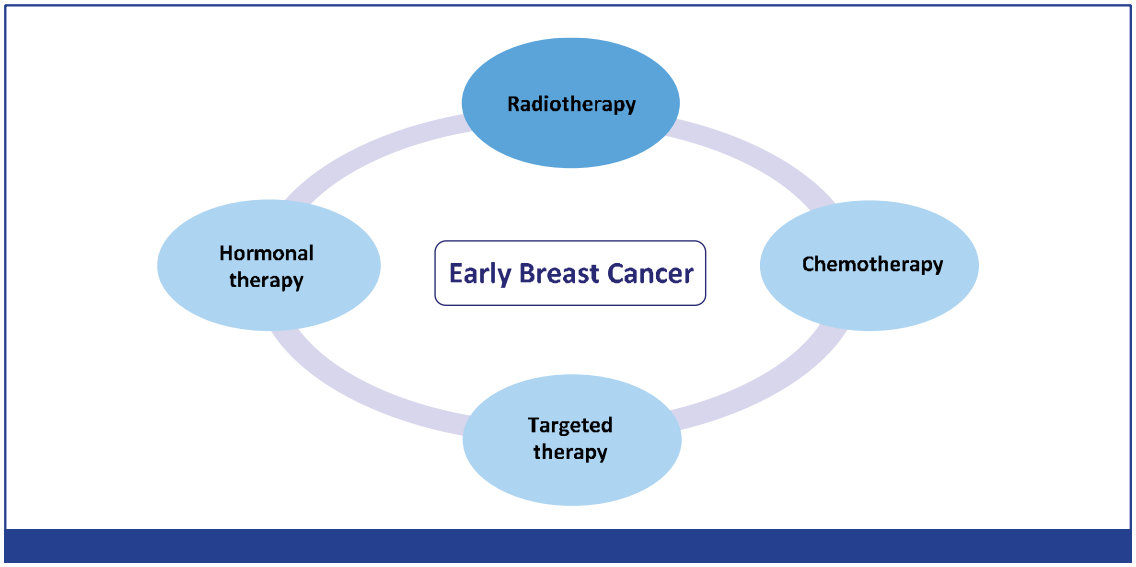
HORMONAL MANIPULATION AND RADIATION

S. Arcangeli, MD

I° AIRB COURSE IN RADIOBIOLOGY

How to sequence systemic therapies and radiotherapy in early breast cancer?

H. Wildiers, MD, PhD[1,2], T. Pecceu, MD[1], C. Weltens, MD, PhD[2,3], P. Neven, MD, PhD[2], S. Peeters, MD, PhD[2,3]

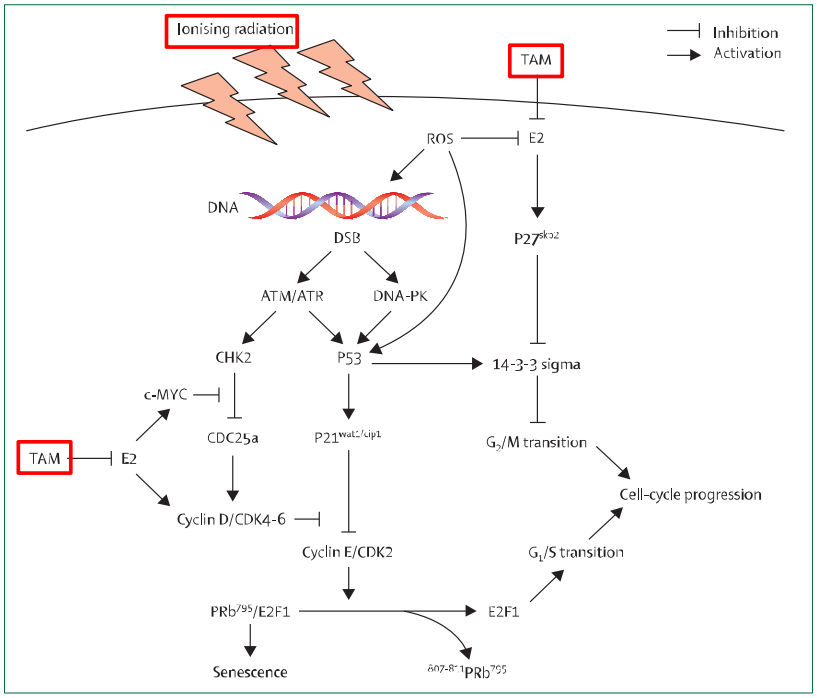


(Belg J Med Oncol 2014;8(3):72-80)

Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale?

Lancet Oncol 2009; 10: 53–60

Cyrus Chargari, Robert Alain Toillon, Dhara MacDermed, Pierre Castadot, Nicolas Magné



I° AIRB COURSE IN RADIOBIOLOGY

Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale?

Lancet Oncol 2009; 10: 53–60

Cyrus Chargari, Robert Alain Toillon, Dhara MacDermed, Pierre Castadot, Nicolas Magné

Author	Patients included	Study arm	Median follow-up (years)	OS (10 years)	DFS	Local recurrence (10 years)	Distant recurrence (10 years)
Pierce et al.[17a]	2690	RT + TAM RT → TAM	10.3	88% 90% p=0.65	83% 83% p=0.76	7% 5% p=0.54	NR NR
Ahn et al.[18a]	1649	RT + TAM RT → TAM	10.0	84% 82% p=0.46	NR NR	10% 14% p=0.86	18% 22% p=0.12
Harris et al.[3a]	278	RT + TAM RT → TAM	8.6	81% 86% p=0.64	85% 76% p=0.35	3% 7% p=0.52	NR NR
Azria et al.[19b]	150	RT + LET RT → LET	2.2	NR	97%[c]	NR	NR

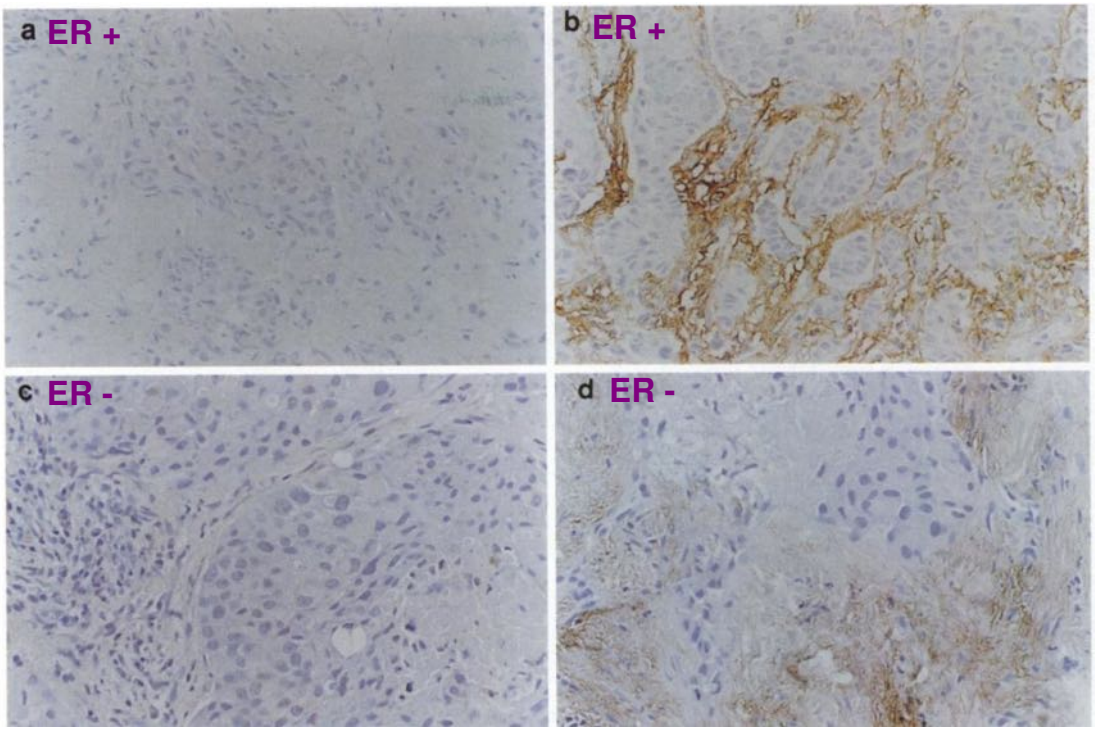
OS-overall survival; DFS-disease free survival; TAM-tamoxifen; RT-radiotherapy; NR-not reported; LET-letrozole.
[a] Retrospective study.
[b] Prospective study.
[c] At 2 years.

the hypothesis that tamoxifen may have another potent action on tumor growth and not function soley as an antagonist of

Received 5/11/92; accepted 6/12/92.

response, prior to surgery. The tissue samples were fixed in 10% buffered formalin and embedded in paraffin; sections (4 μm) and placed on gelatin-coated slides.

For the immunohistochemical localization of TGF-βs (15), were permeabilized with 1 mg/ml hyaluronidase in 0.1 M sod



tracellular staining for TGF-β1.

shown to exert a number of nonhormonal as well as hormonal effects. One nonhormonal effect of tamoxifen is the induction of transforming growth factor-β (TGF-β) secretion. TGF-β has been implicated in the pathogenesis of radiation-induced fibrosis. *Purpose:* We investigated the development of lung fibrosis in breast cancer patients who were treated after mastectomy with radiotherapy, with or without simultaneous adjuvant treatment with tamoxifen. *Methods:* Data from 196 women were included in the analysis.

Table 2. Incidence of marked lung fibrosis after postoperative radiotherapy adjuvant tamoxifen, in 84 randomly assigned patients with

	RT + tamoxifen, No. with fibrosis/total (% of total)
12 fractions*	15/24 (63%)†
22 fractions	5/14 (36%)†

*Refers to the number of fractions into which the total radiation dose was
†Cochran–Mantel–Haenszel test for association between lung fibrosis and number of fractions; $P = .01$.

cosmetic outcome of lumpectomy followed by postoperative radiotherapy. Wazer et al. (*24*) found a borderline significant ($P = .06$) increase in the risk of

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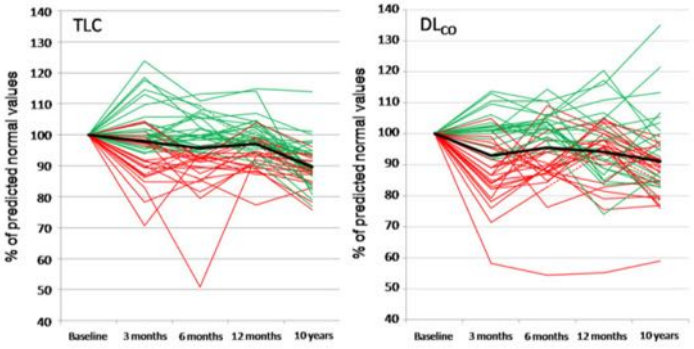
CHANGES IN PULMONARY FUNCTION UP TO 10 YEARS AFTER LOCOREGIONAL BREAST IRRADIATION

KATRIEN ERVEN, M.D.,* CAROLINE WELTENS, M.D., PH.D.,* KRISTIAAN NACKAERTS, M.D., PH.D.,[y] STEFFEN FIEUWS, PH.D.,[z] MARC DECRAMER, M.D., PH.D.,[y] AND YOLANDE LIEVENS, M.D., PH.D.*

Variable	*n*	VC	FEV_1	TLC	DL_{CO}
Radiotherapy					
Left side	23	95	99	89	90
Right side	25	94	93	90	93
p Value		0.89	0.053*	0.63	0.30
Chemotherapy					
Yes	15	96	98	93	93
No	33	94	95	91	90
p Value		0.29	0.46	0.39	0.54
Hormonal therapy					
Yes	19	94	96	87	93
No	29	95	96	91	91
p Value		0.42	0.87	0.012*	0.41
Smoker at baseline					
Yes	12	98	97	89	91
No	36	93	95	90	91
p Value		0.077	0.63	0.96	0.97
Postmenopausal					
Yes	21	93	94	89	91
No	27	96	97	90	92
p Value		0.062	0.32	0.57	0.90
Age >50 y					
Yes	26	93	94	88	92
No	22	96	98	92	91
p Value		0.19	0.21	0.022	0.83
BMI >25 kg/m^2					
Yes	18	94	96	89	93
No	30	95	96	90	90
p Value		0.53	0.76	0.78	0.30
Early decrease >mean					
Yes	26	93	92	88	87
No	22	96	100	91	96
p Value		0.23	0.0045*	0.078	0.0009*



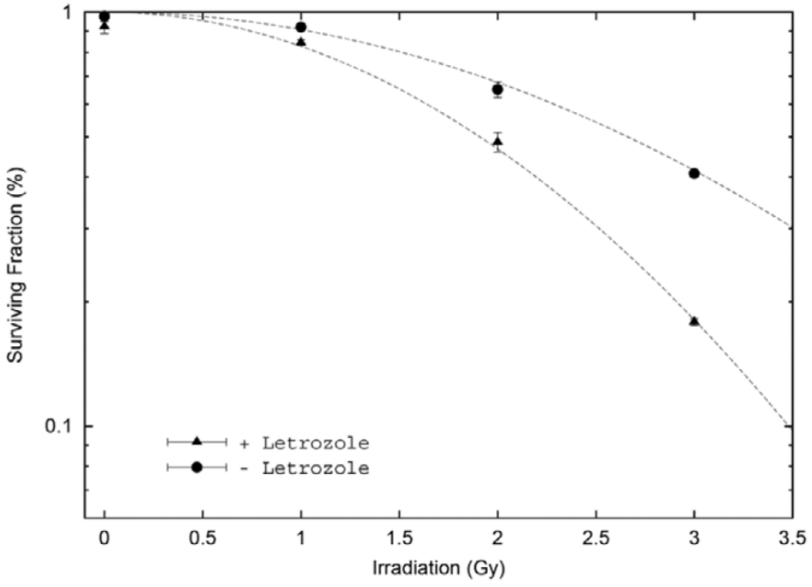
Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 701–707, 2012

Research article

Open Access

Letrozole sensitizes breast cancer cells to ionizing radiation

David Azria[1], Christel Larbouret[2], Severine Cunat[3], Mahmut Ozsahin[4], Sophie Gourgou[5], Pierre Martineau[6], Dean B Evans[7], Gilles Romieu[8], Pascal Pujol[3] and Andre Pèlegrin[2]



Breast Cancer Res 2005, **7**:R156-R163

Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial

David Azria, Yazid Belkacemi, Gilles Romieu, Sophie Gourgou, Marian Gutowski, Khalil Zaman, Carmen Llacer Moscardo, Claire Lemanski, Michael Coelho, Barry Rosenstein, Pascal Fenoglietto, Nigel E A Crompton, Mahmut Ozsahin

Lancet Oncol 2010; 11: 258–65

	Concurrent group (N=55)	Sequential group (N=57)
EORTC QLQ-C30 functional scales		
Physical function	83·7 (20–100)	80·8 (25–100)
Role function	82·4 (0–100)	82·5 (0–100)
Social function	90·0 (0–100)	88·2 (0–100)
Emotional function	76·1 (0–100)	71·5 (0–100)
Cognitive function	78·8 (0–100)	76·6 (0–100)
Global health status/QoL	70·6 (0–100)	65·4 (8–100)
EORTC QLQ-C30 symptom scales		
Fatigue	22·8 (0–100)	28·6 (0–100)
Nausea and vomiting	4·8 (0–100)	4·4 (0–50)
Pain	23·6 (0–100)	29·3 (0–100)
Dyspnoea	16·4 (0–100)	20·5 (0–100)
Sleep disturbance	33·3 (0–100)	40·6 (0–100)
Appetite	8·0 (0–100)	7·6 (0–100)
Constipation	13·9 (0–100)	19·6 (0–100)
Diarrhoea	9·1 (0–100)	7·7 (0–67)
Financial effect	7·9 (0–100)	7·1 (0–100)
EORTC QLQ-23 functional scales		
Body image	85·6 (0–100)	84·0 (0–100)
Sexual function	77·3 (17–100)	86·7 (33–100)
Sexual enjoyment	58·7 (0–100)	59·5 (33–100)
Future perspective	68·5 (0–100)	63·2 (0–100)
EORTC QLQ-23 symptom scales		
Systemic therapy side effects	18·5 (0–71)	20·2 (0–67)
Breast symptoms	13·2 (0–89)	14·9 (0–100)
Arm symptoms	15·2 (0–100)	20·5 (0–100)
Hair loss	28·8 (0–100)	37·5 (0–100)

Data are mean (range). EORTC=European Organisation for Research and Treatment of Cancer. QoL=quality of life.

Table 5: Mean scores from two quality-of-life questionnaires at month 24

	Concurrent group (N=74)				Sequential group (N=75)			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
During radiotherapy								
Baseline	72	2	0	0	26	44	4	1
Week 1	58	5	0	0	59	9	1	0
Week 2	45	19	1	0	51	15	1	0
Week 3	31	34	3	0	35	31	4	0
Week 4	14	40	11	2	20	34	13	2
Week 5	6	41	16	4	8	35	18	3
Week 6	1	15	11	2	2	14	13	1
After radiotherapy								
Week 3	28	35	4	0	22	45	3	1
Week 6	42	22	4	0	58	9	2	0
Week 12	54	14	4	0	60	14	1	0

Data are n.

Table 4: Acute radiation-induced toxic effects of the skin

I° AIRB COURSE IN RADIOBIOLOGY

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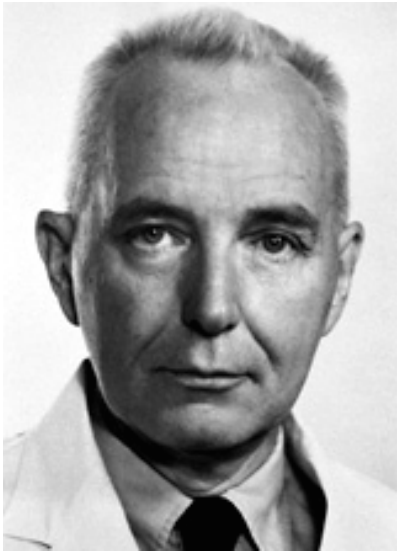
- **in-vitro studies support the notion of antagonistic effects of concurrent tamoxifen and radiotherapy on tumour cells**
- **in-vivo research suggests a synergistic effect that could be attributable to micro-environmental changes in tumour responsiveness to ionising radiation and hormone therapy**

CHARLES HUGGINS

Endocrine-induced regression of cancers

Nobel Lecture, December 13, 1966



I° AIRB COURSE IN RADIOBIOLOGY

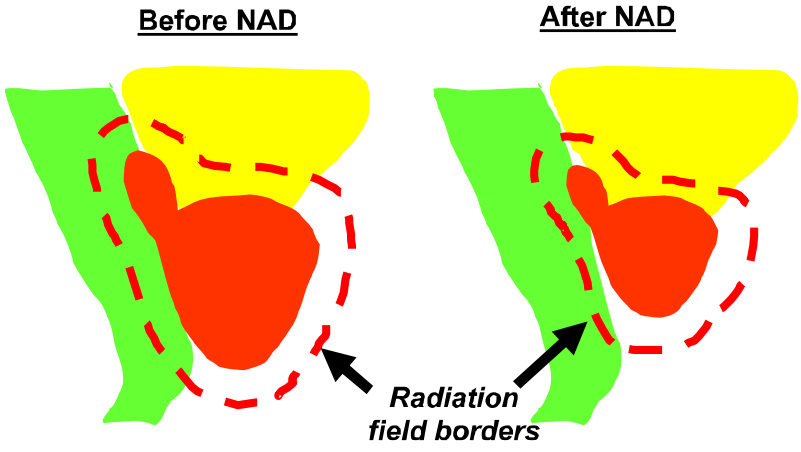
Seminar article

Why does androgen deprivation enhance the results of radiation therapy?

Jennifer Y. Wo, M.D.[a,*], Anthony L. Zietman, M.D.[b]

[a] *Harvard Radiation Oncology Program, Boston, MA 02114, USA*
[b] *Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114, USA*

Technical advantages: Volume Reduction



Urologic Oncology: Seminars and Original Investigations 26 (2008) 522–529

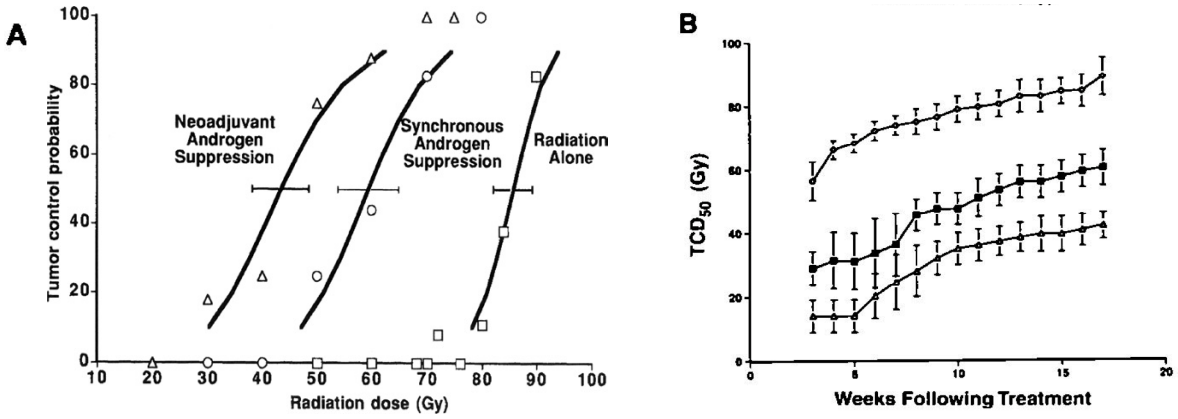
Seminar article

Why does androgen deprivation enhance the results of radiation therapy?

Jennifer Y. Wo, M.D.[a,*], Anthony L. Zietman, M.D.[b]

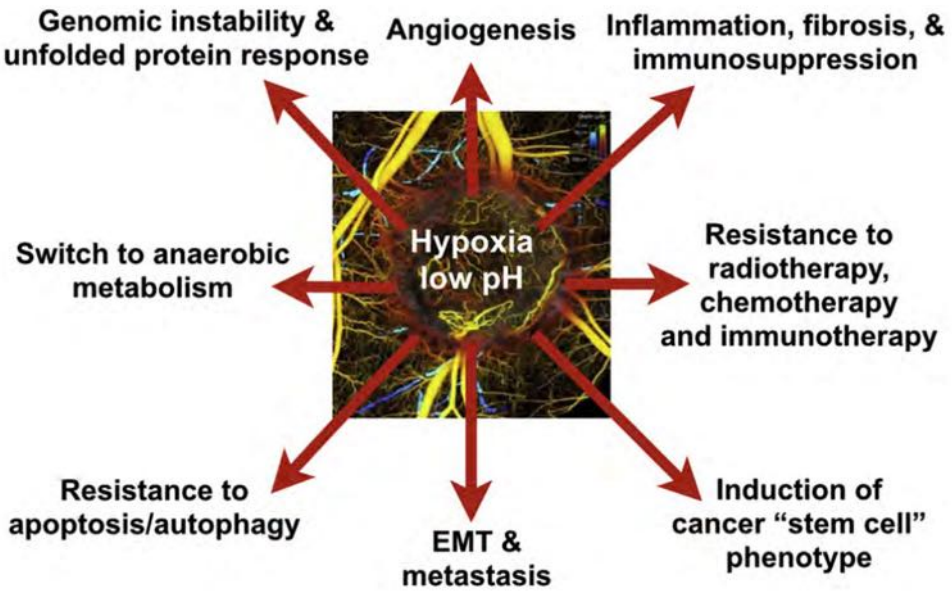
[a] Harvard Radiation Oncology Program, Boston, MA 02114, USA
[b] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114, USA

Biological advantages: prior ADT increase the probability of eradicating tumor by irradiation



Urologic Oncology: Seminars and Original Investigations 26 (2008) 522–529

Treatment failure and poor prognosis of PCa could be due to the anomalous and inefficient pattern of vascularization, leading to intermittent/chronic hypoxia



Published OnlineFirst April 1, 2012; DOI: 10.1158/1078-0432.CCR-11-2711

Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

Tumor Hypoxia Predicts Biochemical Failure following Radiotherapy for Clinically Localized Prostate Cancer

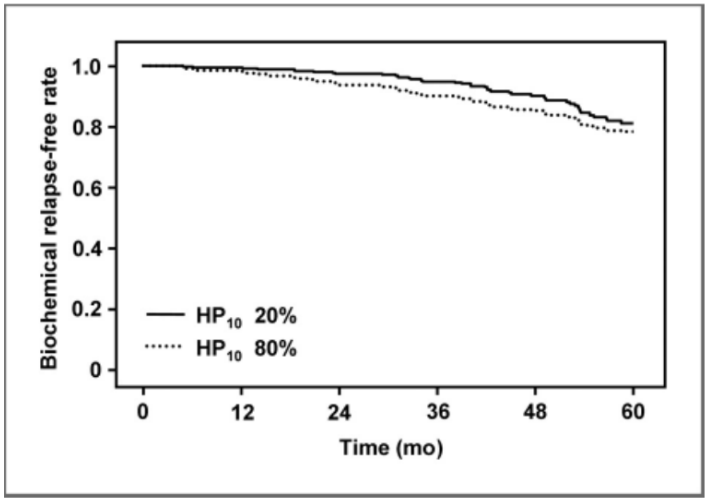


Table 2. Multivariate predictive models for biochemical and LRFRs

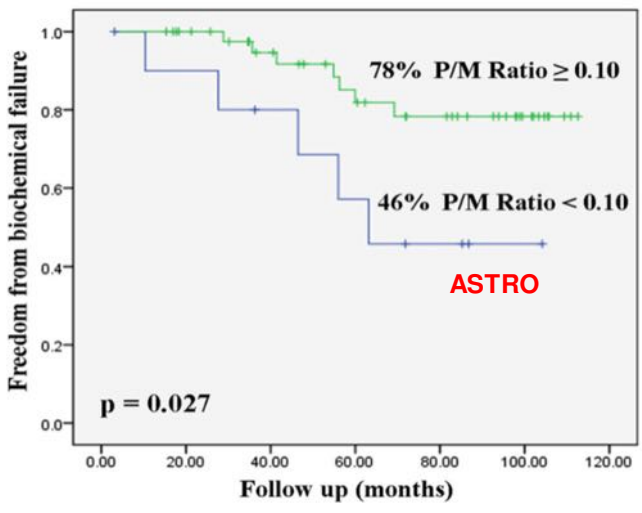
Variable	HR	P
Entire cohort of 247 patients with prostate cancer, bRFR		
Gleason score[a]	2.66	0.015
PSA	1.075	<0.001
HP_{10}[b]	1.023	0.019
HP_{10} with time[c]	0.9995	0.001
142 patients with bulk[d] tumor at the site of the oxygen measurements, bRFR		
Age	1.073	0.021
PSA	1.085	<0.001
HP_{10}[b]	1.036	0.004
HP_{10} with time[c]	0.9992	<0.001
70 patients with prostate biopsies for local control, LRFR		
HP_{10}[b]	1.037	0.043
HP_{10} with time[c]	0.9991	0.032

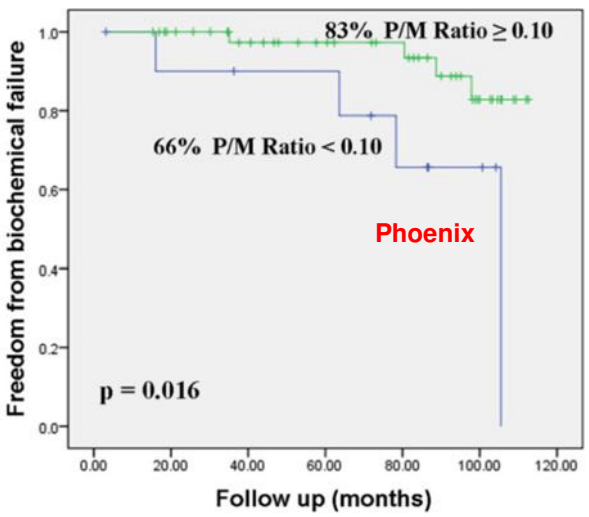
NOTE: No effect of age, clinical T-category, the proportion of positive diagnostic biopsy cores, radiotherapy dose, or the use of hormonal therapy on either bRFR or LRFR.
[a]Gleason 8 versus 6 or 7.
[b]Effect of HP_{10} on outcome (bRFR or LRFR) at the completion of treatment.
[c]HP_{10} time dependence. Time expressed in months from the date of the oxygen measurements.
[d]See text for definition of bulk tumor.

I° AIRB COURSE IN RADIOBIOLOGY

Hypoxic Prostate/Muscle Po_2 Ratio Predicts for Outcome in Patients With Localized Prostate Cancer: Long-Term Results

Aruna Turaka, M.D.,* Mark K. Buyyounouski, M.D., M.S.,* Alexandra L. Hanlon, Ph.D.,† Eric M. Horwitz, M.D.,* Richard E. Greenberg, M.D.,‡ and Benjamin Movsas, M.D.§

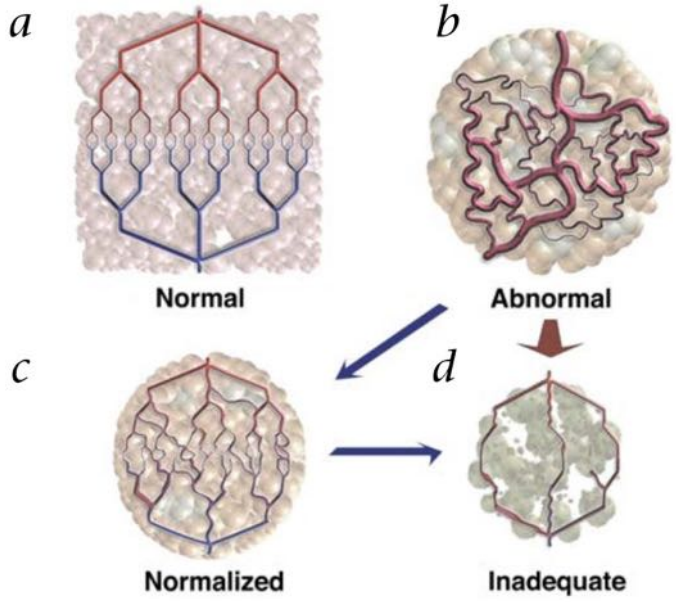




Int J Radiation Oncol Biol Phys, Vol. 82, No. 3, pp. e433–e439, 2012

Anti-angiogenic therapy was proposed in 1971 as a means to treat solid tumors and in 1976 as a method of cancer prevention. Here we propose that this form of therapy, judiciously applied, can normalize the tumor vasculature and improve the delivery of therapeutics.

Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy



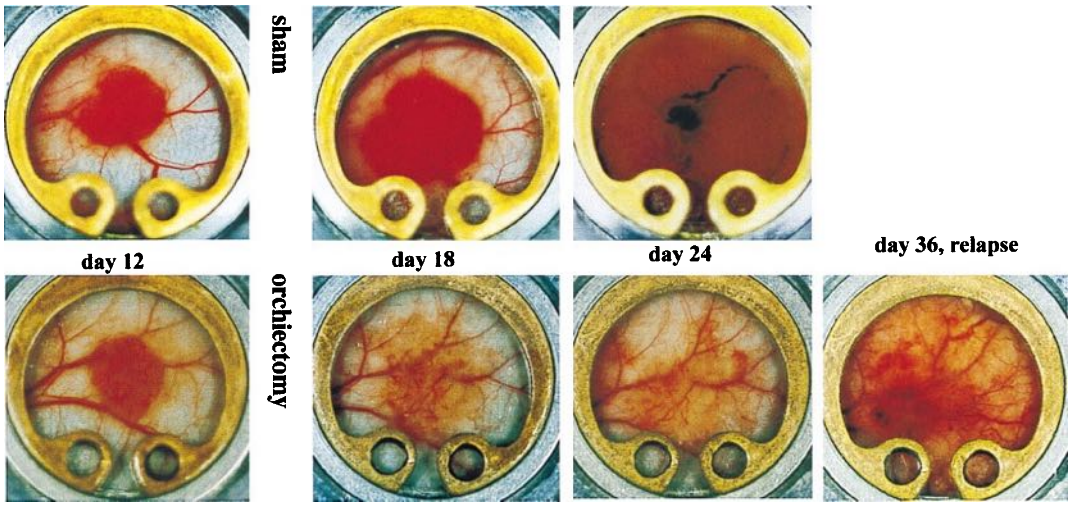
I° AIRB COURSE IN RADIOBIOLOGY

Endothelial cell death, angiogenesis, and microvascular function after castration in an androgen-dependent tumor: Role of vascular endothelial growth factor

(vascular regression/permeability/vascular density)

RAKESH K. JAIN*†, NINA SAFABAKHSH*‡, AXEL SCKELL*§, YI CHEN*, PING JIANG*, LAURA BENJAMIN¶, FAN YUAN*‖, AND ELI KESHET¶

Proc. Natl. Acad. Sci. USA 95 (1998)



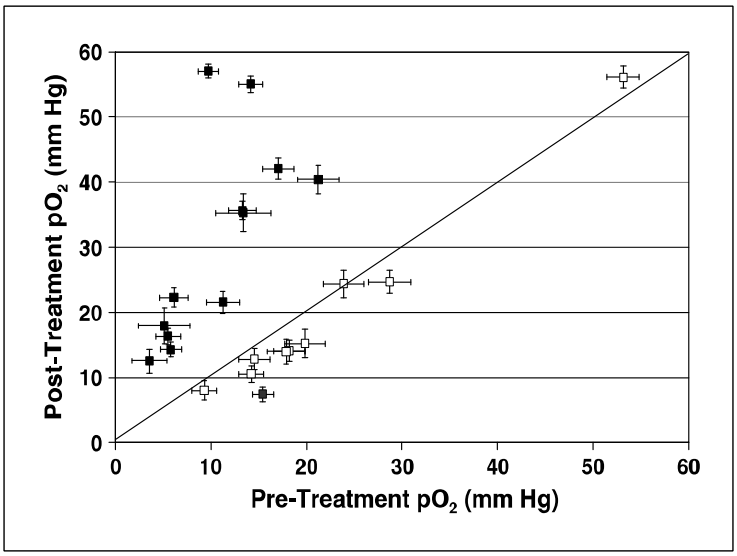
Hormone withdrawal inhibits VEGF expression and angiogenesis in hormone-dependent PCa, thereby mimicking anti-VEGF therapy

Priority Report

Androgen Withdrawal in Patients Reduces Prostate Cancer Hypoxia: Implications for Disease Progression and Radiation Response

Michael Milosevic,[1,5] Peter Chung,[1,5] Chris Parker,[9] Robert Bristow,[1,4,5,8] Ants Toi,[2,6] Tony Panzarella,[3,7] Padraig Warde,[1,5] Charles Catton,[1,5] Cynthia Menard,[1,5] Andrew Bayley,[1,5] Mary Gospodarowicz,[1,5] and Richard Hill[4,8]

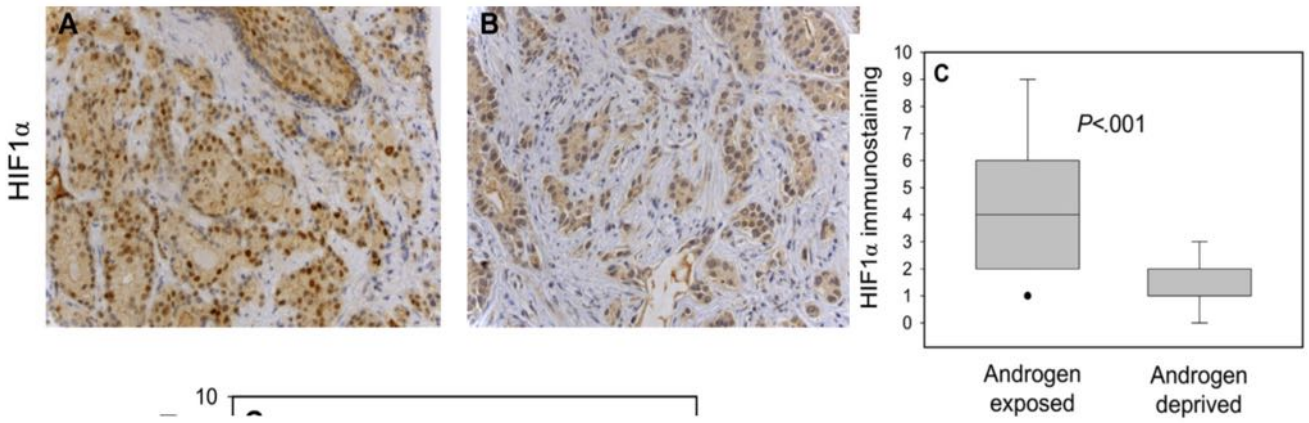
pO2 increased from 6.4 to 15 mmHg



Cancer Res 2007; 67: (13). July 1, 2007

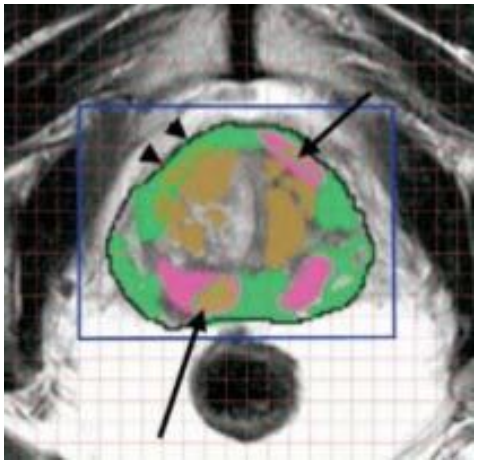
Hypoxia-Independent Downregulation of Hypoxia-Inducible Factor 1 Targets by Androgen Deprivation Therapy in Prostate Cancer

Harald Bull Ragnum, MD,* Kathrine Røe, PhD,*,# Ruth Holm, PhD,† Ljiljana Vlatkovic, MD,† Jahn Marthin Nesland, PhD,†,** Eva-Katrine Aarnes, MSc,* Anne Hansen Ree, PhD,#,** Kjersti Flatmark, PhD,‡,§ Therese Seierstad, PhD,||,†† Wolfgang Lilleby, PhD,¶ and Heidi Lyng, PhD*



Int J Radiation Oncol Biol Phys, Vol. 87, No. 4, pp. 753–760, 2013

Importance of monitoring changes in tumor hypoxia during ADT



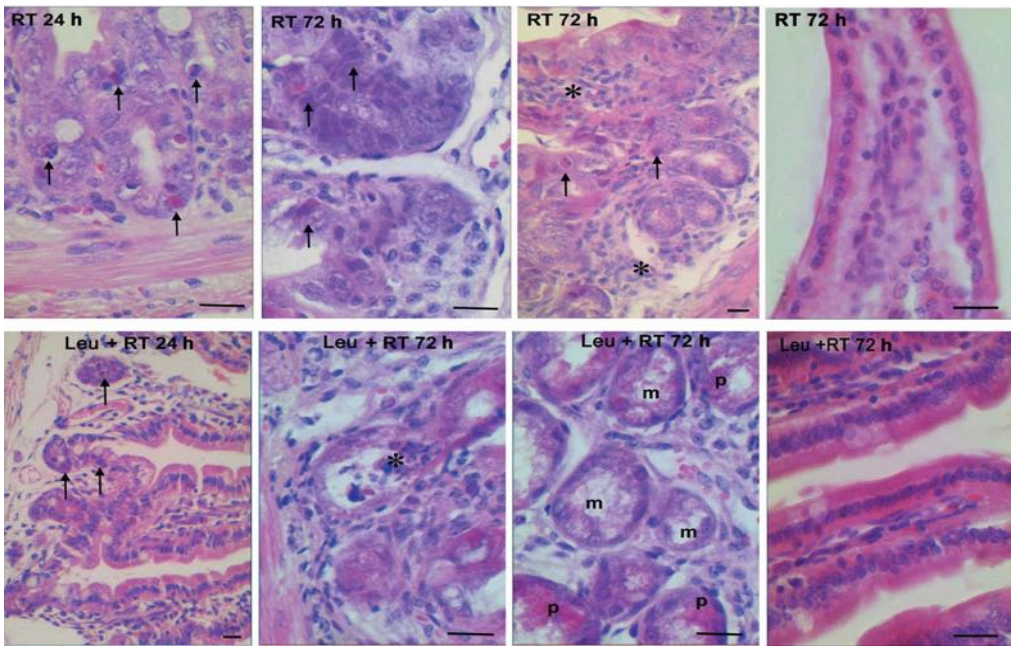
Hypoxia biomarker such HIF1a could be helpful for planning RT initiation and potential use of hypoxia-targeted therapy.

I° AIRB COURSE IN RADIOBIOLOGY

ANTICANCER RESEARCH *35*: 3875-3884 (2015)

Protective Effect of Leuprorelin on Radiation-induced Intestinal Toxicity

MONICA MANGONI[1], MARIANGELA SOTTILI[1], CHIARA GERINI[1], ROSSELLA FUCCI[1], ALESSANDRO PINI[2], LAURA CALOSI[2], PIERLUIGI BONOMO[1], BEATRICE DETTI[1], DANIELA GRETO[1], ICRO MEATTINI[1], GABRIELE SIMONTACCHI[1], MAURO LOI[1], DANIELE SCARTONI[1], ILARIA FURFARO[1], STEFANIA PALLOTTA[3] and LORENZO LIVI[1]



European Association of Urology

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			**Locally advanced**

European Association of Urology 2015

Intermediate risk PCa	**Radiotherapy**	In intermediate-risk PCa, the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A

High risk PCa	**Radiotherapy**	In patients with high-risk localised PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yr is recommended).	A
		In patients with **locally advanced cN0** PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr is recommended).	A

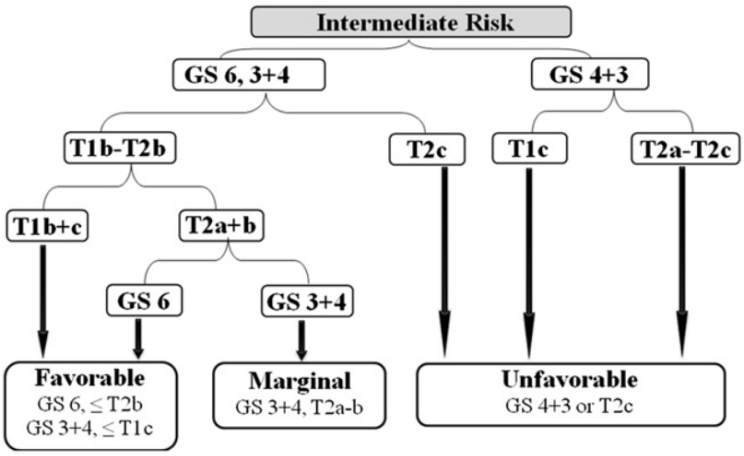
I° AIRB COURSE IN RADIOBIOLOGY

Synthesis of Trials Data

- **Overall Survival Benefit**
  - **EORTC 22863** – 3 yrs vs. 0 (18.3% at 10 yrs)
  - **TROG 9601** – 6 months vs. 0 (13.3% at 3 yrs)
  - **DFCI 95096** – 6 months vs. 0 (13% at 8 yrs)
  - **RTOG 8610** – 4 months vs. 0 (8.8% at 10 yrs)
  - **RTOG 9408** – 4 months vs. 0 (5% at 10 yrs)
  - **RTOG 9910** – 9 months vs. 4 months (1% at 10 yrs)
  - **EORTC 22961** – 3 yrs vs. 6 months (3.8% at 5 yrs)

Are these results transferable in daily clinical practice ?

- **Population**: inhomogeneity of intermediate risk group



- **Intervention**: use of ineffective RT total dose
- **Outcomes**: improvement in OS and DFS likely overestimated

I° AIRB COURSE IN RADIOBIOLOGY

CLINICAL INVESTIGATION Prostate

WHAT DOSE OF EXTERNAL-BEAM RADIATION IS HIGH ENOUGH FOR PROSTATE CANCER?

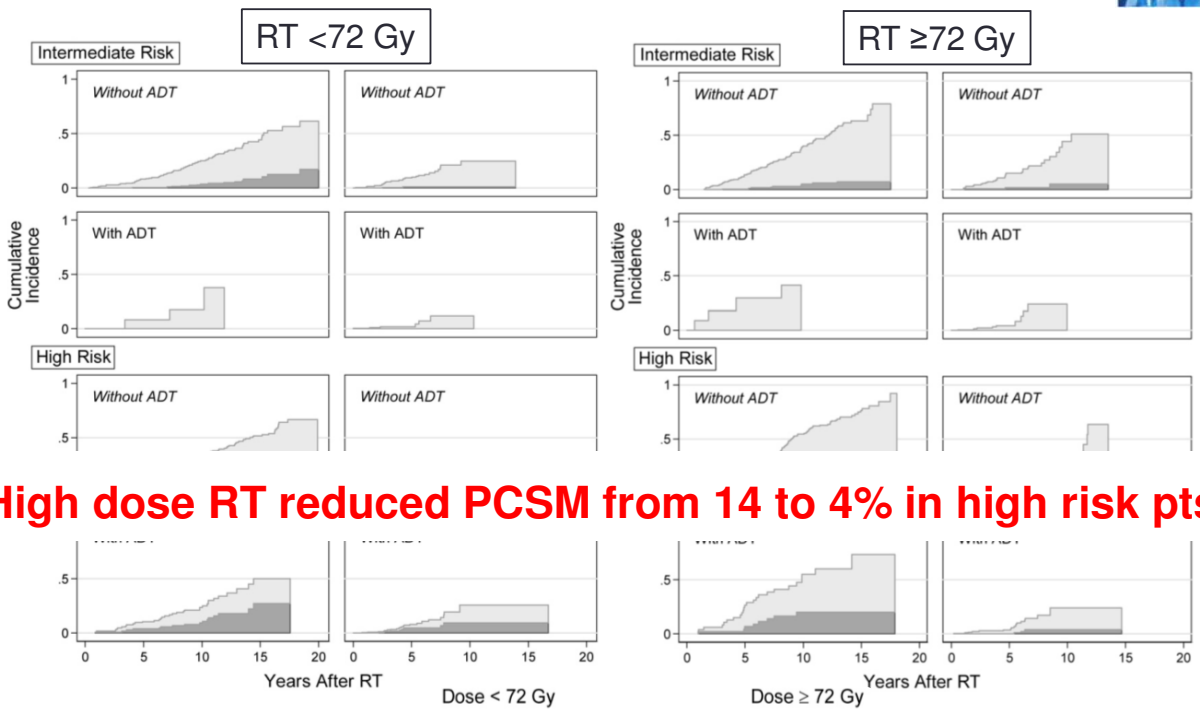
THOMAS N. EADE, F.R.A.N.Z.C.R.,* ALEXANDRA L. HANLON, PH.D.,† ERIC M. HORWITZ, M.D.,* MARK K. BUYYOUNOUSKI, M.D.,* GERALD E. HANKS, M.D.,* AND ALAN POLLACK, M.D., PH.D.*

A decrease in BF secondary to dose escalation should translate into a reduction in distant spread (10). Our results more precisely define this relationship, showing that RT dose causes an 8% reduction in the risk of distant metastases for each 1 Gy delivered. We anticipate that as our median follow-up increases, the benefit of dose escalation will strengthen, because higher initial doses will proportionally increase local control and prevent the late wave of distant metastasis due to persistent local disease (34, 35). Follow-up >10 years is required

Int J Rad Oncol Biol Phys 2008

Prostate cancer-specific mortality after definitive radiation therapy: Who dies of disease?

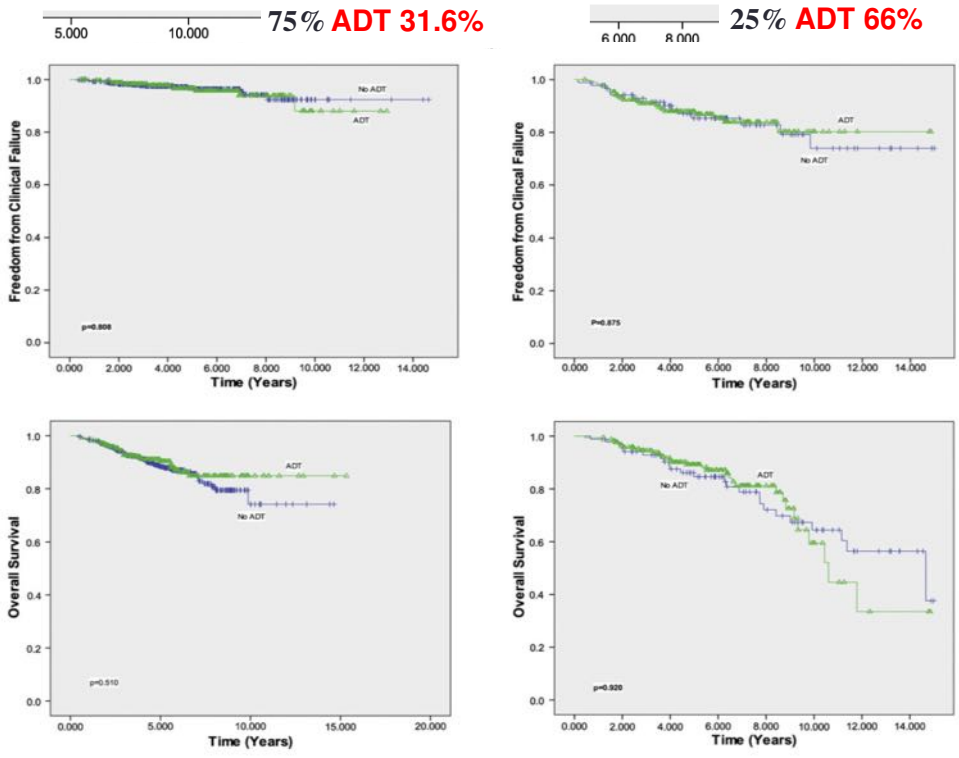
Outcomes of 2675 men with localised PC treated with RT ± ADT from 1987–2007



High dose RT reduced PCSM from 14 to 4% in high risk pts

CLINICAL INVESTIGATION — Prostate

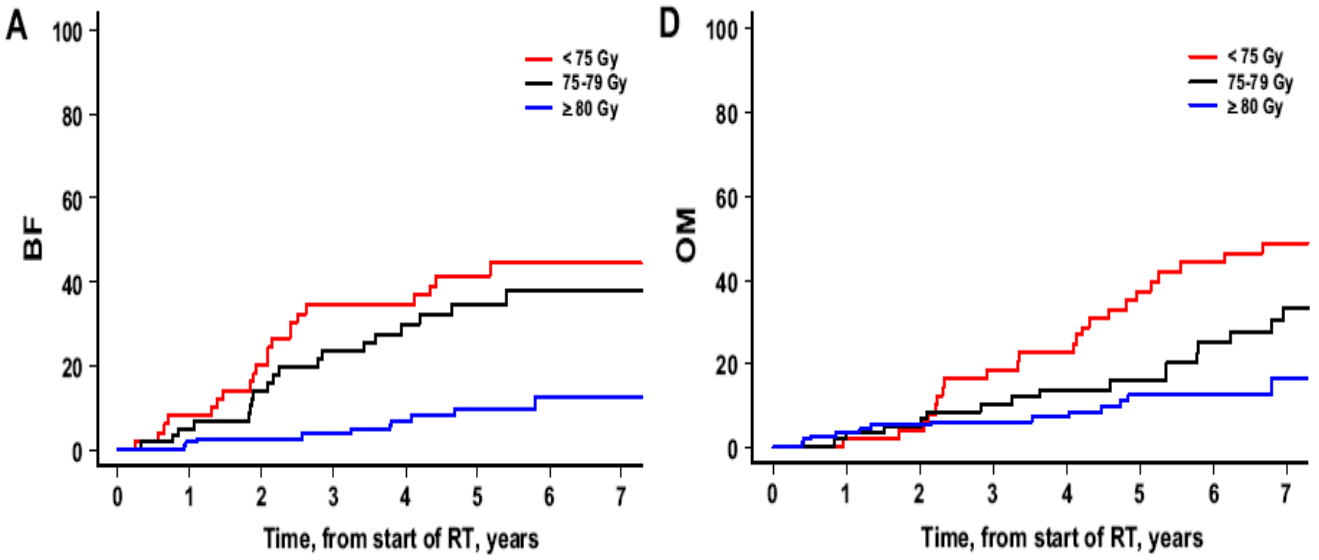
LACK OF BENEFIT FOR THE ADDITION OF ANDROGEN DEPRIVATION THERAPY TO DOSE-ESCALATED RADIOTHERAPY IN THE TREATMENT OF INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER



CLINICAL INVESTIGATION

RADIOTHERAPY DOSES OF 80 GY AND HIGHER ARE ASSOCIATED WITH LOWER MORTALITY IN MEN WITH GLEASON SCORE 8 TO 10 PROSTATE CANCER

NIRAJ PAHLAJANI, M.D.,* KAREN J. RUTH, M.S.,† MARK K. BUYYOUNOUSKI, M.D.,‡



Int J Rad Oncol Biol Phys 2012

I° AIRB COURSE IN RADIOBIOLOGY

RT + long vs. long ADT

Very HR PCa

- **PCS IV. #NCT00223171** – 70 Gy RT + 18 months HT vs. 36 months HT
  - no OS neither PSCM benefit at median follow up of 6.4 yrs
  - T3-T4; PSA >20; GS >7; N0

EORTC 22961 vs. PCS IV

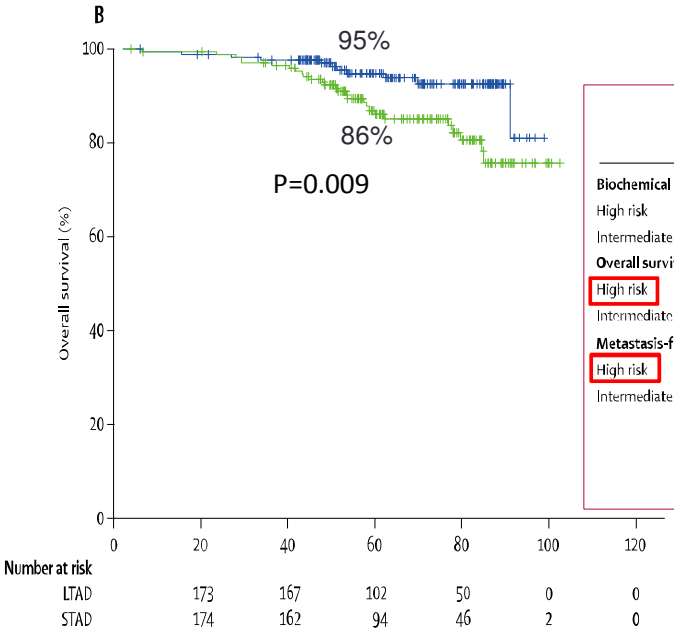
Study	N. pts	Median f-up (years)	5-year Survival (%)		
Duration of ADT			6 months	18 months	36 months
EORTC[1]	970	6.4	80.6		85.3
PCS IV[2]	630	6.4		86.8	92.1

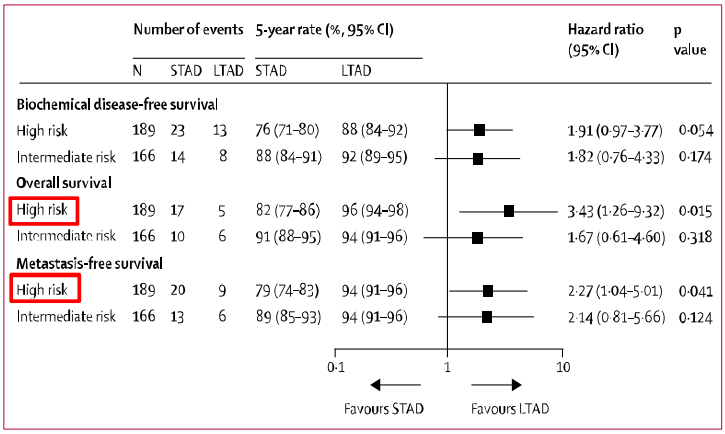
[1] Bolla M et al. N Engl J Med 2009

[2] Nabid A, et al. JCO 2013;31(S6):3 (abs)

High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial

Lancet Oncol 2015; 16: 320–27





I° AIRB COURSE IN RADIOBIOLOGY

High dose RT ± ADT

Ongoing Trials

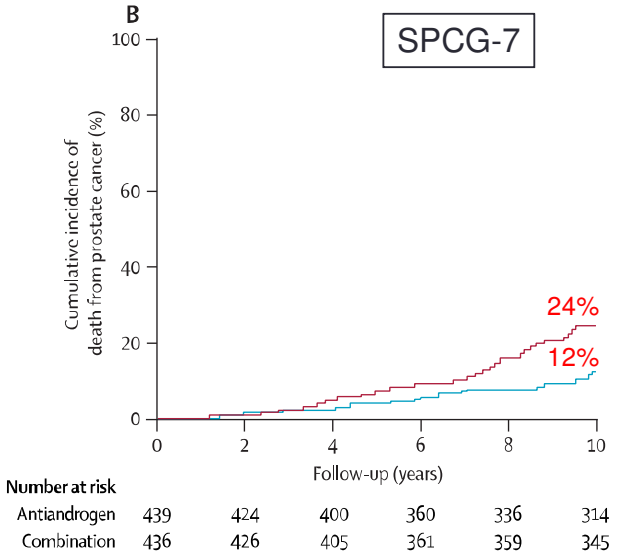
- **RTOG 0815** – 79.2 Gy RT ± 6 months HT in IR-HR PCa

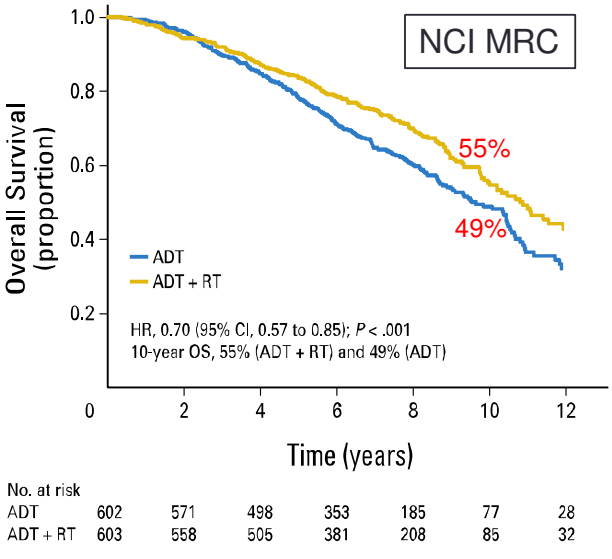
  The only trial stratified by Adult Comorbidity Evaluation-27 comorbidity score

- **EORTC 22991** – 70 Gy/74 Gy/78 Gy RT ± 6 months HT in IR PCa

  - 819 pts from 14 European Countries

ADT ± RT





10 yrs	ADT+RT	ADT	p
bF	26%	75%	< 0.001
CSS	88%	76%	< 0.001
OS	70%	61%	0.004

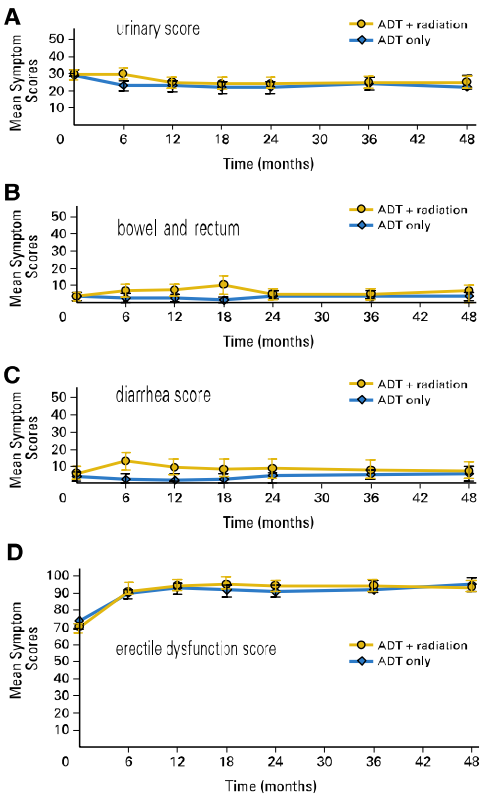
10 yrs	ADT+RT	ADT	p
TTP	63%	27%	< 0.001
CSS	68%	46%	< 0.001
OS	55%	49%	0.001

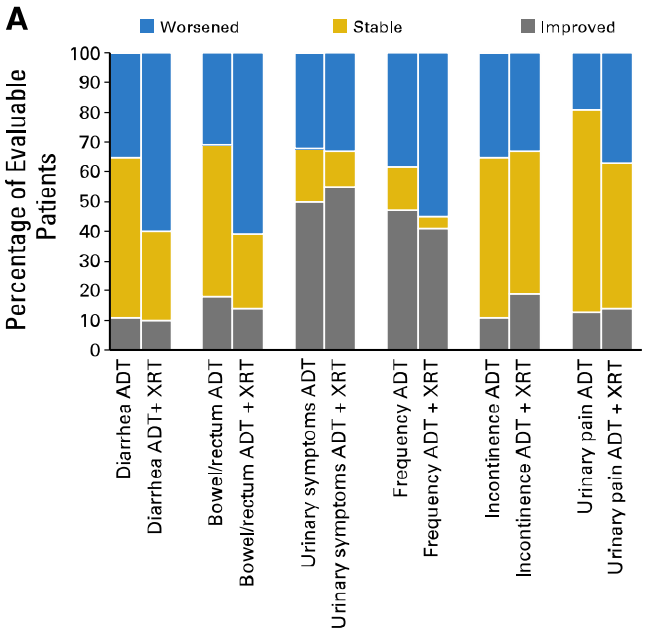
I° AIRB COURSE IN RADIOBIOLOGY

ADT ± RT

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Quality-of-Life Outcomes From the NCIC CTG PR3/MRC PR07 Randomized Trial

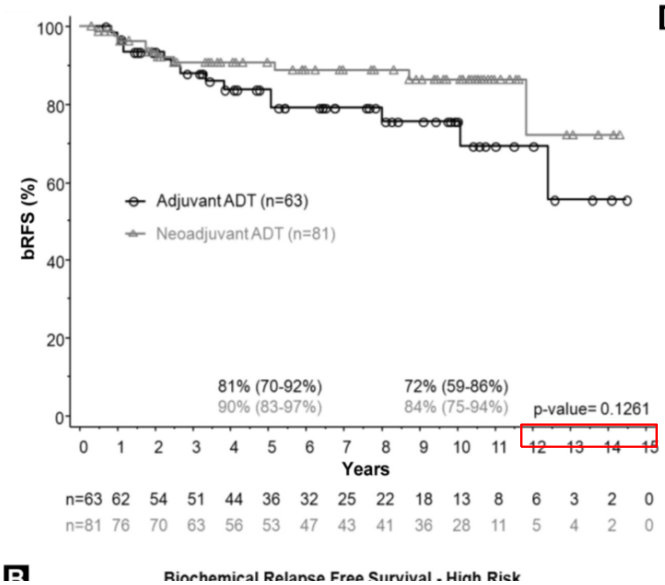


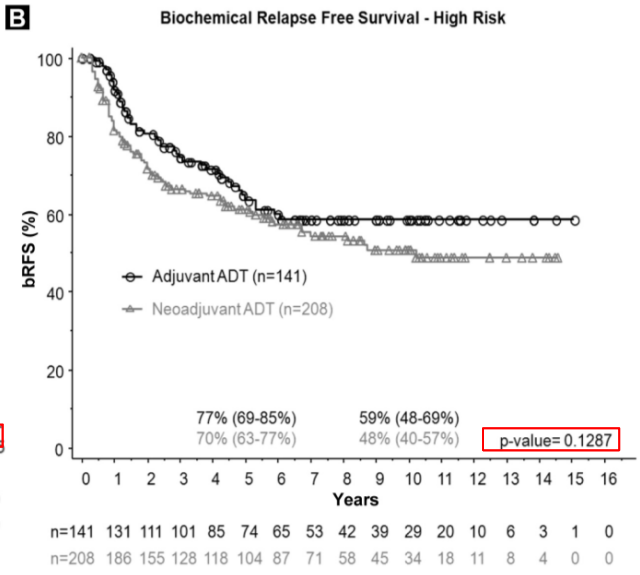


Original Study

Clinical Genitourinary Cancer Month 2015

Adjuvant Versus Neoadjuvant Androgen Deprivation With Radiotherapy for Prostate Cancer: Does Sequencing Matter?





B Biochemical Relapse Free Survival - High Risk

The synergy between RT and ADT is independent of the sequencing of both

...more in

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Combination of androgen deprivation therapy and radiotherapy for localized prostate cancer in the contemporary era

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Received 14 February 2014; received in revised form 18 August 2014; accepted 1 October 2014