Targeting Tumor Hypoxia in Patients

Kathy Han, MD, MSc

Department of Radiation Oncology, University of Toronto

Radiation Medicine Program, Princess Margaret Cancer Centre

Toronto, Ontario, Canada

Objectives

- Identify ways of measuring hypoxia in human tumors.
- Describe the relationship between hypoxia in human tumors and clinical outcome.
- Understand ways of targeting hypoxia in human tumors and opportunities for future research and clinical development.

What have we learned about hypoxia?

Hypoxia:

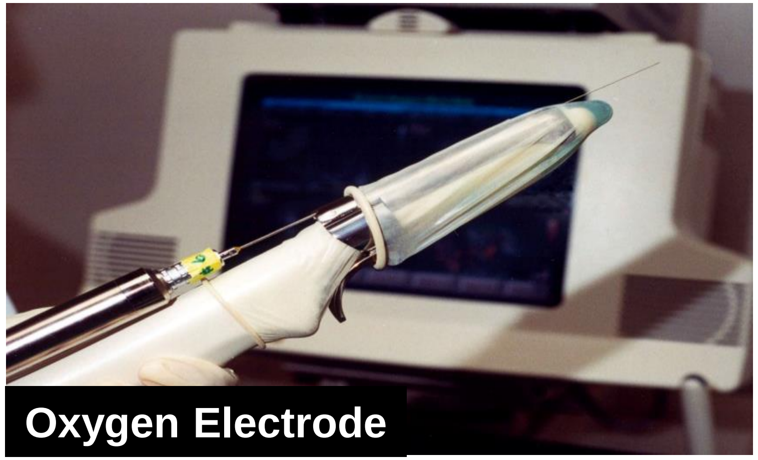
- Activates cell survival pathways
- Maintains cancer stem cells
- Alters DNA repair and contributes to genomic instability
- Selects for hypoxia tolerant, clinically aggressive cell populations
- Increases metastatic potential
- Contributes to treatment resistance

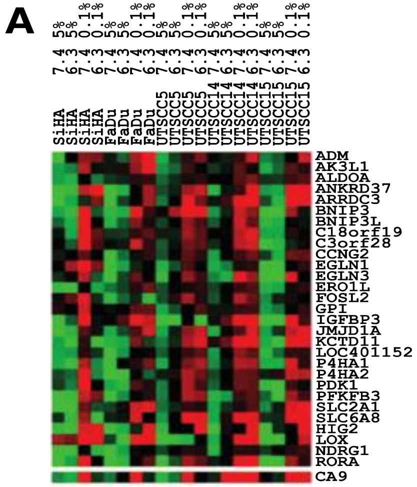
Clinical Implications of Hypoxia

- Most solid human tumors contain hypoxia.
- The extent of hypoxia is highly variable within individual tumors, among patients and over time.
- Tumor hypoxia is associated with poor local control after radiotherapy.
- Tumor hypoxia is associated with aggressive clinical behavior and the development of metastases regardless of treatment modality.
- Hypoxia targeted treatments are effective in selected patients.

Measuring Hypoxia in Patients

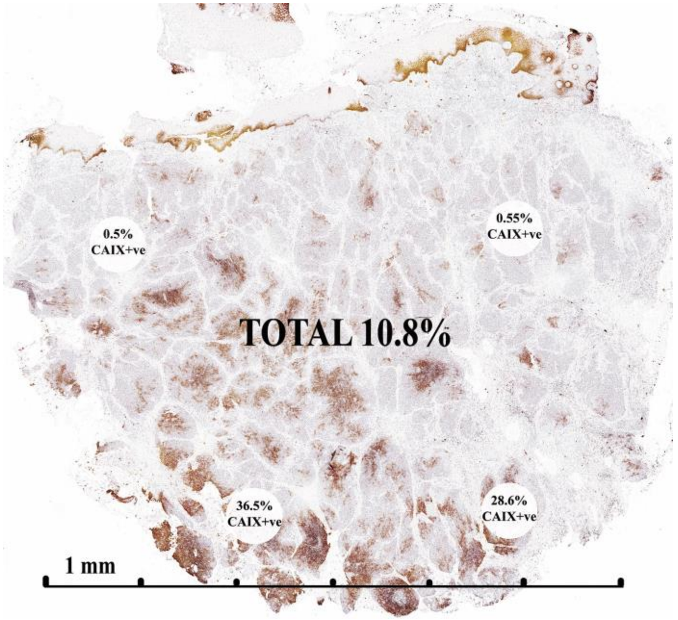
- Direct oxygen measurements
  (polarographic electrodes)
- Drugs that bind in hypoxia
  - pimonidazole, EF5 (exogenous)
- Endogenous biomarkers
  - HIF1α, HIF2α , CA-IX, GLUT-1, VEGF, …
- Gene signatures
- Imaging
  - MRI
  - PET with hypoxia tracer
    (e.g. F-MISO, FAZA)





Hypoxia is Heterogeneous

Spatial and time-dependent variability confounds
the identification of clinically relevant hypoxia

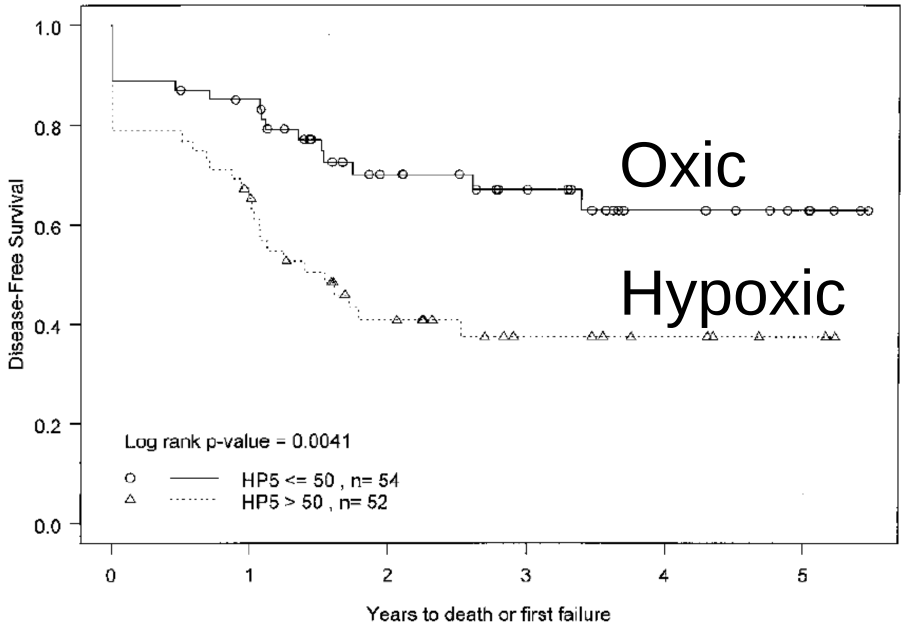


Solutions: Multiple hypoxic markers (gene signatures)
Serial, whole-tumor imaging assessment

Iakovlev and Hedley, 2007

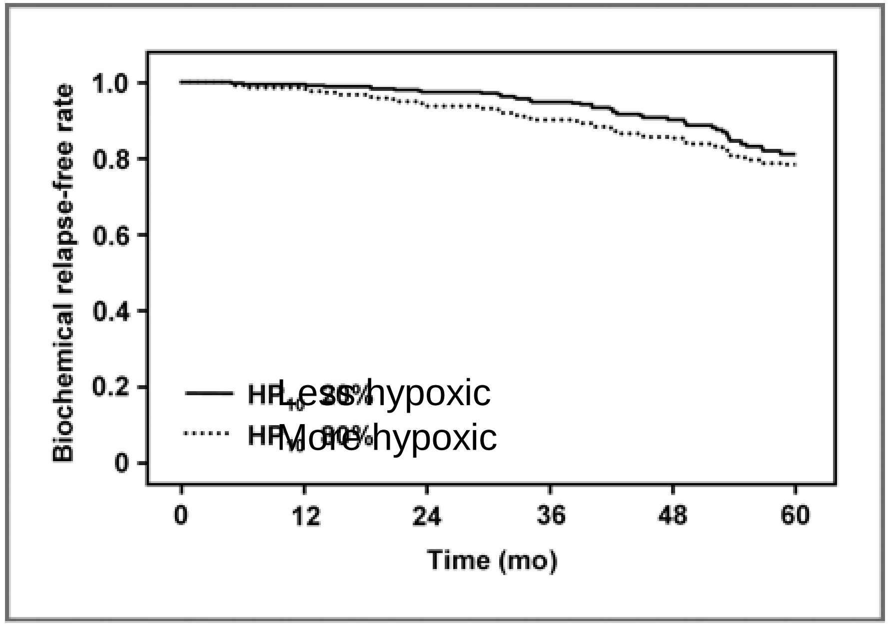
Tumor Hypoxia (pO2 electrode) and Survival

Cervical Cancer



Fyles et al, JCO 2002

Prostate Cancer



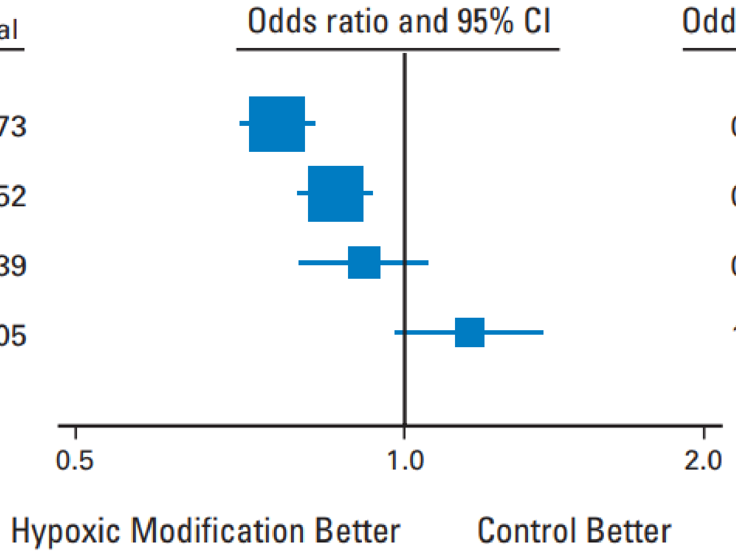
Milosevic et al, Clin Cancer Res 2012

Tumor hypoxia is associated with inferior survival

Hypoxic modification improves locoregional control and survival: systematic review

Data from 86 randomized trials including 10,108 patients

Endpoint	Hypoxic modification Events	Hypoxic modification Total	Control Events	Control Total	Odds ratio	95% CI
Loco-regional control	2,144	4,416	2,465	4,473	0.77	0.71 to 0.84
Survival	3,237	4,921	3,405	4,952	0.87	0.80 to 0.95
Distant metastasis	452	2,332	480	2,339	0.93	0.81 to 1.07
Complications	374	2,424	310	2,305	1.17	1.00 to 1.38



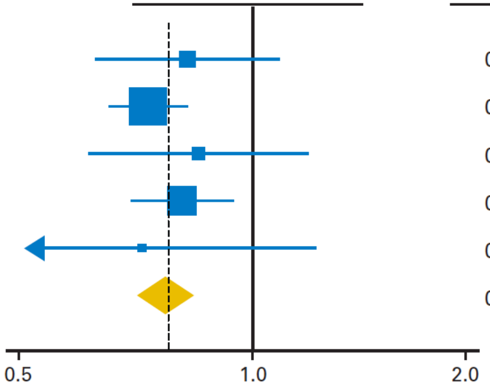
Different methods: hyperbaric oxygen (26 trials), normobaric oxygen or carbogen (5 trials), hypoxic radiosensitizers (54 trials), or both hyperbaric oxygen and hypoxic sensitizer (1 trial)

Overgaard, J Clin Oncol 2007

Hypoxic modification significantly improves the effect of RT

Tumor Site	Hypoxic modification Events	Hypoxic modification Total	Control Events	Control Total	Odds ratio	95% CI
Bladder	185	402	206	403	0.82	0.62 to 1.08
Head and Neck	1,179	2,261	1,336	2,225	0.73	0.64 to 0.82
Lung	196	309	212	315	0.84	0.61 to 1.17
Uterine cervix	499	1,308	601	1,383	0.80	0.69 to 0.94
Other	88	132	104	141	0.71	0.42 to 1.20
All	2,147	4,412	2,459	4,467	0.76	0.70 to 0.83

Odds ratio and 95% CI

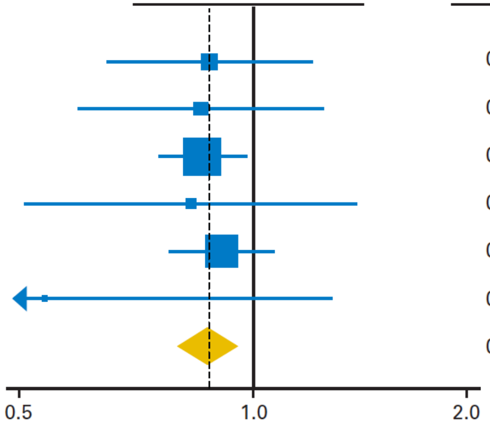


Locoregional Control

Hypoxic Modification Better Control Better

Tumor Site	Hypoxic modification Events	Hypoxic modification Total	Control Events	Control Total	Odds ratio	95% CI
Bladder	254	400	258	388	0.88	0.65 to 1.18
CNS	394	474	403	473	0.86	0.60 to 1.21
Head and Neck	1,415	2,163	1,483	2,157	0.86	0.76 to 0.98
Lung	375	416	385	420	0.83	0.52 to 1.33
Uterine cervix	765	1,358	839	1,429	0.91	0.78 to 1.05
Other	71	89	79	90	0.55	0.24 to 1.24
All	3,274	4,900	3,447	4,957	0.87	0.80 to 0.95

Odds ratio and 95% CI



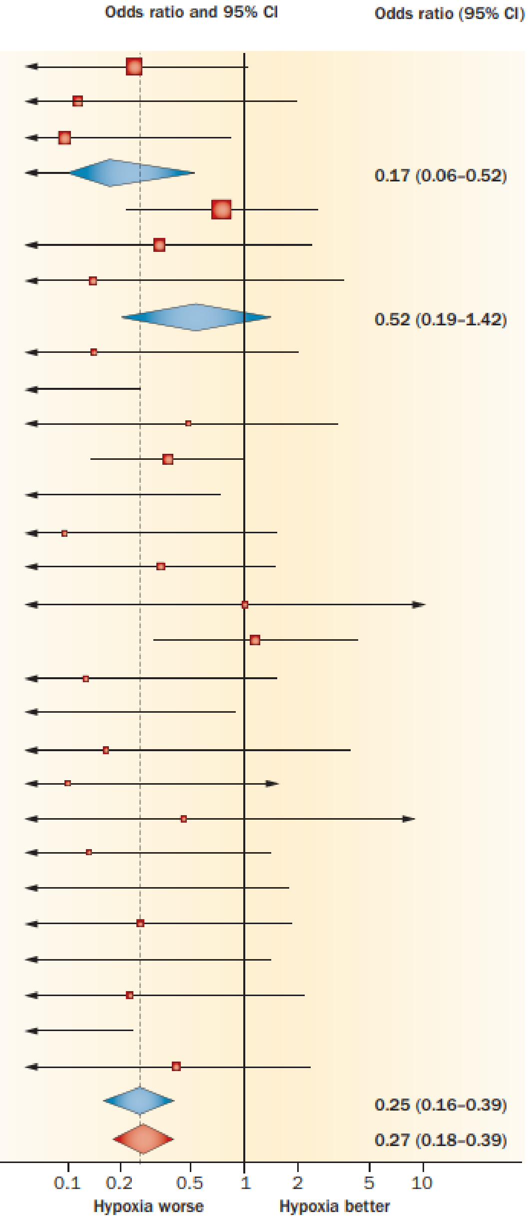
Overall Survival

Hypoxic Modification Better Control Better

Overgaard J Clin Oncol 2007

Meta-analysis: uniform tendency for poor response to RT for hypoxic tumors

Study	Tumour	Tracer	Events/total No hypoxia	Events/total Hypoxia	Odds ratio (95% CI)
Loncaster (2002)[97]	Cervix	DCE MRI	3/25	9/25	
Mayr (2010)[98]	Cervix	DCE MRI	0/16	17/82	
Andersen (2012)[99]	Cervix	DCE MRI	1/41	8/40	
DCE MRI all			**4/82**	**34/147**	**0.17 (0.06–0.52)**
Hermans (1999)[87]	HNSCC	CTperf	9/21	10/20	
Bisdas (2009)[88]	HNSCC	CTperf	2/11	4/10	
Truong (2011)[89]	HNSCC	CTperf	0/6	2/6	
CT perfusion all			**11/38**	**16/36**	**0.52 (0.19–1.42)**
Urtasun (1996)[102]	HNSCC	IAZA	3/10	3/4	
Dehdashti (2003)[70]	Lung	CuATSM	0/8	6/6	
Lehtiö (2004)[52]	HNSCC	FETNIM	4/9	5/8	
Rajendran (2006)[53]	HNSCC	FMISO	10/37	18/36	
Rischin (2006)[28]	HNSCC	FMISO	1/10	8/13	
Thornwarth (2006)[54]	HNSCC	FMISO	1/6	4/6	
Li (2006)[104]	Lung	Tc-HL91	8/16	12/16	
Eschmann (2007)[55]	HNSCC	FMISO	2/4	4/8	
Dehdashti (2008)[71]	Cervix	CuATSM	9/22	6/16	
Dietz (2008)[72]	Rectal	CuATSM	1/9	4/8	
Khamly (2008)[56]	Sarcoma	FAZA	3/9	7/8	
Spence (2008)[57]	CNS	FMISO	9/11	11/11	
Dirix (2009)[58]	HNSCC	FMISO	2/6	5/6	
Lee (2009)[59]	HNSCC	FMISO	0/7	1/11	
Li (2010)[60]	Lung	FETNIM	8/13	12/13	
Schuetz (2010)[47]	Cervix	FAZA	0/10	2/5	
Kikuchi (2011)[61]	HNSCC	FMISO	3/10	5/8	
Minagawa (2011)[73]	HNSCC	CuATSM	0/5	6/10	
Mortensen (2012)[62]	HNSCC	FAZA	1/17	7/25	
Yue (2012)[63]	Oesophagus	FETNIM	1/14	11/14	
Zips (2012)[64]	HNSCC	FMISO	3/13	5/12	
PET/SPECT all			**69/244**	**142/244**	**0.25 (0.16–0.39)**
All studies			**84/364**	**192/427**	**0.27 (0.18–0.39)**



OR 0.27

Especially true for studies using hypoxic PET tracers, but also when hypoxia was indirectly identified using the perfusion-based methods CT and DCE–MRI.

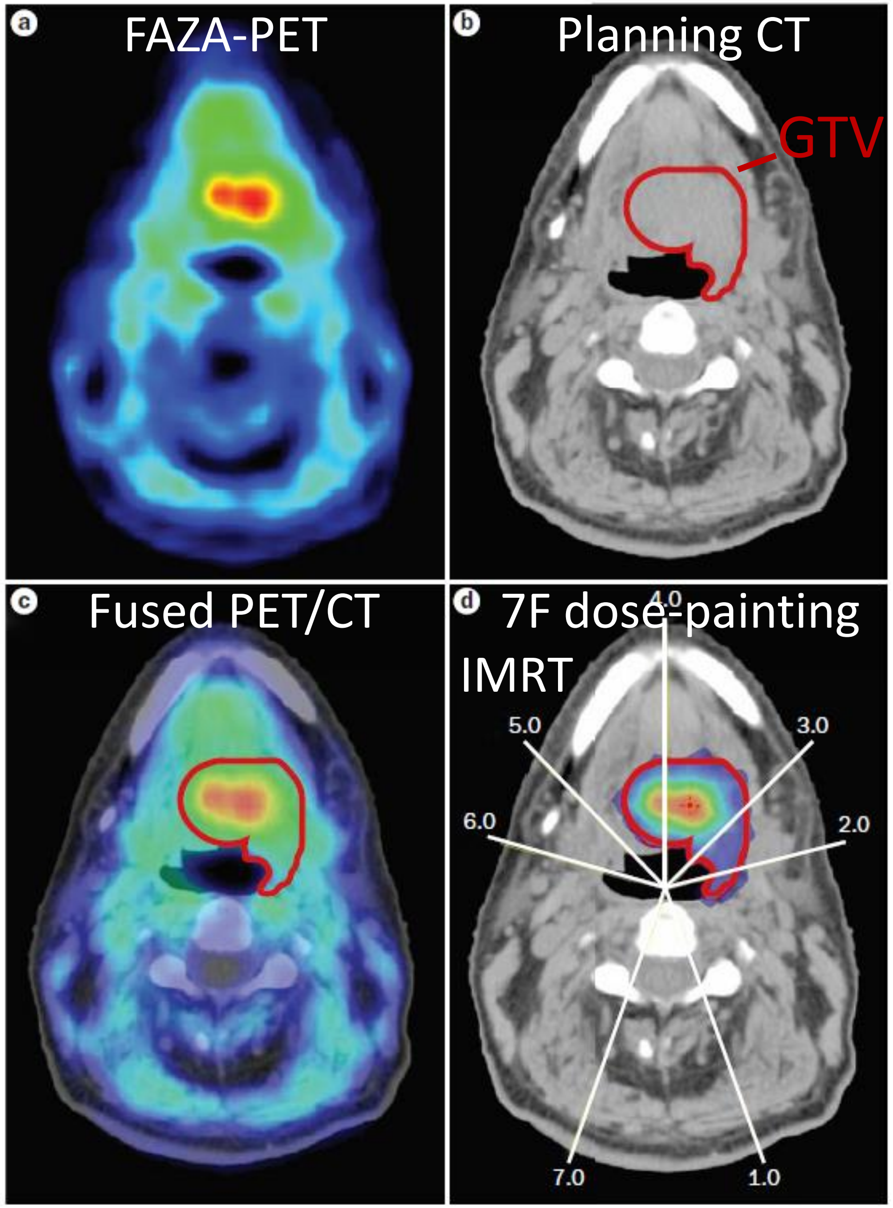
Horsman et al, Nat Rev Clin Oncol 2012

Targeting Hypoxia in Patients

1. RT dose escalation
   – "Dose painting"
2. Improved oxygen supply
   – Treat anemia, hyperbaric O_2, carbogen, nicotinamide
3. Hypoxic cell radiation sensitization (mimicks radiosensitizing properties of oxygen)
   – Misonidazole, pimonidazole, nimorazole, etanidazole
4. Hypoxic cell cytotoxins (activated under hypoxic conditions)
   – Tirapazamine, TH-302
5. Metabolic targeting
   - Angiogenesis, O_2 consumption (Metformin), exercise

1. RT Dose Escalation

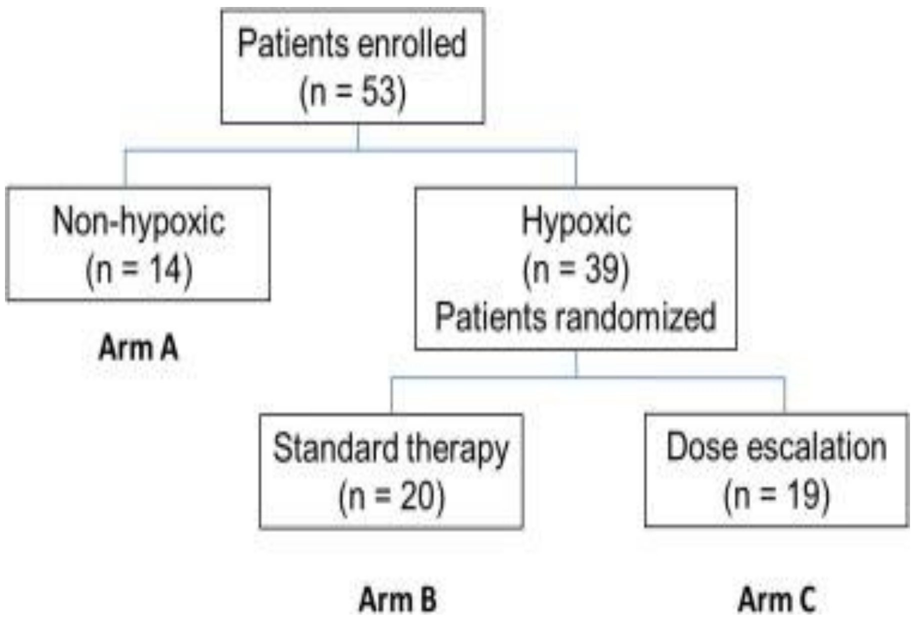
Dose Painting

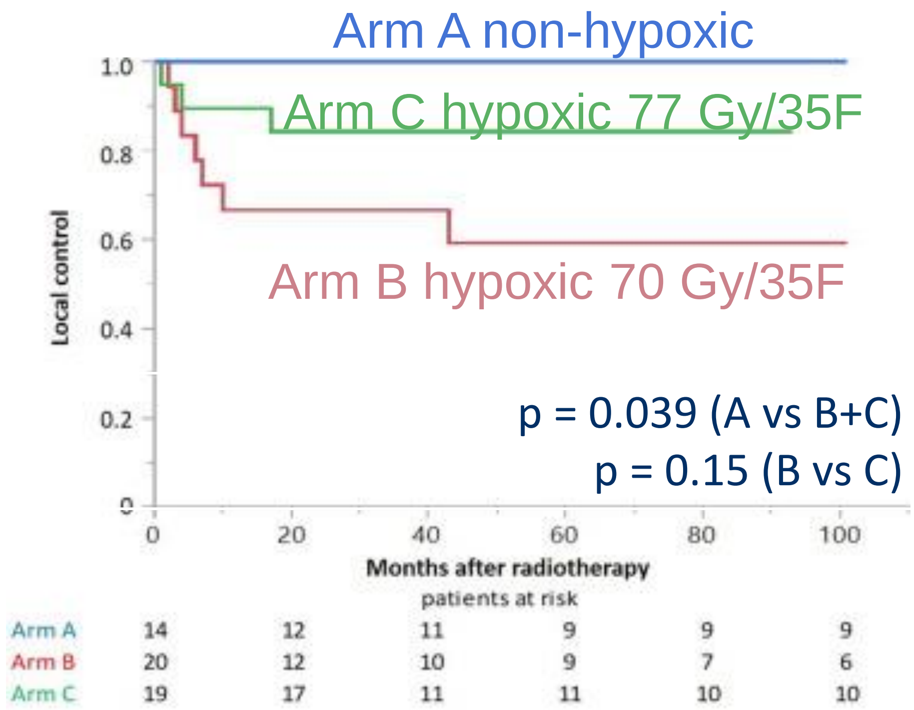


Horsman et al, Nat Rev Clin Oncol 2012

Dose Escalation to Hypoxic Tumor Region

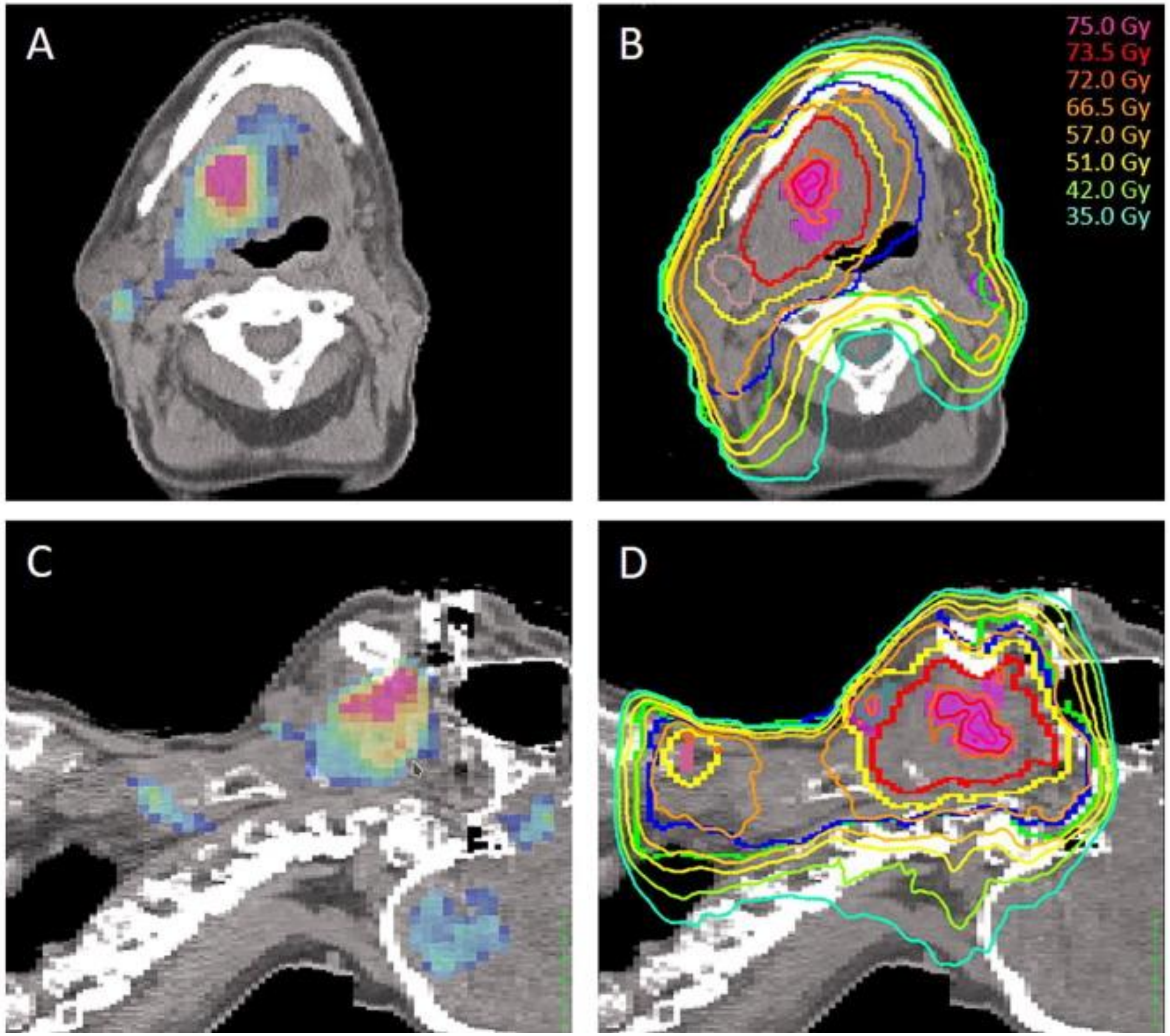
- Randomized phase II trial in HN cancer 2009-2017
- Patients assigned treatment arm based on baseline dynamic F-MISO PET





Welz et al, Radiother Oncol 2022

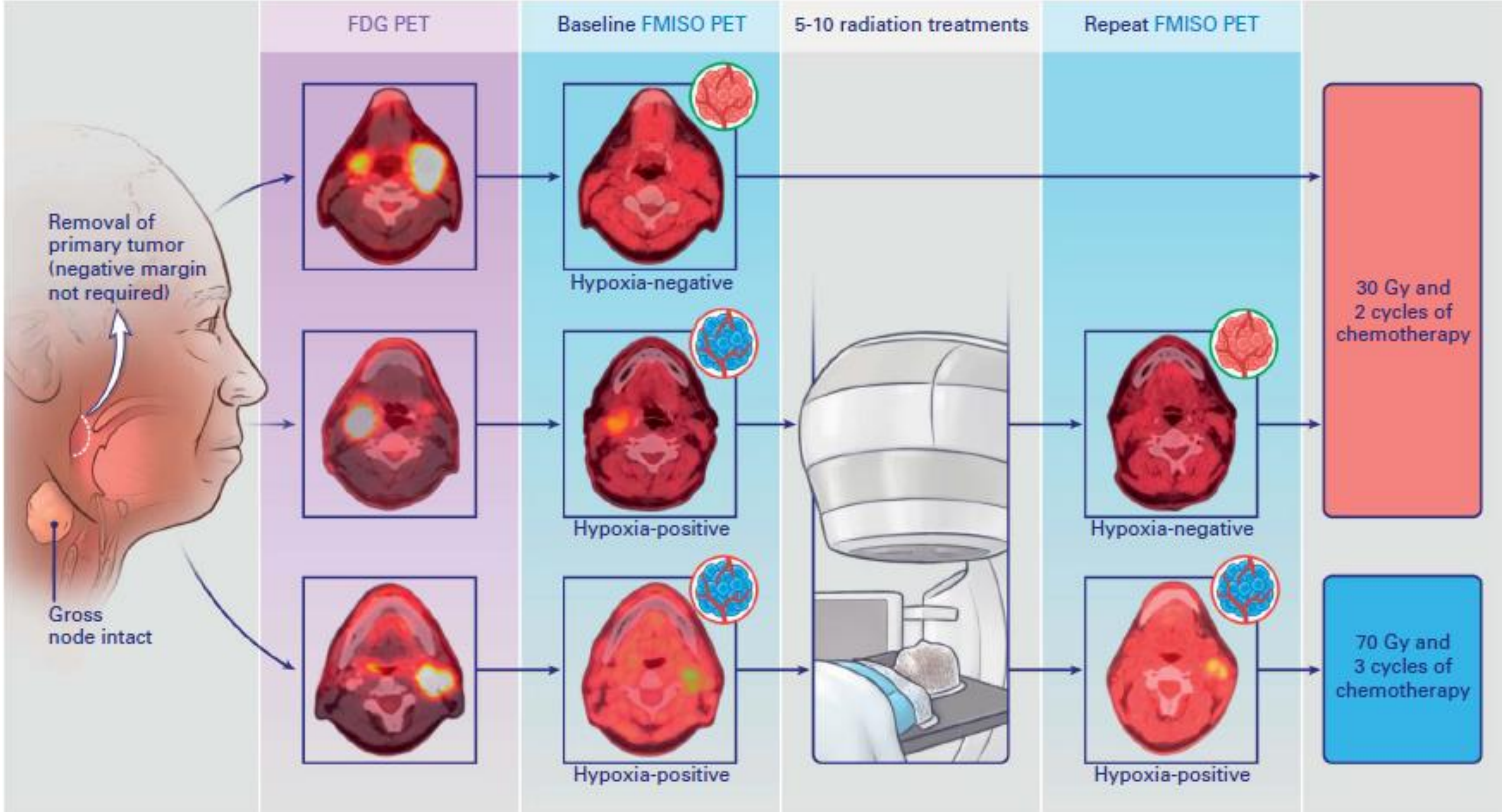
Dose Escalation to Hypoxic Tumor Region



70 Gy to the macroscopic tumor (GTV) + simultaneous integrated boost of 77 Gy to the hypoxic volume

Welz et al, Radiother Oncol 2022

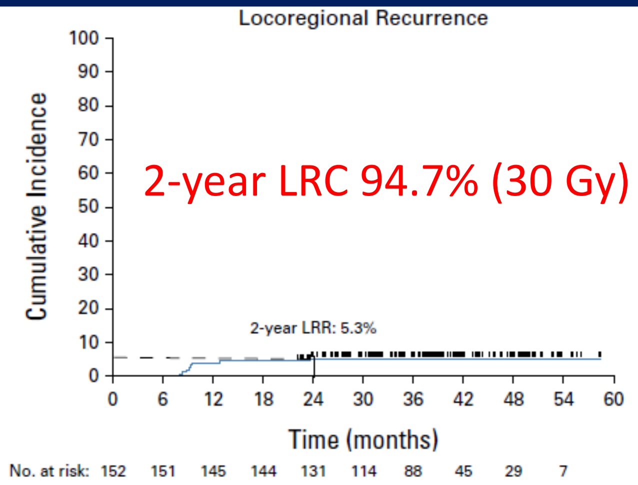
Dose De-Escalation for Non-Hypoxic HPV+ OPC (single-arm phase II)

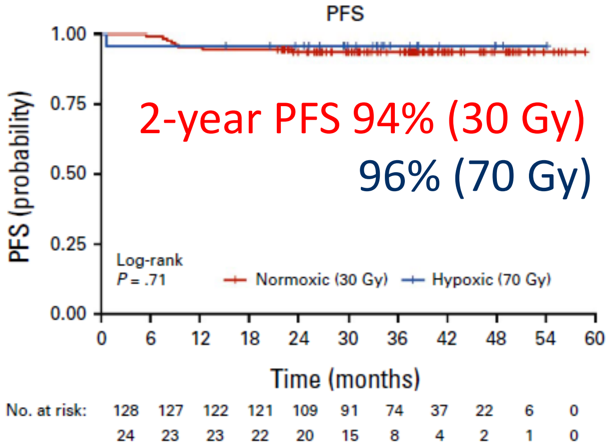


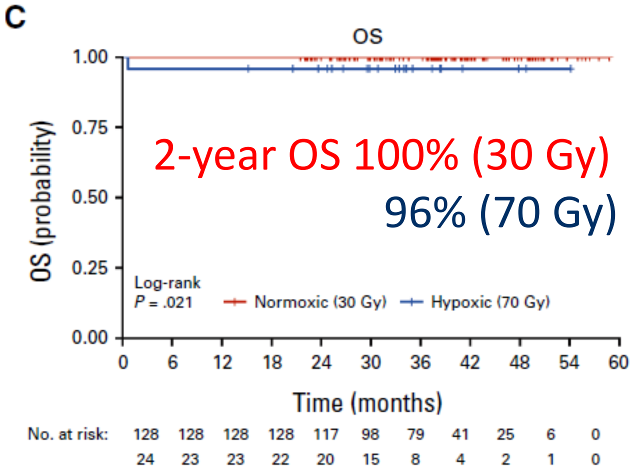
Primary objective: achieving 2-year locoregional control rate 95%

Lee et al, JNCI 2024

Dose De-Escalation for Non-Hypoxic HPV+ OPC







Acute grade 3-4 toxicities more common in 70 Gy (58%) than 30 Gy (32%).

Late grade 3-4 toxicities occurred only in the 70 Gy cohort (4.5%)

Tumor hypoxia is a promising approach to direct dosing of curative-intent chemoRT for HPV+ OPC with preserved efficacy and substantially reduced toxicity.

Lee et al, JNCI 2024

2. Improved Oxygen Supply

Transfusion to Correct Anemia

Br. J. Cancer (1978) **37**, Suppl. III, 302

DEFINITIVE EVIDENCE FOR HYPOXIC CELLS INFLUENCING CURE IN CANCER THERAPY

R. S. BUSH, R. D. T. JENKIN, W. E. C. ALLT, F. A. BEALE, H. BEAN, A. J. DEMBO AND J. F. PRINGLE

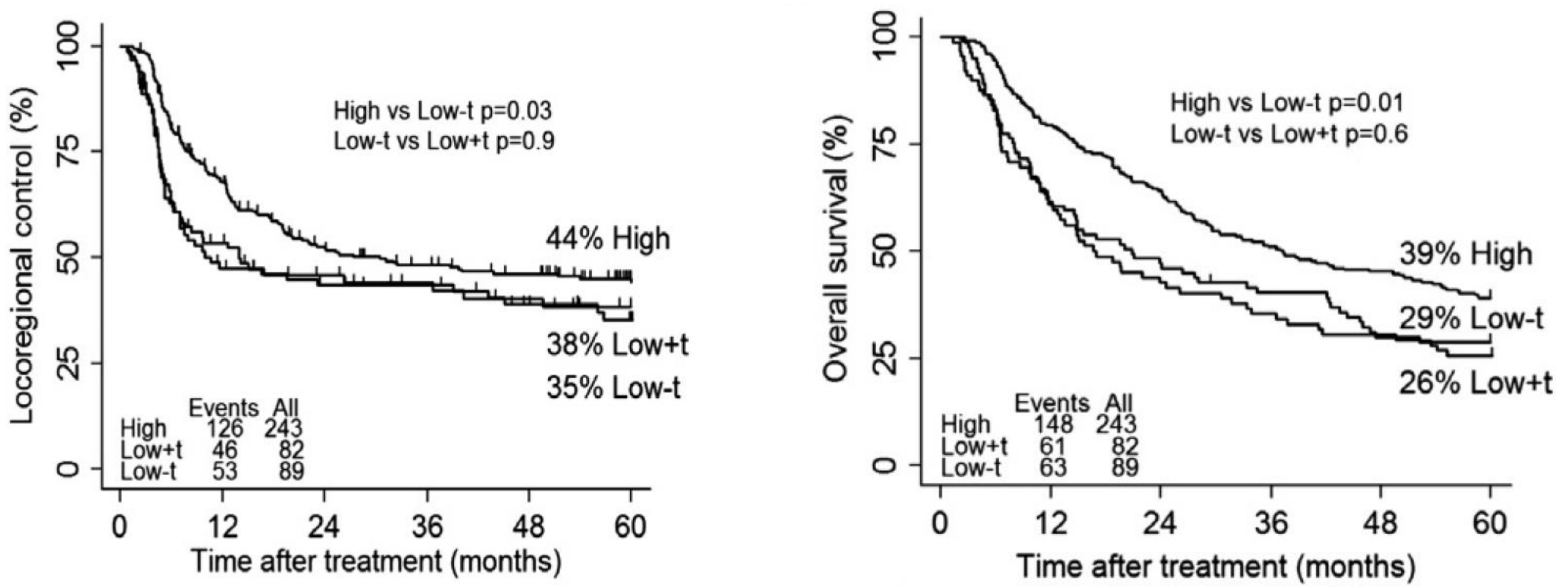
From the Ontario Cancer Institute, incorporating The Princess Margaret Hospital, Toronto, Canada

Summary.—From an analysis of 2803 patients with carcinoma of the cervix treated by radiation therapy, a 62% cure rate can be shown. In those patients with Stage IIb and III disease, a haemoglobin level during treatment of below 12 g% was associated with a significantly higher pelvic recurrence rate, and also lower cure rate, than for those with a haemoglobin level 12 g% or more. A prospective study shows that the correction of anaemia is associated with a decreased pelvic recurrence rate and an increased cure rate consistent with tumour hypoxia being greater in anaemic patients than in those with a normal haemoglobin level. It is also consistent with the thesis that hypoxia controls the radiation local control rate in patients with advanced carcinoma of the cervix.

- Severe anemia may contribute to hypoxia.
- Anemia is associated with poor clinical outcomes in cervical cancer, but hemoglobin levels are strongly correlated with tumor size.
- Apparent benefit of transfusion in older studies possibly confounded by differences in tumor size

Transfusion to Correct Anemia

Patients with low pre-treatment hemoglobin in DAHANCA 5 RCT randomized to transfusion or not



Anemia associated with poor outcome in head and neck cancer but no benefit of transfusion

Hoff et al, Radiother Oncol 2011

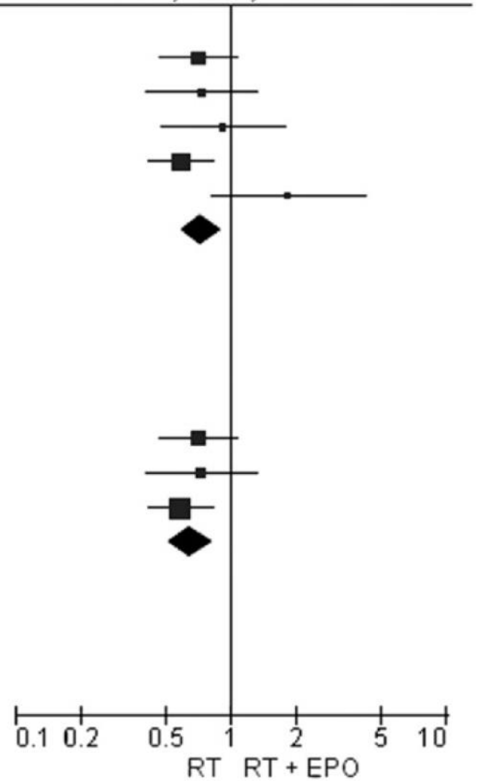
Erythropoetin to Correct Anemia

Worse survival in patients receiving RT+EPO,

possibly due to stimulation of tumor EPO receptors

Study or Subgroup	RT + EPO Events	RT + EPO Total	RT Events	RT Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Overall survival						
Henke 2003	71	180	82	171	27.5%	0.71 [0.46, 1.08]
Hoskin 2004	122	151	127	149	13.5%	0.73 [0.40, 1.33]
Machtay 2007	37	72	37	69	11.3%	0.91 [0.47, 1.77]
Overgaard 2007	97	255	133	260	40.5%	0.59 [0.42, 0.83]
Rosen 2003	28	47	19	43	7.2%	1.84 [0.81, 4.19]
Subtotal (95% CI)		**705**		**692**	**100.0%**	**0.73 [0.58, 0.91]**
Total events	355		398			
Heterogeneity: Chi² = 6.79, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 2.82 (P = 0.005)						
1.1.2 Without studies supplementing iron to intervention group only						
Henke 2003	71	180	82	171	33.7%	0.71 [0.46, 1.08]
Hoskin 2004	122	151	127	149	16.6%	0.73 [0.40, 1.33]
Overgaard 2007	97	255	133	260	49.7%	0.59 [0.42, 0.83]
Subtotal (95% CI)		**586**		**580**	**100.0%**	**0.65 [0.51, 0.83]**
Total events	290		342			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 3.46 (P = 0.0005)						

Peto Odds Ratio
Peto, Fixed, 95% CI



Lambin et al, Cochrane Database of Systematic Reviews, 2009

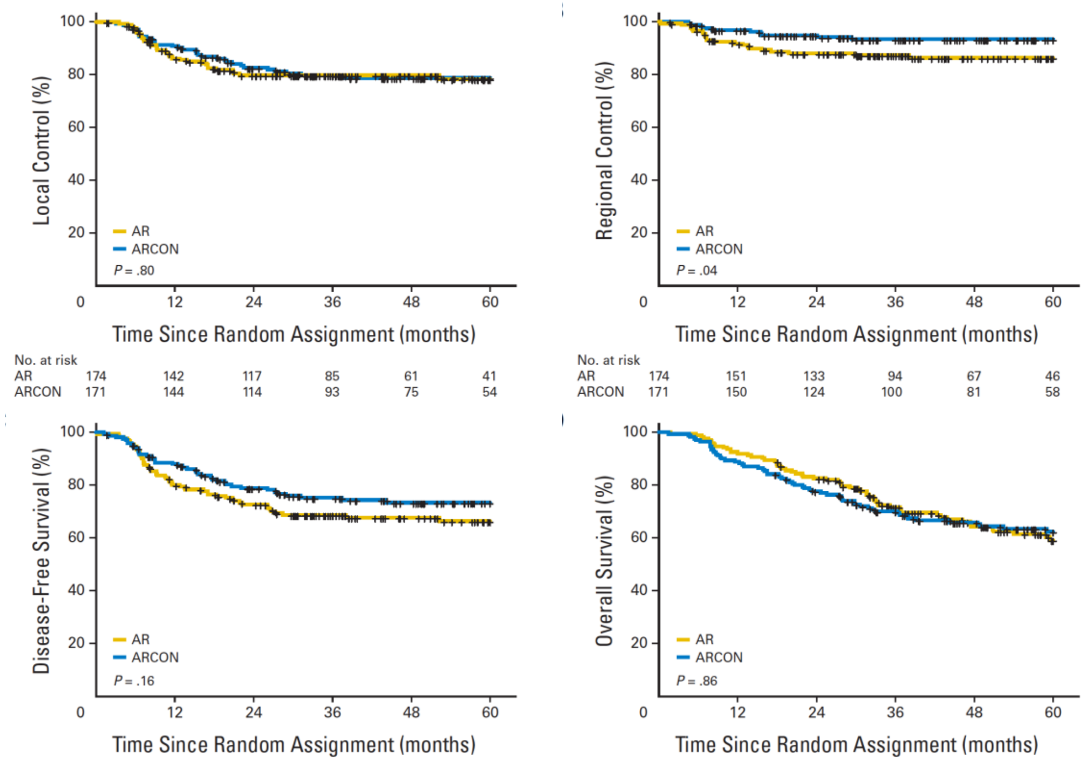
Carbogen and Nicotinamide

ARCON

- Accelerated RT
  - Tumor repopulation
- Carbogen
  - 95-97% O_2, 2-5% CO_2
  - ↓ chronic hypoxia
- Nicotinamide
  - ↓ acute hypoxia
- Promising phase I-II studies in 1990's
  - H&N, bladder, glioblastoma

ARCON in Laryngeal Cancer (Phase III RCT)

ARCON improved 5-year regional control (93% vs 86%)

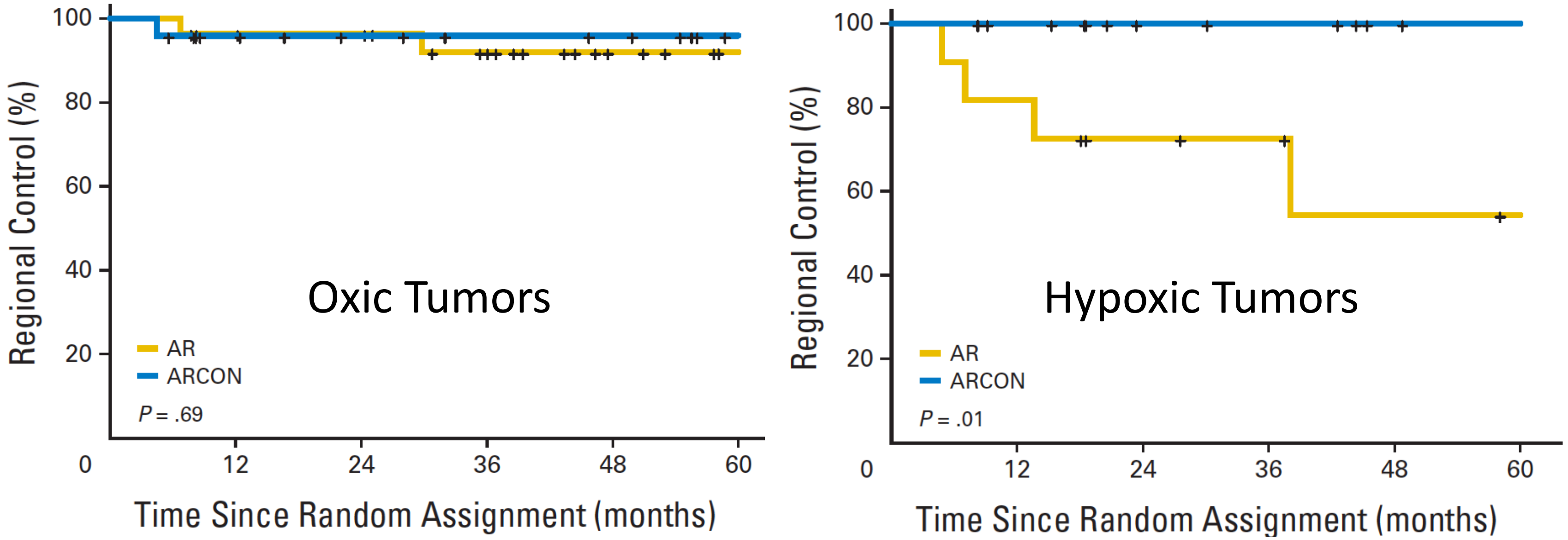


345 patients with T2-T4 laryngeal cancer randomized to receive accelerated RT (AR) ± carbogen and nicotinamide (ARCON)

Janssens et al, JCO 2012

ARCON in Laryngeal Cancer

Benefit of carbogen and nicotinamide only in patients with hypoxic laryngeal tumors

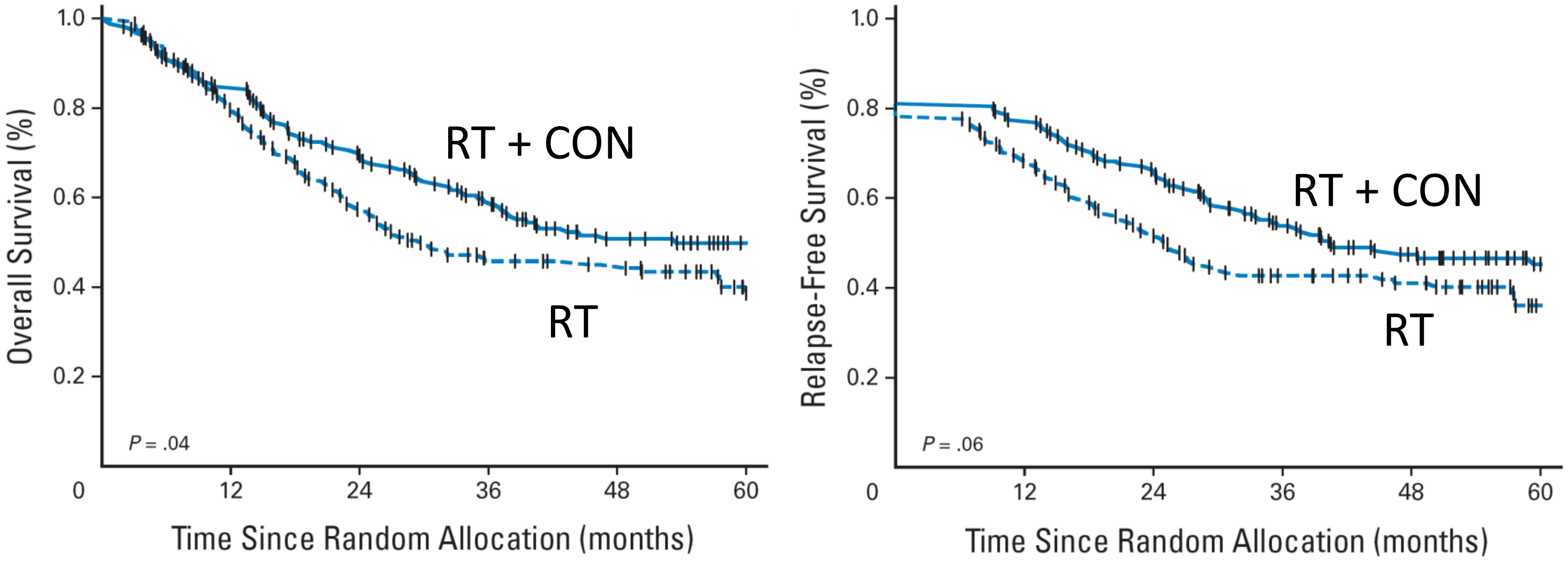


79/345 patients with pimonidazole before treatment

Janssens, 2010

Carbogen and Nicotinamide in Bladder Cancer

Standard RT + carbogen and nicotinamide improved 3-year overall survival & local relapse-free survival



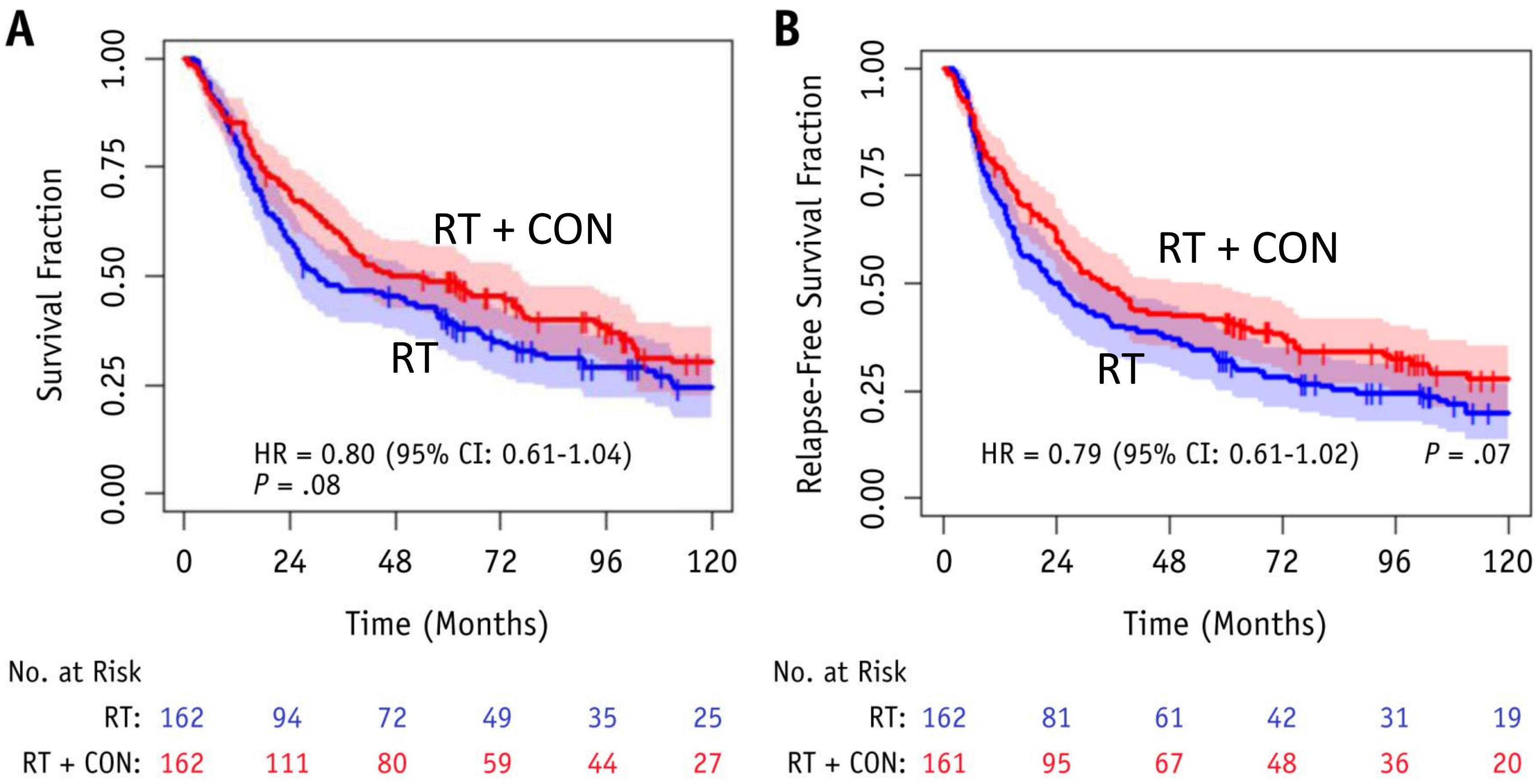
333 patients with T1-T4a bladder cancer randomized to receive RT ± carbogen and nicotinamide

Hoskin et al, JCO 2010

Carbogen and Nicotinamide in Bladder Cancer: Long Term Outcomes

The improvement in long-term (10 year) overall survival was not statistically significant…

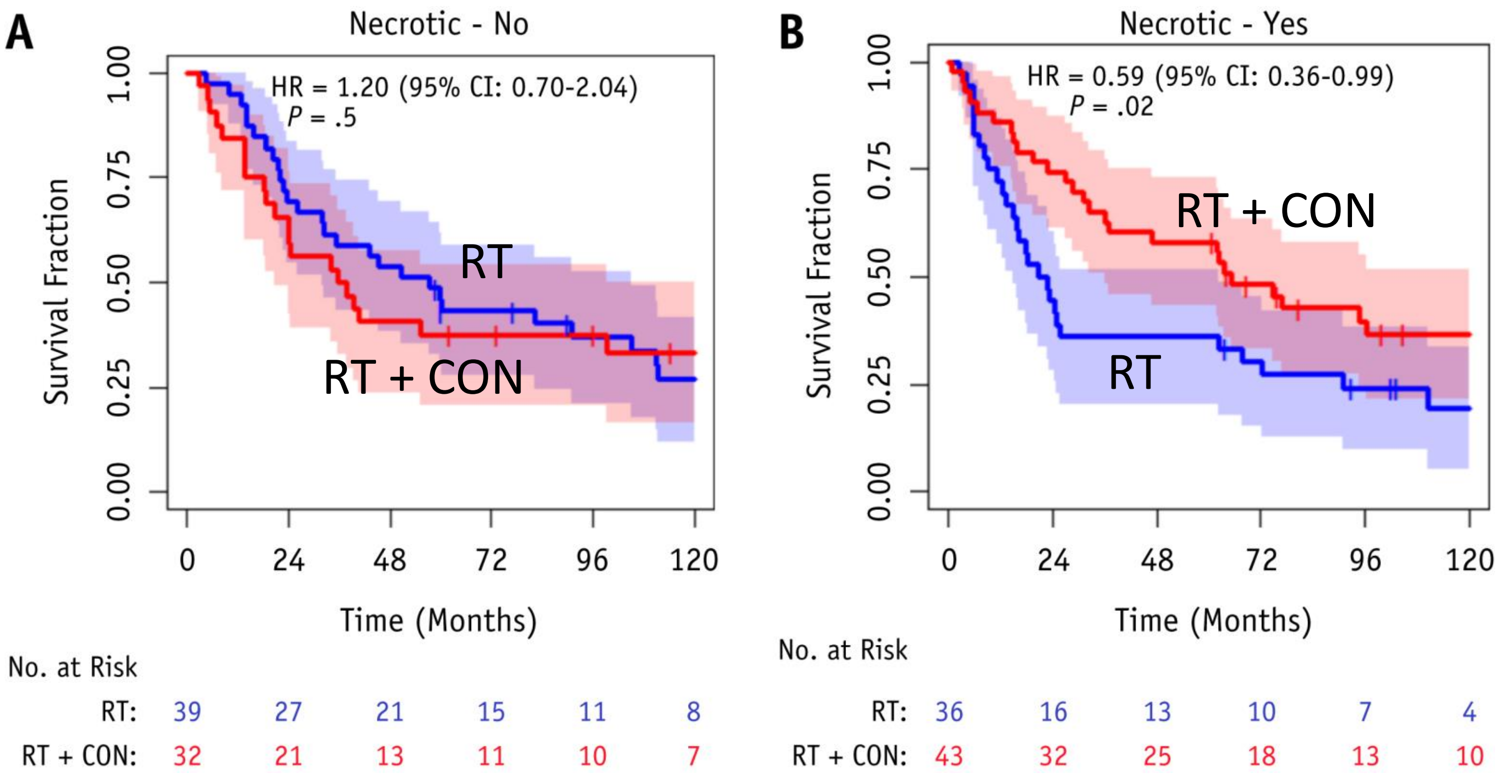
30% in RT + CON vs 24% in RT alone patients (p = 0.08)



Hoskin et al, IJROBP 2021

Carbogen and Nicotinamide in Bladder Cancer: Long Term Outcomes

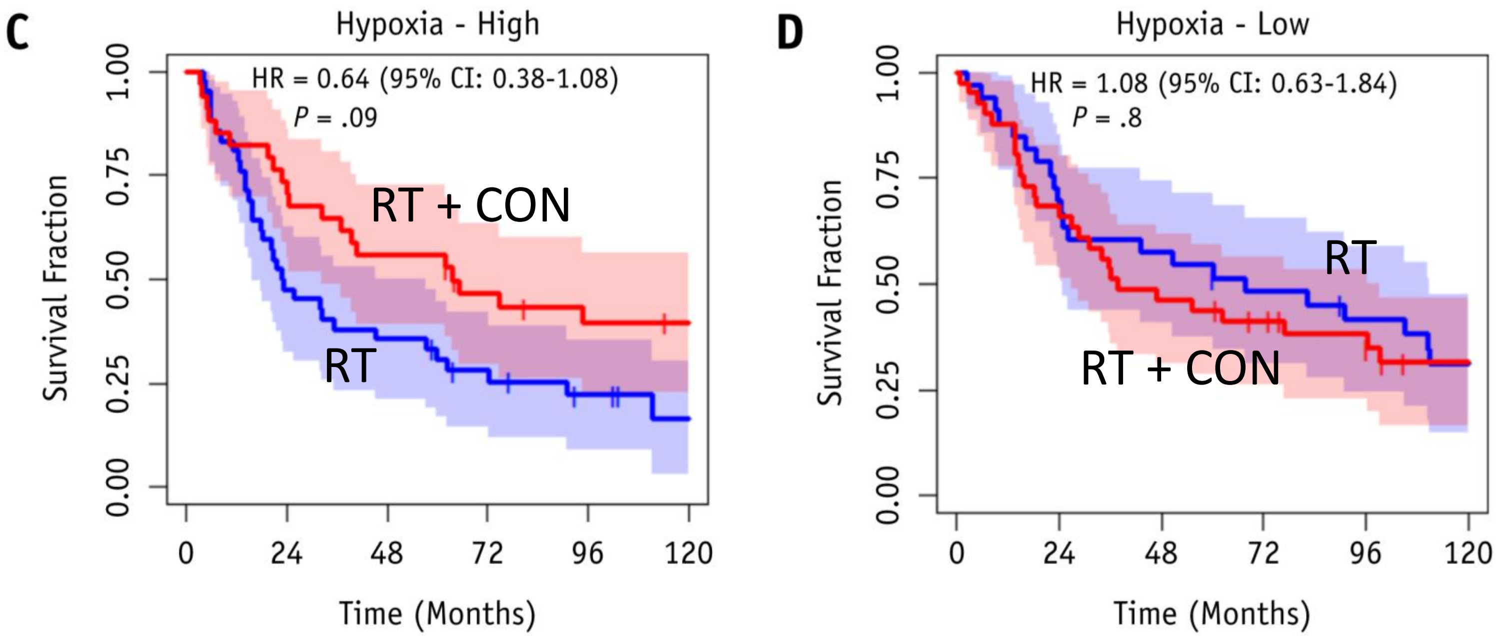
Benefit of CON only in patients with tumor necrosis



Hoskin et al, IJROBP 2021

Carbogen and Nicotinamide in Bladder Cancer: Long Term Outcomes

Benefit of CON only in patients with high-hypoxia gene score



No. at Risk

RT:	42	20	15	10	6	3
RT + CON:	34	25	19	14	11	10

No. at Risk

RT:	33	23	19	15	12	9
RT + CON:	41	28	19	15	12	7

Hoskin et al, IJROBP 2021

3. Hypoxic Cell Radiation Sensitization

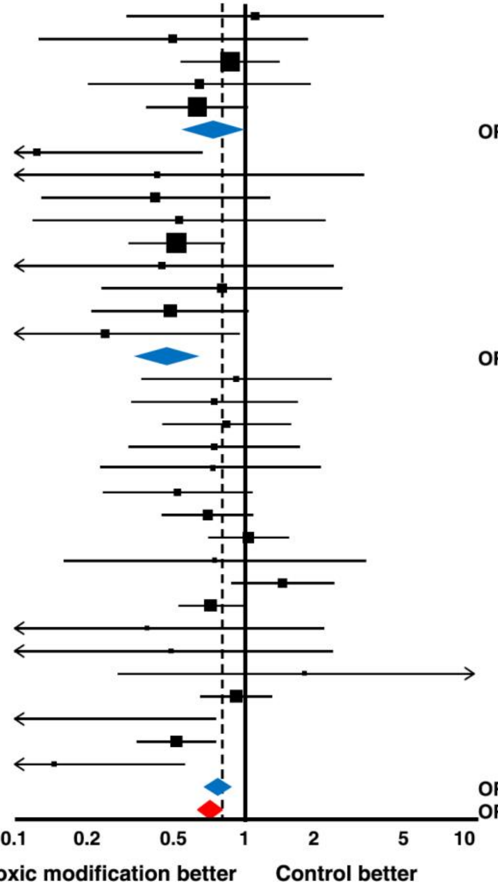
Hypoxic Cell Radiation Sensitizers

- Bioreductive nitroimidazole drugs
  - Misonidazole, etanidazole, nimorazole
- High electron affinity
- Bind in hypoxic tumor regions and **mimic the radio-sensitizing effect of oxygen**
- Numerous phase III studies in HN cancer, cervical cancer and other tumors

Misonidazole

Targeting HN Cancer Hypoxia During RT

	Trial	Modification	Events / Total: Hypoxic modification	Events / Total: Control	Odds ratio and 95% CI	
Normobaric oxygen	1970 Evans 1	O2	7 / 15	11 / 25		
	1975 Evans 2	O2	13 / 20	19 / 24		
	1979 RTOG 70-02	Carbogen	53 / 121	63 / 133		
	2005 Mendenhall	Carbogen	6 / 50	9 / 51		
	2010 ARCON	Carb+Nic	32 / 171	47 / 174		
	Subtotal (Normobaric oxygen)		**111 / 377**	**149 / 407**	**OR: 0.73 (0.53-1.00)**	**p=0.05**
Hyperbaric oxygen	1968 van den Brenk	HBO	5 / 17	10 / 13		
	1971 Tobin 1971	HBO	5 / 9	6 / 8		
	1973 Chang 1973	HBO	8 / 26	13 / 25		
	1973 Shigamatsu	HBO	8 / 15	11 / 16		
	1977 MRC 1.trial	HBO	51 / 125	87 / 151		
	1979 MRC 3.trial	HBO	3 / 9	8 / 15		
	1979 Sause	HBO	8 / 21	10 / 23		
	1986 MRC 2.trial	HBO	21 / 53	29 / 50		
	1999 Haffty	HBO	13 / 23	21 / 25		
	Subtotal (Hyperbaric oxygen)		**122 / 298**	**195 / 326**	**OR: 0.46 (0.33-0.64)**	**p<0.001**
Hypoxic sensitizer	1982 Sealy 1	MISO	11 / 50	11 / 47		
	1983 Brunin	MISO	15 / 51	18 / 50		
	1984 MRC 10 fx	MISO	51 / 82	53 / 80		
	1984 MRC 20 fx	MISO	25 / 43	30 / 46		
	1984 Panis	MISO	14 / 26	16 / 26		
	1986 Sealy 2	HBO/MISO	34 / 60	46 / 64		
	1986 EORTC 228111	MISO	103 / 167	114 / 163		
	1987 European trial	ETA	94 / 187	92 / 187		
	1987 IAEA study	Ornidazole	13 / 18	14 / 18		
	1987 RTOG 79-15	MISO	113 / 147	104 / 150		
	1989 Dahanca 2	MISO	182 / 328	187 / 294		
	1989 RTOG 79-04	MISO	16 / 21	17 / 19		
	1989 Galecki	Metro	3 / 18	5 / 17		
	1992 Giaux	MISO	28 / 30	23 / 26		
	1995 RTOG 85-27	ETA	154 / 252	159 / 252		
	1996 Huilgol	AK-2123	2 / 9	7 / 9		
	1998 Dahanca 5	NIM	104 / 219	125 / 195		
	2006 Ullal	AK-2123	8 / 23	18 / 23		
	Subtotal (Hypoxic sensitizer)		**970 / 1731**	**1039 / 1666**	**OR: 0.76 (0.66-0.88)**	**p<0.001**
All trials with hypoxic modification			**1203 / 2406**	**1383/ 2399**	**OR: 0.71 (0.63-0.80)**	**p<0.001**

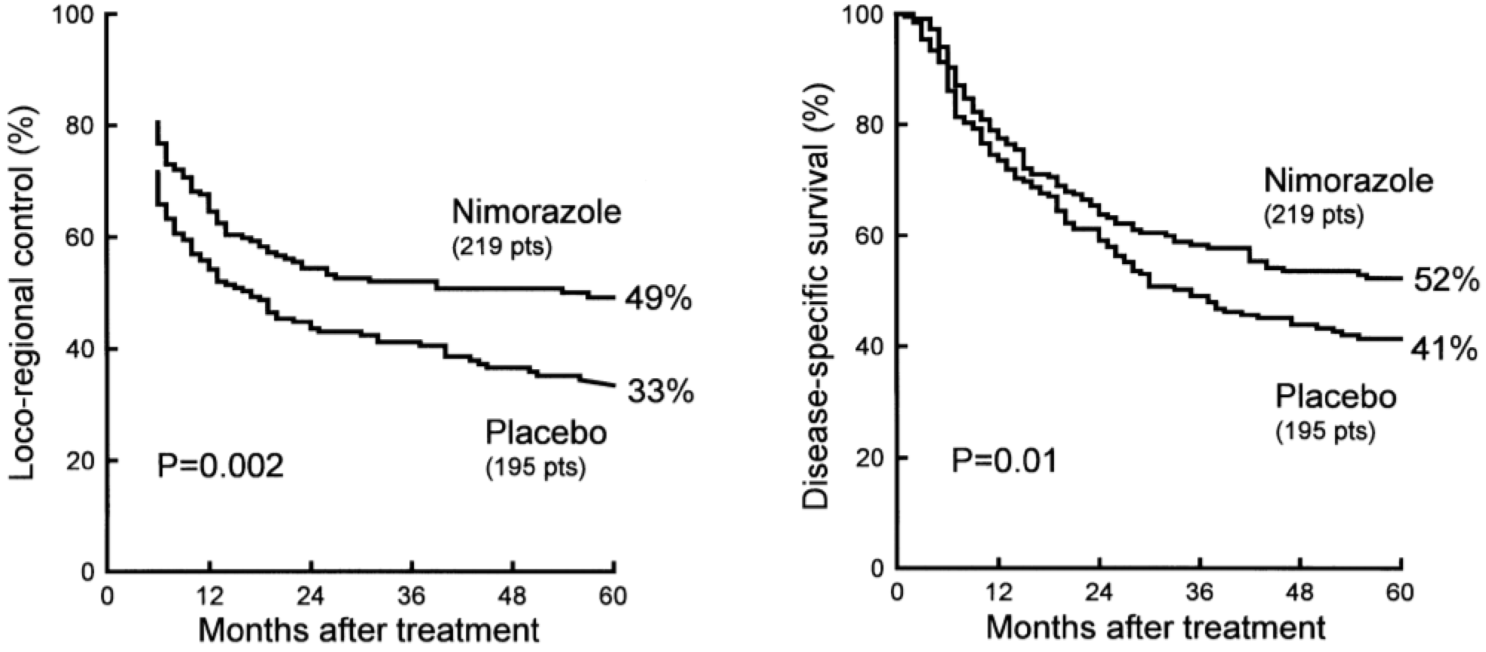


Test for heterogeneity: p = 0.12

Overgaard et al, Radiother Oncol 2011

Hypoxic Cell Sensitization in HN Cancer

DAHANCA 5 (*1980's*):
422 patients randomized to RT + Nimorazole or placebo
Nimorazole ↑ locoregional control & disease-specific survival



Led to 2 validation studies (EORTC 1219 and NIMRAD)

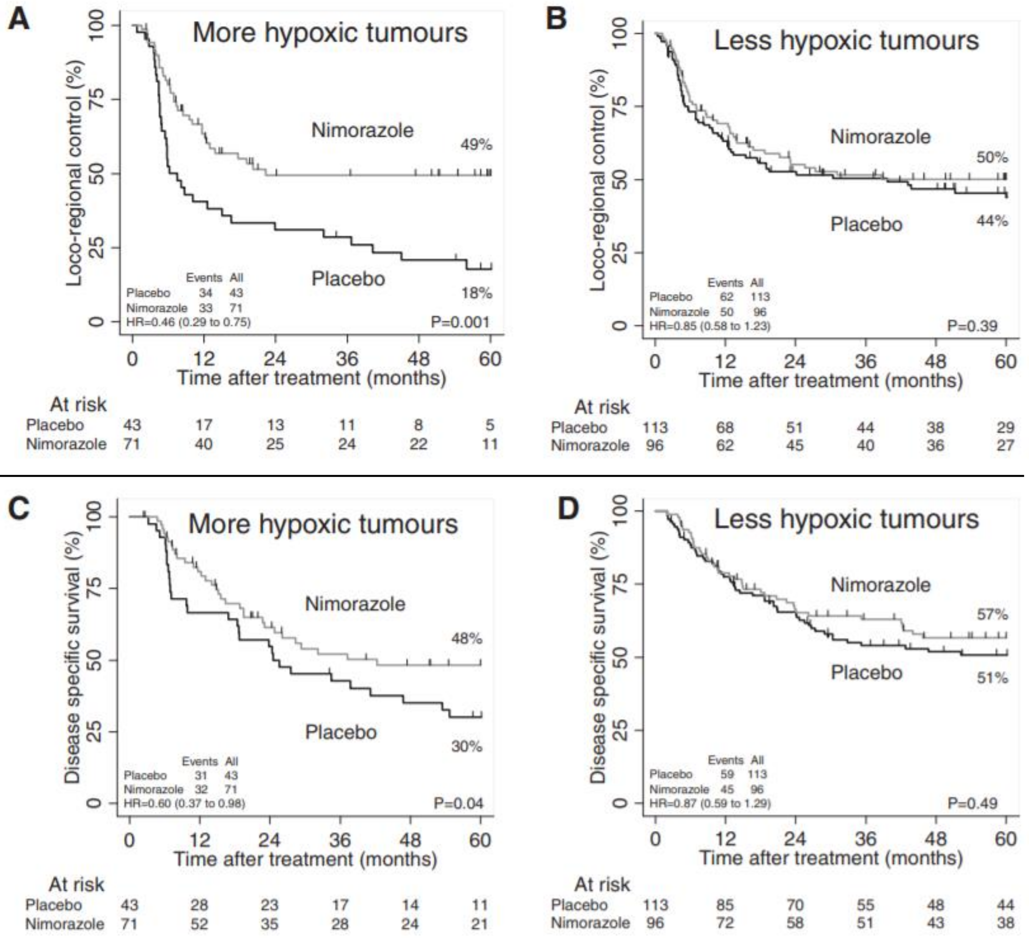
Overgaard et al, Radiother Oncol 1998

Patient selection is crucial …

Benefit of Nimorazole only in patients with hypoxic tumors (15 gene hypoxia signature)

Locoregional control

Disease-specific survival



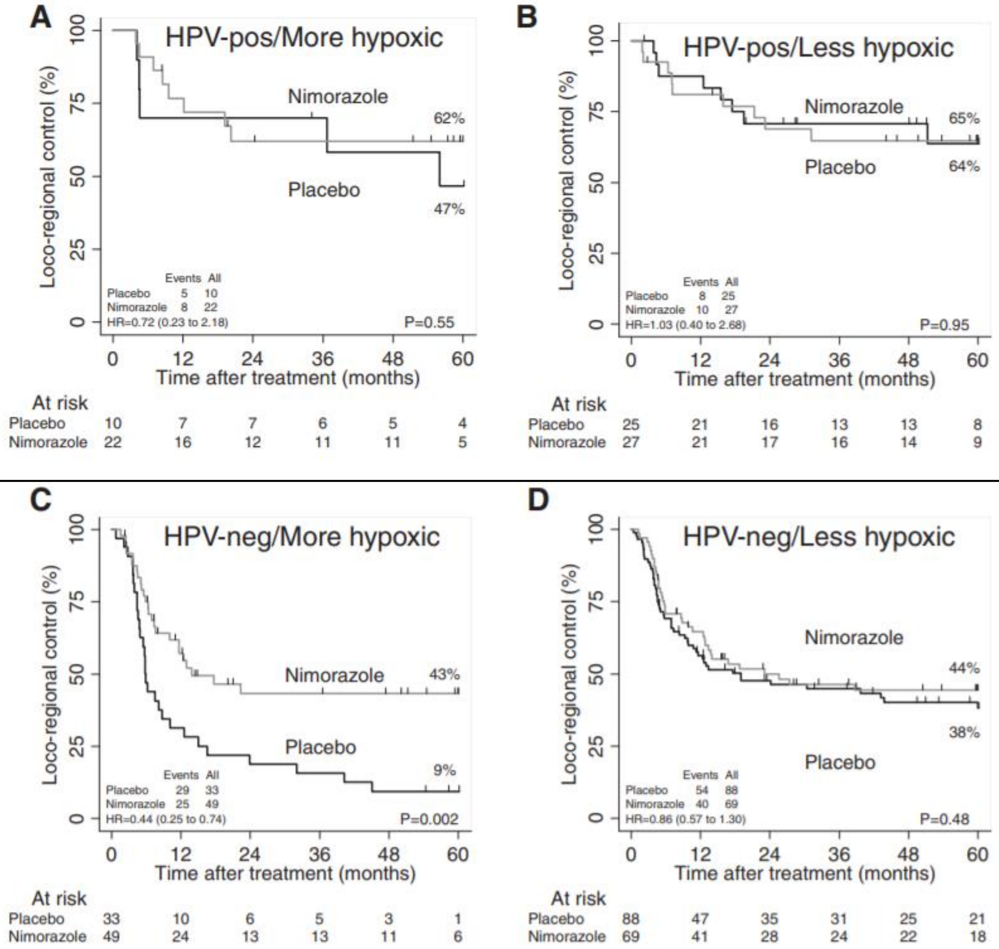
Toustrup et al, Radiother Oncol 2012

Hypoxia is not always important …

Benefit of Nimorazole only in patients with hypoxic <u>and</u> HPV negative tumors (15 gene hypoxia signature)

HPV +

HPV -

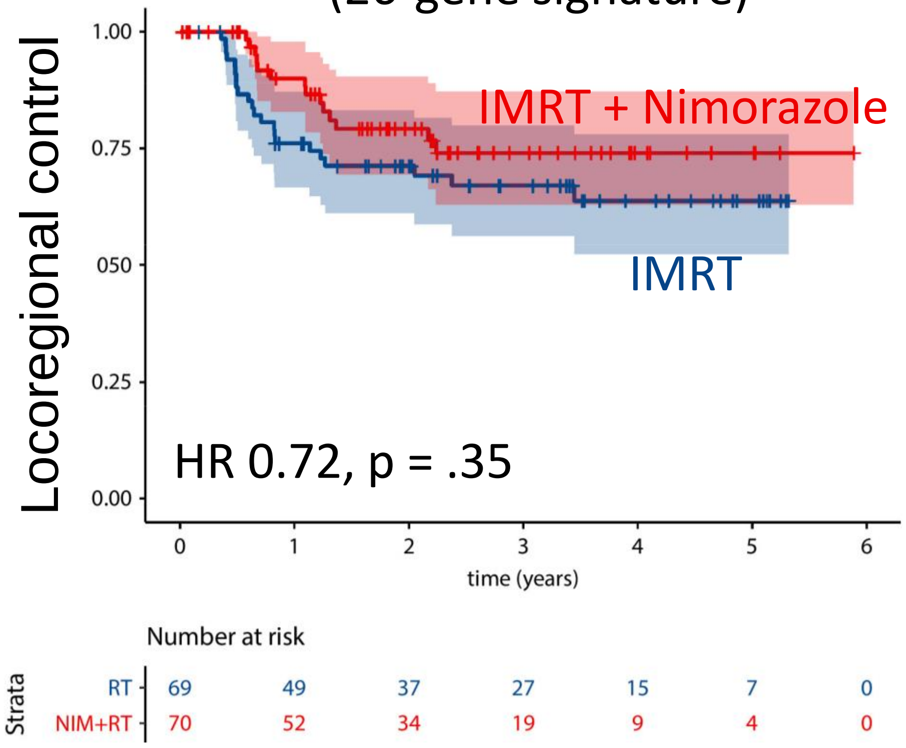


Toustrup et al, Radiother Oncol 2012

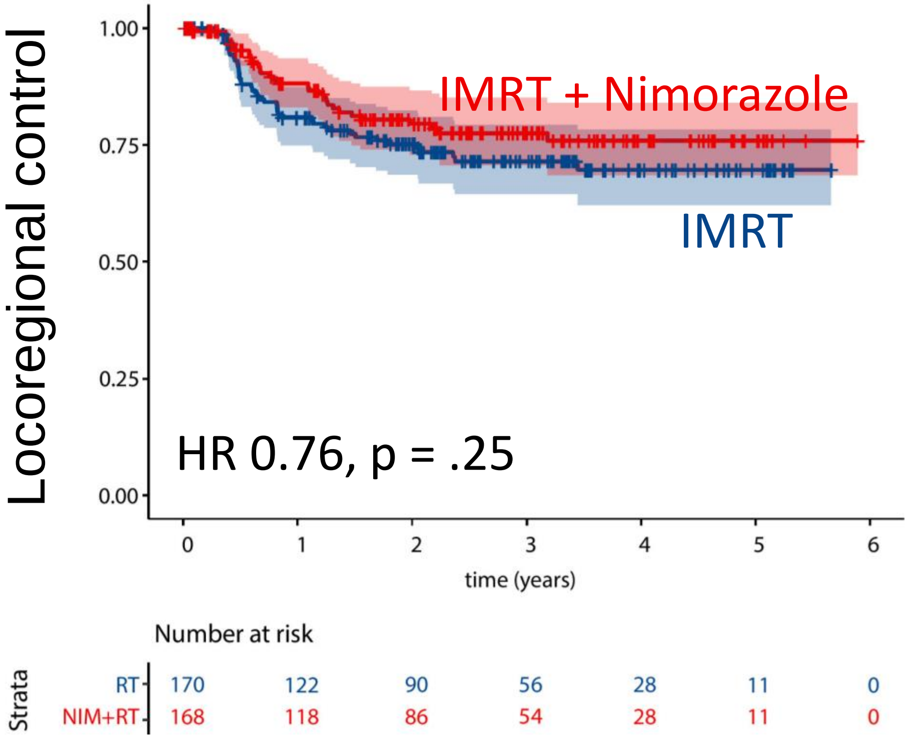
NIMRAD – older/less fit HN patients

- 340 patients randomized to IMRT + Nimorazole or placebo
- **Nimorazole did not improve locoregional control**
  - Post hoc analysis: no benefit in HPV –ve HNSCC

Hypoxia-High Group
(26-gene signature)



All Patients

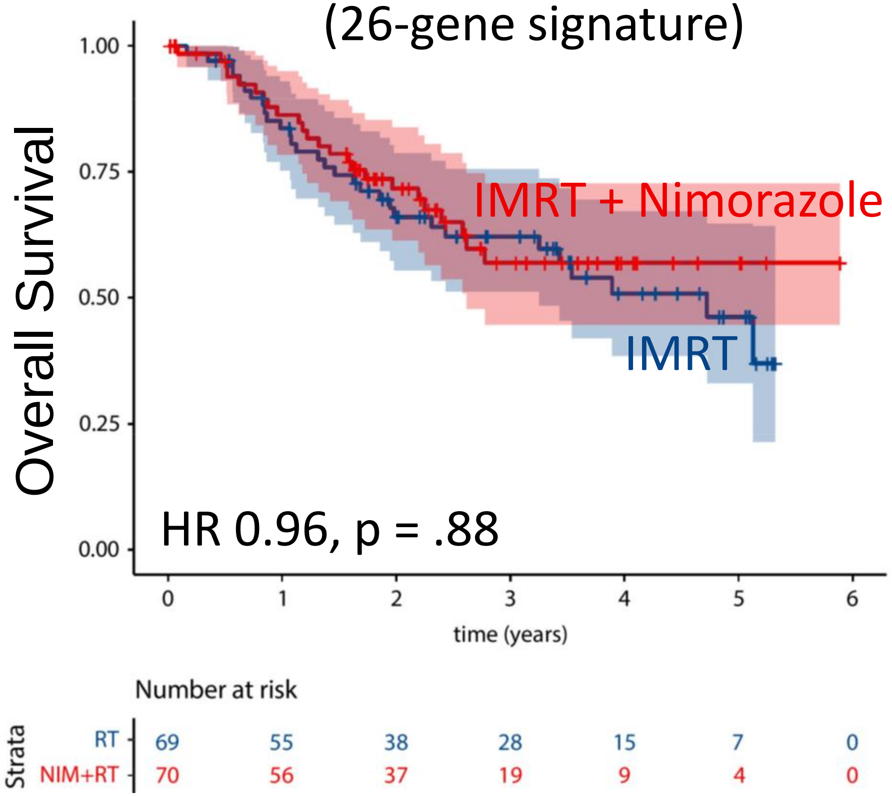


Thomson et al, IJROBP 2023

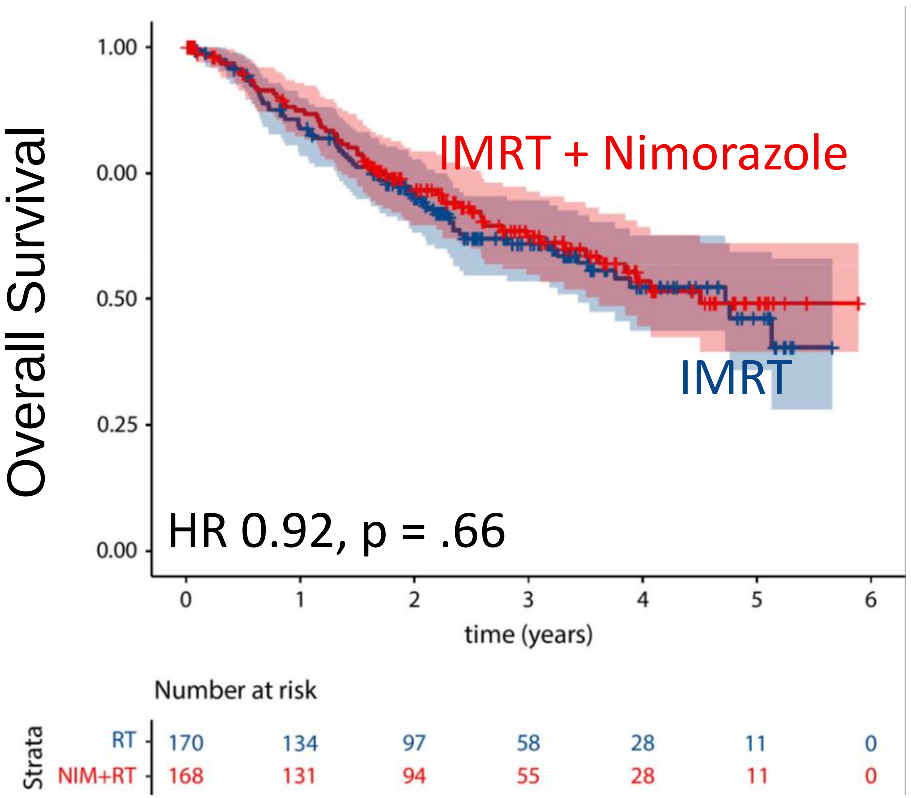
NIMRAD – older/less fit HN patients

- Nimorazole did not improve overall survival
- Nimorazole caused more acute nausea

Hypoxia-High Group
(26-gene signature)



All Patients



Radiation Oncology UNIVERSITY OF TORONTO | Temerty Medicine

Thomson et al, IJROBP 2023

4. Hypoxic Cell Cytotoxins

Hypoxic Cell Cytotoxins

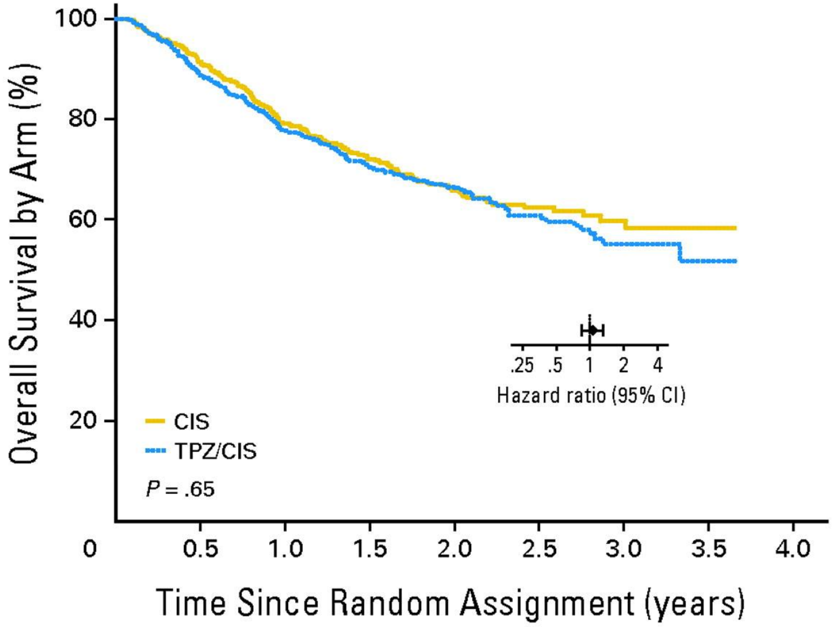
- Bioreductive cytotoxic drugs that are **activated under hypoxic conditions**
- DNA damage leading to cell death
- Tirapazamine, TH-302
- Complement the cell killing effects of RT
- Potentiate cisplatin cell killing
- Bystander effect
- Promising results in phase I/II clinical trials

Tirapazamine in HN Cancer (Phase III RCT)

HeadSTART (*2000's*):

861 patients randomized to RTCT ± Tirapazamine

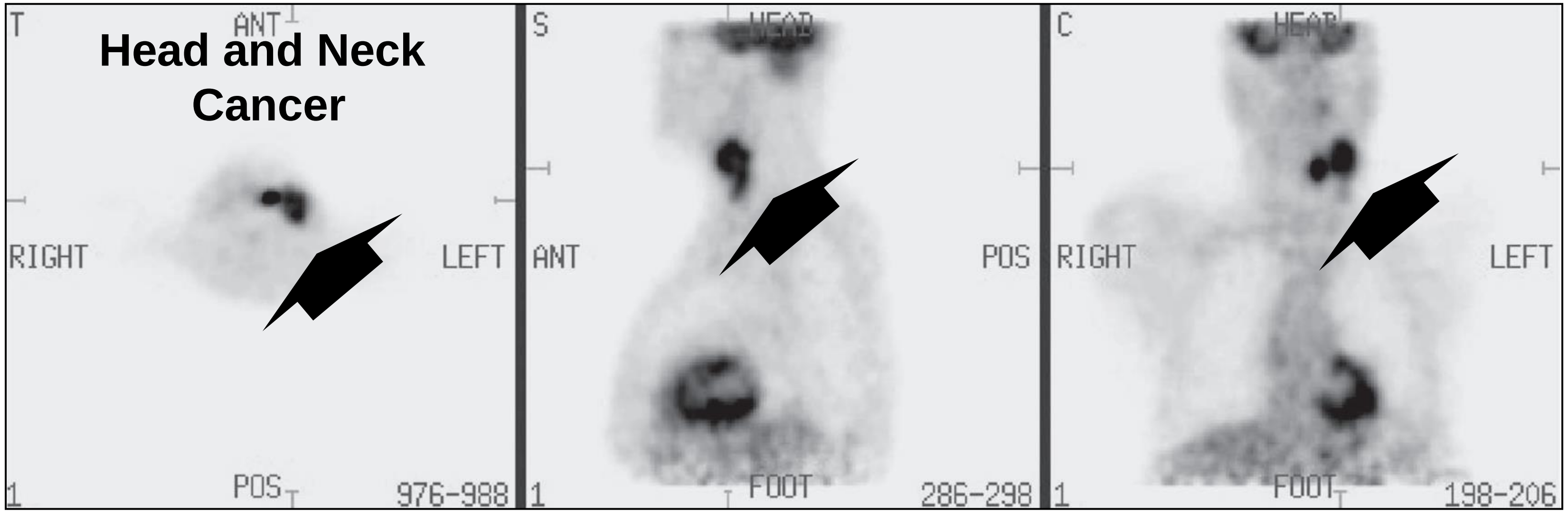
No benefit of targeting hypoxia



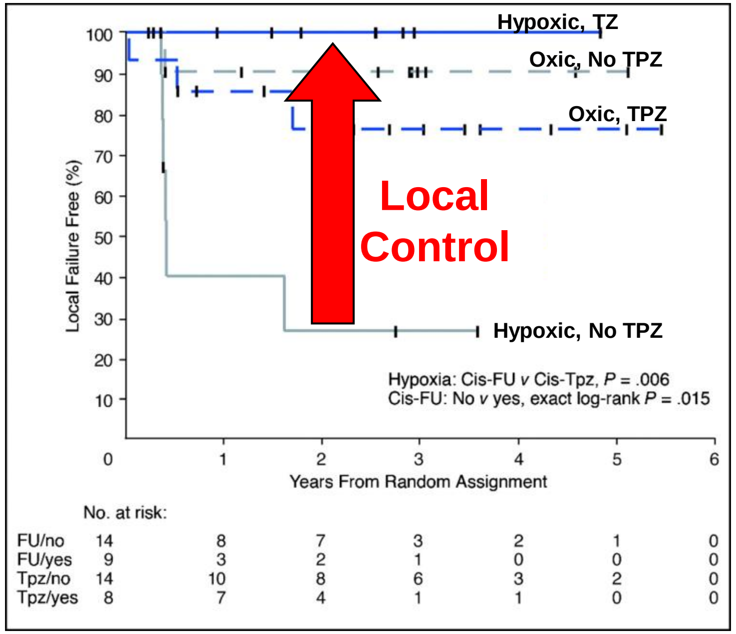
No. at risk									
CIS	428	389	332	294	248	91	45	6	0
TPZ/CIS	425	374	326	291	252	98	42	7	0

Rischin et al, JCO 2010

Patient selection is crucial …

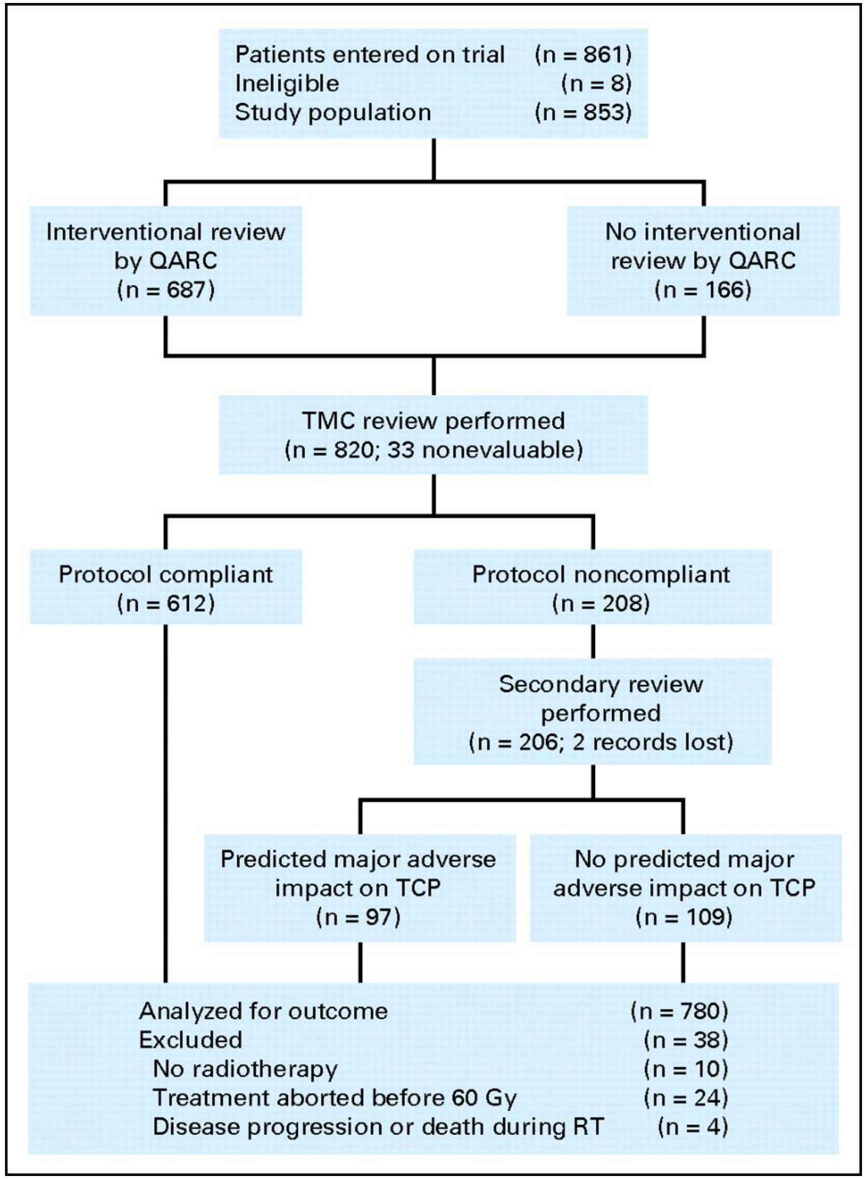


- H&N cancer
- RT with or without TPZ
- Benefit of TPZ only in patients with hypoxic tumors identified using PET imaging



Rischin et al, JCO 2006

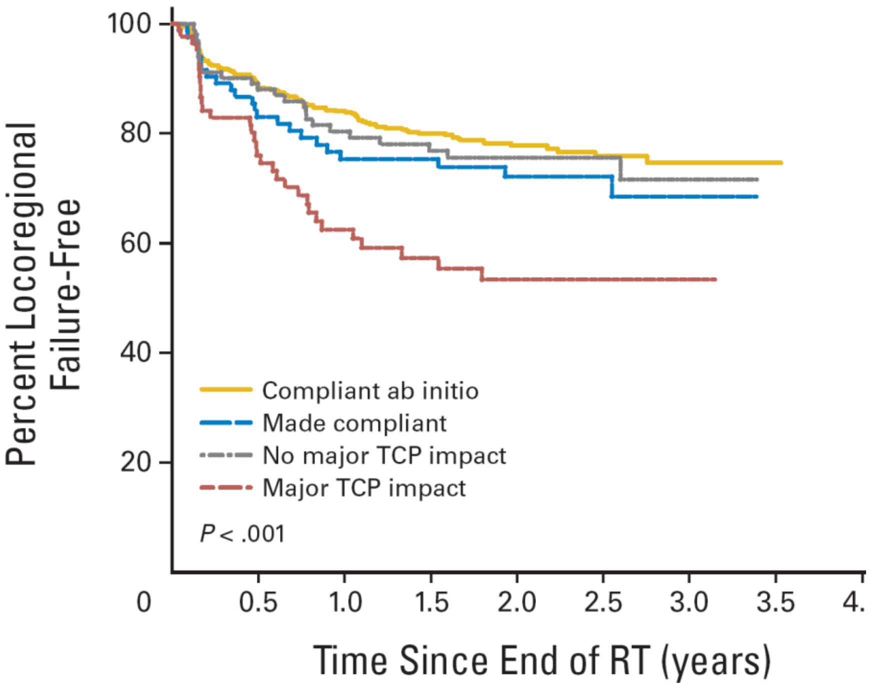
The Importance of High Quality Radiotherapy

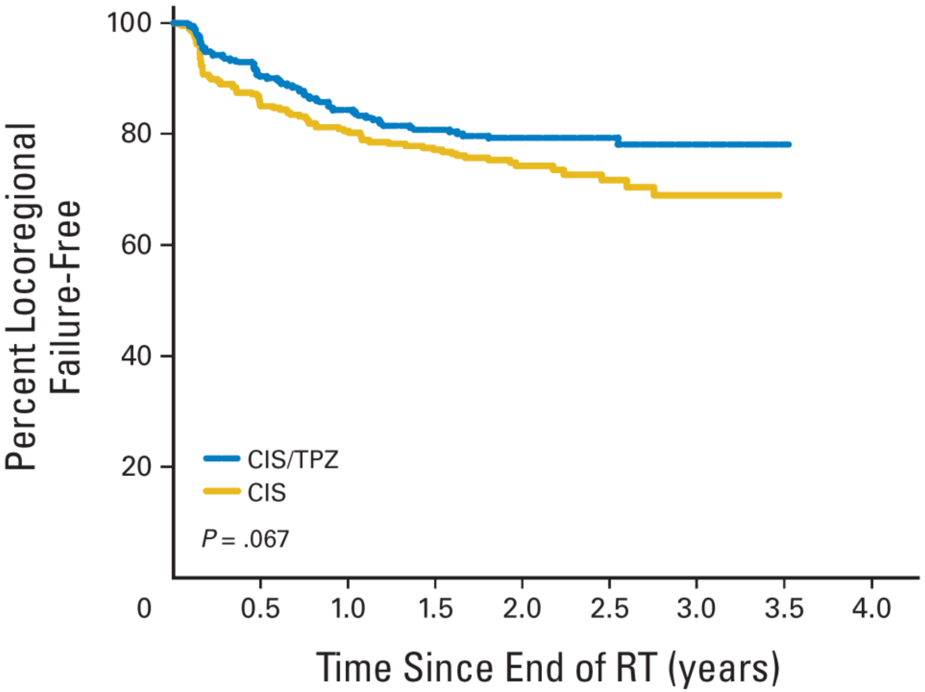


Peters et al, JCO 2010

The Importance of High Quality Radiotherapy

Technically poor radiation treatment can mask biology





Effect of TPZ with good RT

Effect of radiotherapy quality
on tumor control probability (TCP)

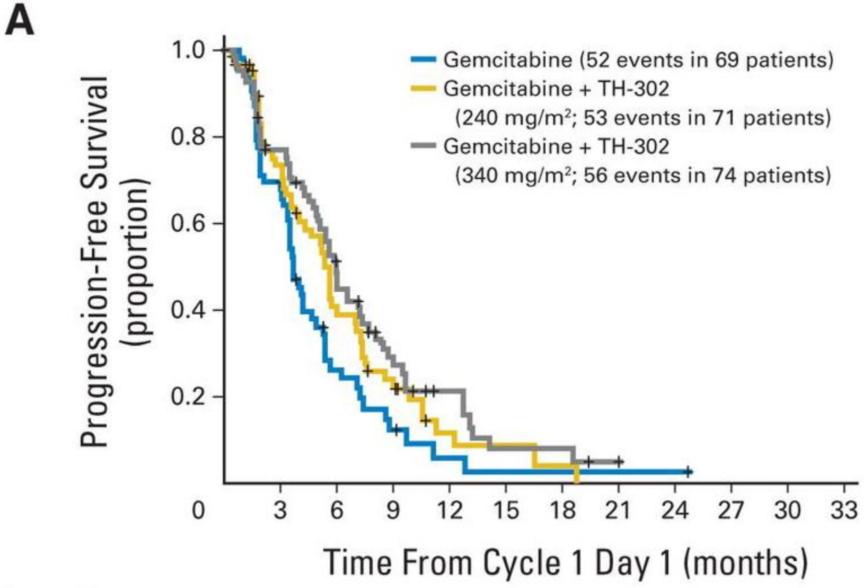
Trend in favor of improved
tumor control

Peters et al, JCO 2010

TH-302 in Pancreatic Cancer (Phase II)

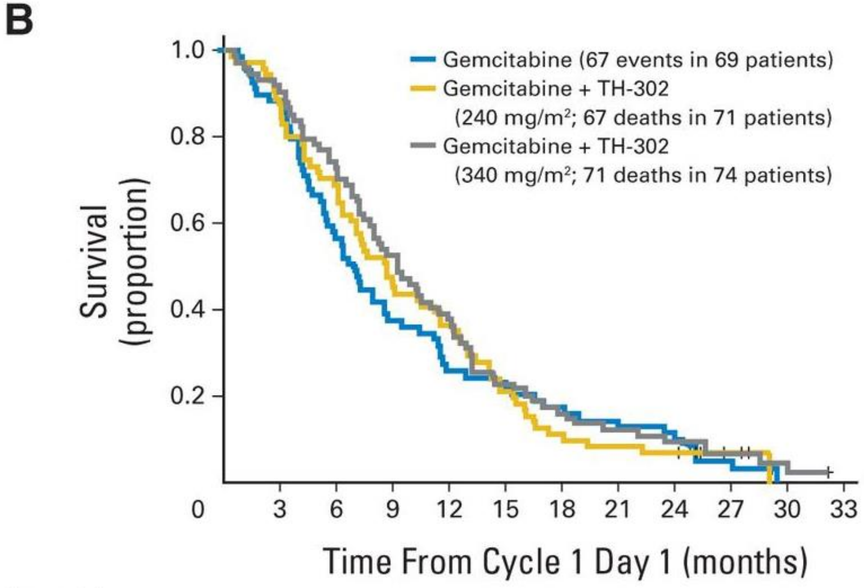
TH-302: Hypoxia activated cytotoxin

PFS was longer with Gem + TH302 Compared to Gem (5.6 vs 3.6 mo)



No. at risk											
Gemcitabine	69	41	13	5	3	1	1	1	1	0	0
Gemcitabine + T240	71	47	22	11	5	3	2	0	0	0	0
Gemcitabine + T340	74	53	33	16	10	4	4	0	0	0	0

No significant difference in OS



No. at risk											
Gemcitabine	69	62	40	27	19	17	13	10	9	4	0
Gemcitabine + T240	71	64	51	34	27	16	9	7	5	2	0
Gemcitabine + T340	74	68	55	40	29	18	13	10	8	5	1

Phase III preliminary results presented at ASCO 2016: OS 8.7 vs 7.6 months, p = 0.059

Borad et al, JCO 2015

5. Metabolic Targeting

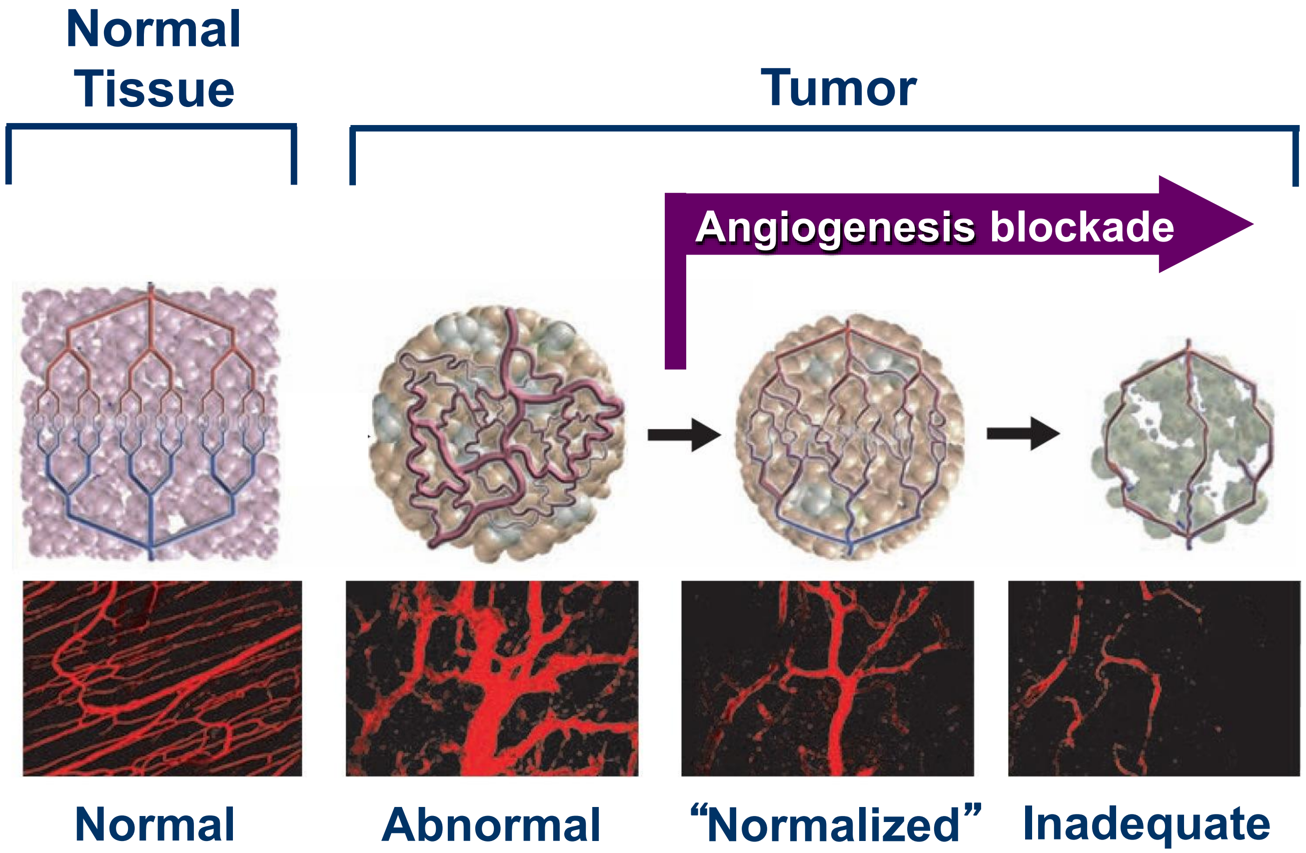
Targeting the Tumor Vasculature

Rationale for targeting the tumor vasculature to improve radiation treatment response:

- Hypoxia and angiogenesis are tightly-coupled aspects of the tumor microenvironment.
- Hypoxia and angiogenesis are important determinants of outcome in patients treated with radiotherapy.
- Targeting angiogenesis may improve RT response by:
  - Altering the balance between oxygen supply and consumption leading to reduced hypoxia.
  - Offsetting RT-induced increases in HIF and VEGF as causes of vascular radioresistance.

Vascular ‘Normalization’

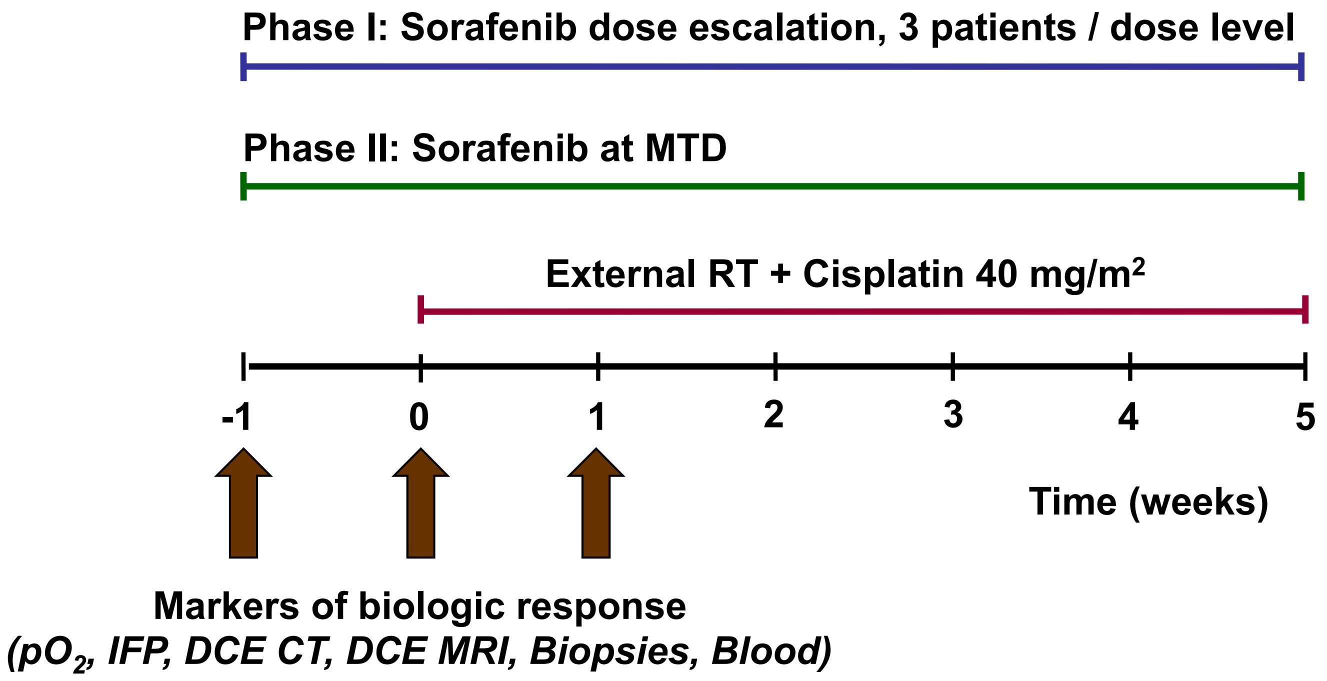
Probably relevant only in very specific circumstances



Modified from Jain, 2005

Targeting Angiogenesis in Cervical Cancer

PMH Phase I-II study of standard RTCT + sorafenib in locally advanced cervical cancer

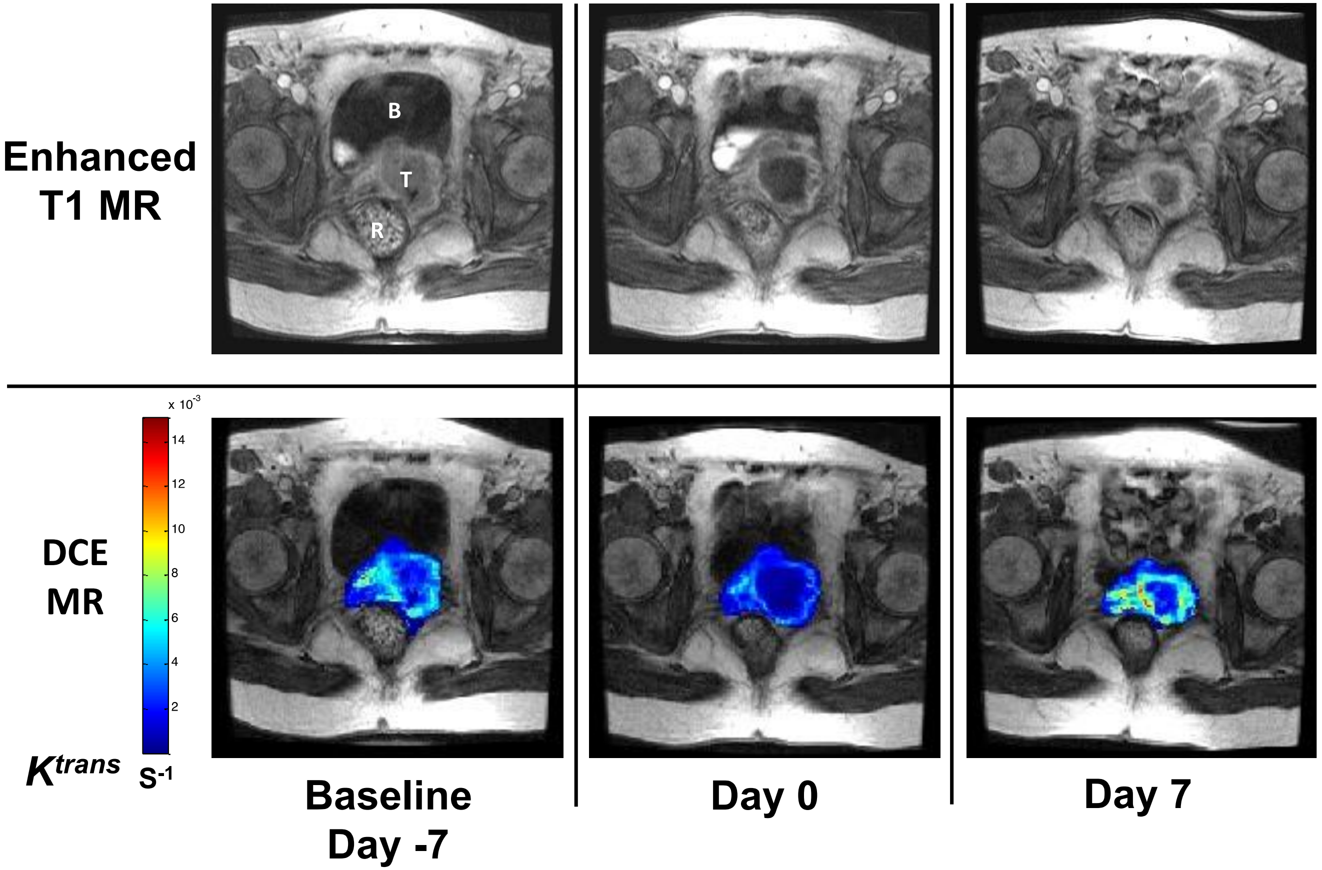


Sorafenib – oral inhibitor of VEGF, PDGF, Raf

Milosevic et al, IJROBP 2016

Sorafenib Increased Tumor Hypoxia

Sorafenib reduced tumor perfusion and increased hypoxia – study closed prematurely

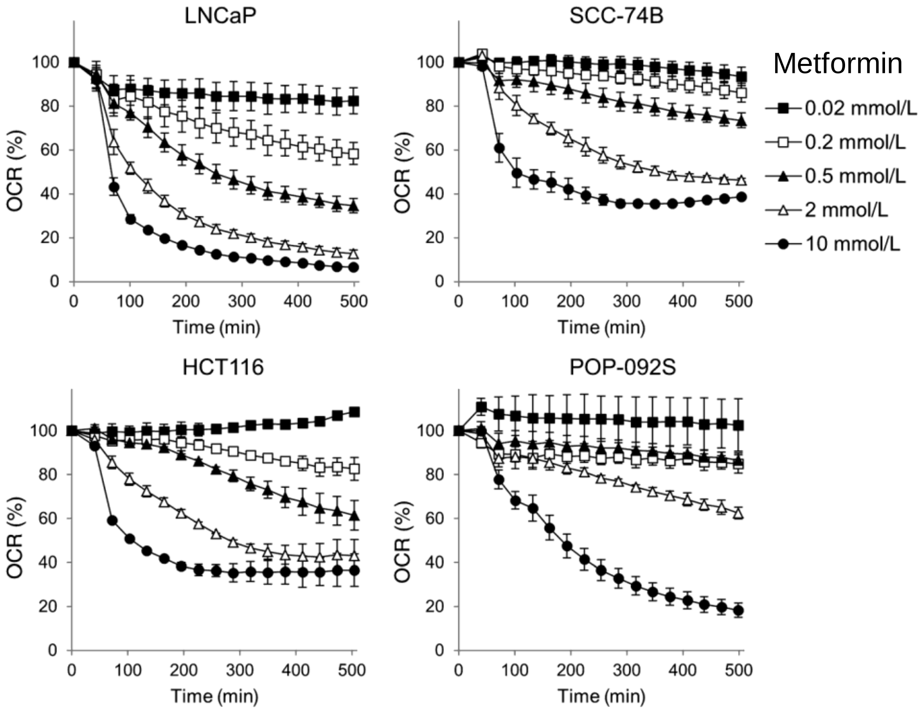


Milosevic et al, IJROBP 2016

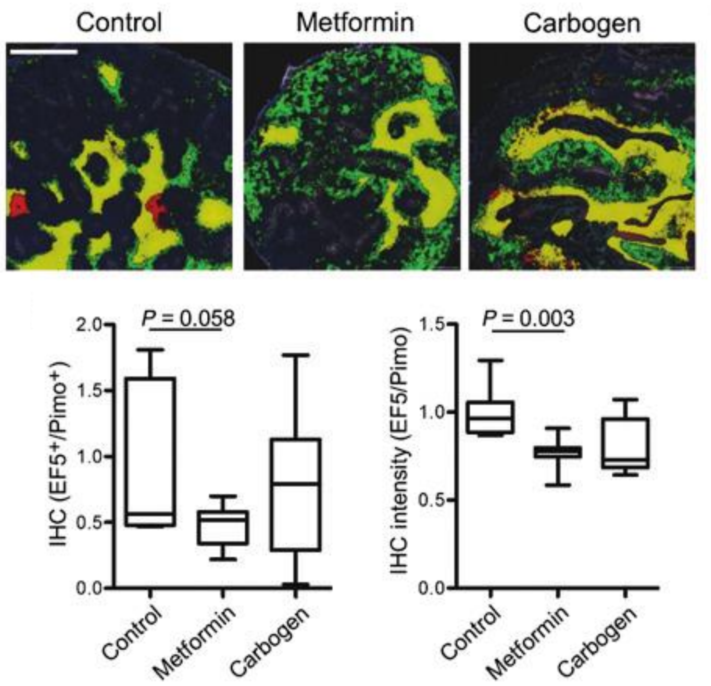
Targeting Cellular Oxygen Consumption

Metformin reduces oxygen consumption and hypoxia

Oxygen consumption



Hypoxia (HCT116)



Zannella and Kortizinsky, Clin Cancer Res 2013

Phase II Trial : Chemoradiation ± Metformin in Cervical Cancer

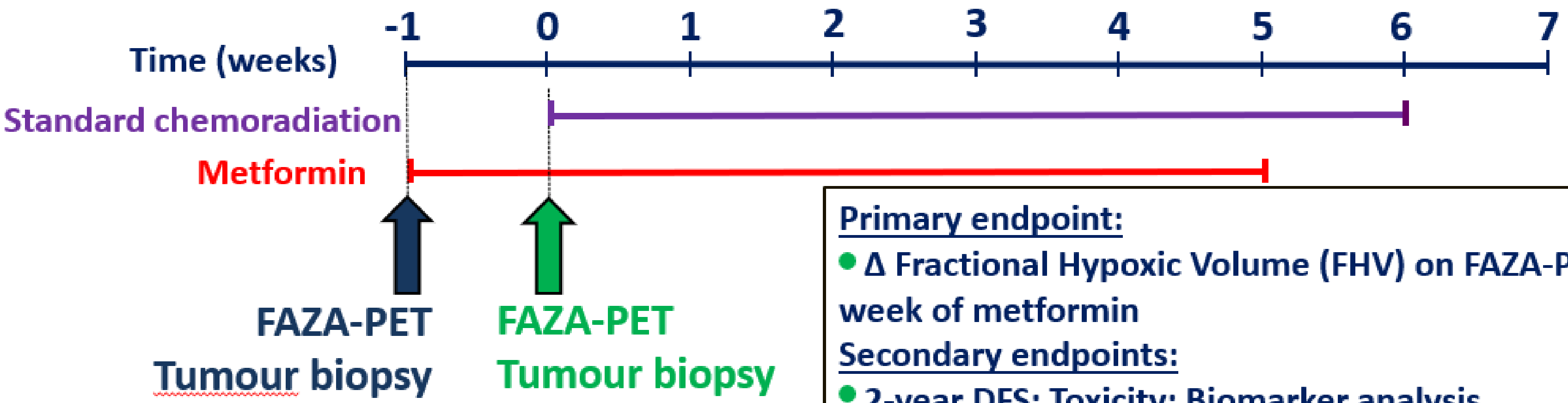
FIGO stage IB – IVA squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the cervix **with FAZA uptake (hypoxic tumor)**

N = 48 planned

RANDOMIZE

2 → Standard chemoradiation + **METFORMIN** (starting 1 week prior to chemoradiation: 850mg QD x 3 days then 850mg BID until the end of external radiation)

1 → Standard chemoradiation



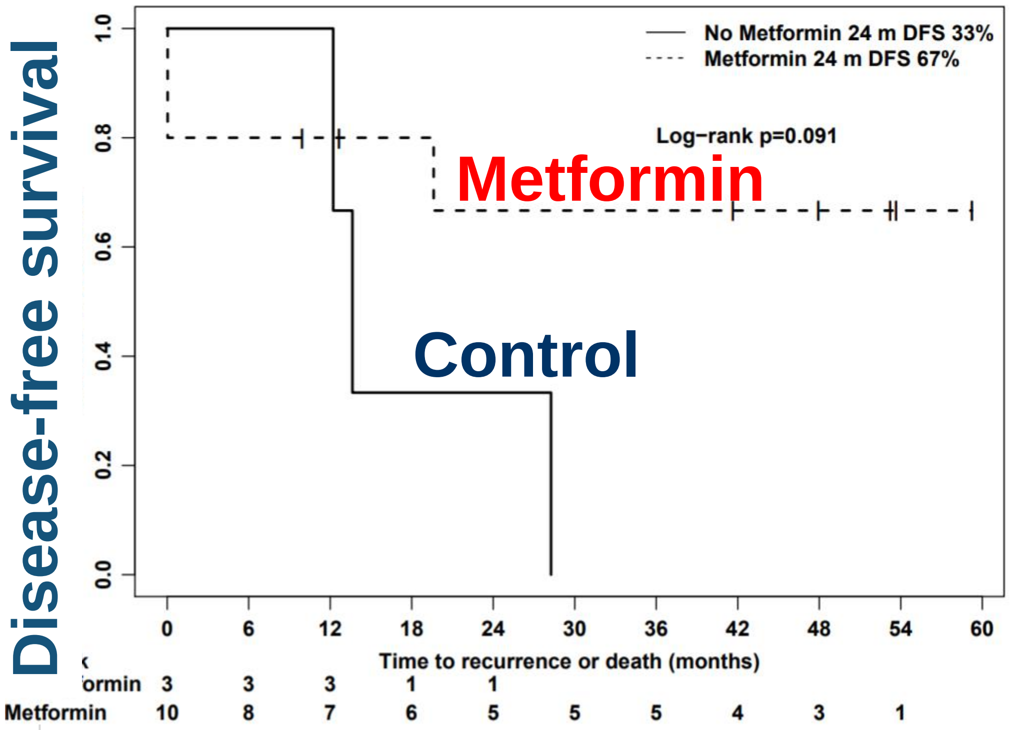
Primary endpoint:
- **Δ Fractional Hypoxic Volume (FHV) on FAZA-PET after 1 week of metformin**

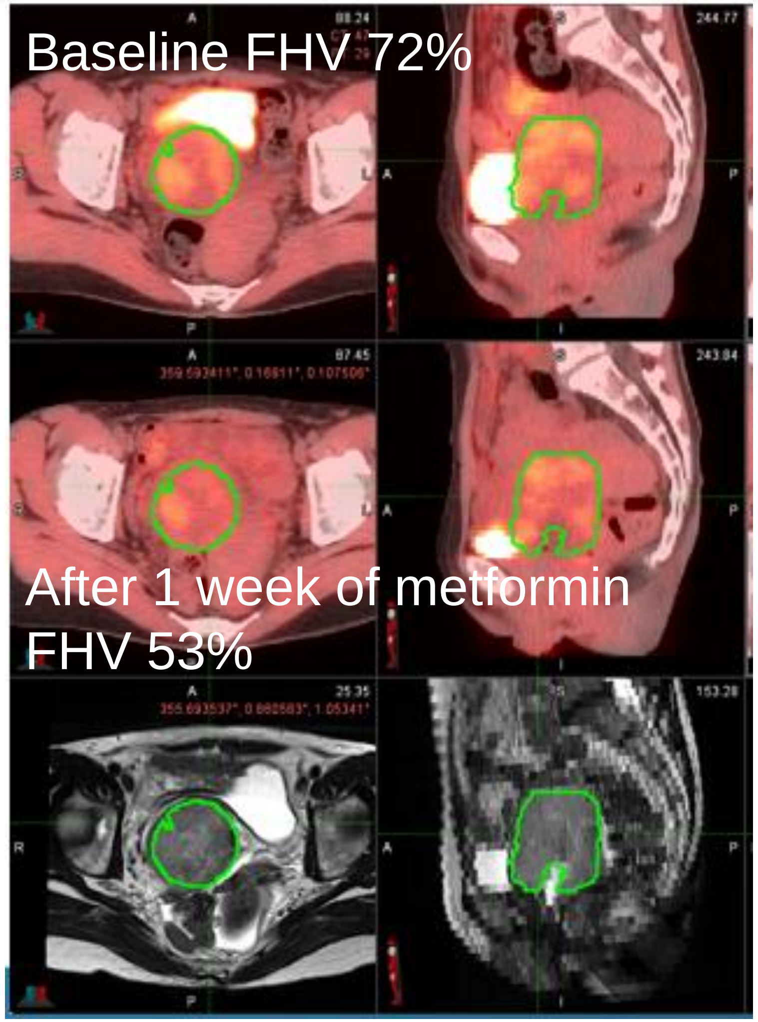
Secondary endpoints:
- **2-year DFS; Toxicity; Biomarker analysis**

Han et al, Clin Cancer Res 2022

Phase II Trial : Chemoradiation ± Metformin in Cervical Cancer

	Average		
	Baseline FHV	1-week FHV	Difference (1wk – baseline)
Metformin	44.4%	34.2%	↓ 10.2%
Control	29.1%	33.8%	↑ 4.7%





Han et al, Clin Cancer Res 2022

Maybe its not that complicated …

Physical Activity and Survival After Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study

Stacey A. Kenfield, Meir J. Stampfer, Edward Giovannucci, and June M. Chan

J Clin Oncol 29:726-732. © 2011

Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model

Danielle J. McCullough,[1] Linda M.-D. Nguyen,[1] Dietmar W. Siemann,[2,3] and Bradley J. Behnke[1,3]

J Appl Physiol 115: 1846–1854, 2013.

Modulation of Blood Flow, Hypoxia, and Vascular Function in Orthotopic Prostate Tumors During Exercise

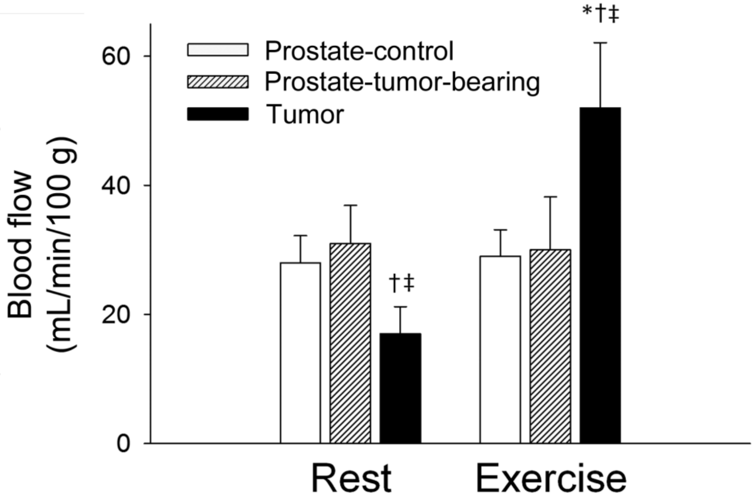
Danielle J. McCullough, John N. Stabley, Dietmar W. Siemann, Bradley J. Behnke

JNCI J Natl Cancer Inst (2014) 106(4): dju036 doi:10.1093/jnci/dju036

Physical Exercise and Tumor Hypoxia

Acute mild-moderate exercise reduces tumor hypoxia

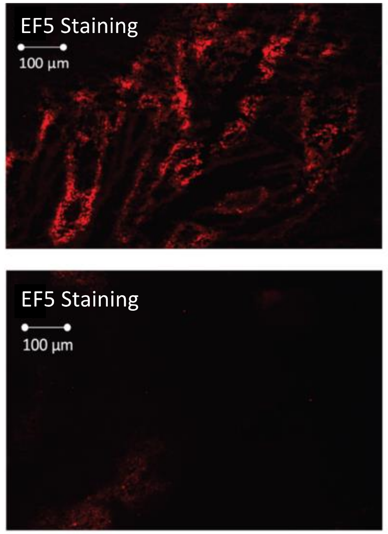
- Dunning R-3327 prostate cancer growing in the rat prostate gland
- Treadmill exercise for 5 min

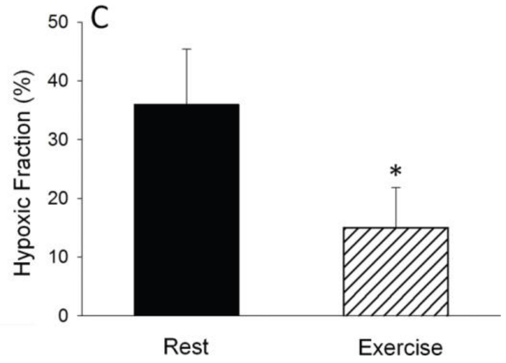


M. Milosevic, 2010

Hypoxia Control

Hypoxia Exercise





McCullough et al, JNCI 2014

Targeting Hypoxia in Patients

1. RT dose escalation
   – "Dose painting"
2. Improved oxygen supply
   – Treat anemia, hyperbaric O_2, carbogen, nicotinamide
3. Hypoxic cell radiation sensitization (mimicks radiosensitizing properties of oxygen)
   – Misonidazole, pimonidazole, nimorazole, etanidazole
4. Hypoxic cell cytotoxins (activated under hypoxic conditions)
   – Tirapazamine, TH-302
5. Metabolic targeting
   - Angiogenesis, O_2 consumption (Metformin), exercise

Objectives

- Identify ways of measuring hypoxia in human tumors.
- Describe the relationship between hypoxia in human tumors and clinical outcome.
- Understand ways of targeting hypoxia in human tumors and opportunities for future research and clinical development.

Summary

- Hypoxia-targeted treatment can improve clinical outcomes in patients receiving radiotherapy.
- Currently available hypoxia-targeted treatments have not permeated routine clinical practice.
- Pre-treatment selection of patients with hypoxic tumors who can benefit from hypoxia-targeted treatments is essential.
- Effective, well tolerated and easily administered hypoxia-targeted treatments are needed.