Targeting Tumor Hypoxia in Patients

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Adapted from Dr. M Milosevic

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:

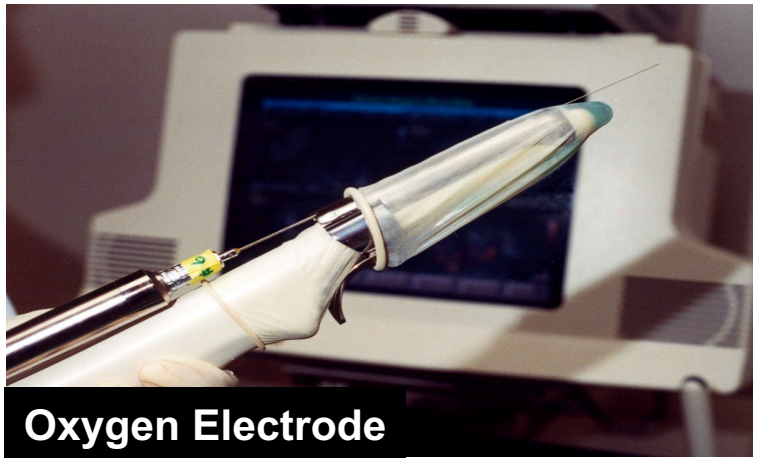
- Activates cell survival pathways
- Maintains cancer stem cells
- Alters DNA repair and contributes to genomic instability
- Selects for hypoxia tolerant, clinically aggressive cell populations
- Increases metastatic potential
- Contributes to treatment resistance

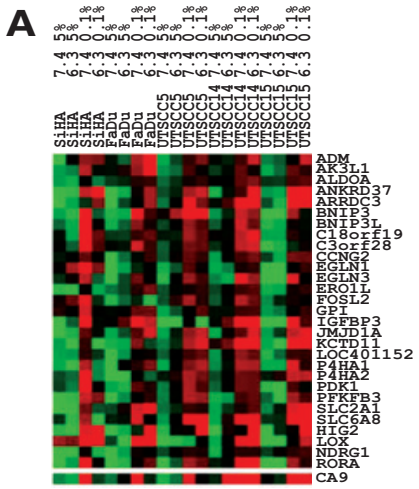
Clinical Implications of Hypoxia

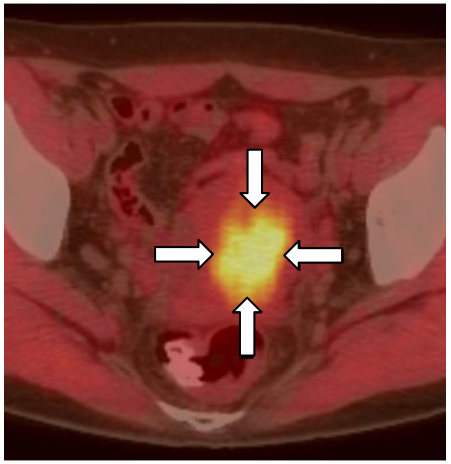
- Most solid human tumors contain hypoxia.
- The extent of hypoxia is highly variable within individual tumors, among patients and over time.
- Tumor hypoxia is associated with poor local control after radiotherapy.
- Tumor hypoxia is associated with aggressive clinical behavior and the development of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

Measuring Hypoxia in Patients

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

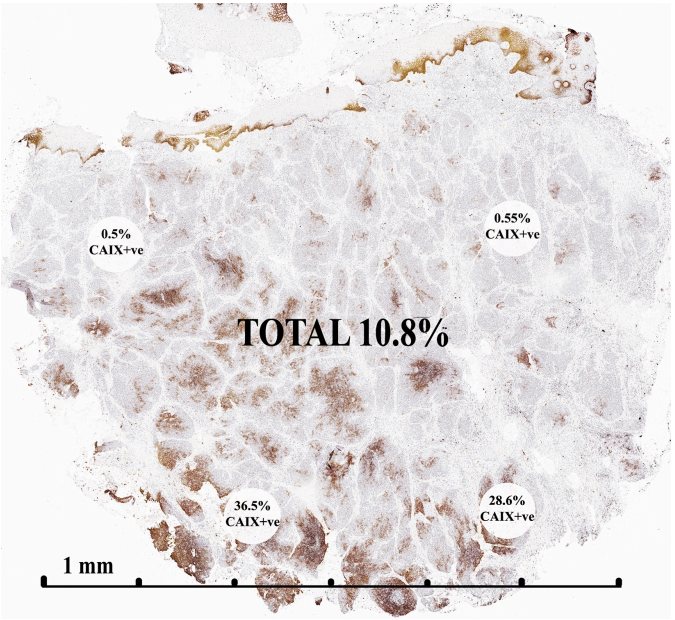






Hypoxia is Heterogeneous

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

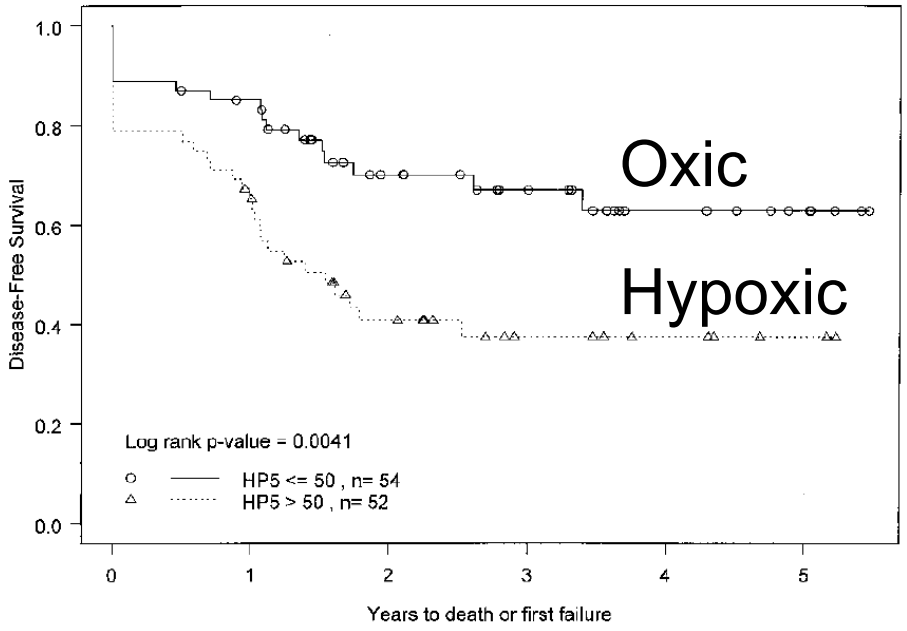


Solutions: Multiple hypoxic markers (gene signatures)
Serial, whole-tumor imaging assessment

Iakovlev and Hedley, 2007

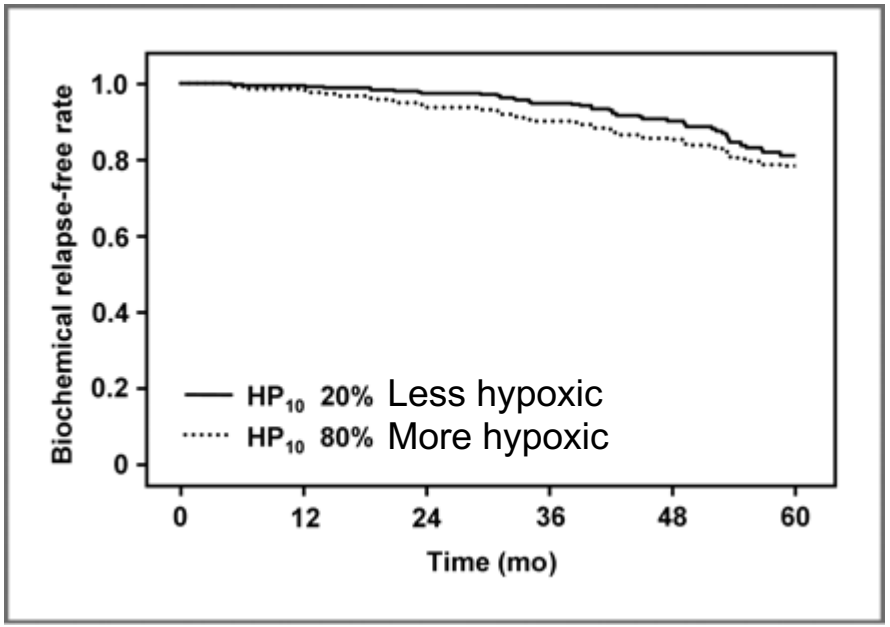
Tumor Hypoxia (pO2 electrode) and Survival

Cervical Cancer



Fyles et al, JCO 2002

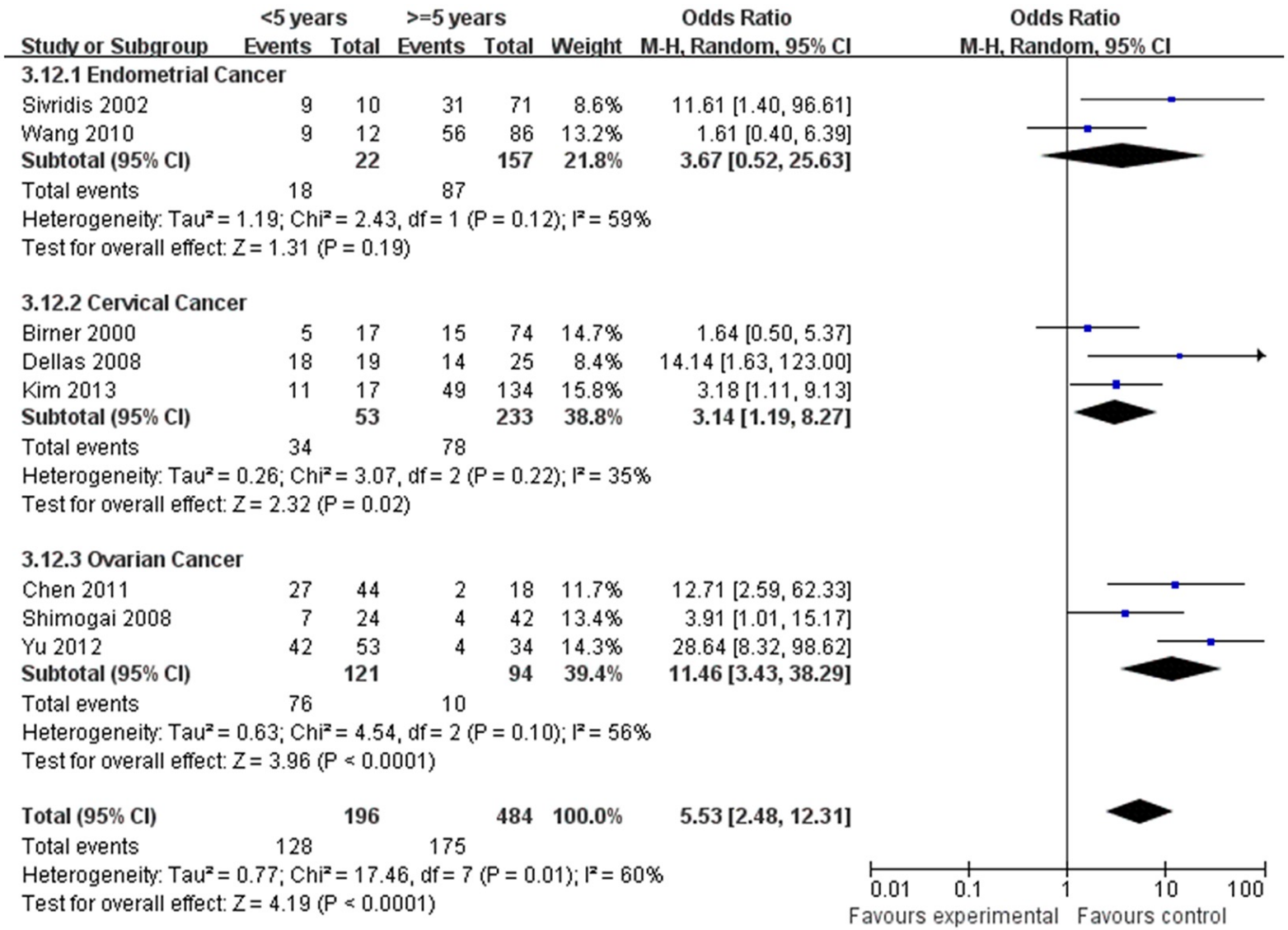
Prostate Cancer



Milosevic et al, Clin Cancer Res 2012

Tumor hypoxia is associated with inferior survival

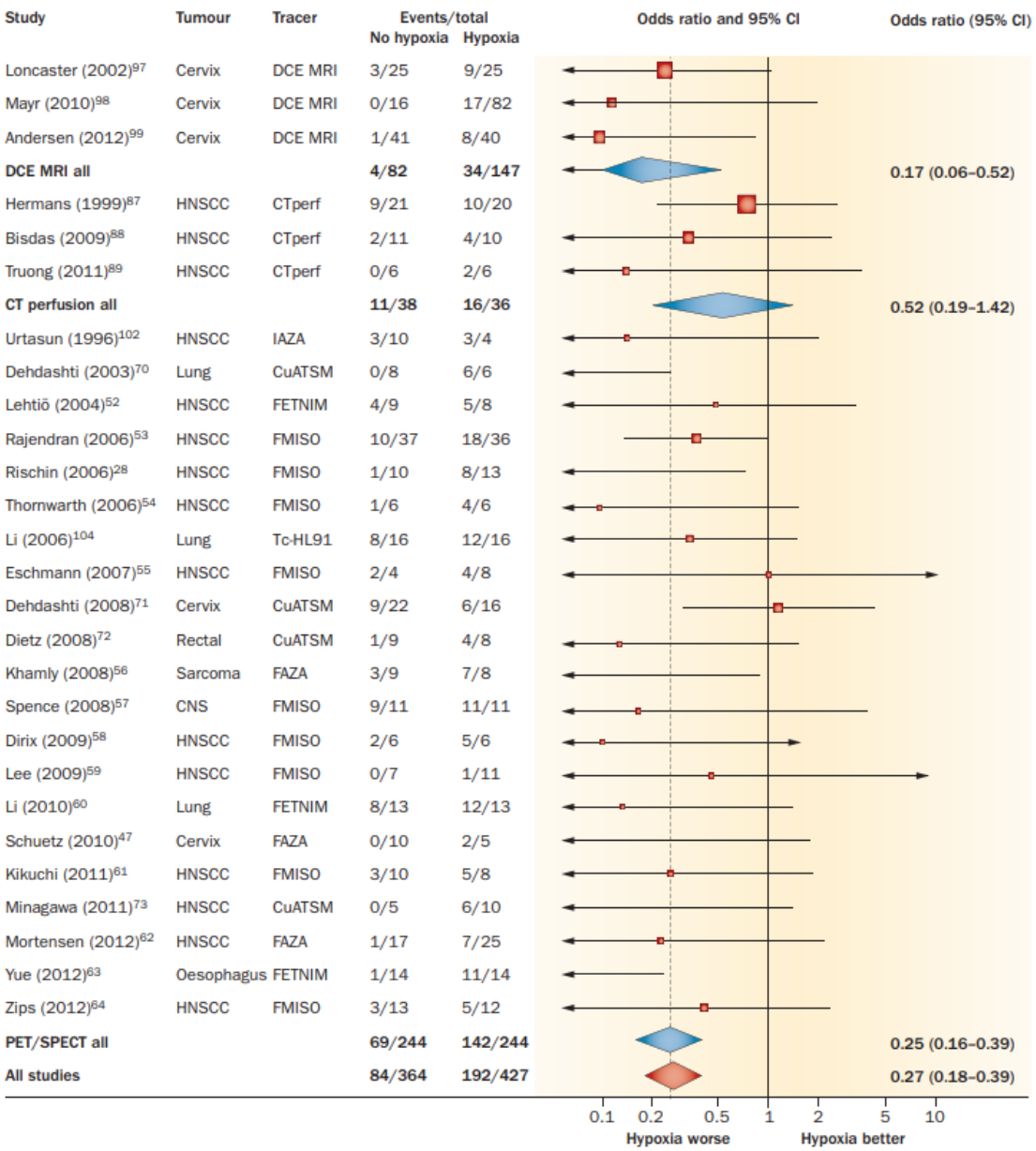
HIF-1α expression is associated with inferior survival



Study or Subgroup	<5 years Events	Total	>=5 years Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.12.1 Endometrial Cancer						
Sivridis 2002	9	10	31	71	8.6%	11.61 [1.40, 96.61]
Wang 2010	9	12	56	86	13.2%	1.61 [0.40, 6.39]
Subtotal (95% CI)		**22**		**157**	**21.8%**	**3.67 [0.52, 25.63]**
Total events	18		87			
Heterogeneity: Tau² = 1.19; Chi² = 2.43, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 1.31 (P = 0.19)						
3.12.2 Cervical Cancer						
Birner 2000	5	17	15	74	14.7%	1.64 [0.50, 5.37]
Dellas 2008	18	19	14	25	8.4%	14.14 [1.63, 123.00]
Kim 2013	11	17	49	134	15.8%	3.18 [1.11, 9.13]
Subtotal (95% CI)		**53**		**233**	**38.8%**	**3.14 [1.19, 8.27]**
Total events	34		78			
Heterogeneity: Tau² = 0.26; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 2.32 (P = 0.02)						
3.12.3 Ovarian Cancer						
Chen 2011	27	44	2	18	11.7%	12.71 [2.59, 62.33]
Shimogai 2008	7	24	4	42	13.4%	3.91 [1.01, 15.17]
Yu 2012	42	53	4	34	14.3%	28.64 [8.32, 98.62]
Subtotal (95% CI)		**121**		**94**	**39.4%**	**11.46 [3.43, 38.29]**
Total events	76		10			
Heterogeneity: Tau² = 0.63; Chi² = 4.54, df = 2 (P = 0.10); I² = 56%						
Test for overall effect: Z = 3.96 (P < 0.0001)						
Total (95% CI)		**196**		**484**	**100.0%**	**5.53 [2.48, 12.31]**
Total events	128		175			
Heterogeneity: Tau² = 0.77; Chi² = 17.46, df = 7 (P = 0.01); I² = 60%						
Test for overall effect: Z = 4.19 (P < 0.0001)						

Jin et al, PLoS One 2015

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



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

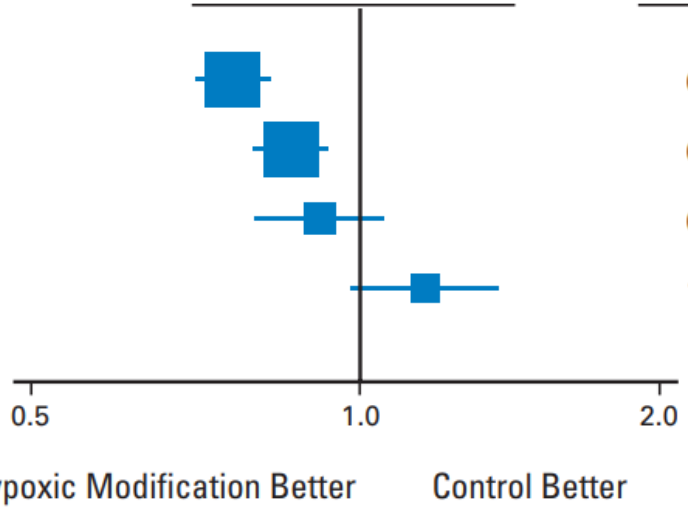
1. RT dose escalation
   - "Dose painting"
2. Improved oxygen supply
   - Treat anemia, hyperbaric O_2, carbogen, nicotinamide
3. Hypoxic cell radiation sensitization

   (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), DNA repair

Hypoxic modification: systematic review

Data from 86 randomized trials including 10,108 patients

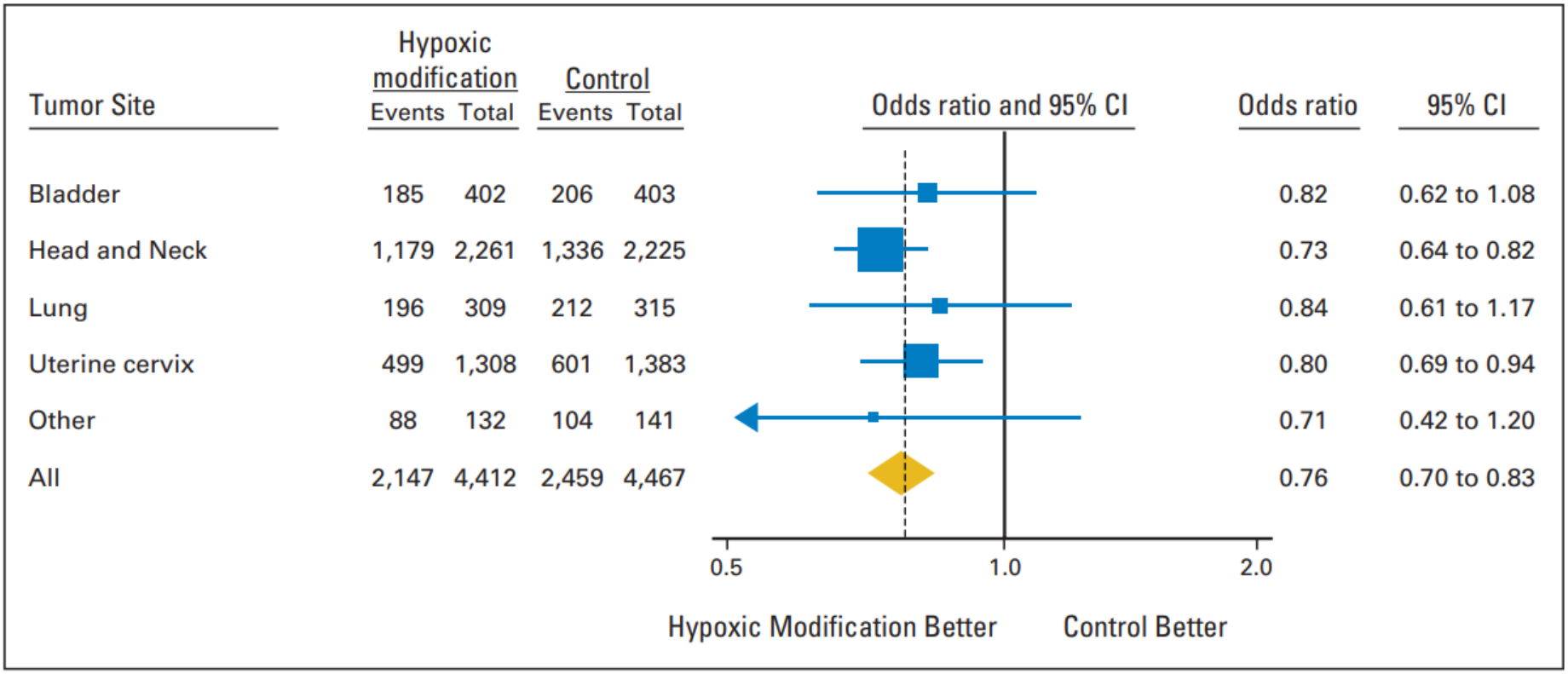
Endpoint	Hypoxic modification Events	Hypoxic modification Total	Control Events	Control Total	Odds ratio	95% CI
Loco-regional control	2,144	4,416	2,465	4,473	0.77	0.71 to 0.84
Survival	3,237	4,921	3,405	4,952	0.87	0.80 to 0.95
Distant metastasis	452	2,332	480	2,339	0.93	0.81 to 1.07
Complications	374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



Overgaard, J Clin Oncol 25:4066-74, 2007

Hypoxic modification: systematic review

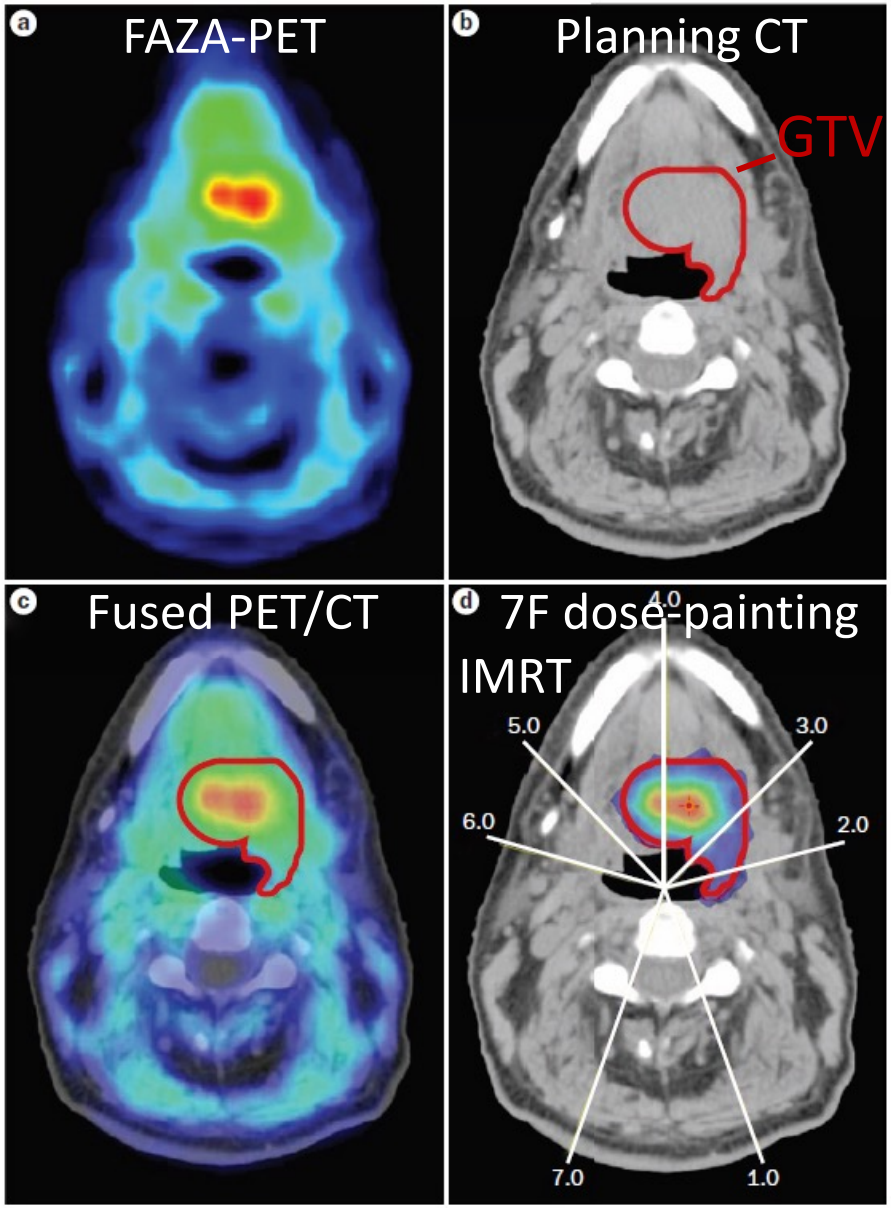
Influence on locoregional control as a function of tumor site



Overgaard, J Clin Oncol 25:4066-74, 2007

1. RT Dose Escalation

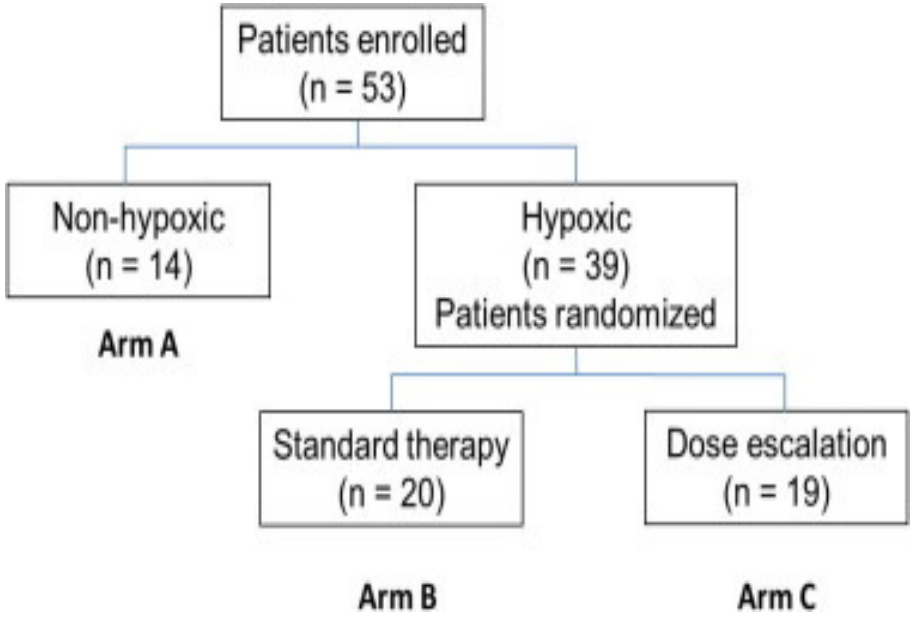
Dose Painting

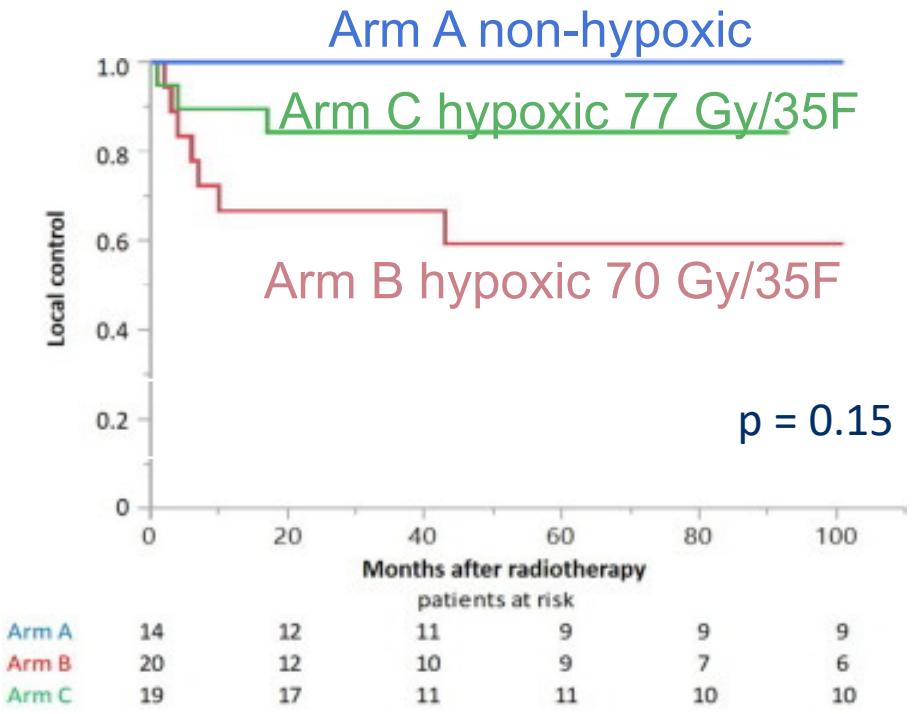


Horsman et al, Nat Rev Clin Oncol 2012

Dose Escalation to Hypoxic Tumor Region

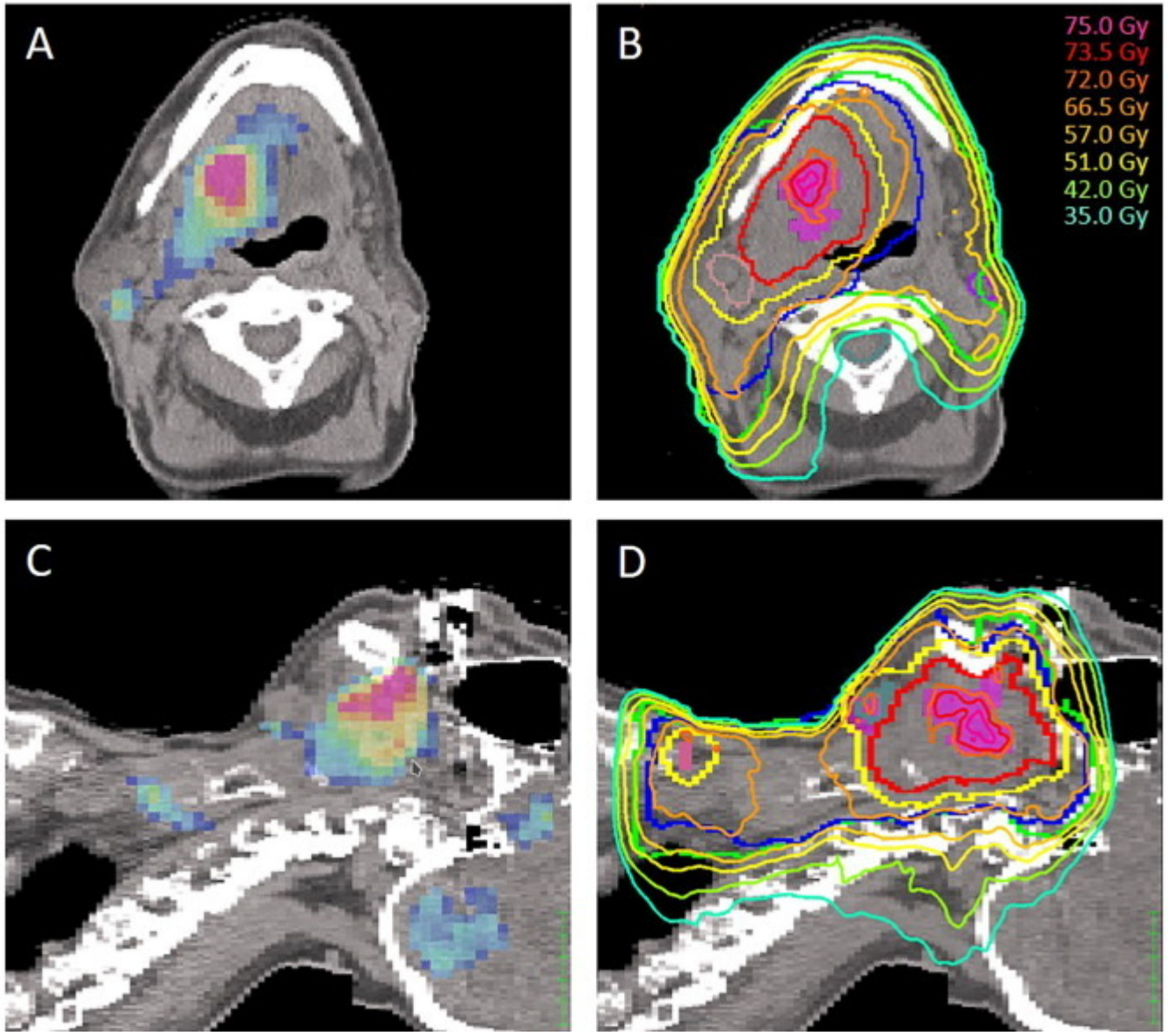
- Randomized phase II trial in HN cancer 2009-2017
- Patients assigned treatment arm based on baseline dynamic F-MISO PET





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

2. Improved Oxygen Supply

Transfusion to Correct Anemia

Apparent benefit of transfusion in cervical cancer possibly confounded by differences in tumor size

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

DEFINITIVE EVIDENCE FOR HYPOXIC CELLS INFLUENCING CURE IN CANCER THERAPY

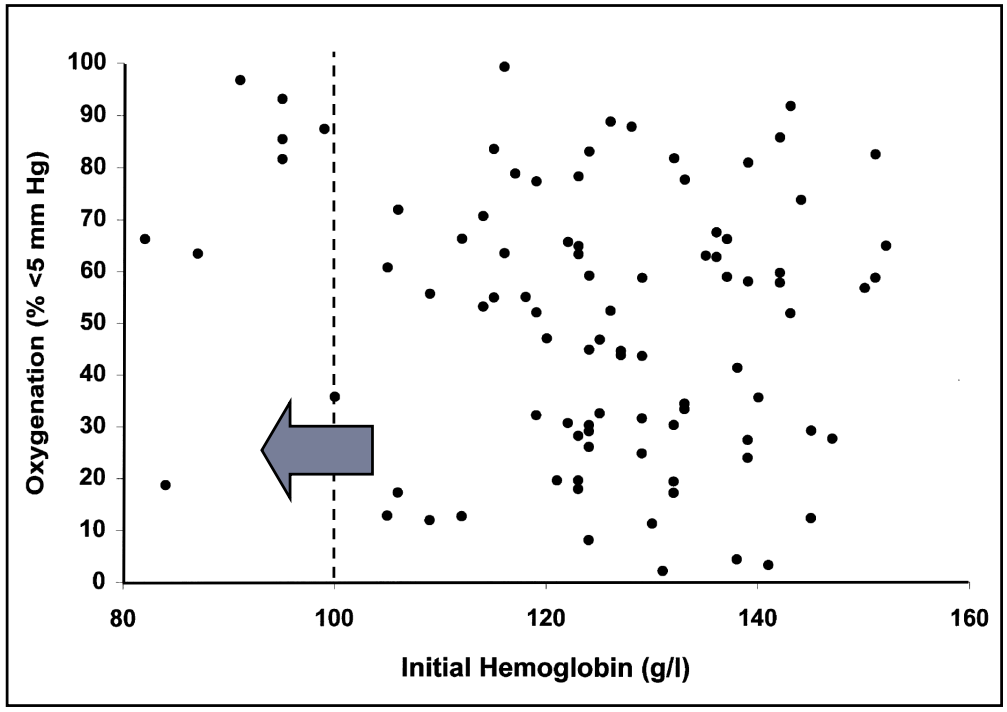
R. S. BUSH, R. D. T. JENKIN, W. E. C. ALLT, F. A. BEALE, H. BEAN, A. J. DEMBO AND J. F. PRINGLE

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.

Anemia and Tumor Hypoxia

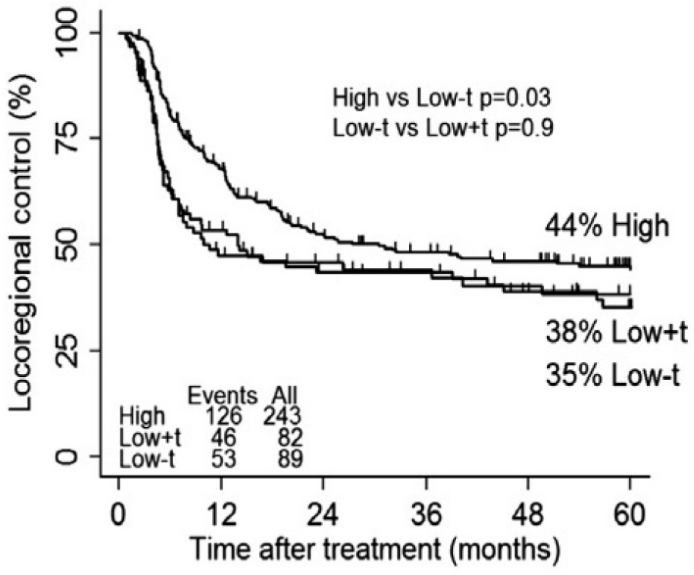
- Anemia is associated with poor clinical outcomes.
- Severe anemia (<100 g/l) may contribute to hypoxia.

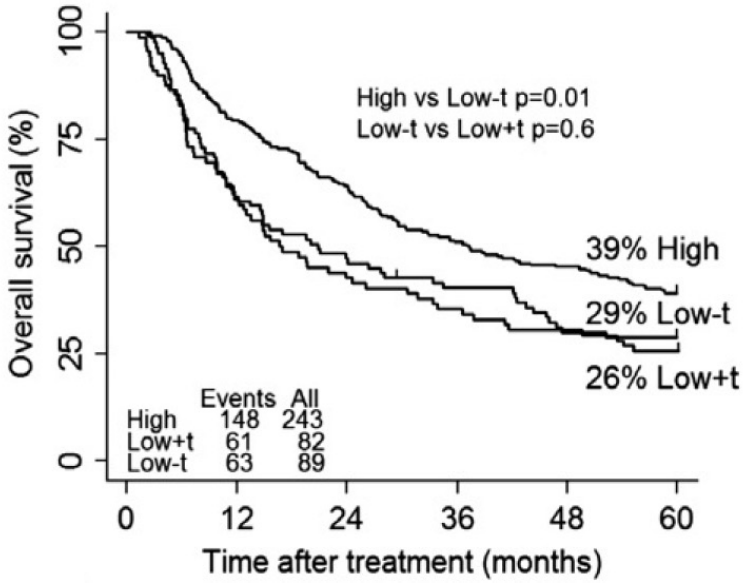


Pre-treatment hemoglobin and hypoxia in cervical cancer

Transfusion to Correct Anemia

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





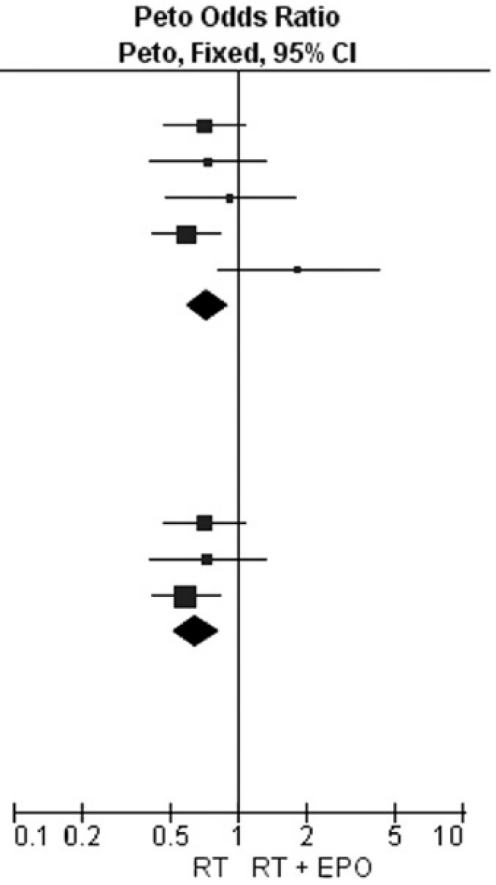
Patients with low pre-treatment hemoglobin in DAHANCA 5 RCT
randomized to transfusion or not

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)						



Lambin et al, Cochrane Database of Systematic Reviews, 2009

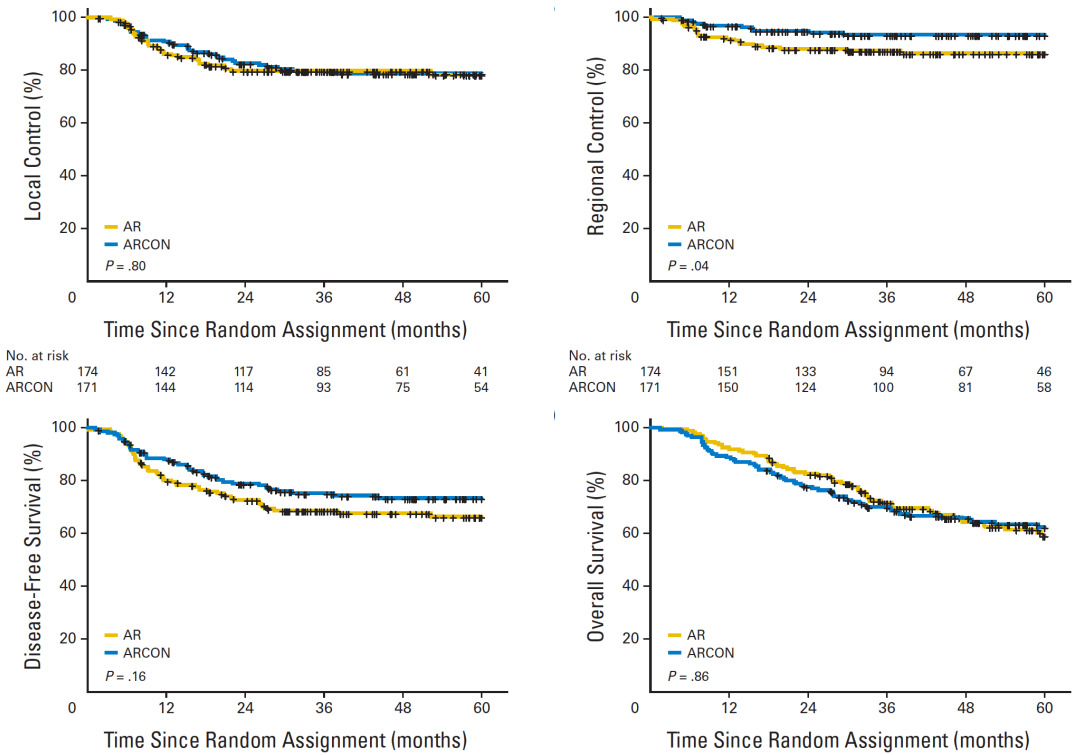
Carbogen and Nicotinamide

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%)

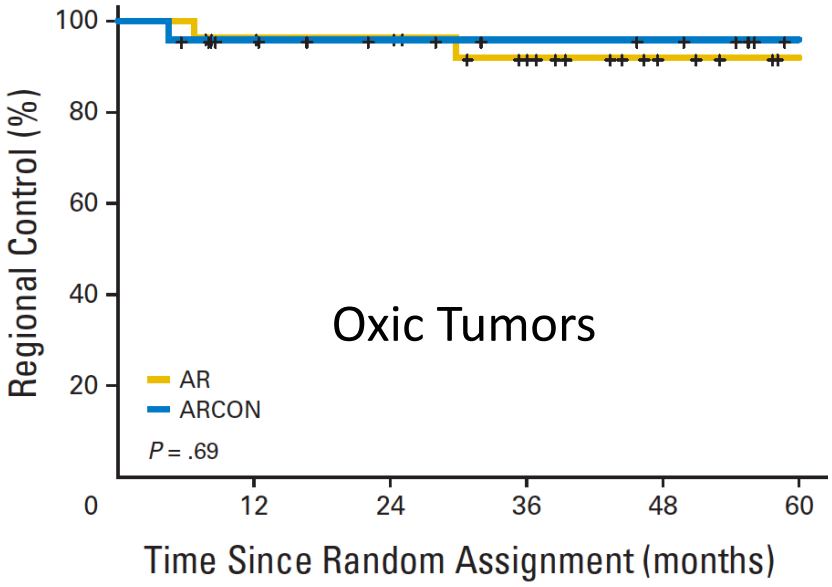


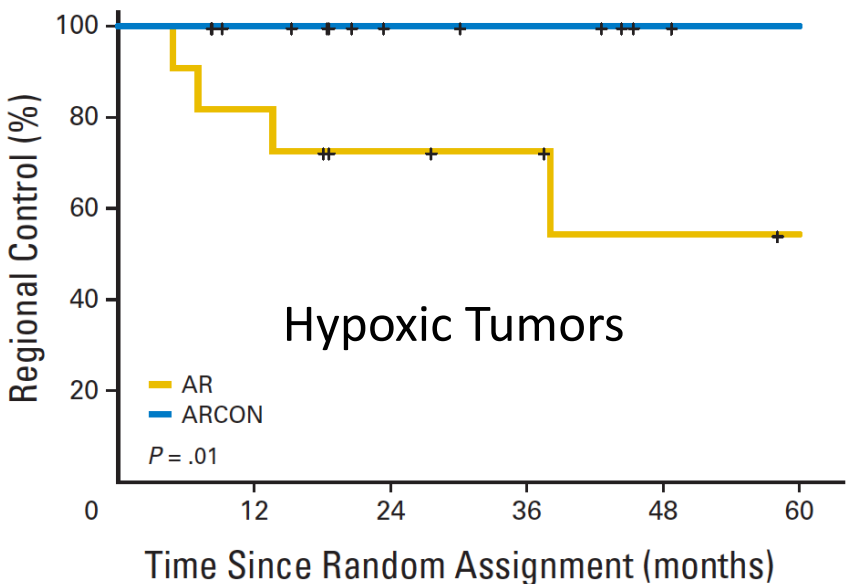
345 patients with T2-T4 laryngeal cancer randomized to receive accelerated RT (AR) ± carbogen and nicotinamide (ARCON)

Janssens et al, JCO 2012

ARCON in Laryngeal Cancer

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



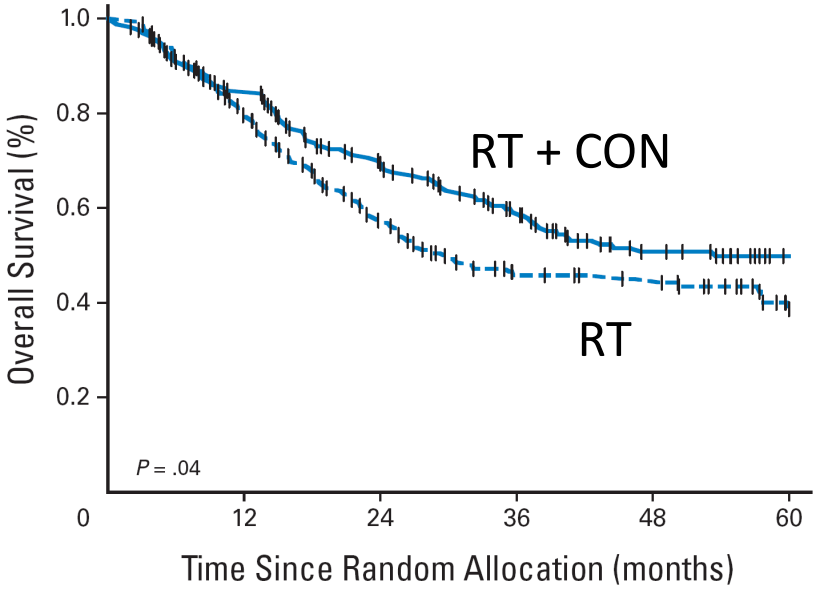


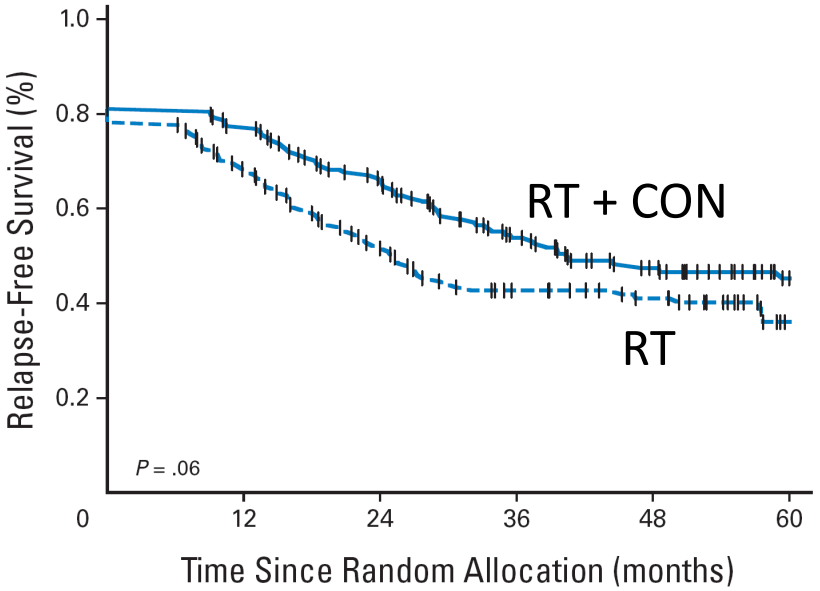
79/345 patients with pimonidazole before treatment

Janssens, 2010

Carbogen and Nicotinamide in Bladder Cancer

Standard RT + carbogen and nicotinamide improved OS & RFS



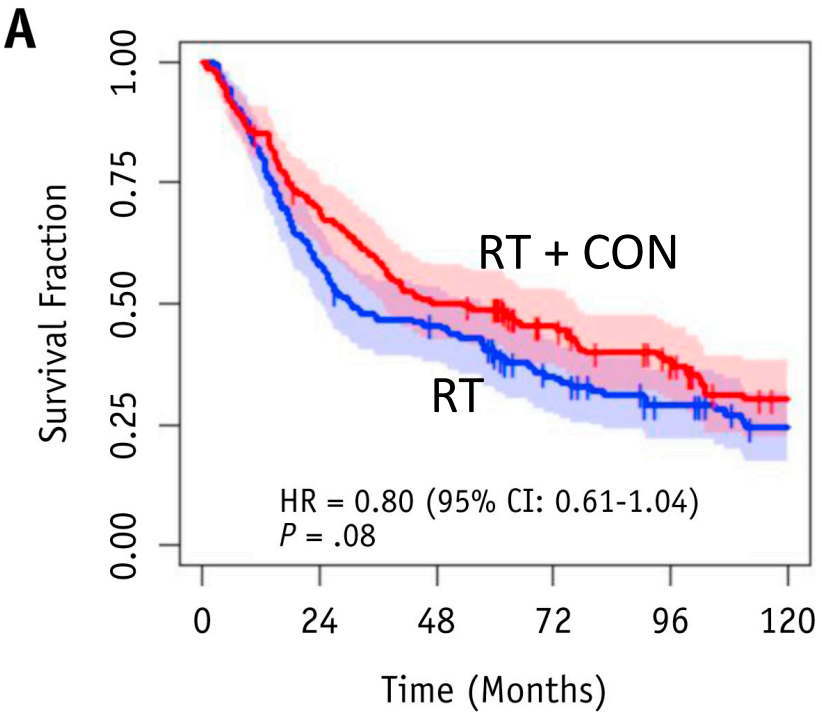


333 patients with T1-T4a bladder cancer randomized to receive RT ± carbogen and nicotinamide

Hoskin et al, JCO 2010

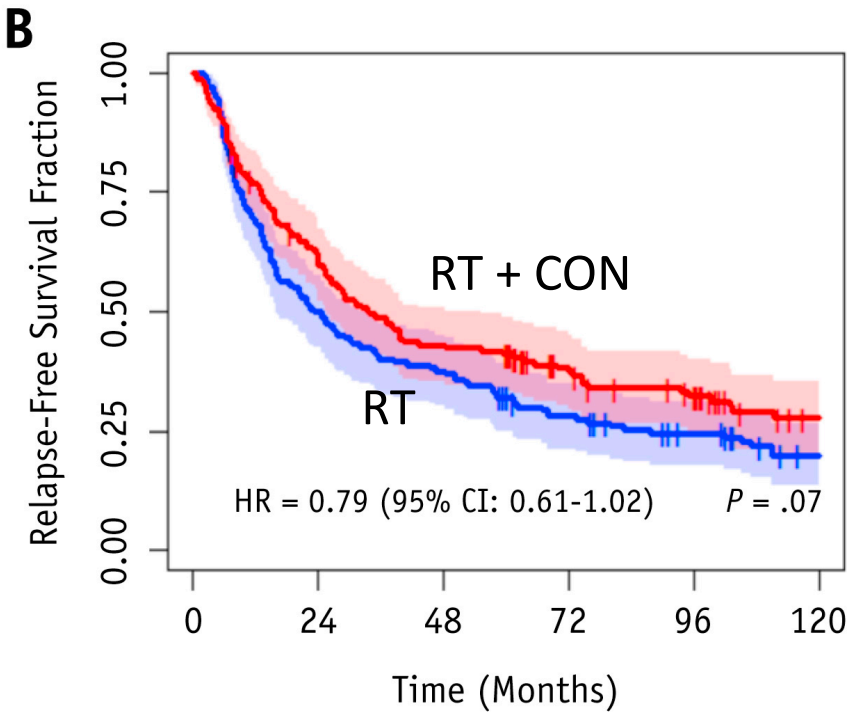
Carbogen and Nicotinamide in Bladder Cancer: Long Term Outcomes

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



No. at Risk

RT:	162	94	72	49	35	25
RT + CON:	162	111	80	59	44	27



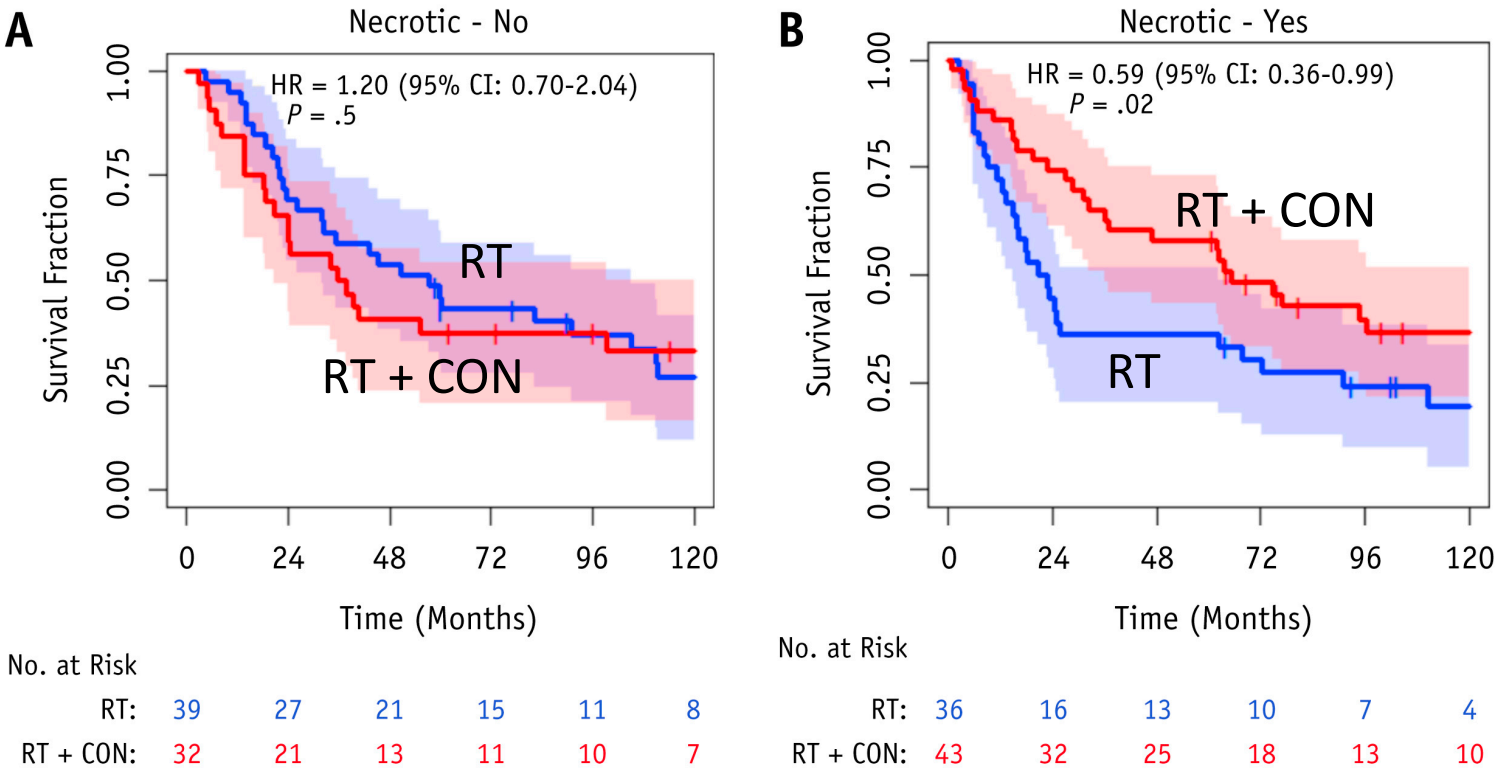
No. at Risk

RT:	162	81	61	42	31	19
RT + CON:	161	95	67	48	36	20

Hoskin et al, IJROBP 2021

Carbogen and Nicotinamide in Bladder Cancer: Long Term Outcomes

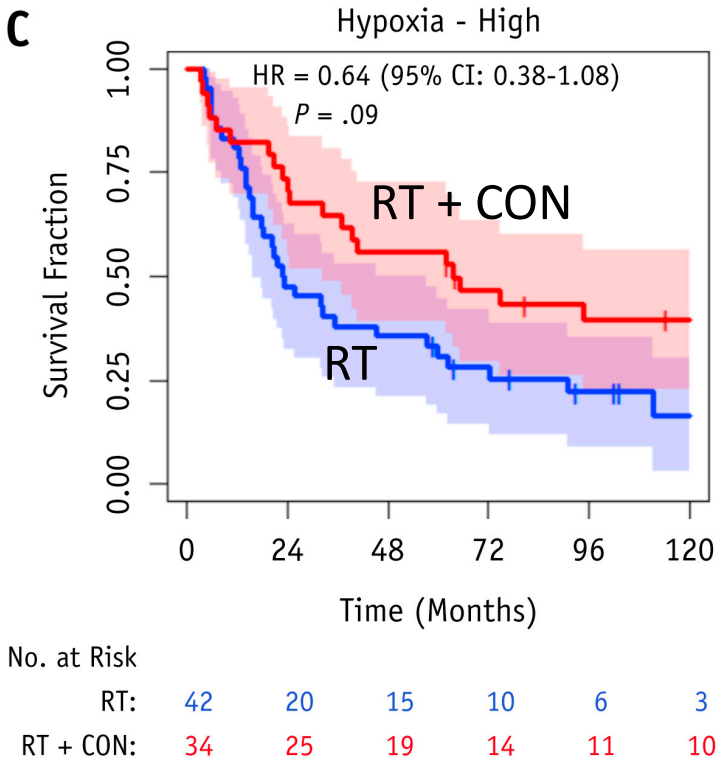
Benefit of CON only in patients with tumor necrosis

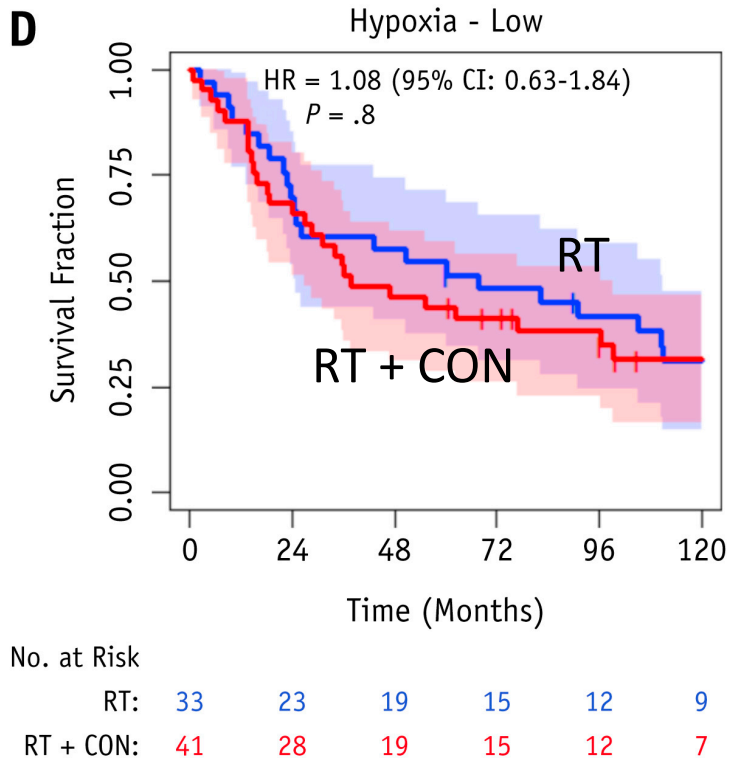


Hoskin et al, IJROBP 2021

Carbogen and Nicotinamide in Bladder Cancer: Long Term Outcomes

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





Hoskin et al, IJROBP 2021

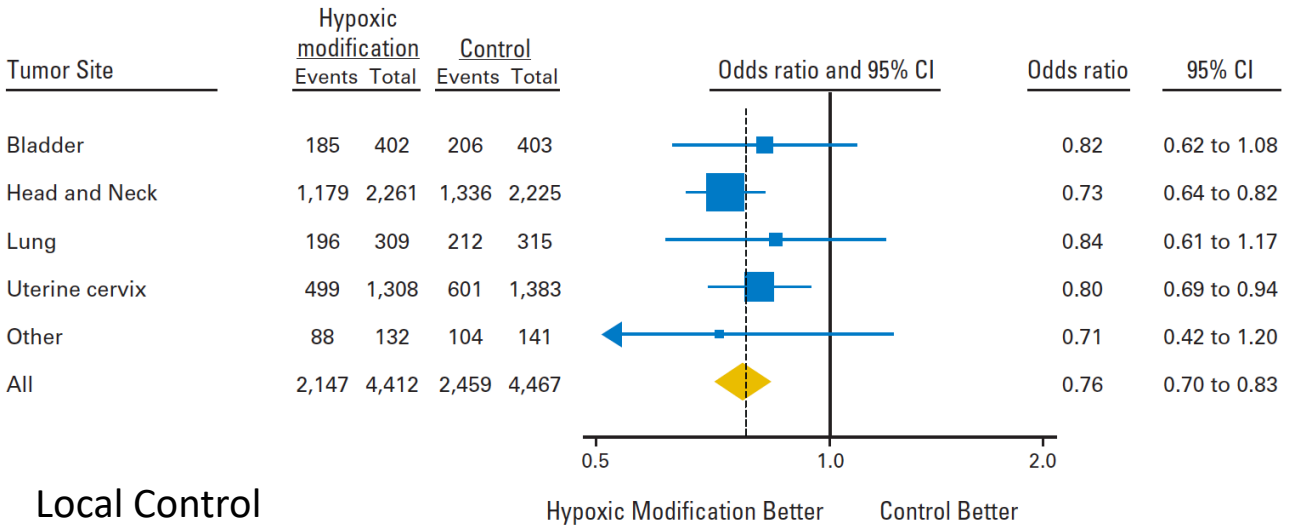
3. Hypoxic Cell Radiation Sensitization

Hypoxic Cell Radiation Sensitizers

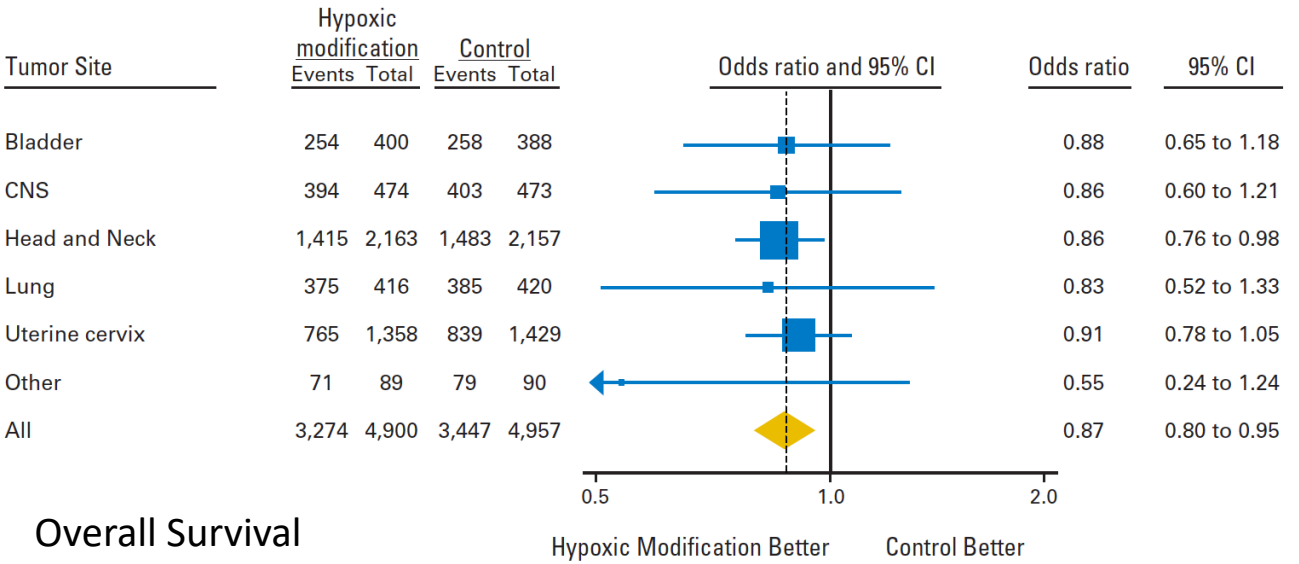
- Bioreductive nitroimidazole drugs
  - Misonidazole, etanidazole, nimorazole
- High electron affinity
- Bind in hypoxic tumor regions and **mimic the radio-sensitizing effect of oxygen**
- Numerous phase III studies in HN cancer, cervical cancer and other tumors

Misonidazole

Modification of tumor hypoxic significantly improves the effect of RT



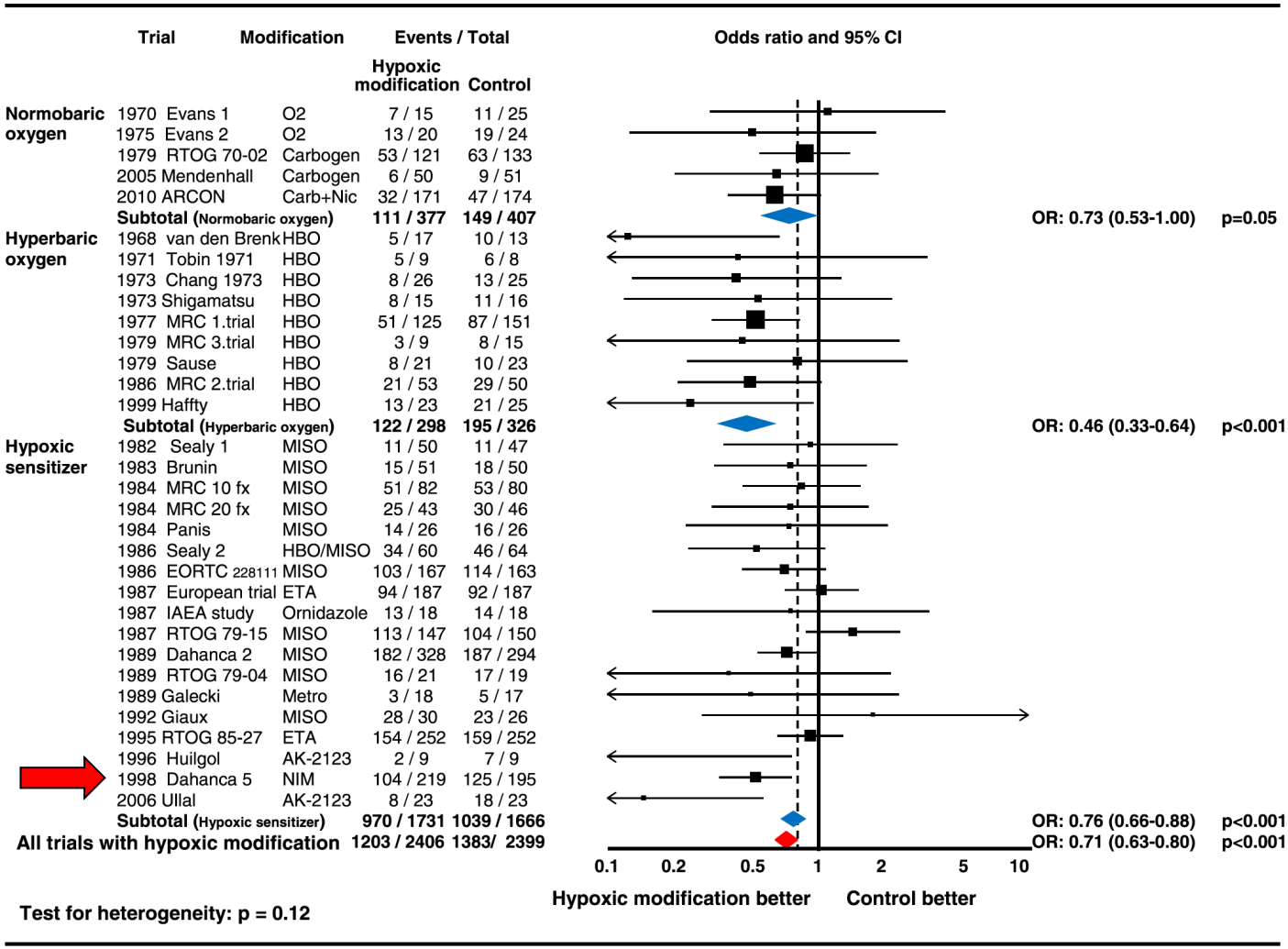
Local Control



Overall Survival

Overgaard, 2007

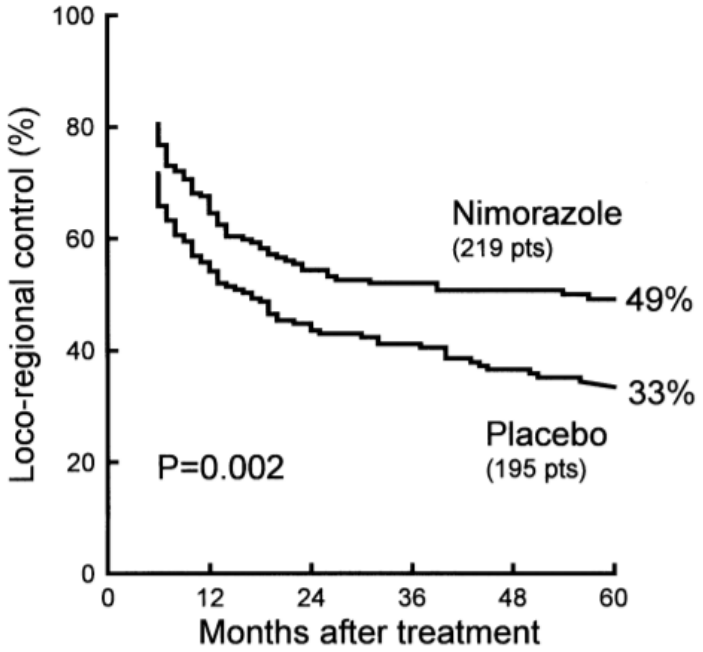
Targeting HN Cancer Hypoxia During RT

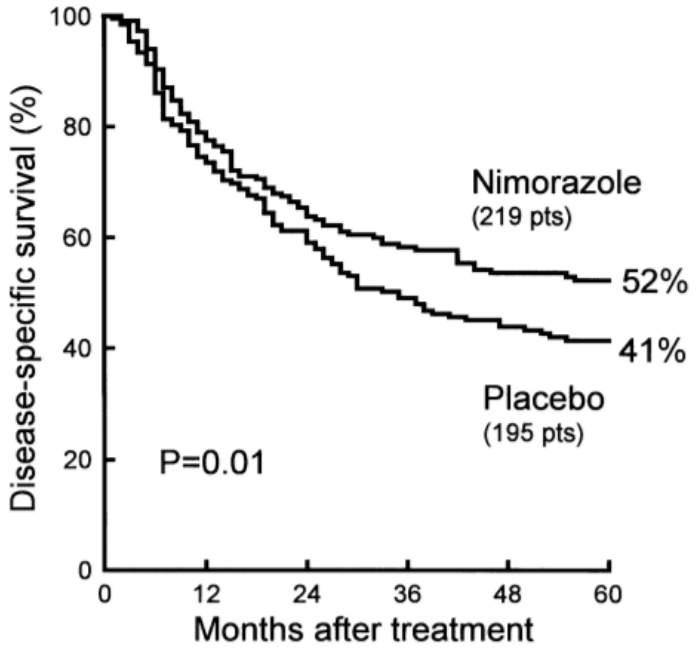


Overgaard et al, Radiother Oncol 2011

Hypoxic Cell Sensitization in HN Cancer

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





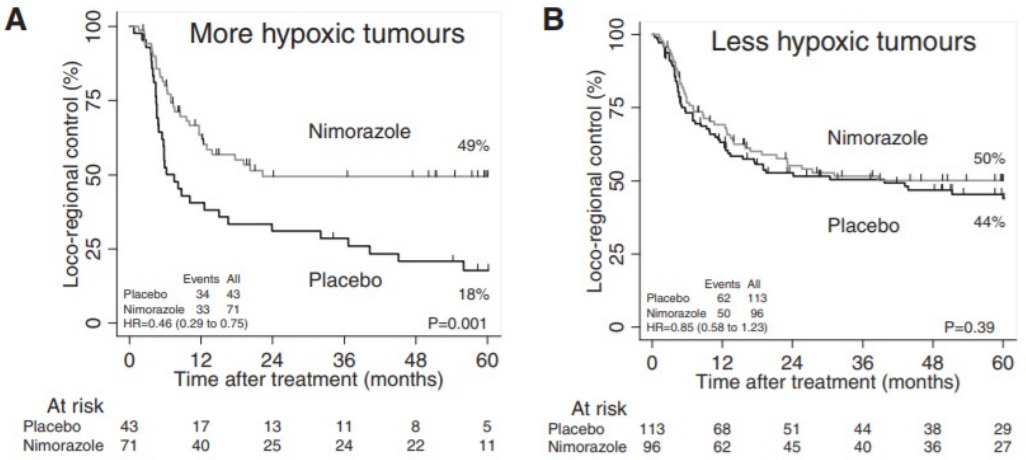
Two ongoing validation studies (EORTC 1219 and NIMRAD)

Overgaard et al, Radiother Oncol 1998

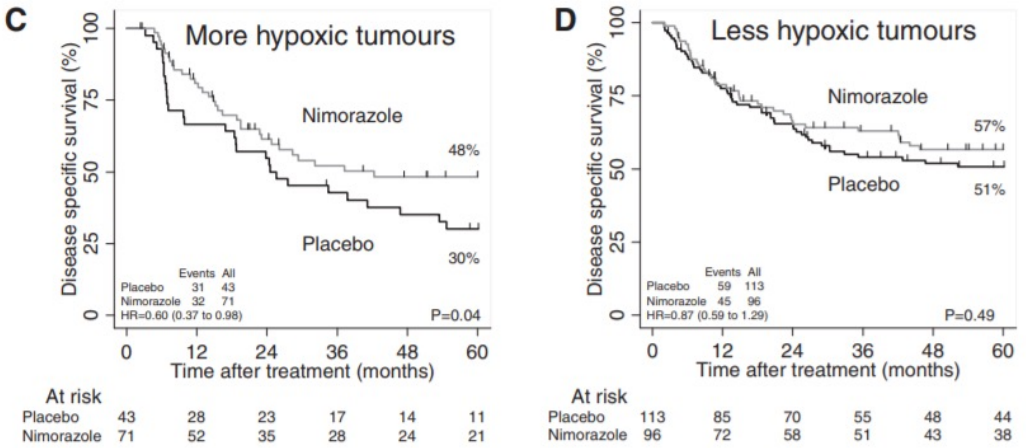
Patient selection is crucial …

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

Locoregional control



Disease-specific survival

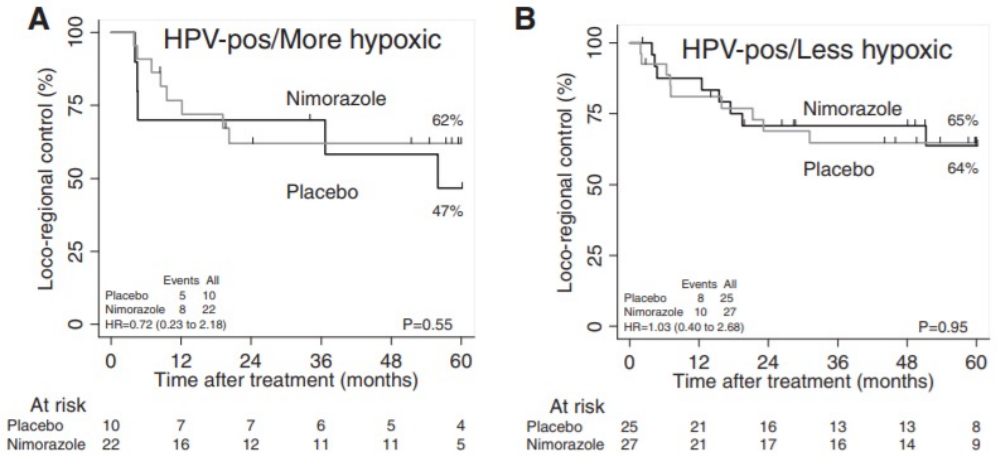


Toustrup et al, Radiother Oncol 2012

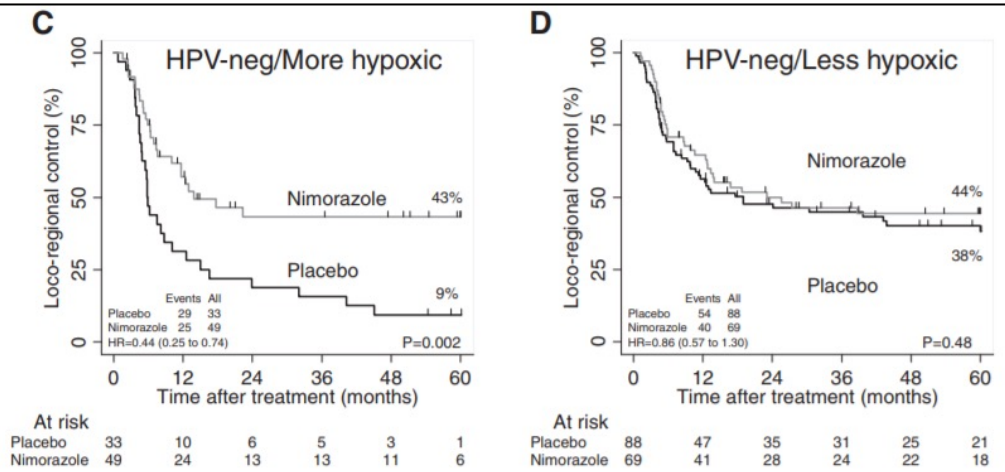
Hypoxia is not always important …

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

HPV +



HPV -



Toustrup et al, Radiother Oncol 2012

4. Hypoxic Cell Cytotoxins

Hypoxic Cell Cytotoxins

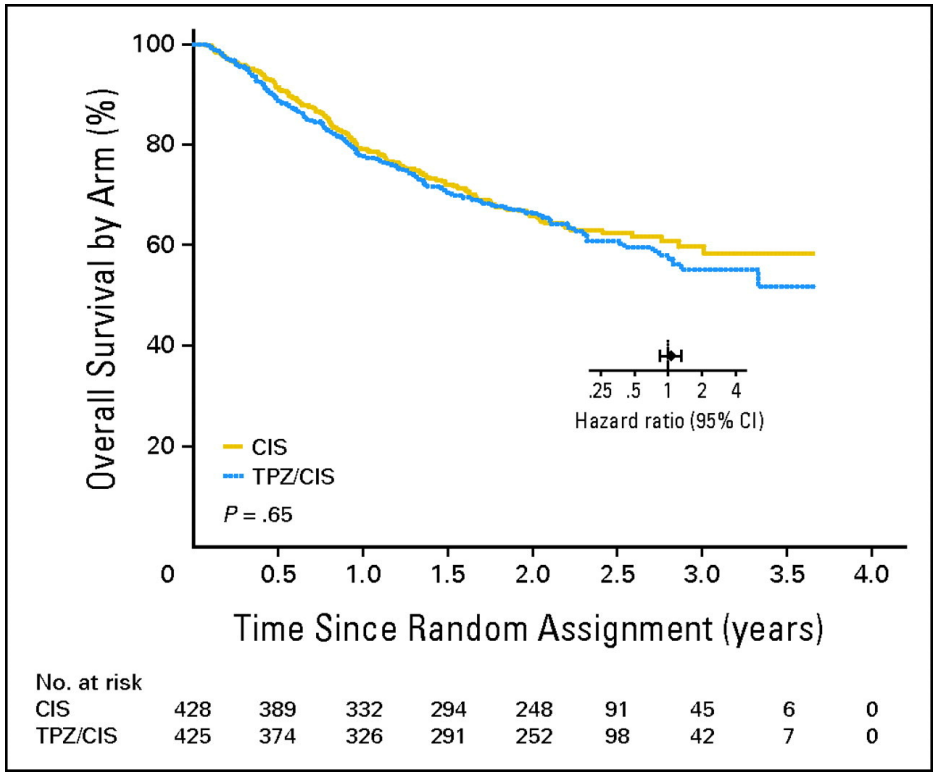
- Bioreductive cytotoxic drugs that are **activated under hypoxic conditions**
- DNA damage leading to cell death
- Tirapazamine, TH-302
- Complement the cell killing effects of RT
- Potentiate cisplatin cell killing
- Bystander effect
- Promising results in phase I/II clinical trials

Tirapazamine in HN Cancer (Phase III RCT)

HeadSTART (*2000's*):

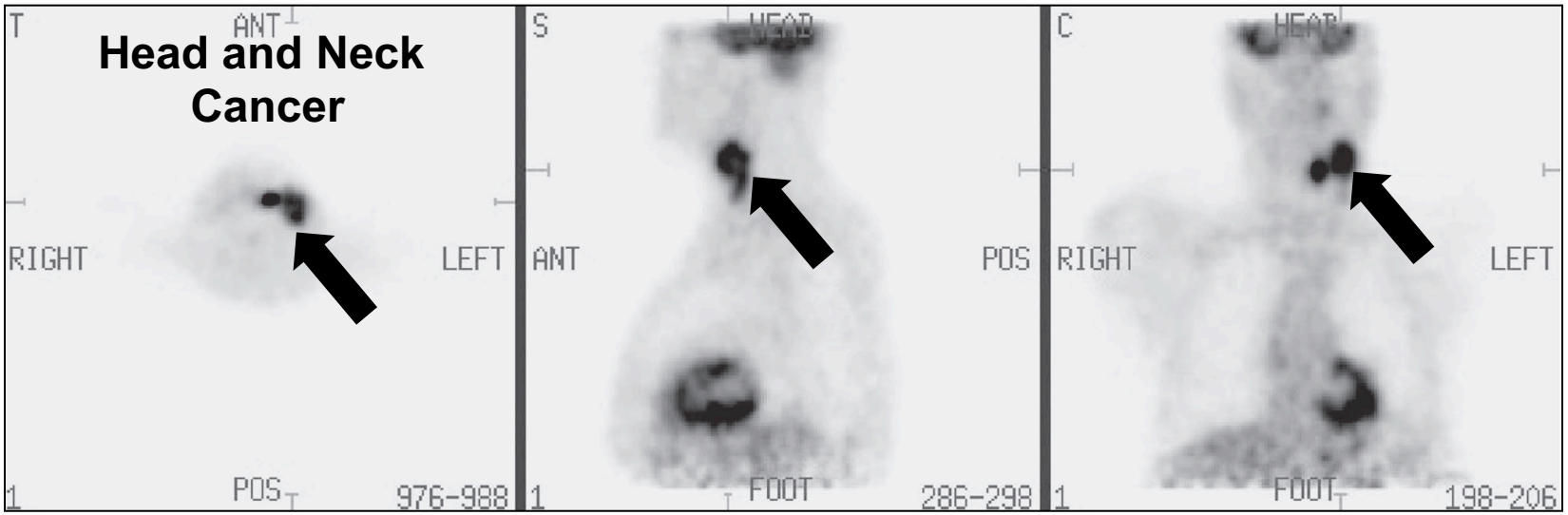
861 patients randomized to RTCT ± Tirapazamine

No benefit of targeting hypoxia

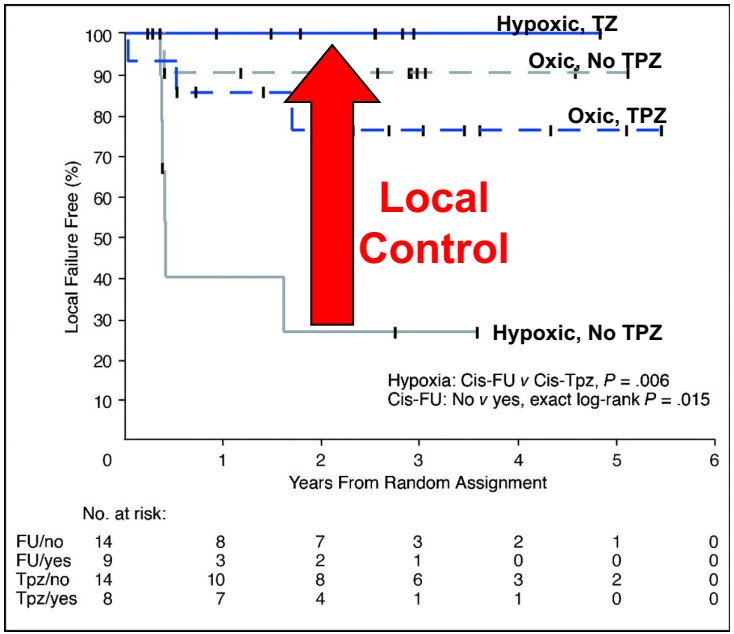


Rischin et al, JCO 2014

Patient selection is crucial …

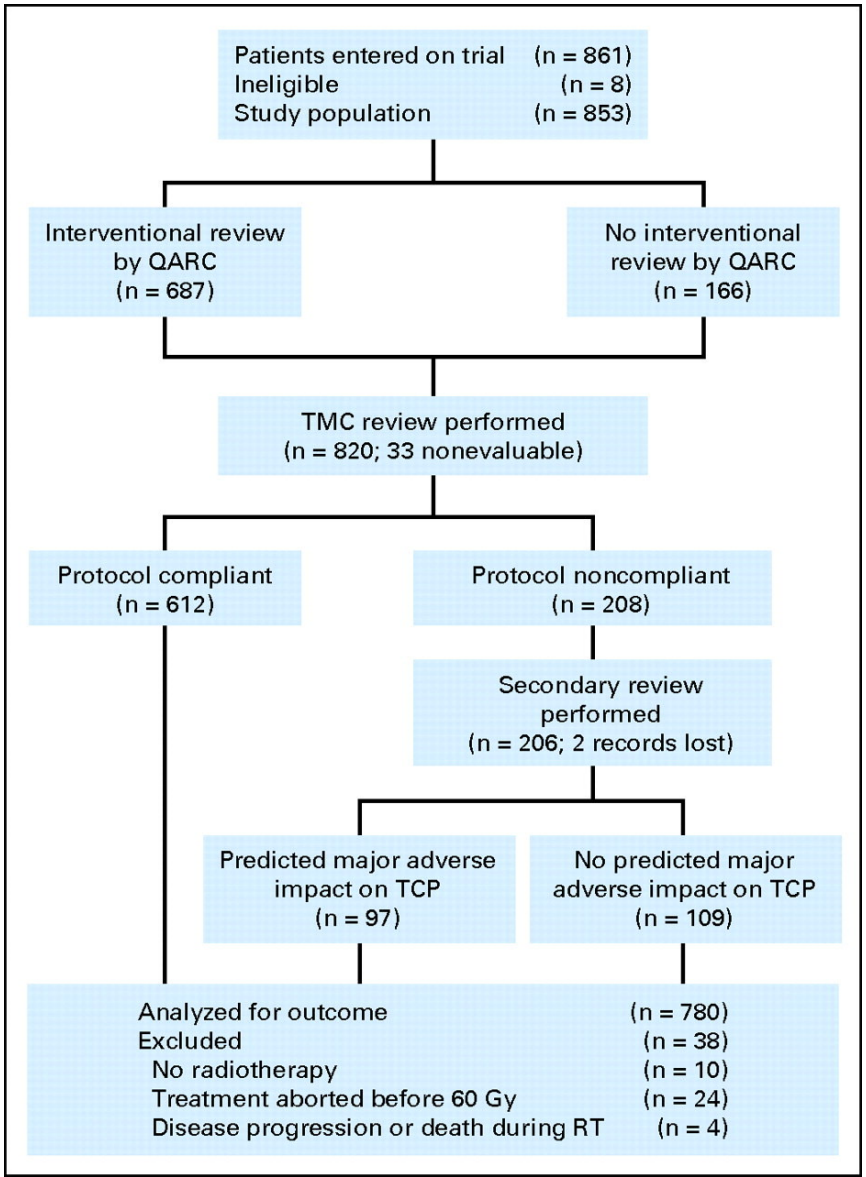


- H&N cancer
- RT with or without TPZ
- Benefit of TPZ only in patients with hypoxic tumors identified using PET imaging



Rischin et al, JCO 2006

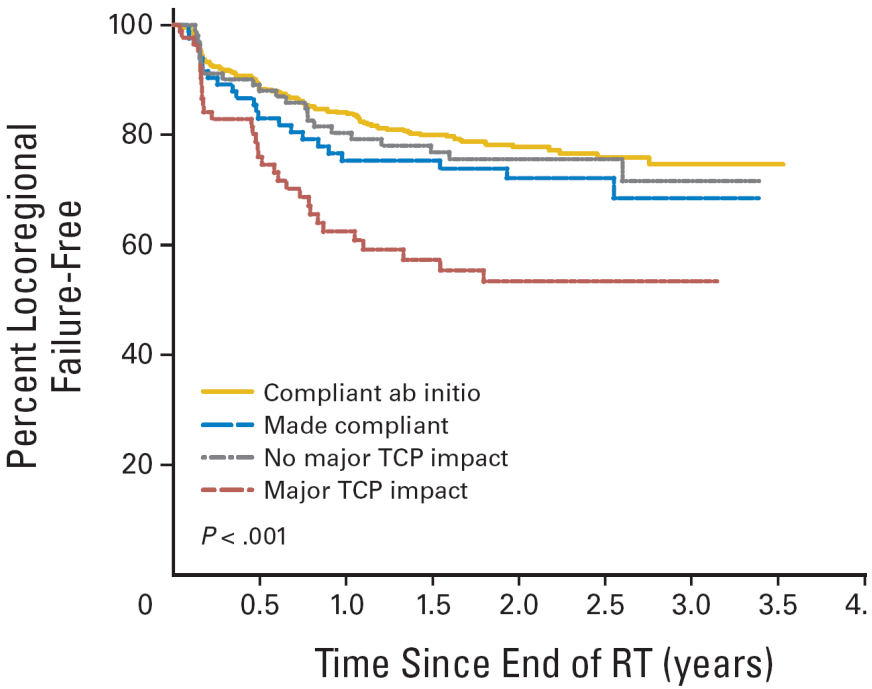
The Importance of High Quality Radiotherapy



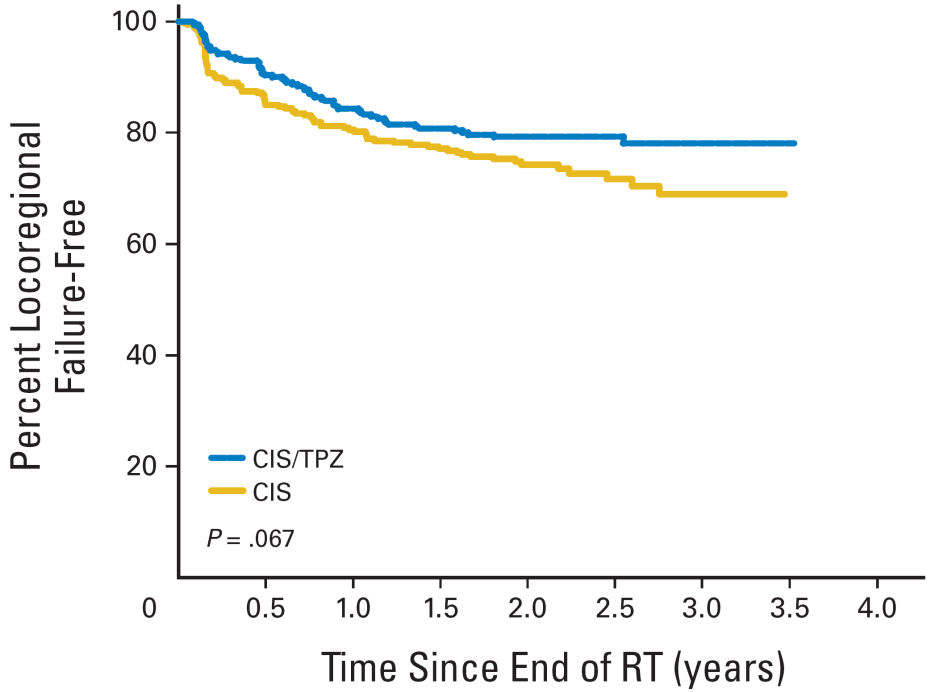
Peters et al, JCO 2010

The Importance of High Quality Radiotherapy

Technically poor radiation treatment can mask biology



Effect of radiotherapy quality on tumor control probability (TCP)



Effect of TPZ with good RT

Trend in favor of improved tumor control

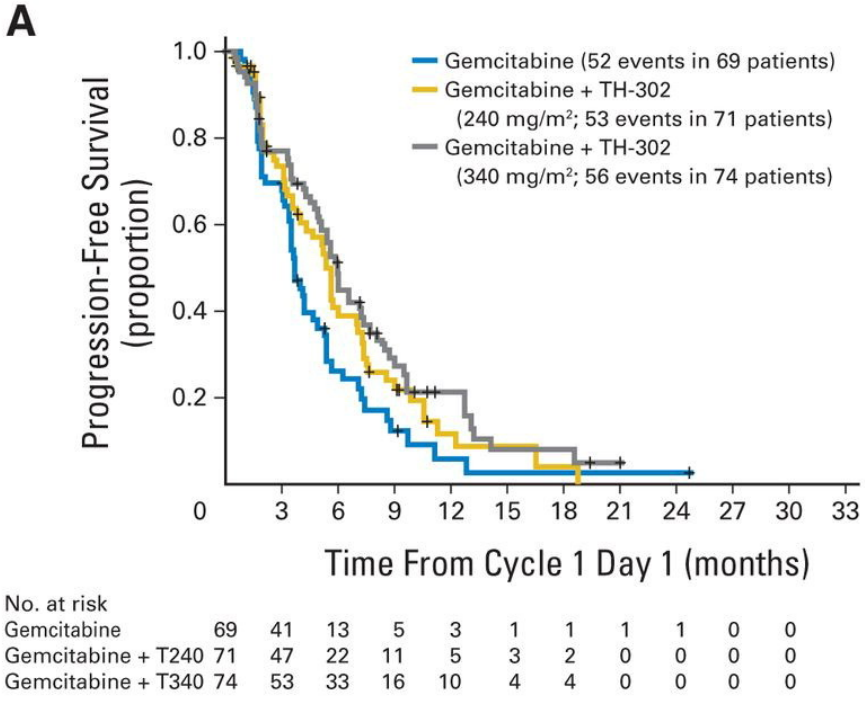
Peters et al, JCO 2010

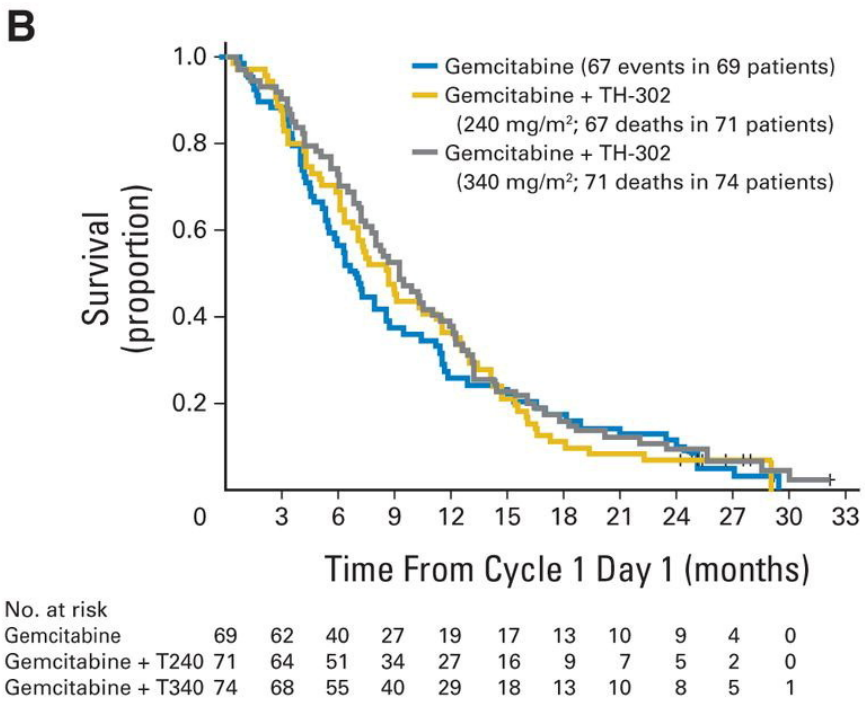
TH-302 in Pancreatic Cancer (Phase II)

TH-302: Hypoxia activated cytotoxin

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

No significant difference in OS





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

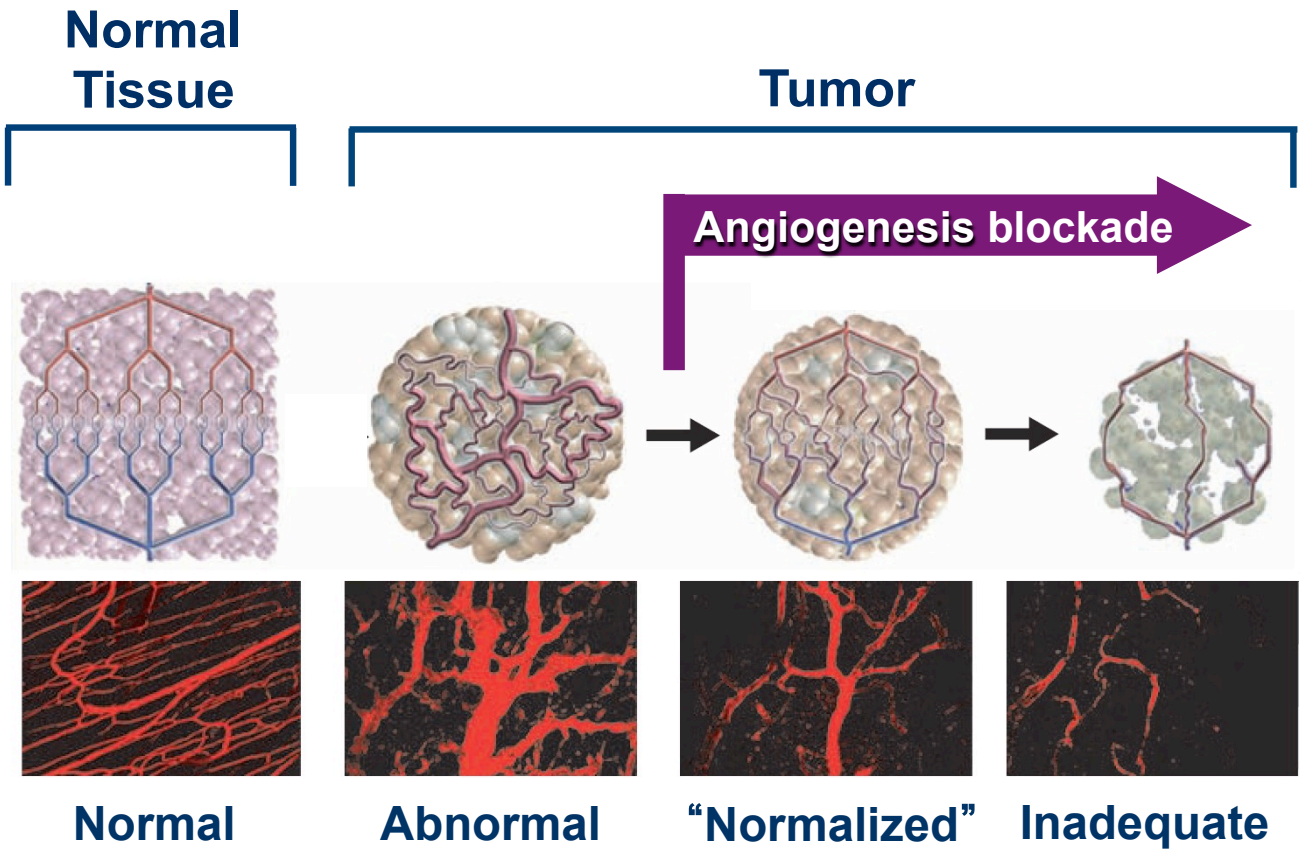
Targeting the Tumor Vasculature

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’

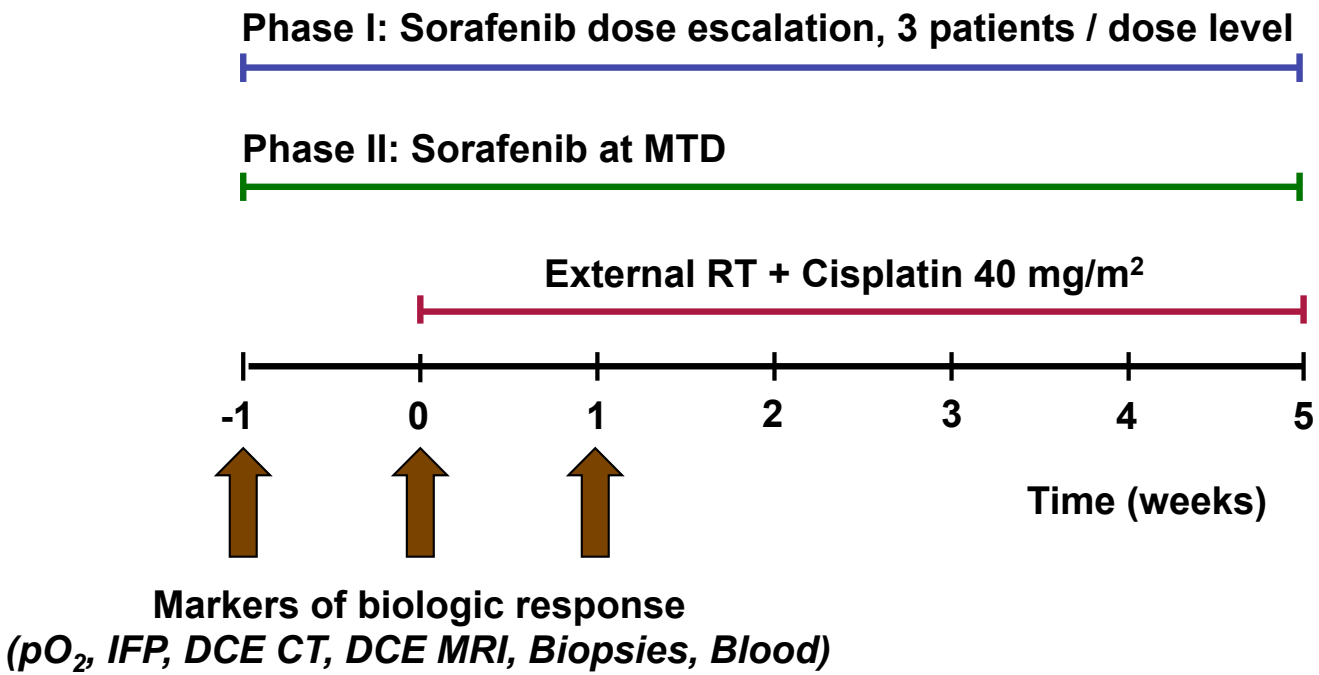
Probably relevant only in very specific circumstances



Modified from Jain, 2005

Targeting Angiogenesis in Cervical Cancer

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

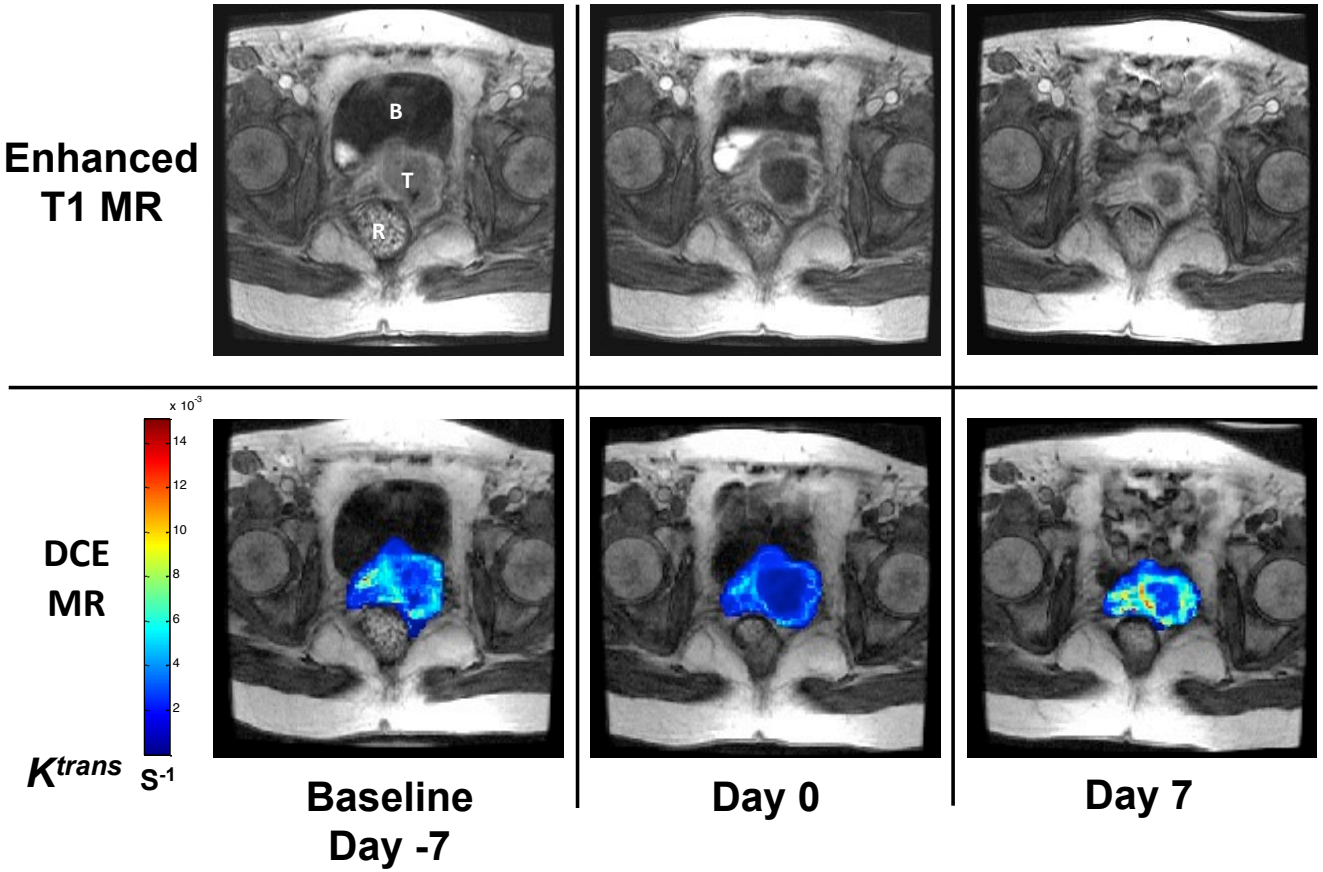


Sorafenib – oral inhibitor of VEGF, PDGF, Raf

Milosevic et al, IJROBP 2016

Sorafenib Increased Tumor Hypoxia

Sorafenib reduced tumor perfusion and increased hypoxia – study closed prematurely

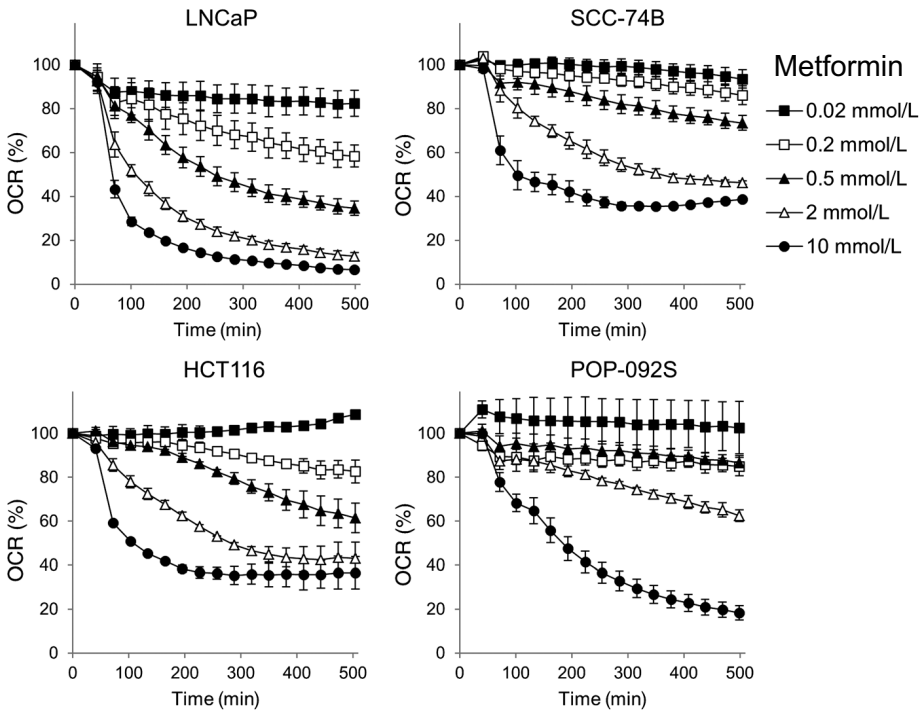


Milosevic et al, IJROBP 2016

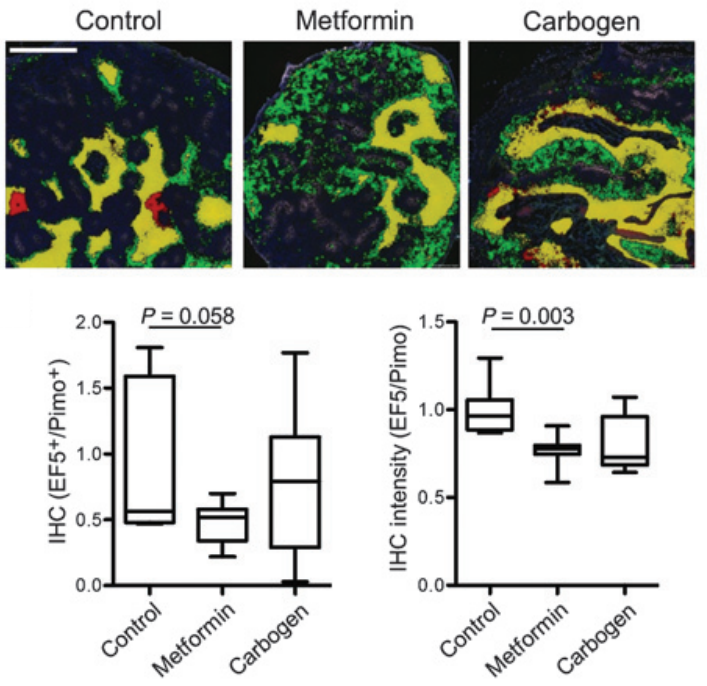
Targeting Cellular Oxygen Consumption

Metformin reduces oxygen consumption and hypoxia

Oxygen consumption



Hypoxia (HCT116)



Zannella and Kortizinsky, Clin Cancer Res 2013

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

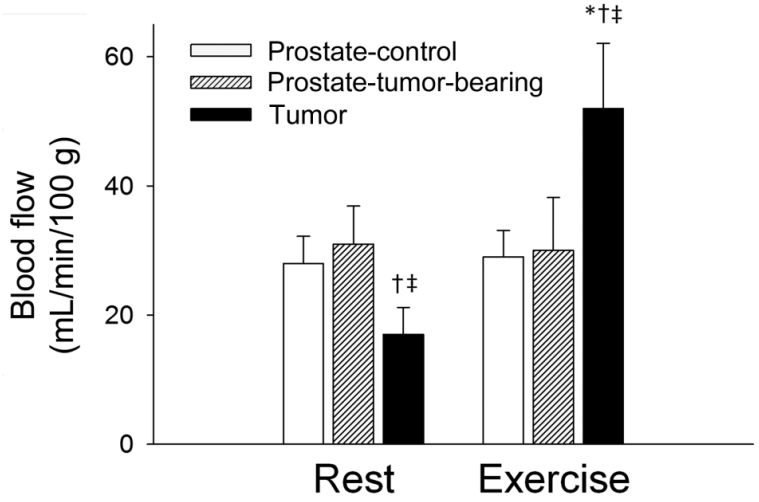
Danielle J. McCullough, John N. Stabley, Dietmar W. Siemann, Bradley J. Behnke

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

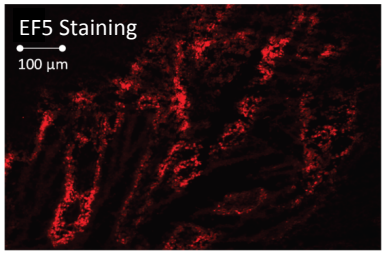
Physical Exercise and Tumor Hypoxia

Acute mild-moderate exercise reduces tumor hypoxia

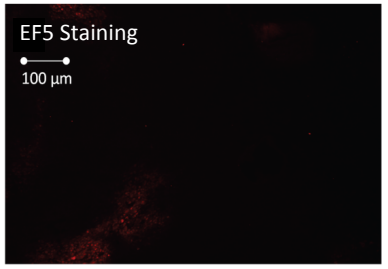
- Dunning R-3327 prostate cancer growing in the rat prostate gland
- Treadmill exercise for 5 min

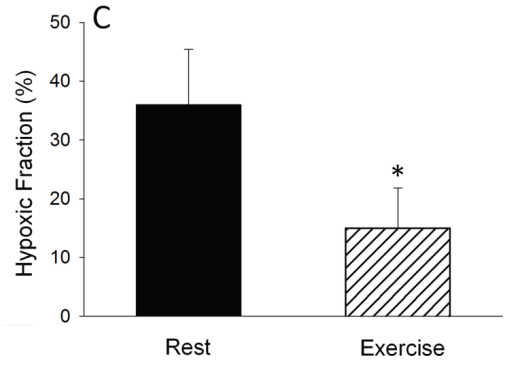


Hypoxia Control



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), DNA repair

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.