

# Surgery/radiotherapy/chemotherapy/hormonal manipulation interactions and treatment damage: the case of prostate cancer



Barbara A. Jereczek-Fossa

European Institute of Oncology  
University of Milan



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Brescia Meetings in Radiation Oncology – 2014 Edition

NORTHWEST PASSAGE:  
KEY-FUNCTIONS PRESERVATION IN ONCOLOGY

Brescia 26.09.2014

European Institute of Oncology

## VALIDATED APPROACHES TO NON METASTATIC PROSTATE CANCER

**Active monitoring** (low-risk) & watchful waiting  
(advanced)

**Active treatment:**

- Radical prostatectomy
- Radiotherapy
- Combination with ADT (surg/RT +/- ADT)**

**Advanced disease: combined treatments**

# DISEASE COURSE in PROSTATE CANCER

Localized PCa

Recurrence

Dissemination

Progression



RT  
SURG  
SURG/RT/ADT  
RT/ADT

RT  
ADT  
RT/ADT

ADT  
RT/ADT

TXT  
ENZA  
ABI

CABA, RT  
Istituto  
Europeo  
di Oncologia

# COMBINED TREATMENT

# Combined treatment

1. RT + ADT
2. Surgery + RT
3. RT + CHT
4. New agents

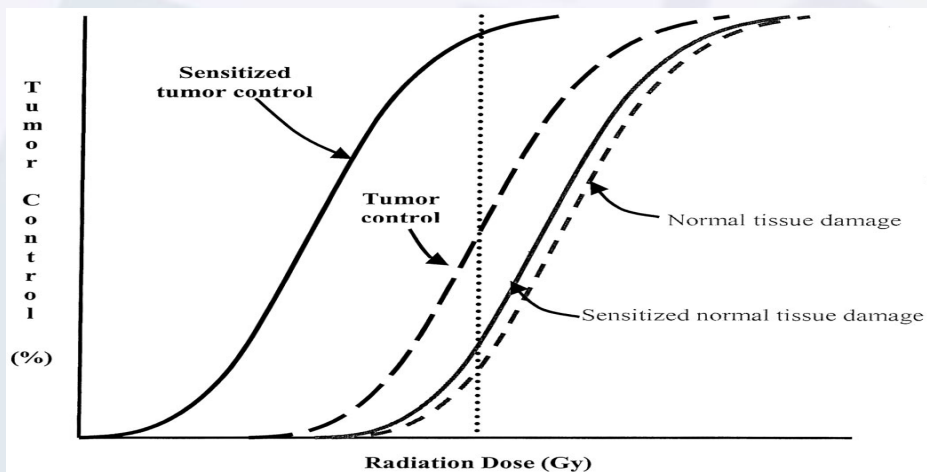
# Cancer survivors park



# RISKS and BENEFITS



# RISKS and BENEFITS



# Combined treatment

1. RT + ADT
2. Surgery + RT
3. RT + CHT
4. New agents

## Does Hormone Treatment Added to Radiotherapy Improve Outcome in Locally Advanced Prostate Cancer?

Meta-Analysis of Randomized Trials

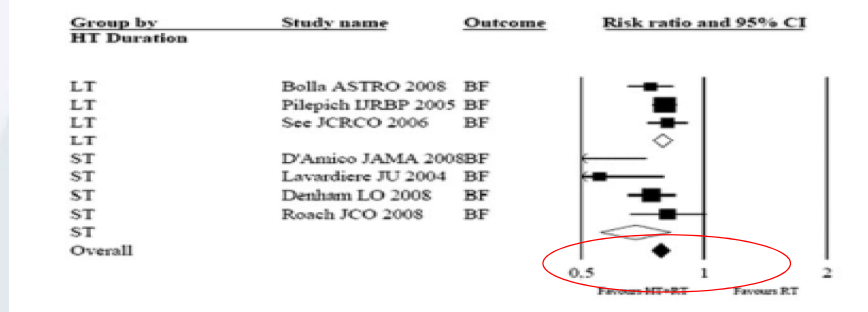
Emilio Brià, MD<sup>1</sup>; Federica Cuppone, MD<sup>1</sup>; Diana Giannarelli, PhD<sup>2</sup>; Michele Milella, MD<sup>3</sup>;  
Enzo Maria Ruggeri, MD<sup>3</sup>; Isabella Sperduti, PhD<sup>2</sup>; Paola Pinnarò, MD<sup>1</sup>; Edmondo Terzoli, MD<sup>3</sup>;  
Francesco Cognetti, MD<sup>1</sup>; and Paolo Carlini, MD<sup>1</sup>

Cancer 2009;115:3446-56.

**Level 1a evidence**

# BIOCHEMICAL CONTROL

## A. Primary Outcome: BF.



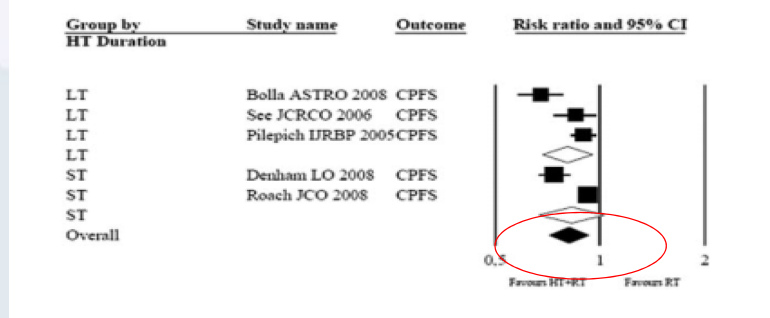
Reduction in biochemical failure - RR 0.76 (10%)

Number needed to treat: 10

**Level 1a evidence**

# CLINICAL PROGRESSION FREE SURVIVAL

## B. Primary Outcome: CPFS.



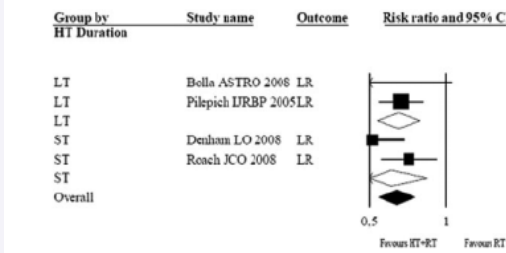
Reduction of the risk of clinical progression RR 0.81 (7.7%)

Number needed to treat: 13

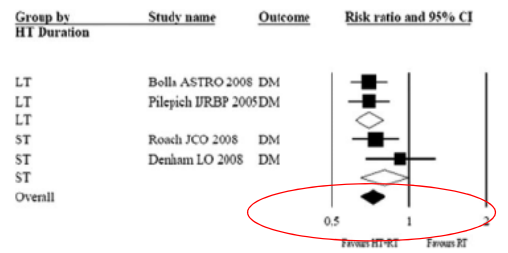
**Level 1a evidence**

# LOCAL AND DISTANT CONTROL

E. Secondary Outcome: LR.



F. Secondary Outcome: DM.

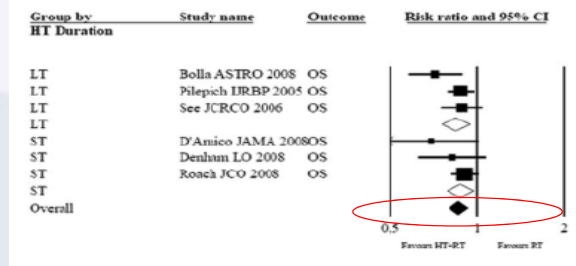


Reduction in local failure and distant metastasis (by 36% and 28%)

**Level 1a evidence**

# OVERALL SURVIVAL

D. Secondary Outcome: OS.



Reduction of the global mortality RR 0.86 (4.9%)

Number needed to treat: 20

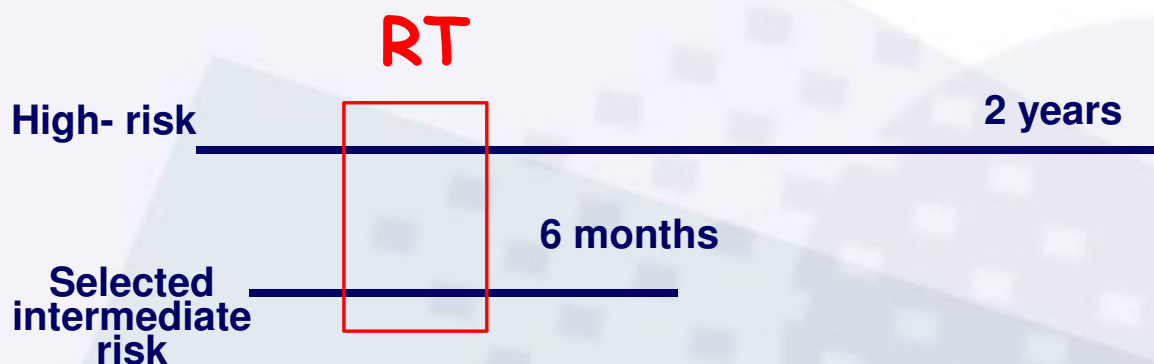
**Level 1a evidence**

# CURRENT EVIDENCE FOR AD/RT

## Randomized trials & meta-analysis

Patient category	Treatment (RT)	Level of evidence
Low risk/very low risk (T1, 2a; PSA < 10, GS < 7)	RT or active monitoring	
Intermediate risk (T2b-c, PSA 10-20, GS 7)	High dose RT or RT + short term AD	1b
High risk/very high (T3-4, PSA > 20, GS 8-10) or N1	RT + long term (2-3y) AD	1a

## TIMING



**AGENT: single LHRH analog +/- antiandrogen**  
**no role for bicalutamide alone**



# TOXICITY

## Does Hormone Treatment Added to Radiotherapy Improve Outcome in Locally Advanced Prostate Cancer?

Meta-Analysis of Randomized Trials

Emilio Bris, MD<sup>1</sup>; Federica Cuppone, MD<sup>1</sup>; Diana Giannarelli, PhD<sup>2</sup>; Michele Milella, MD<sup>3</sup>; Enzo Maria Ruggeri, MD<sup>4</sup>; Isabella Sperduti, PhD<sup>5</sup>; Paola Pinnaro, MD<sup>6</sup>; Edmondo Terzoli, MD<sup>7</sup>; Francesco Cognetti, MD<sup>8</sup>; and Paolo Carlini, MD<sup>9</sup>

**...No difference in toxicity...**

(under-evaluated?)

**Level 1a evidence?**



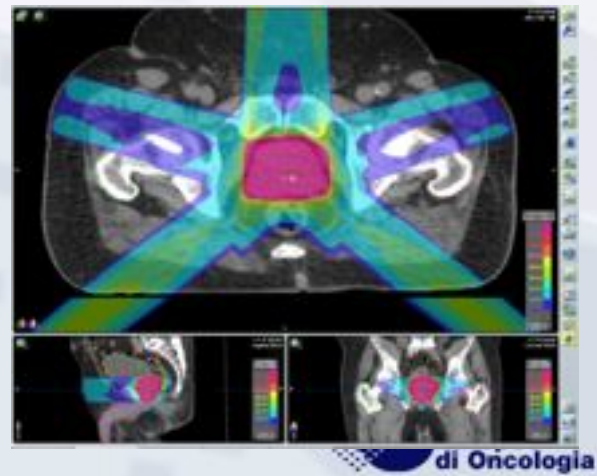
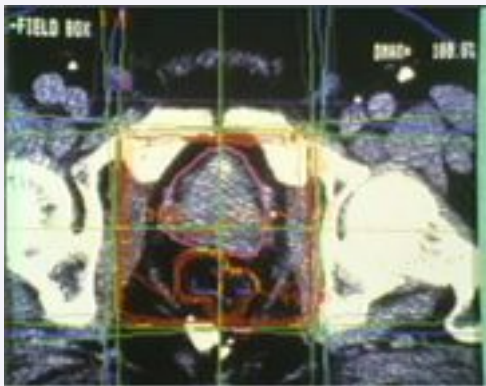
## MAJOR CONCERNS

1. Cardiac toxicity
2. Diabetes mellitus
3. Bone fractures

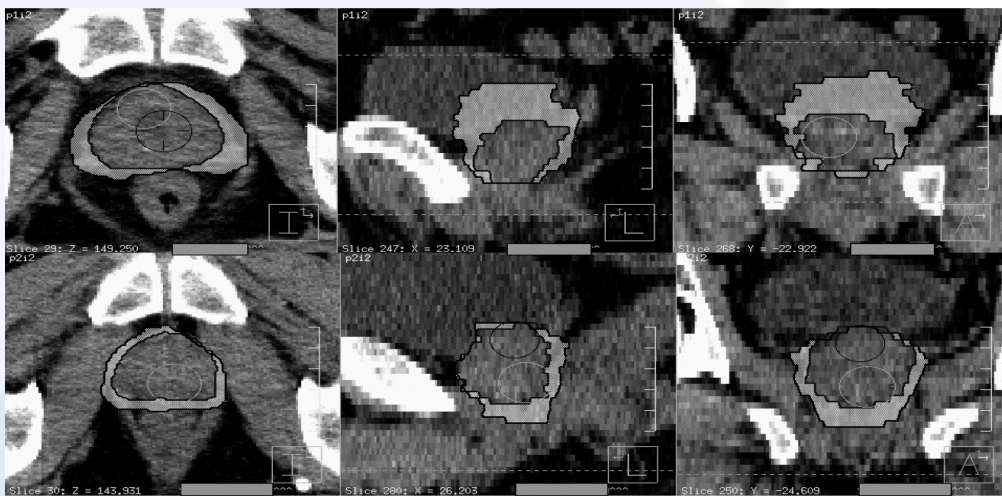
## MAJOR CONCERNS

1. Cardiac toxicity
  2. Diabetes mellitus
  3. Bone fractures
- METABOLIC  
SYNDROME**

## LOCAL TOXICITY?

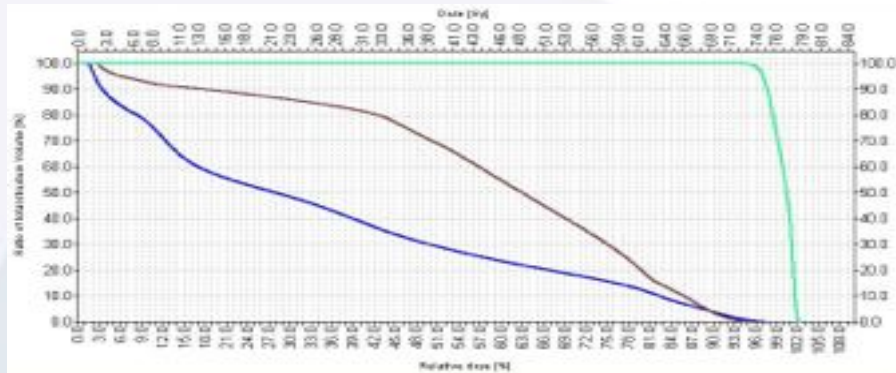


## NEOADJUVANT: DOWNSIZING



**Most of the reduction: in the first 2-3 months**

# NEOADJUVANT: DOWNSIZING



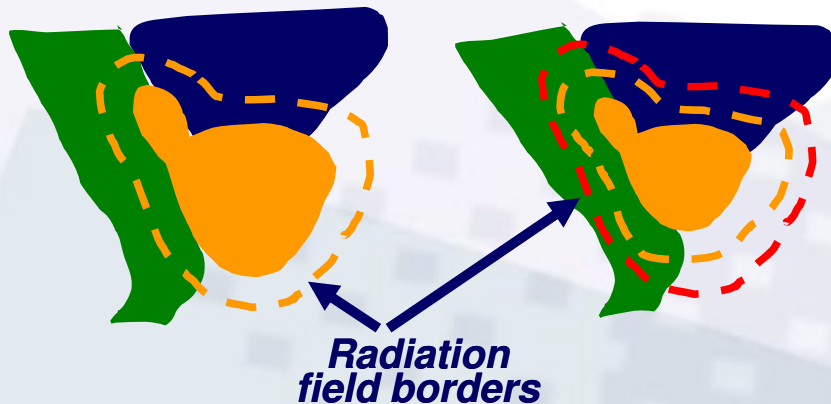
AD allows for:

- ↓ rectal volume in high-dose area by 18-28%
- ↓ bladder volume in high-dose area by 45-50%
- ↓ bowel volume in high-dose area by 12-100%

Zelevsky, 1997

Istituto Europeo di Oncologia

# PITFALLS OF DOWNSIZING



- Higher RT doses to rectum and bladder if RT + AD start together (if prostate RT only)

- Effect on late toxicity?

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## Review – Prostate Cancer

## Functional Outcomes and Complications Following Radiation Therapy for Prostate Cancer: A Critical Analysis of the Literature

Lars Budäus<sup>a,\*</sup>, Michel Bolla<sup>b</sup>, Alberto Bossi<sup>c</sup>, Cesare Cozzarini<sup>d</sup>, Juanita Crook<sup>e</sup>, Anders Widmark<sup>f</sup>, Thomas Wiegel<sup>g</sup>

“...Established risk factors for acute or late toxicities after RT include:

- advanced age,
- larger rectal volume,
- a history of previous abdominal surgery,
- the use of concomitant androgen deprivation,
- preexisting diabetes mellitus,
- haemorrhoids,
- and inflammatory bowel disease...”

Budaus et al. 2011



# BJC

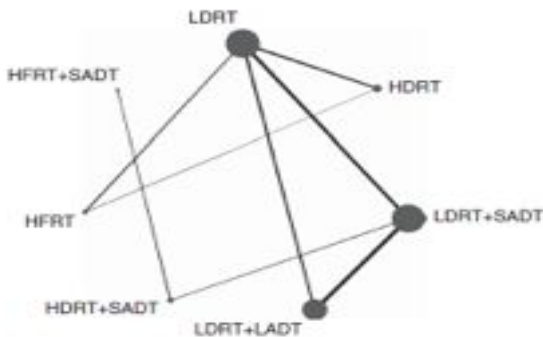
FULL PAPER

British Journal of Cancer (2014) 110, 2396–2404 | doi: 10.1038/bjc.2014.197

Keywords: EBRT; prostate cancer; network meta-analysis

## Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

Z Zhu<sup>1</sup>, J Zhang<sup>1</sup>, Y Liu<sup>1</sup>, M Chen<sup>1</sup>, P Guo<sup>2</sup> and K Li<sup>1,3</sup>



**HypoRT + Short ADT:**

- Most efficacious
- Highest toxicity



# Combined treatment

1. RT + ADT
2. Surgery + RT
3. RT + CHT
4. New agents

Lancet 2005; 366: 572-78

## Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911)

Michel Bolla, Hein van Poppel, Laurence Collette, Paul van Caugh, Kris Vekemans, Luigi Di Pozzo, Theo M de Reijke, Antony Verbooy,  
Jean-François Bassot, Roland van Velthoven, Jean-Marc Marichal, Pierre Scalfiet, Karin Haustermans, Marianne Pivrot, for the European  
Organization for Research and

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

### Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific Antigen: ARO 96-02/AUO AP 09/95

Thomas Wrigel, Dirk Bontje, Uweka Sreeni, Alessandro Sposasso, Reinhard Galle, Stephan Skudelny,  
Norbert Willich, Axel  
Peter Alikhan, Udo Rul,  
Wolfgang Hinkelbein, et al.

From the Department of Radiation  
Oncology, University Hospital Groningen,  
Groningen, The Netherlands; and the  
Department of Radiation Oncology, University  
Hospital Groningen, Groningen, The Netherlands.

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Vol. 181, 956-961, March 2009  
Printed in U.S.A.  
DOI:10.1016/j.juro.2008.11.032

### Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial

Ian M. Thompson,\*†, Catherine M. Tangen, Jorge Parekh, M. Scott Lucia,  
Gary Miller,† Dean Trayan, Edward Messing, Jeffrey Forman, Joseph Chin,  
Gregory Swanson, Edith Carby-Hagins and E. David Crawford

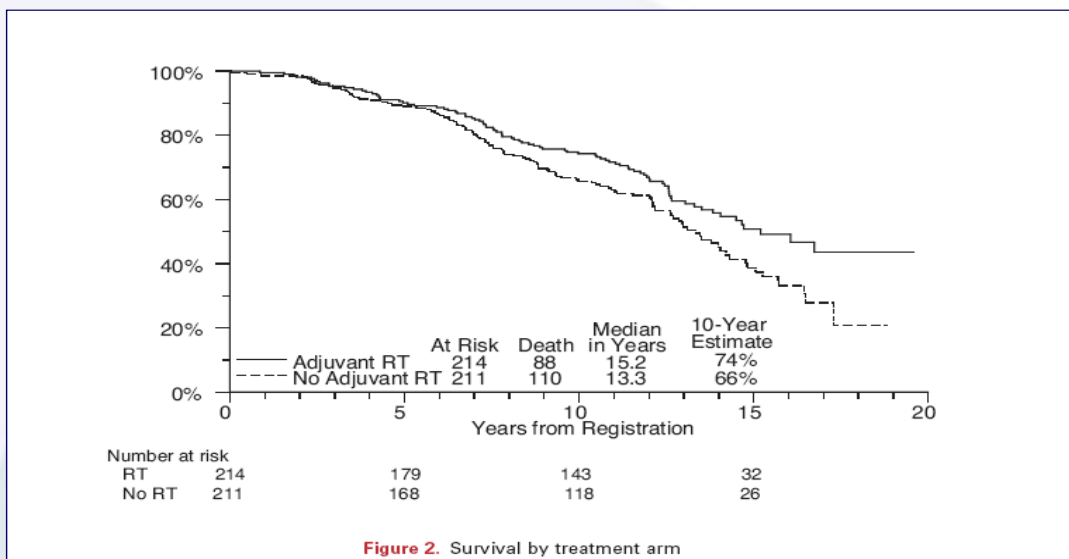
From the University of Texas Health Science Center at San Antonio (M.T., D.T., G.M., and M.S.L.), and the University of Texas Health Science Center at San Antonio, Texas; The Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland (C.M.T.); The Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland (J.F.); The University of Colorado Health Sciences Center, Denver, Colorado (E.M.); The Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland (G.S.); The Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland (E.C.H.); and the University of Western Ontario, Department of Radiation Oncology, London, Ontario (E.D.C.)

# HIGH EVIDENCE: 3 RANDOMISED STUDIES

Trial	Inclusion criteria	Pts	F-up	Biochemical control (%)	Clinical progression free survival (%)	Metastasis free survival (%)	Overall survival (%)
EORTC 22911 2012	pT3 N0 M0 or R1	1005 (968 eligible)	5y	74% vs. 52% <b>&lt; 0.0001</b>	85% vs. 75% <b>0.004</b>	94% vs. 94% 0.6	92% vs. 93% 0.6
SWOG 87-94 2009	pT3 N0 M0 or R1	431 (425 eligible)	12.7y	10y: 53% vs. 25% <b>&lt; 0.001</b>	10y: 70% vs. 50% <b>0.001</b>	10y: 71% vs. 61% <b>0.016</b>	10y: 74% vs. 66% <b>0.023</b>
ARO96-AUOAP 09/95 2009	pT3 N0 M0 and undetectable PSA	388 (307 eligible)	5y	72% vs. 54% <b>0.0015</b>	-	-	-



# OVERALL SURVIVAL



# Adjuvant radiotherapy following radical prostatectomy for prostate cancer (Review)

Daly T, Hickey BE, Lehman M, Francis DP, See AM

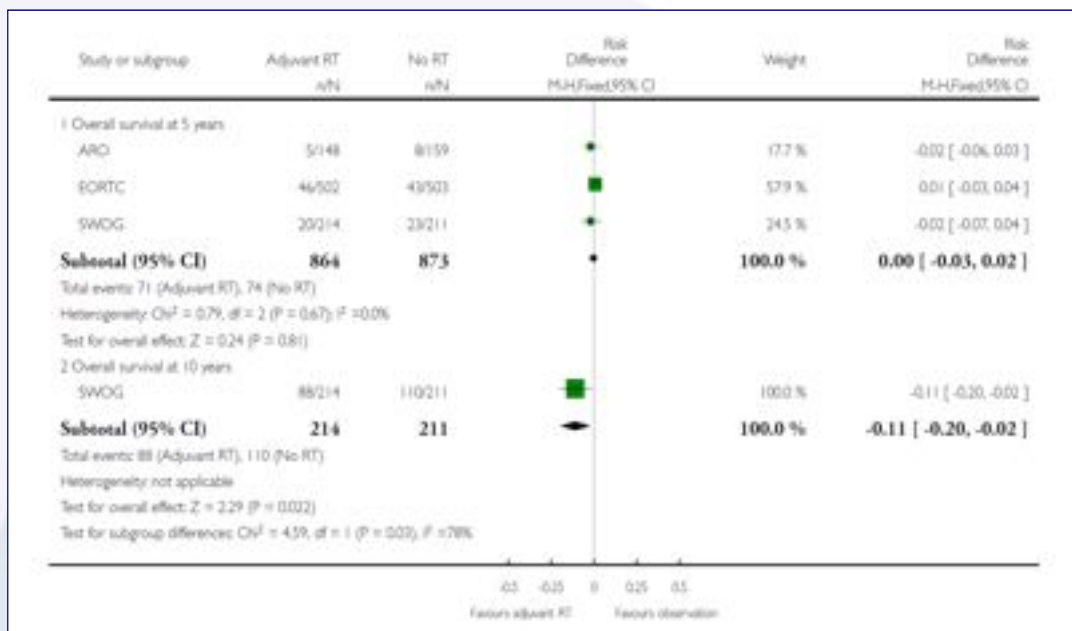


THE COCHRANE  
COLLABORATION®

2011

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di Oncologia

## OVERALL SURVIVAL AT 10 YEARS



Istituto  
Europeo  
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## TOXICITY

“Genitourinary and gastrointestinal toxicity is moderate:

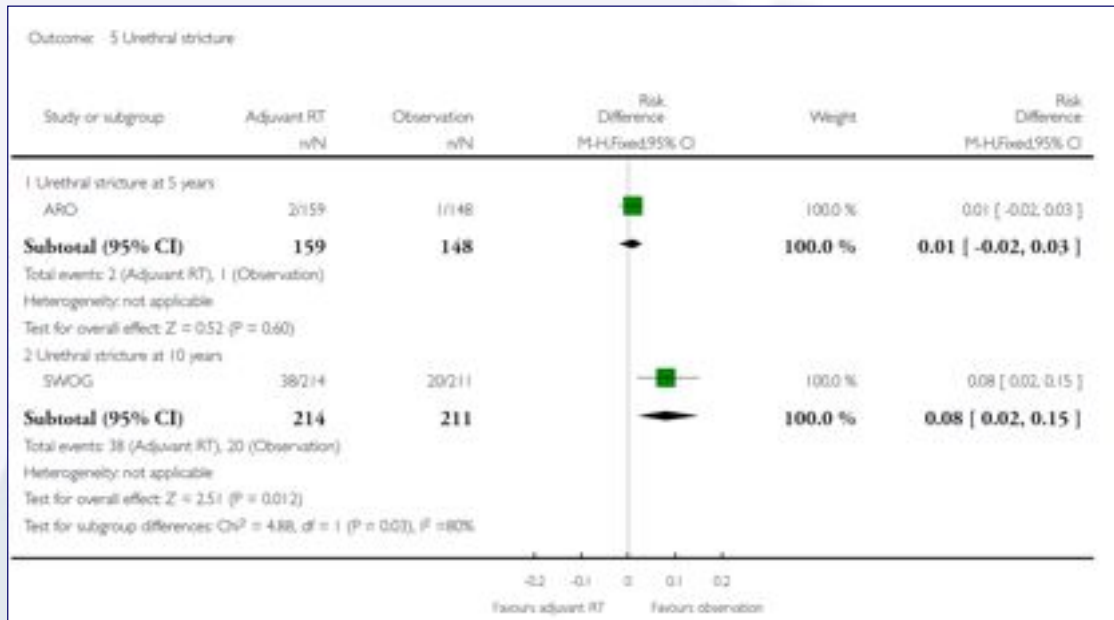
...with late side effects (> G2)

between 3% (ARO) and < 5% (EORTC)...”

## SWOG: QUALITY OF LIFE

	RT	No RT
Erectile dysfunction	=	=
QoL at 3 months	worse	better
QoL at 2 years	=	=
QoL at 3 years	better	worse

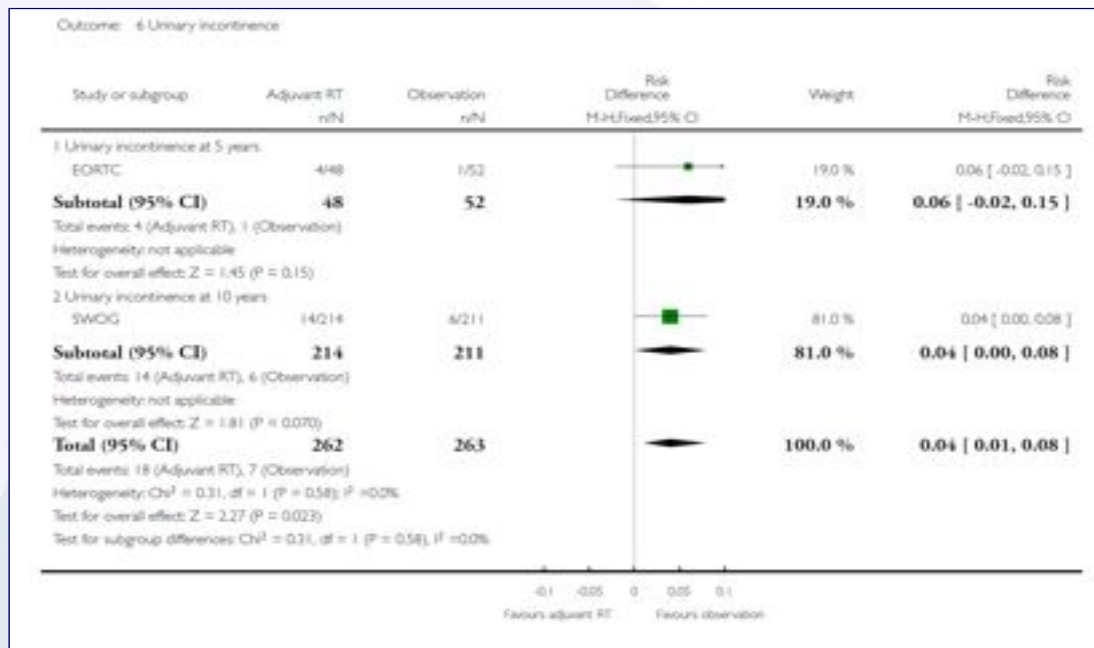
# URETHRAL STRICTURE



Daly 2011

di Oncologia

# URINARY INCONTINENCE



Daly 2011

di Oncologia

# IMPACT OF SURGERY

Surgery was done before entry into the study. Surgery consisted of retropubic approach, negative ilio-obturator lymphadenectomy, prostatectomy with total removal of the prostate gland and of the seminal vesicles. A unilateral or bilateral nerve-sparing technique was applied provided the procedure did not increase the risk of macroscopically positive surgical margins.

EORTC

Surgery was done before entry onto the study. Surgery consisted of open RP and pelvic lymphadenectomy (including the prostate gland and seminal vesicles). A uni- or bilateral nerve-sparing technique was allowed when it did not involve an increased risk of positive surgical margins.

ARO

S8794 was a randomized multi-institutional study of adjuvant RT for pathologically advanced prostate cancer after radical prostatectomy. Eligible patients with clinical T1-2 prostate cancer must have undergone radical prostatectomy within 16 weeks before randomization and must have had at least 1 criterion of pathological T1 disease such as extracapsular tumor extension, positive margins or seminal vesicle invasion. All patients had to have a negative bone scan and were initially required to have had a negative pelvic lymphadenectomy. Starting in

SWOG



# ROBOTIC SURGERY

## Evidence-Based Comparison of Robotic and Open Radical Prostatectomy

William T. Lowrance<sup>1,\*</sup>, Tatum V. Tarin<sup>1</sup>, and Shahrokh F. Shariat<sup>2</sup>

<sup>1</sup>Department of Surgery (Urology Service), Memorial Sloan-Kettering Cancer Center, New York; <sup>2</sup>Department of Urology and Medical Oncology, Weill Cornell Medical Center, New York

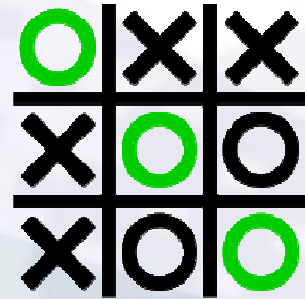
**Trend for lower PSM rate in RALP**

**Tendency to deliver salvage RT**



# TRIFECTA

1. Continent
2. Potent
3. Cured of cancer



Memorial Sloan Kettering  
Bianco et al 2005



## TRIFECTA dati IEO

BJUI  
BJU International

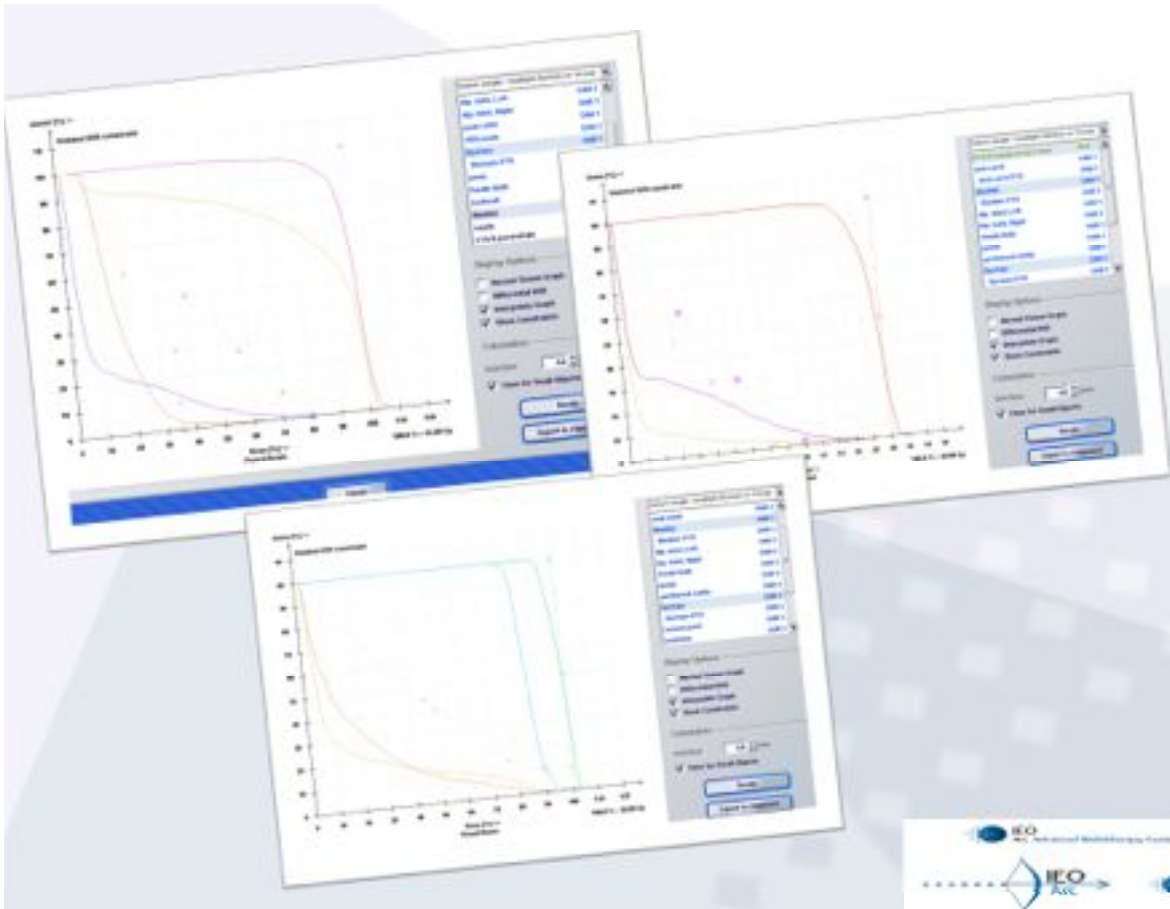
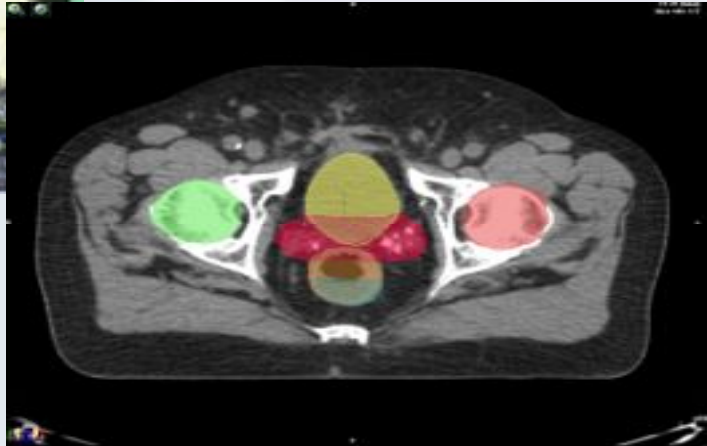
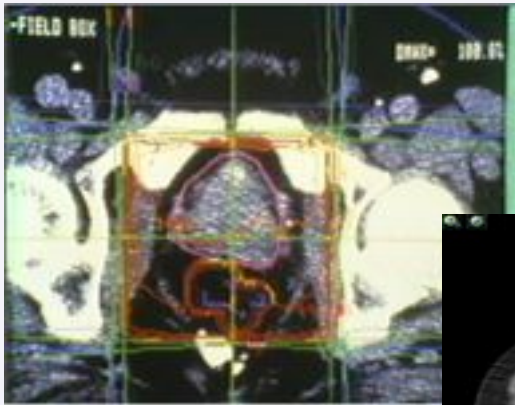
**Reporting combined outcomes with Trifecta and survival, continence, and potency (SCP) classification in 337 patients with prostate cancer treated with image-guided hypofractionated radiotherapy**

Barbara A. Jereczek-Fossa<sup>\*§</sup>, Dario Zerini<sup>\*</sup>, Cristiana Fodor<sup>\*</sup>, Luigi Santoro<sup>§</sup>,  
Andrea Maucieri<sup>\*§</sup>, Marianna A. Gerardi<sup>\*§</sup>, Barbara Vischioni<sup>††</sup>, Raffaella Cambria<sup>†</sup>,  
Cristina Garibaldi<sup>†</sup>, Federica Cattani<sup>†</sup>, Andrea Vavassori<sup>\*</sup>, Deliu V. Matei<sup>‡</sup>,  
Gennaro Musi<sup>‡</sup>, Ottavio De Cobelli<sup>‡§</sup> and Roberto Orecchia<sup>\*††</sup>

Departments of <sup>\*</sup>Radiation Oncology, <sup>†</sup>Medical Physics, <sup>‡</sup>Urology, and <sup>§</sup>Epidemiology and Biostatistics of the European Institute of Oncology, <sup>††</sup>University of Milan, Milan, and <sup>†††</sup>Centro Nazionale di Adroterapia Oncologica (CNAO), Pavia, Italy



# IMPACT OF RT



# WARNING

## Higher-than-expected Severe (Grade 3–4) Late Urinary Toxicity After Postprostatectomy Hypofractionated Radiotherapy: A Single-institution Analysis of 1176 Patients

Cesare Cozzarini<sup>1,2</sup>, Claudio Fiorino<sup>3</sup>, Chiara Deantoni<sup>4</sup>, Alberto Briganti<sup>5</sup>, Mariangela La Macchia<sup>6</sup>, Barbara Noris Chioda<sup>7</sup>, Paola Maria Vittoria Ranca Nazareno Suardi<sup>8</sup>, Flavia Zerbetto<sup>9</sup>, Riccardo Calandrino<sup>3</sup>, Francesco Montorsi Nadia Di Muzio<sup>1</sup>

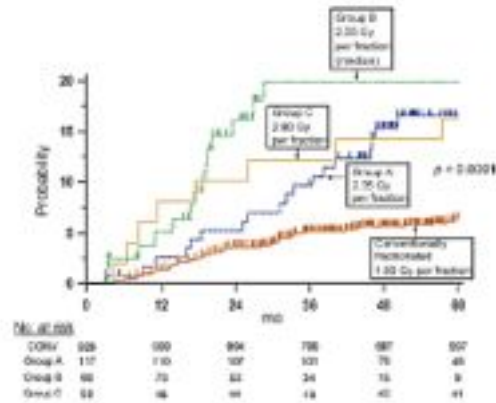


Fig. 2 – Risk of 5-yr severe (Grade  $\geq 3$ ) late urinary toxicity in the conventionally fractionated and hypofractionated cohorts. CONV = conventionally fractionated.

### REPORT DOSIMETRICO TRATTAMENTO IMRT

Limiti dose-volume, organi a rischio

	Valori raccomandati per dose frazione 2.7 Gy	Valori dal piano di cura	Valori raccomandati per dose frazione 2 Gy	Valori dal piano di cura
Retto Vv _____ cm <sup>3</sup>	V <sub>rect</sub> < 3 %	%	V <sub>rect</sub> < 3 %	%
	V <sub>rect</sub> < 10 cm <sup>3</sup>	cm <sup>3</sup>	V <sub>rect</sub> < 10 cm <sup>3</sup>	cm <sup>3</sup>
	V <sub>rect</sub> < 10%	%	V <sub>rect</sub> < 10% <sup>1,2</sup>	%
	V <sub>rect</sub> < 20%	%	V <sub>rect</sub> < 20% <sup>1,2</sup>	%
	V <sub>rect</sub> < 30%	%	V <sub>rect</sub> < 30% <sup>1,2</sup>	%
Parete post. sferoconica anca	V <sub>rect</sub> < 45% <sup>2</sup>	%	V <sub>rect</sub> < 45% <sup>2</sup>	%
	V <sub>rect</sub> < 1 cm <sup>3</sup>	cm <sup>3</sup>	V <sub>rect</sub> < 1 cm <sup>3</sup>	cm <sup>3</sup>
Cervice anale	V <sub>rect</sub> < 60%	%	V <sub>rect</sub> < 60%	%
	V <sub>rect</sub> < 40%	%	V <sub>rect</sub> < 40%	%
	D <sub>rect</sub> < 35Gy	Gy	D <sub>rect</sub> < 40Gy	Gy
Vescica urinaria Vv _____ cm <sup>3</sup>	V <sub>ves</sub> < 15%	%	V <sub>ves</sub> < 15%	%
	V <sub>ves</sub> < 15% <sup>1,2</sup>	%	V <sub>ves</sub> < 15% <sup>1,2</sup>	%
	V <sub>ves</sub> < 25%	%	V <sub>ves</sub> < 25% <sup>1,2</sup>	%
	V <sub>ves</sub> < 30%	%	V <sub>ves</sub> < 30% <sup>1,2</sup>	%
	V <sub>ves</sub> < 50%	%	V <sub>ves</sub> < 50% <sup>1,2</sup>	%
	V <sub>ves</sub> < 80%	%	V <sub>ves</sub> < 80% <sup>1,2</sup>	%
Teste femoral	V <sub>test</sub> < 50%	%	V <sub>test</sub> < 50%	%
	D <sub>test</sub> < 50Gy	Gy	D <sub>test</sub> < 57Gy	Gy
Intestino cavità peritoneale Vv _____ cm <sup>3</sup>	V <sub>int</sub> < 1 cm <sup>3</sup>	cm <sup>3</sup>	V <sub>int</sub> < 1 cm <sup>3</sup>	cm <sup>3</sup>
	D <sub>int</sub> < 30Gy	Gy	D <sub>int</sub> < 40Gy	Gy
	V <sub>int</sub> < 195 cm <sup>3</sup> <sup>1,2</sup>	cm <sup>3</sup>	V <sub>int</sub> < 195 cm <sup>3</sup> <sup>1,2</sup>	cm <sup>3</sup>

## ONGOING STUDIES

Study	Status	Study design	RT volumes
RTOG 96-01	Closed (3/2003)	Salvage RT +/- ADT	Prostatic bed only
RADICALS	ongoing	<b>Adjuvant RT vs. salvage RT +/-ADT</b>	Prostatic bed only
RTOG 05-34	ongoing	Salvage RT +/- ADT	Prostatic bed vs. prostatic bed + pelvis
SAKK	ongoing	Salvage RT (64 vs. 70 Gy)	Prostatic bed only

## Combined treatment

1. **RT + ADT**
2. **Surgery + RT**
3. **RT + CHT**
4. **New agents**

# DOCETAXEL

Docetaxel-based chemotherapy

the first demonstrated overall survival benefit in hormone refractory prostate cancer **CRPC castration resistant cancer**)

**SWOG 9916 Petrylak 2004**

**TAX 327 Tannock 2004**

**Chemotherapy added to local therapy  
in non-metastatic high risk patients?**

# CHEMOTHERAPY AND RT

**SWOG 9024** phase II feasibility but low activity of **5-FU** added to RT in T3-T4

Swanson 2006

**RTOG 9902** phase III 397 high risk pts

Rosenthal 2009

RT + 2y AD

RT + 2 y AD + 4 TEE  
(paclitaxel, etoposide, estramustine)

**excess tromboembolic tox (closed earlier)**

Acute hematological tox  
GI  
GU  
Toxic death (neutropenia)  
AML  
Late tox

↑  
↑  
no difference  
2 pts  
3 pts  
no difference



# CHEMOTHERAPY AND RT

## SWOG S9921

### mitoxantrone+ADT vs ADT

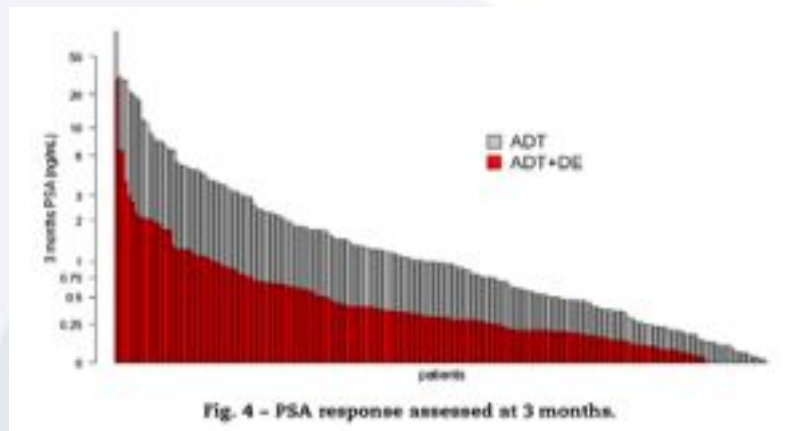
**accrual** to this study was halted  
after determination of  
3 cases of **acute myelogenous  
leukemia** in the mitoxantrone arm

A phase III trial of docetaxel-estramustine in high-risk localised prostate cancer: A planned analysis of response, toxicity and quality of life in the GETUG 12 trial ☆



Local treatment: RT 87%, surgery 6%, none 6%

# RESULTS



Too early for OS (few events)

Higher toxicity and lower QoL in CHEMOTHERAPY Arm

Fizazi et al. Eur J Cancer 2012



## Clinical Genitourinary Cancer 2014

### Original Study

Phase I Trial of Weekly Docetaxel, Total Androgen Blockade, and Image-Guided Intensity-Modulated Radiotherapy for Localized High-Risk Prostate Adenocarcinoma

David T. Marshall,<sup>1</sup> Stephen Ramey,<sup>1</sup> Ali-Reza Golshayan,<sup>1</sup> Thomas E. Keane,<sup>1</sup>  
Andrew S. Kraft,<sup>1</sup> Uzair Chaudhary<sup>2</sup>

Limited IMRT volume

Acceptable tox



## ONGOING RESEARCH

- ❑ 10 ongoing phase III studies on **docetaxel-based regimens** in high-risk localized cancer:

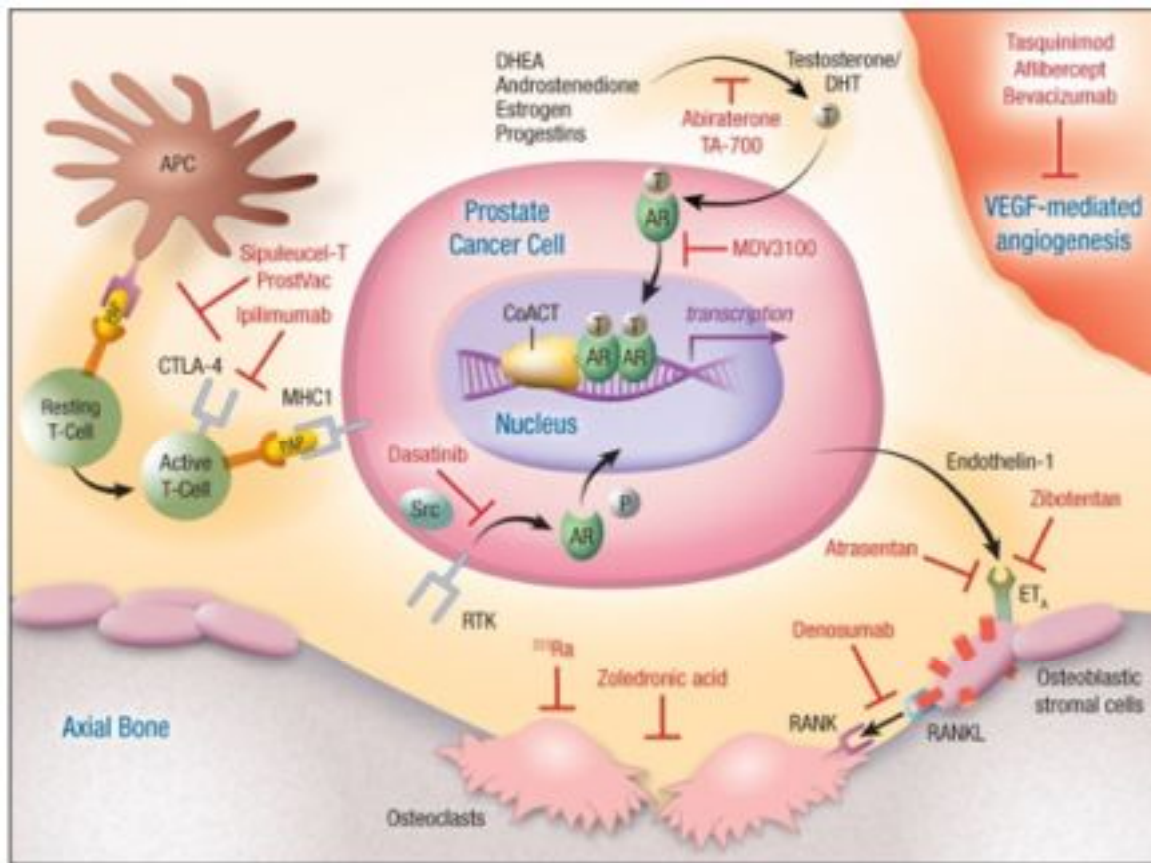
RTOG 0521 RT/AD +/- adj Docetaxel+prednisone

- ❑ RTOG 0621 (phase II) adj post-prostatectomy RT/AD + Docetaxel

- ❑ Novel agents...

## Combined treatment

1. RT + ADT
2. Surgery + RT
3. RT + CHT
4. New agents



## FDA APPROVED AGENTS IN CASTRATION RESISTANT PROSTATE CANCER

- ❑ **Cabazitaxel:** novel taxane that can evade multidrug-resistant proteins
- ❑ **Abiraterone:** androgen biosynthesis inhibitor
- ❑ **Denosumab:** monoclonal antibody for RANK-L (signalling pathways promoting bone resorption)
- ❑ **Sipuleucel T:** vaccine (autologous peripheral blood mononuclear cells, obtained by leukapheresis and cultured with PAP, reinfused to induce response to PAP-expressing cancer cells)
- ❑ **Enzalutamide....**
- ❑ **Radium-223.....**

Agent	MOA	Studies	Trial Results
<b>Abiraterone Acetate</b>	Potent and selective inhibitor of CYP17 alpha-hydroxylase and C17,20-lyase	Phase III studies post- and pre-docetaxel with prednisone	COU-AA-301 <sup>7,20</sup> Met endpoint of OS OS: HR 0.74; 95% CI 0.638-0.859; p < 0.0001 26% reduction in risk for death COU-AA-302 <sup>8</sup> met endpoint of rPFS and trend in OS OS: HR 0.79; 95% CI 0.66-0.95; p = 0.0151 21% reduction in risk of death rPFS: HR 0.43 ; 95% CI 0.35-0.52 ; p < 0.0001 57% reduction in rPFS Other combination trials ongoing
<b>Enzalutamide</b>	AR antagonist, inhibits nuclear translocation and blocks DNA binding of the receptor and activation	Phase III studies post- and pre-docetaxel	AFFIRM <sup>9</sup> met endpoint of OS OS: HR 0.63; 95% CI 0.529-0.752; p < 0.0001 37% reduction in risk of death PREVAIL <sup>11</sup> met endpoints of OS and rPFS OS: HR 0.706; 95% CI 0.60-0.84; p < 0.0001 rPFS: HR 0.186; 95% CI 0.15-0.23; p < 0.0001 MO CRPC PROSPER trial recruiting and other trials ongoing <sup>41</sup>
<b>Orteronel (TAK-700)</b>	Selective, non-steroidal, small-molecule inhibitor of 17,20-lyase	Phase III studies post- and pre-docetaxel with prednisone	ELM-PC5 did not meet primary endpoint of OS <sup>25</sup> OS: HR 0.886; 95% CI 0.739-1.062; p = 0.1898 Substantial regional differences in OS were seen rPFS: HR 0.76; 95% CI 0.653-0.885; p = 0.00038 ELM-PC4 Fully recruited-ongoing <sup>23</sup> Others: orteronel vs. bicalutamide in mCRPC patients failing first-line LHRH agonists or surgical castration <sup>28</sup> Orteronel vs. bicalutamide in hormone-naive prostate cancer patients failing on LHRH agonists <sup>29</sup>
<b>Galeterone (TOK-001)</b>	AR antagonist and AR degrader and a CYP17 lyase inhibitor	Phase I/II ARMOR 1 and ARMOR 2	ARMOR 2 <sup>32</sup> Reformulated galeterone Significant improvements in PSA response at 12 weeks in CRPC as compared with ARMOR1 MI treatment naive 2,550 mg OD PSA response: 90% $\geq$ 30% and 81% $\geq$ 50%
<b>ARN-509</b>	AR antagonist, inhibits nuclear translocation and DNA binding of the receptor	Phase I/II	N = 30 with doses 30 mg to 480 mg PSA declines at 12 weeks $\geq$ 50% in 46.7% <sup>43</sup> Phase II trial recruited <sup>44</sup>
<b>ODM-201 ORM-15341 (main metabolite)</b>	No CYP inhibition or induction with therapeutic doses	Phase I/II	MO CRPC Spartan trial recruiting <sup>45</sup> ARCADES Trial <sup>46</sup> Chemotherapy, CYP17i-naive $\geq$ 50% PSA: 65% Post-chemotherapy/CYP17i-naive $\geq$ 50% PSA 32% Post-CYP17i $\geq$ 50% PSA: 9% MO CRPC trial planned

Abbreviations: MOA, mode of action; OS, overall survival; HR, hazard ratio; CI, confidence interval; rPFS, radiographic progression-free survival; AR, androgen receptor; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; LHRH, luteinizing-hormone releasing hormone; OD, every day.

**Sternberg et al ASCO 2014**

**Istituto Europeo di Oncologia**

## NOVEL AGENTS + RT...

At least 6 ongoing phase III studies on docetaxel-prednisone plus a novel agent

1. First toxicity profile and activity in CRPC

2. Then will they be tested in locally advanced cancer?

**Istituto Europeo di Oncologia**

# NEW TOXICITY

Niyazi et al. Radiation Oncology 2011, 6:177  
<http://www.ro-journal.com/content/6/1/177>



REVIEW

Open Access

## Radiotherapy and "new" drugs-new side effects?

Maximilian Niyazi<sup>1†</sup>, Cornelius Maihoefer<sup>1†</sup>, Mechthild Krause<sup>2</sup>, Claus Rödel<sup>3</sup>, Wilfried Budach<sup>4</sup> and Claus Belka<sup>1†</sup>

Niyazi et al. Radiat Oncol 2011;6:177



International Journal of  
Radiation Oncology  
biology • physics

[www.rodjournal.org](http://www.rodjournal.org)

Clinical Investigation: Genitourinary Cancer

### Phase II Study of Long-Term Androgen Suppression With Bevacizumab and Intensity-Modulated Radiation Therapy (IMRT) in High-Risk Prostate Cancer

Jacqueline Vuky, M.D.,\* Huong T. Pham, M.D.,<sup>†</sup> Sarah Warren, B.A.,<sup>‡</sup> Erika Douglass, B.A.,<sup>‡</sup> Kasra Badiozamani, M.D.,<sup>†</sup> Berit Madsen, M.D.,<sup>§</sup> Alex Hsi, M.D.,<sup>§</sup> and Guobin Song, M.D.<sup>†</sup>

**Late** toxicity was concerning,  
with higher than  
anticipated levels of GU or GI toxicity  
**50% pts: late bleeding complications**



## Dose-dependent response of tumor vasculature to radiation therapy in combination with Sunitinib depicted by three-dimensional high-frequency power Doppler ultrasound

Ahmed El Kaffas · Anoja Giles · Gregory J. Czarnota

**Radiosensitizing effect of sunitinib is  
linked to a **vascular normalization****

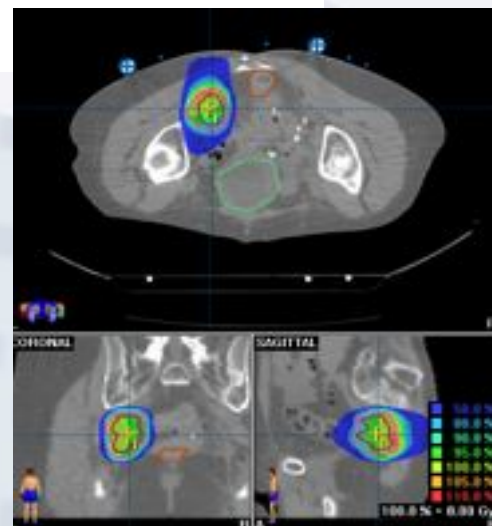


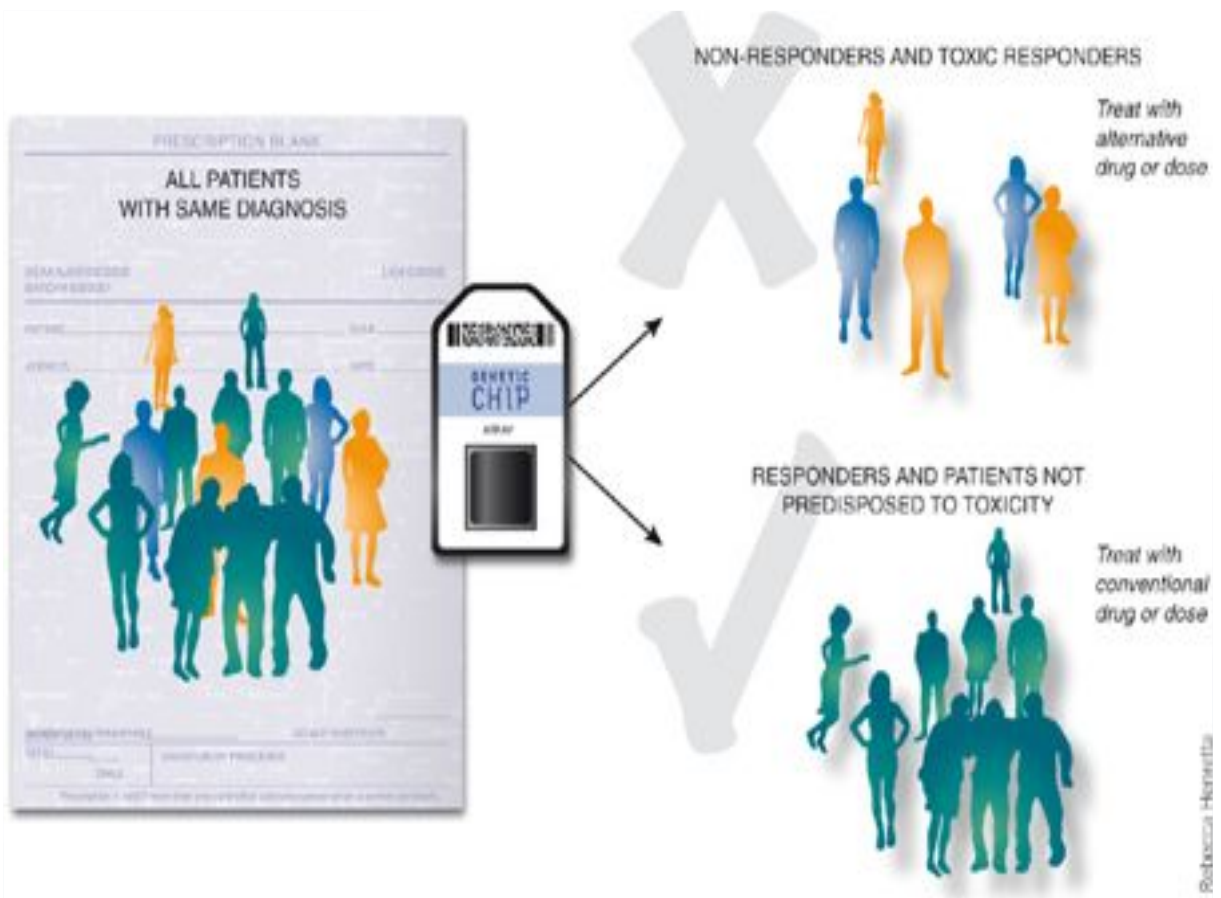
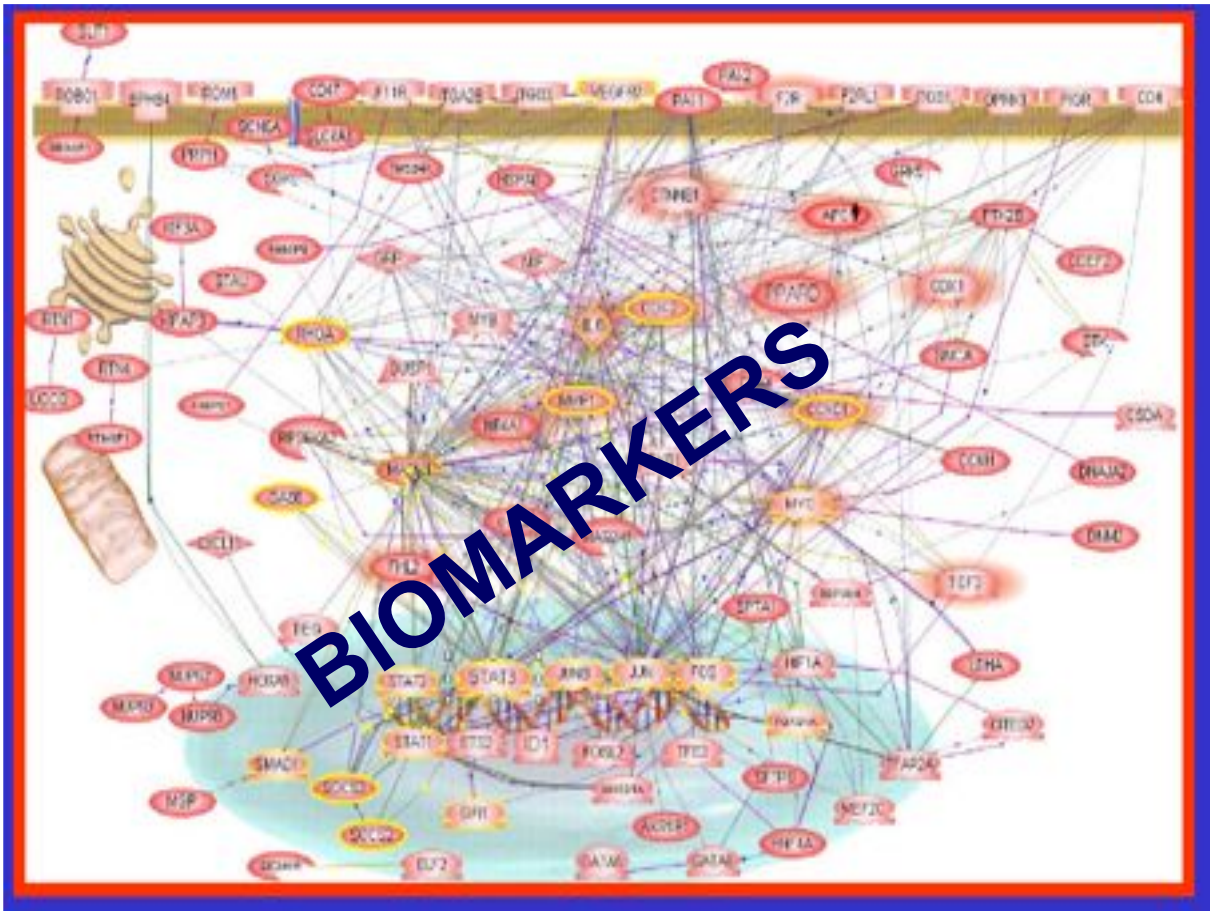
## Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases

Final report of a prospective clinical trial

Johnny Kao · Chien-Ting Chen · Charles C. L. Tong ·  
Stuart H. Packer · Myron Schwartz · Shu-hsia Chen ·  
Max W. Song

- Promising results
- Feasible
- Increased **acute** toxicity







# Paradigm shift in health care:

## PERSONALIZED MEDICINE

## HIGH PRECISION MEDICINE



**Thank you**

