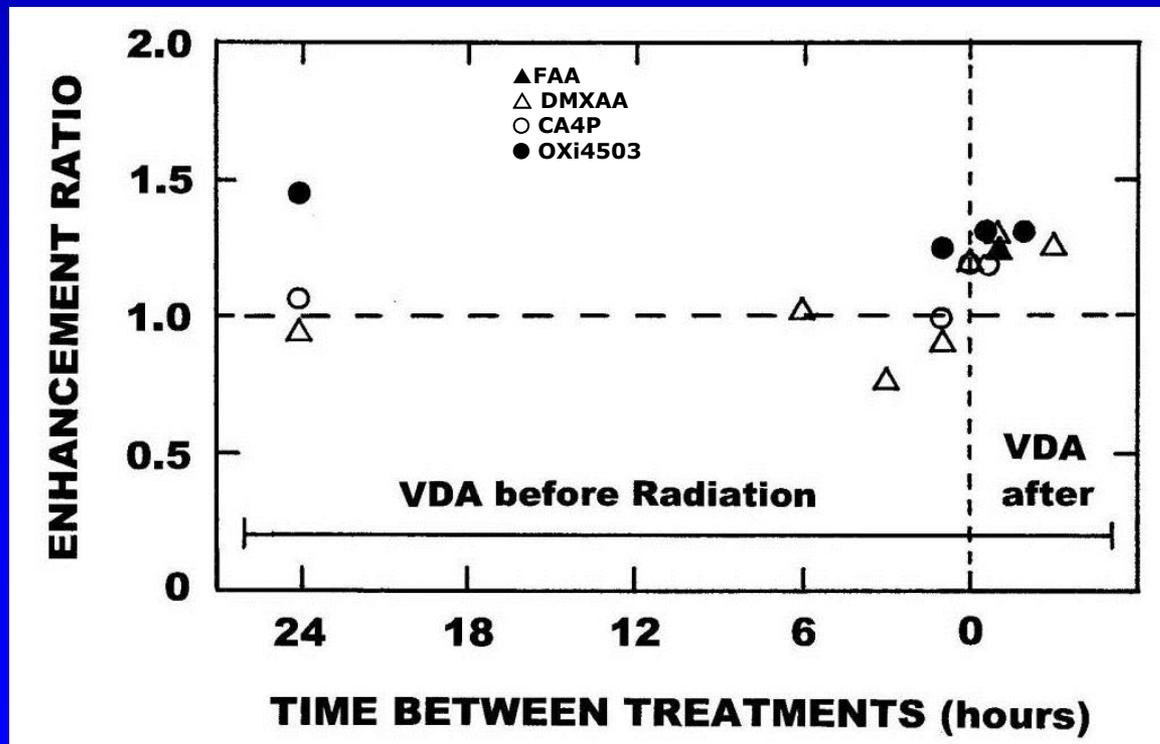






Vascular disrupting agents and hypoxia

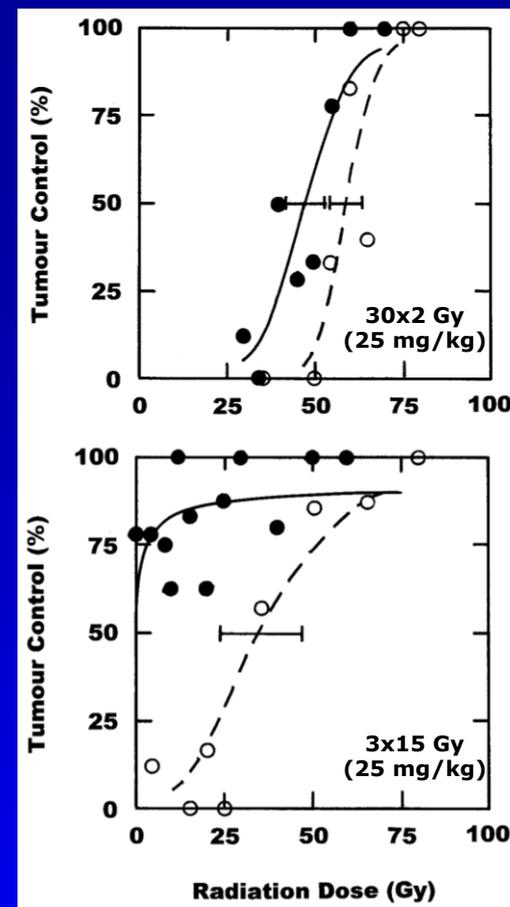
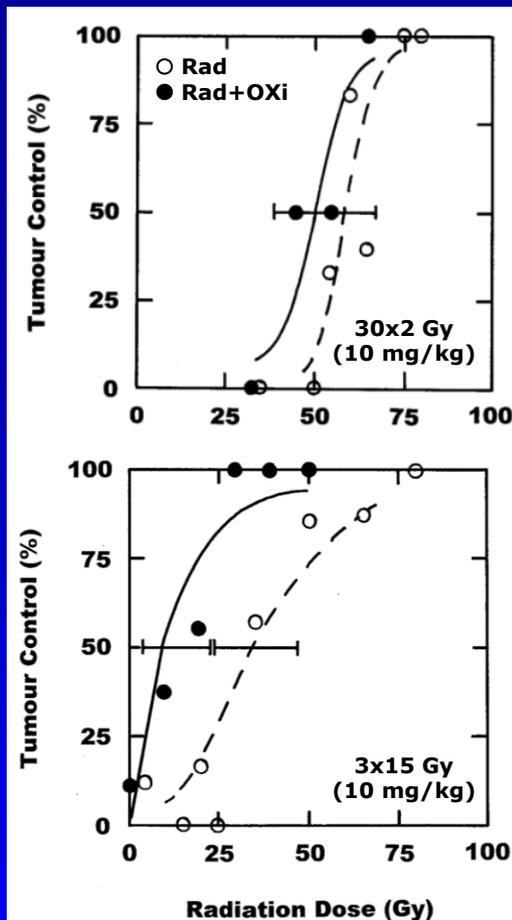
<i>Treatment</i>	<i>pO₂ values ≤ 5 mmHg (%)</i>	<i>Relative necrotic fraction</i>
Controls	51 ± 6	1.0 ± 0.1
FAA (150 mg/kg)	72 ± 8*	n.d.
DMXAA (20 mg/kg)	87 ± 10*	6.3 ± 0.4*
CA4P (250 mg/kg)	91 ± 5*	3.1 ± 0.3*
OXi4503 (50 mg/kg)	77 ± 6*	4.6 ± 0.5*
Clamping	97 ± 2*	n.d.



Iversen et al. (2013) *Acta Oncol.* 52:1320-1326



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Radiation + Drug Treatment	TCD50 Dose (\pm 95% CI)	ER (\pm 95% CI)
30 x 2 Gy	59 Gy (54-64)	1.0
30 x 2 Gy + OXi4503 (10 mg/kg)	52 Gy (48-57)*	1.13 (1.03-1.24)*
30 x 2 Gy + OXi4503 (25 mg/kg)	47 Gy (42-53)*	1.26 (1.13-1.41)*
3 x 15 Gy	33 Gy (24-46)	1.0
3 x 15 Gy + OXi4503 (10 mg/kg)	12 Gy (8-19)**	2.75 (1.77-4.29)**
3 x 15 Gy + OXi4503 (25 mg/kg)	<1.0 Gy	not possible



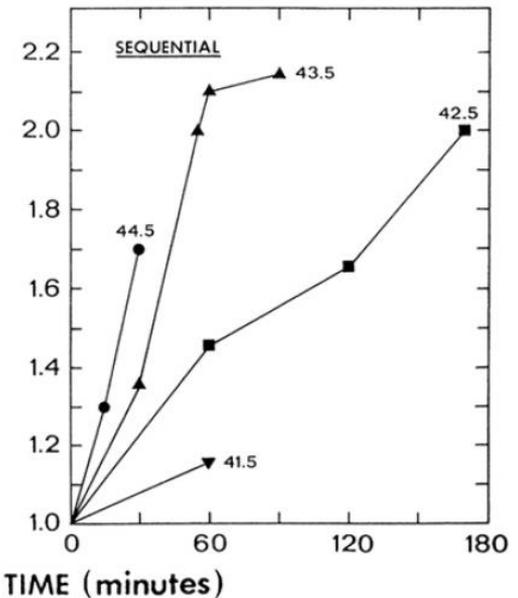
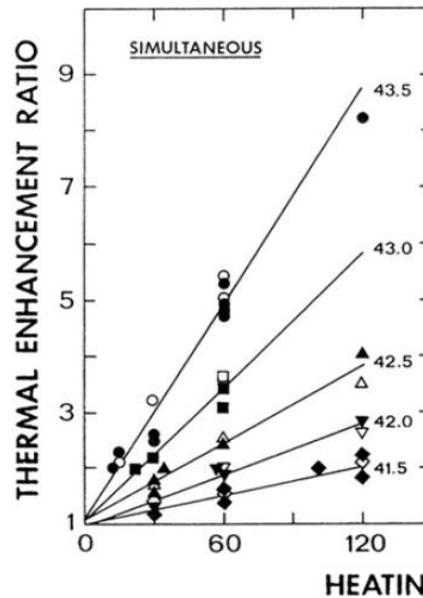
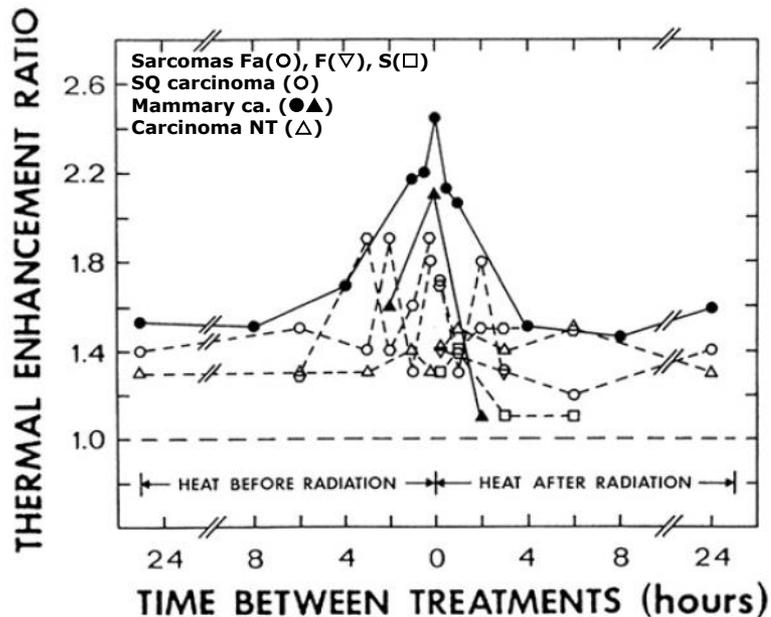
Hyperthermia: a potent enhancer of radiotherapy

Table 1 – Meta analysis of all clinical trials in which patients were randomised to receive radiation alone or radiation with hyperthermia*

Tumour site	No. of trials	No. of patients/lesions	Radiation alone (%)	Radiation + hyperthermia (%)	Odds ratio (95% CI)
Advanced breast	2	143	67	68	1.06 (0.52–2.14)
Chest wall	4	276	38	59	2.37 (1.46–3.86)
Cervix	4	248	52	77	3.05 (1.77–5.27)
Rectum	2	258	9	19	2.27 (1.08–4.76)
Bladder	1	101	51	73	2.61 (1.14–5.98)
Prostate	1	49	79	81	1.16 (0.28–4.77)
Melanoma	1	70/128	31	56	2.81 (1.36–5.80)
Head and neck	5	274	33	51	2.08 (1.28–3.39)
Mixed	3	442	34	39	1.24 (0.84–1.82)
All trials	23	1861	38	52	1.80 (1.50–2.16)

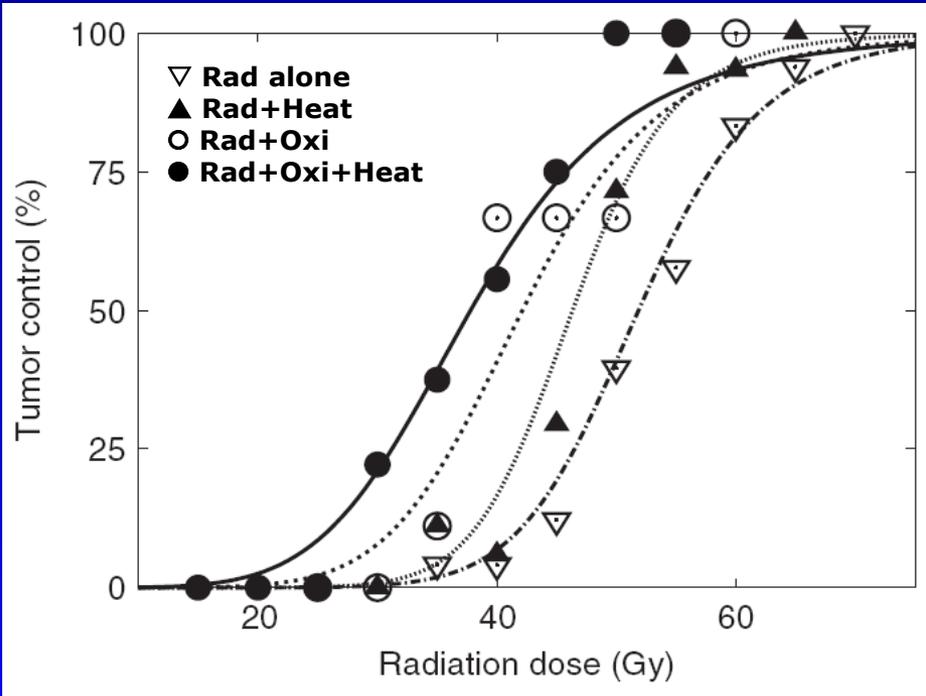
CI, confidence interval. *All results are for loco-regional control.

Horsman & Overgaard (2007) Clin. Oncol. 19:418-426



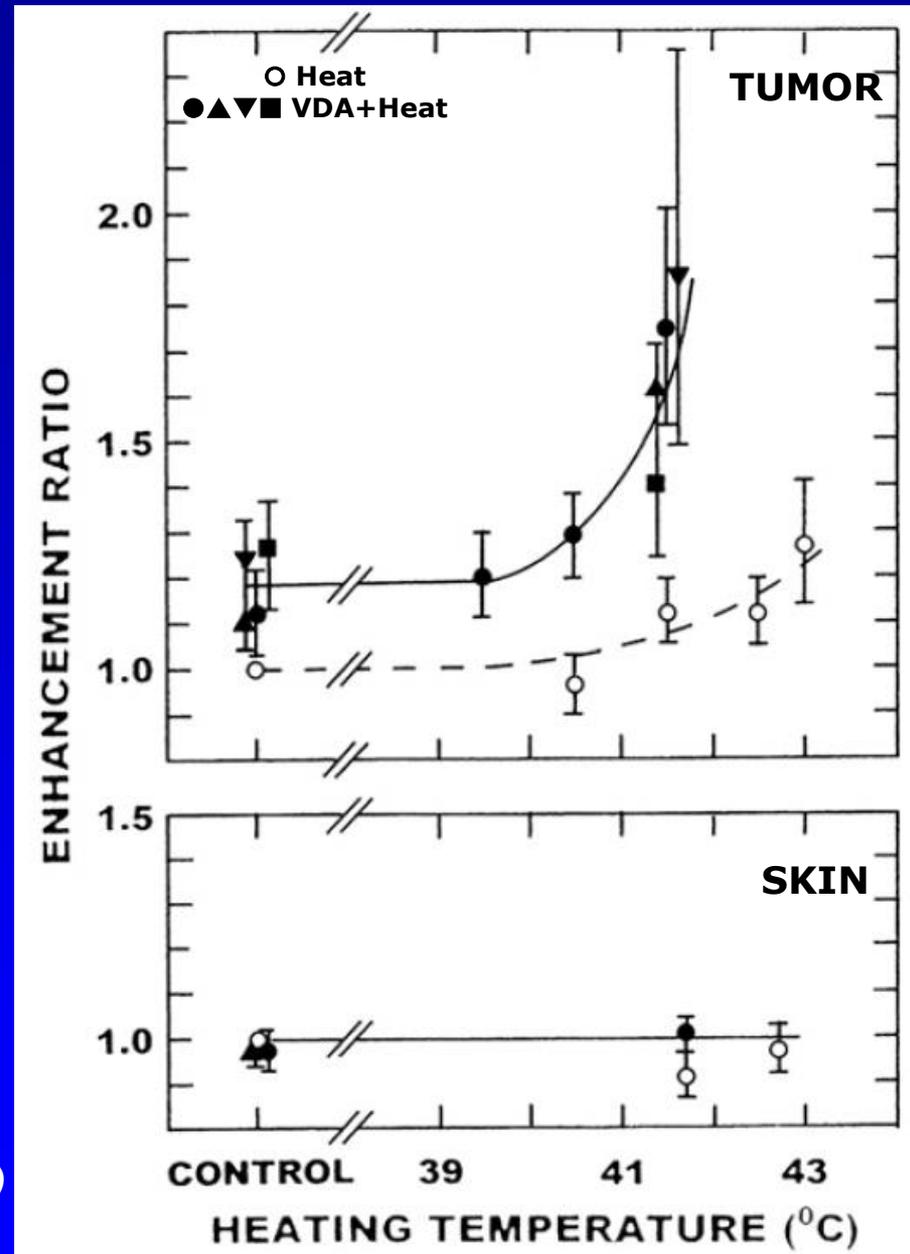
Horsman & Overgaard (1989) Hyperthermia & Oncology 2:113-45

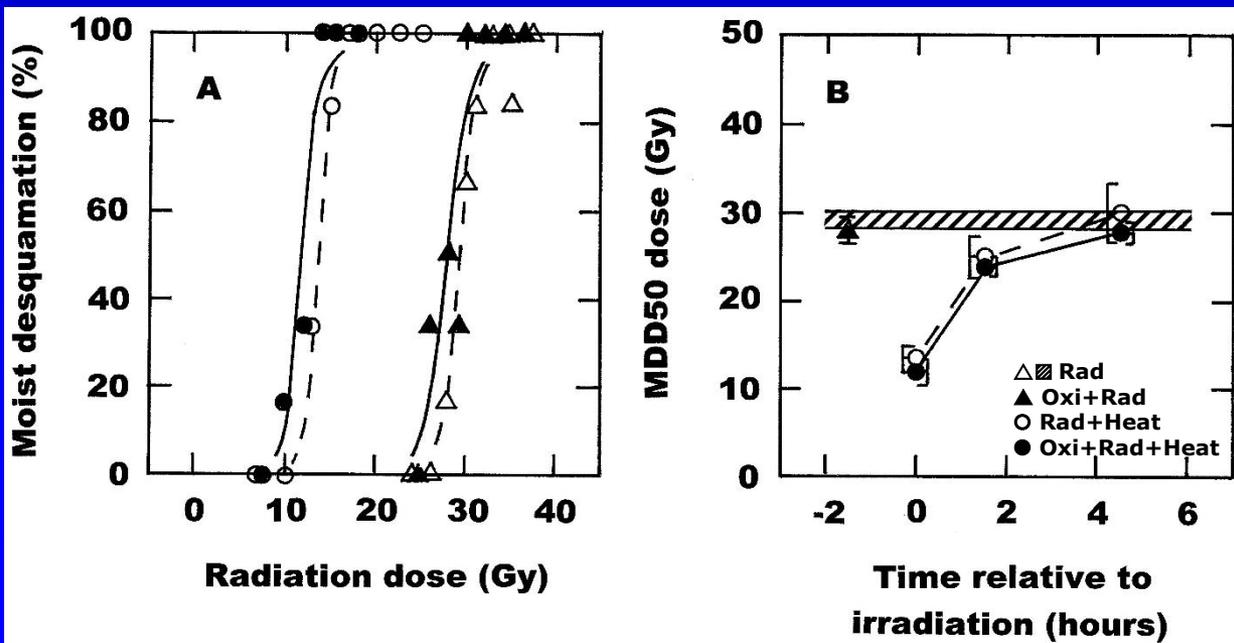
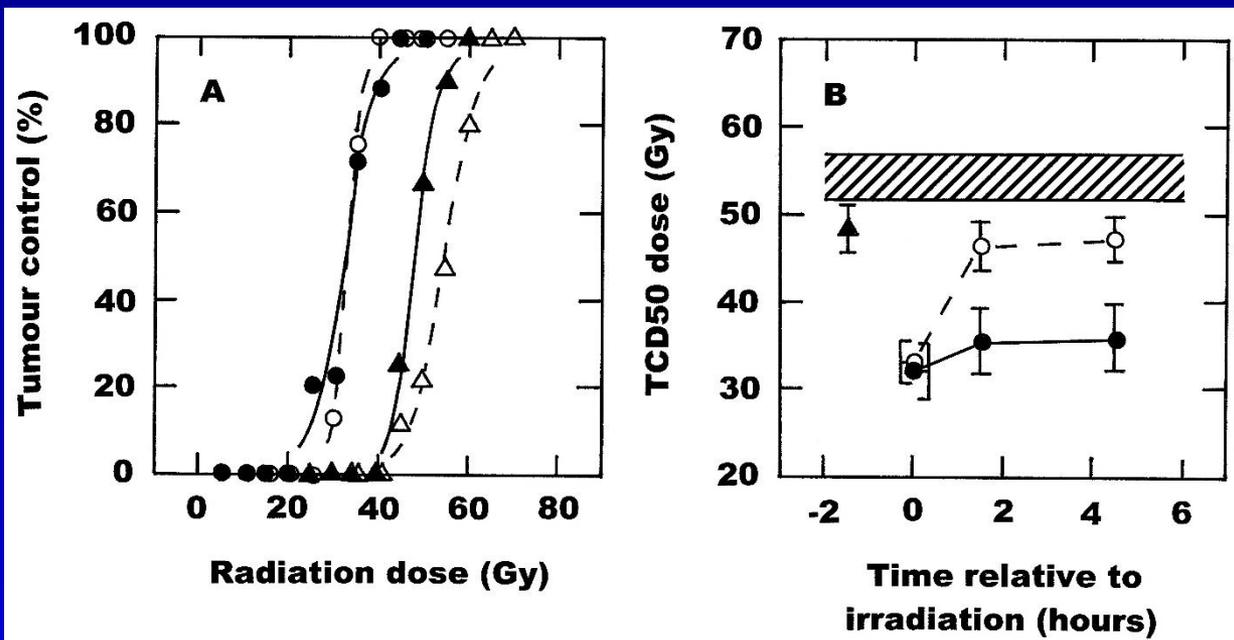
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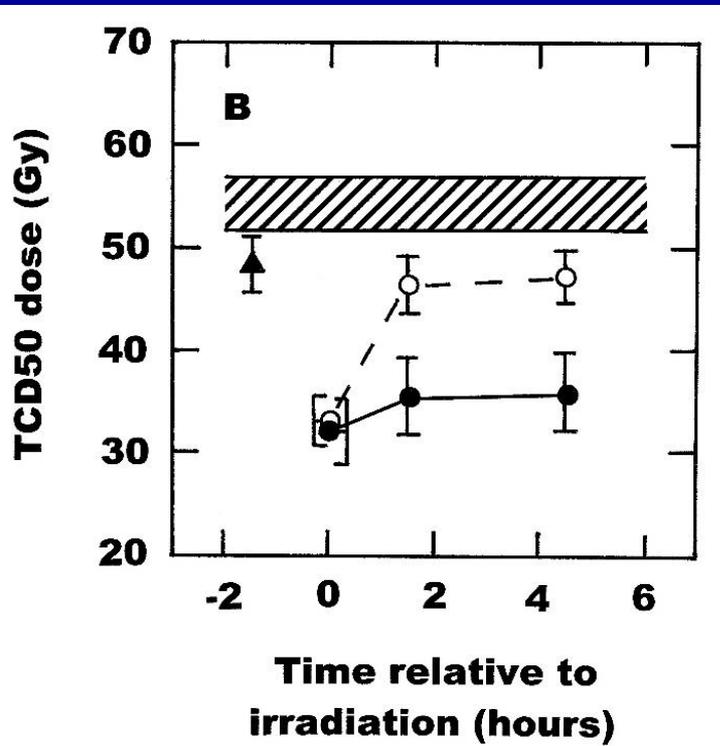
Hokland & Horsman (2007) *Int. J. Hyperthermia* 23:599-606

Horsman & Overgaard (2007) *Clin. Oncol.* 19:418-426

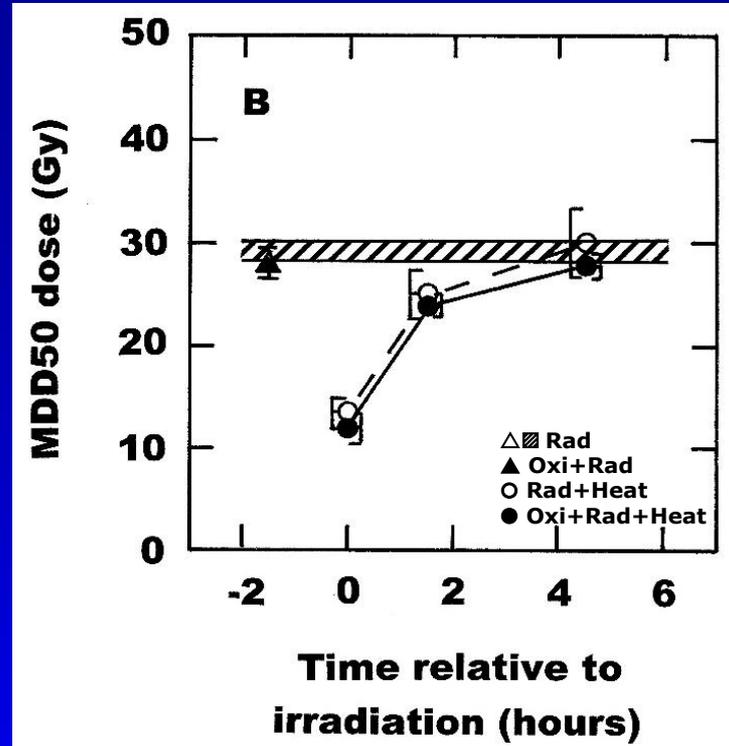




Tumour



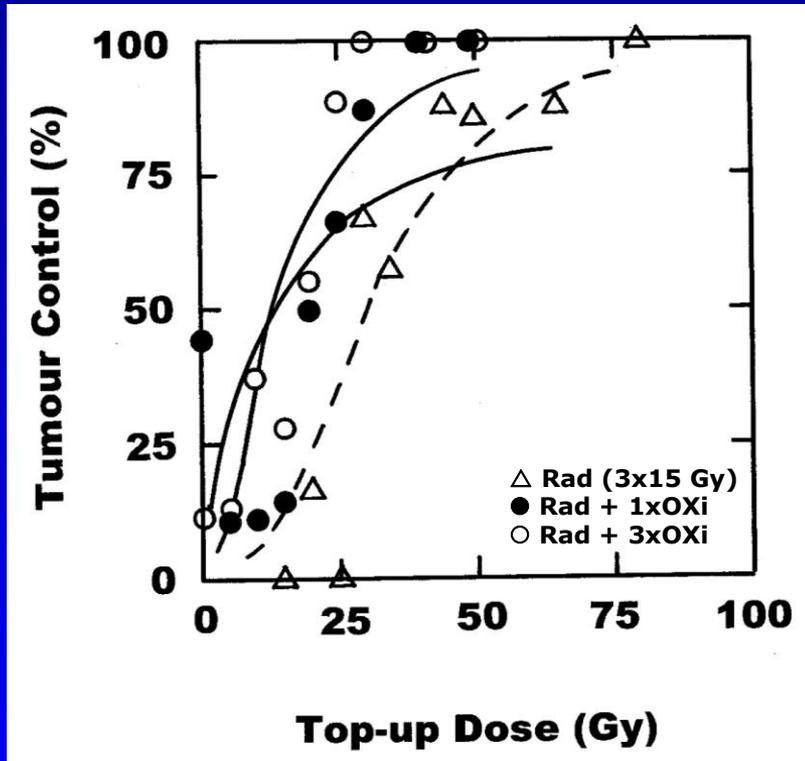
Skin



Treatment	Enhancement Ratios		Therapeutic Gain
	<i>Tumour</i>	<i>Skin</i>	
Rad-0h-Heat	1.64 (1.53-1.76)	2.17 (2.00-2.34)	0.76 (0.60-0.91)
Oxi-Rad-0h-Heat	1.70 (1.55-1.87)	2.47 (2.26-2.69)	0.69 (0.50-0.88)
Rad-4h-Heat	1.11 (1.05-1.18)	0.98 (0.89-1.07)	1.13 (1.01-1.26)
Oxi-Rad-4h-Heat	1.52 (1.38-1.67)	1.06 (1.01-1.11)	1.43 (1.22-1.65)

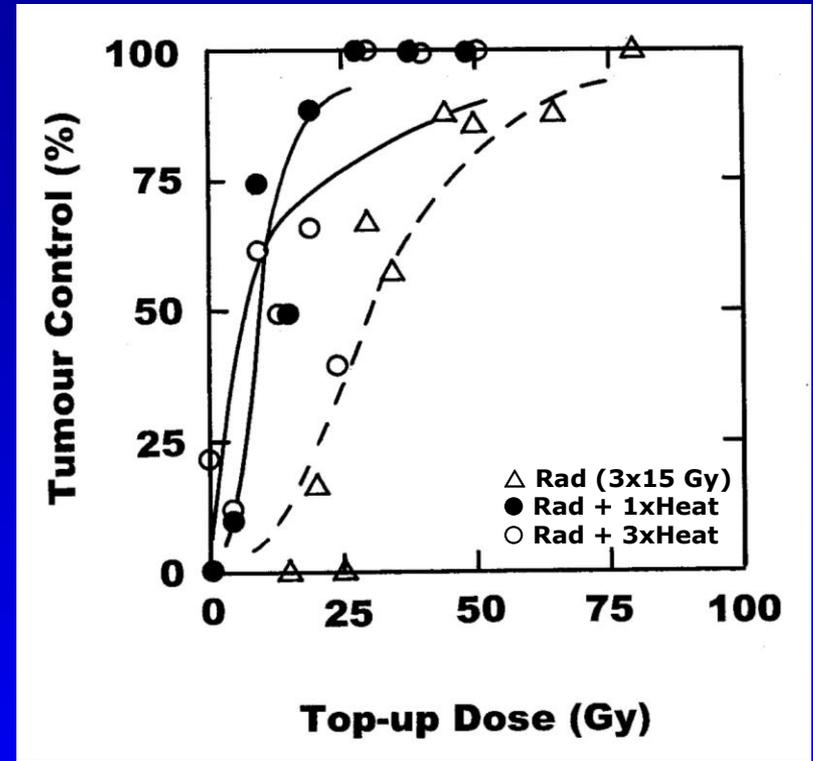
OXi4503

Rad – 1-hour – Oxi (10 mg/kg)



Hyperthermia

Rad – 4-hours – Heat (41.5°C; 60 mins)

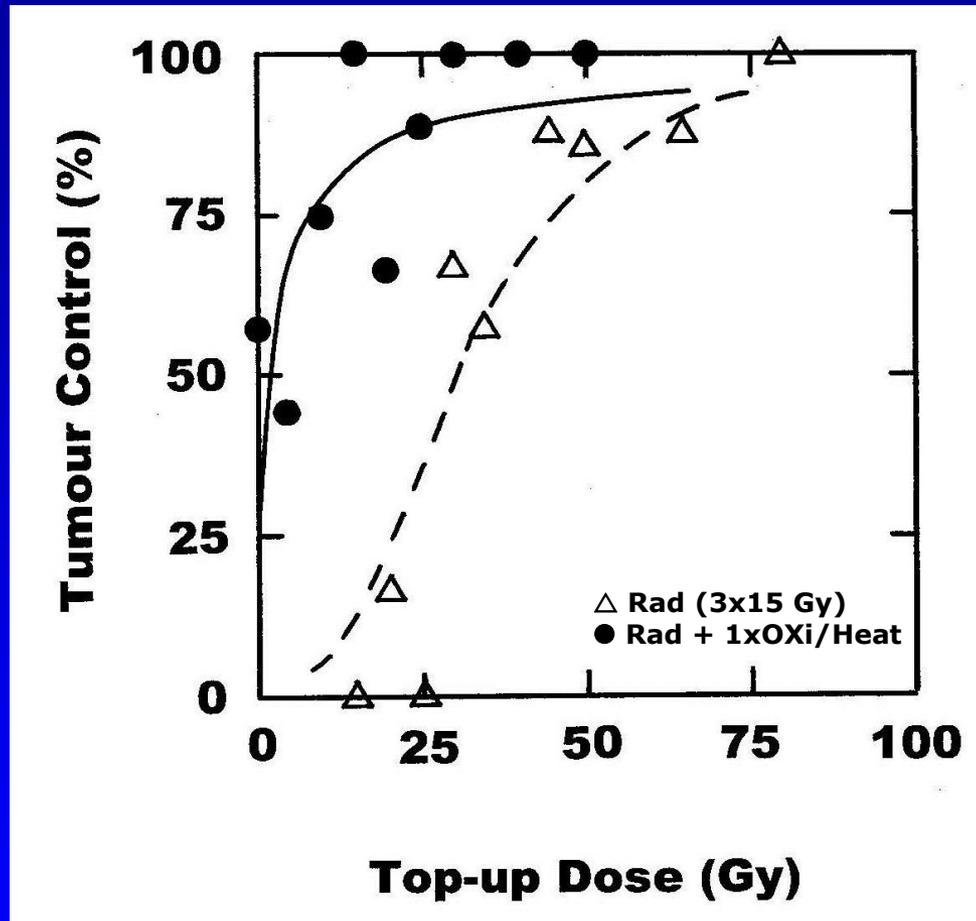


Treatment	TCD50 dose (± 95% CI)
Rad (3x15 Gy)	30 Gy (23-38)
Rad + 1xOXi	12 Gy (6-25)
Rad + 3xOXi	12 Gy (8-19)

Treatment	TCD50 dose (± 95% CI)
Rad (3x15 Gy)	30 Gy (23-38)
Rad + 1xHeat	10 Gy (7-15)
Rad + 3xHeat	9 Gy (5-17)



Radiation – 1-hour – OXi4503 – 3-hours – Heat



Treatment	TCD50 dose (± 95% CI)
Rad (3x15 Gy)	30 Gy (23-38)
Rad + 1xOXi/Heat	2 Gy (1-9)



Current clinical status of vascular disrupting agents.

VDA	Company	Stage of clinical development	Indication	Combination	Status
<i>Flavonoid</i>					
DMXAA (ASA404)	Novartis	Phase II	NSCLC ^a SCLC ^b Prostate cancer Urothelial carcinoma	Carboplatin, paclitaxel Carboplatin, paclitaxel Docetaxel Docetaxel Docetaxel	Stopped
		Phase III (1800 mg/m ²)	NSCLC ^a	Carboplatin, paclitaxel	
<i>Tubulin binding</i>					
CA-4-P (fosbretabulin)	OXiGENE	Phase I/II Phase II Phase II Phase II Phase II	Anaplastic thyroid cancer Anaplastic thyroid cancer Ovarian cancer Solid tumors NSCLC ^a	Radiotherapy Carboplatin, paclitaxel Carboplatin, paclitaxel Carboplatin, paclitaxel, bevacizumab Bevacizumab	Ongoing
		Phase II	Epithelial ovarian, fallopian tube or primary peritoneal carcinoma	Bevacizumab	
		Phase II/III (60 mg/m ²)	Anaplastic thyroid cancer	Carboplatin, paclitaxel	
AVE8062 (Ombrabulin)	Sanofi-Aventis	Phase II Phase II Phase III (25 mg/m ²)	Ovarian cancer NSCLC ^a Soft tissue sarcoma	Carboplatin, paclitaxel Taxane, platinum Cisplatin	Ongoing
CA-1-P (OXi4503)	OXiGENE	Phase I			Ongoing
TZT-1027 (Soblidotin)	Daichi	Phase II Phase II	Soft tissue sarcoma NSCLC ^a		Ongoing
ZD6126	AstraZeneca/Angiogene	Phase II	Renal cell carcinoma Colorectal cancer	Oxaliplatin, 5-fluorouracil, leucovorin	Stopped
NPI-2358	Nereus	Phase I/II	NSCLC ^a	Docetaxel	Ongoing
EPC2407 (Crinobulin)	EpiCept	Phase I/II	Anaplastic thyroid cancer	Cisplatin	Ongoing
CYT997	YM Biosciences	Phase I/II Phase II	Glioblastoma Multiple myeloma	Carboplatin	Ongoing
BNC105	Bionomics	Phase I/II	Renal cell carcinoma	Everolimus	Ongoing
MN-029	Medicnova	Phase I			Stand by

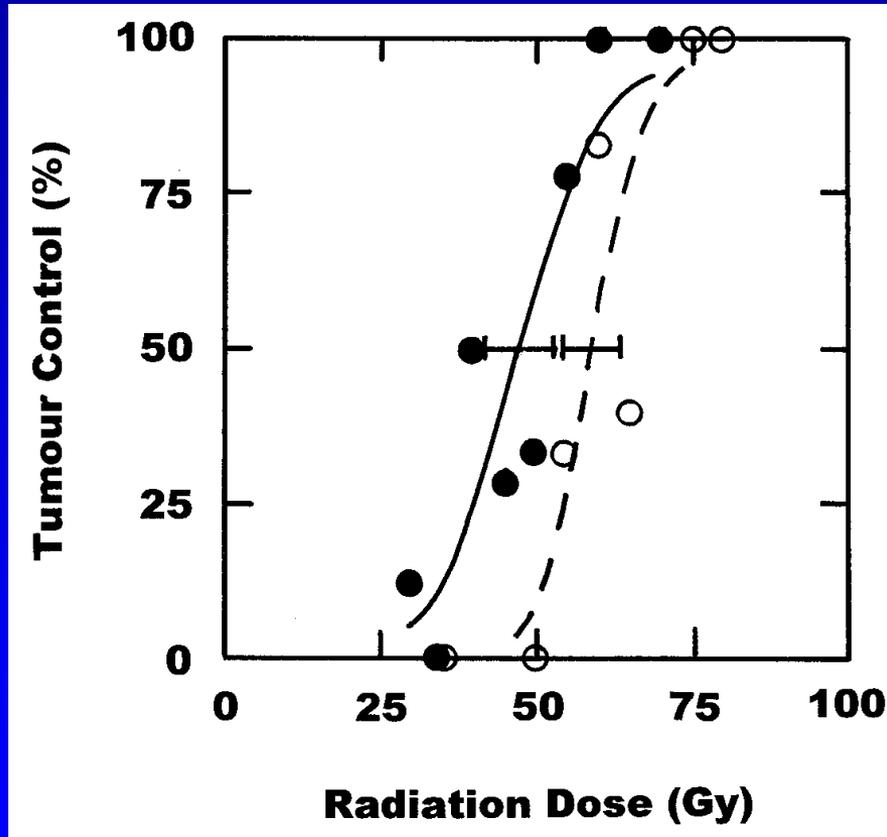
Identified from *PubMed* and *ClinicalTrials.gov* search.



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Radiation (30 x 2 Gy + Clamped top-up) \pm OXi4503 (i.p.)

OXi4503: 3 x 25 mg/kg



OXi4503: 3 x 10 mg/kg

