Indicazioni all'associazione OT – RT alla luce dell'evidenza nel trattamento radicale

Marco A. Signor

RT oncologica
A.O.U. "S.Maria della Misericordia" Udine

Evidenze sui Razionali: radiobiologico

1. Riduzione dei clonogeni, sincronizzazione cellulare, induzione dell'apoptosi con Effetto sopraAdditivo
2. Blocco del ripopolamento
3. Aumento effetto Ossigeno
4. "Normalization of tumor vasculature"

Science 2005;307:58–62

Microvasc Res 2007;74:72–84

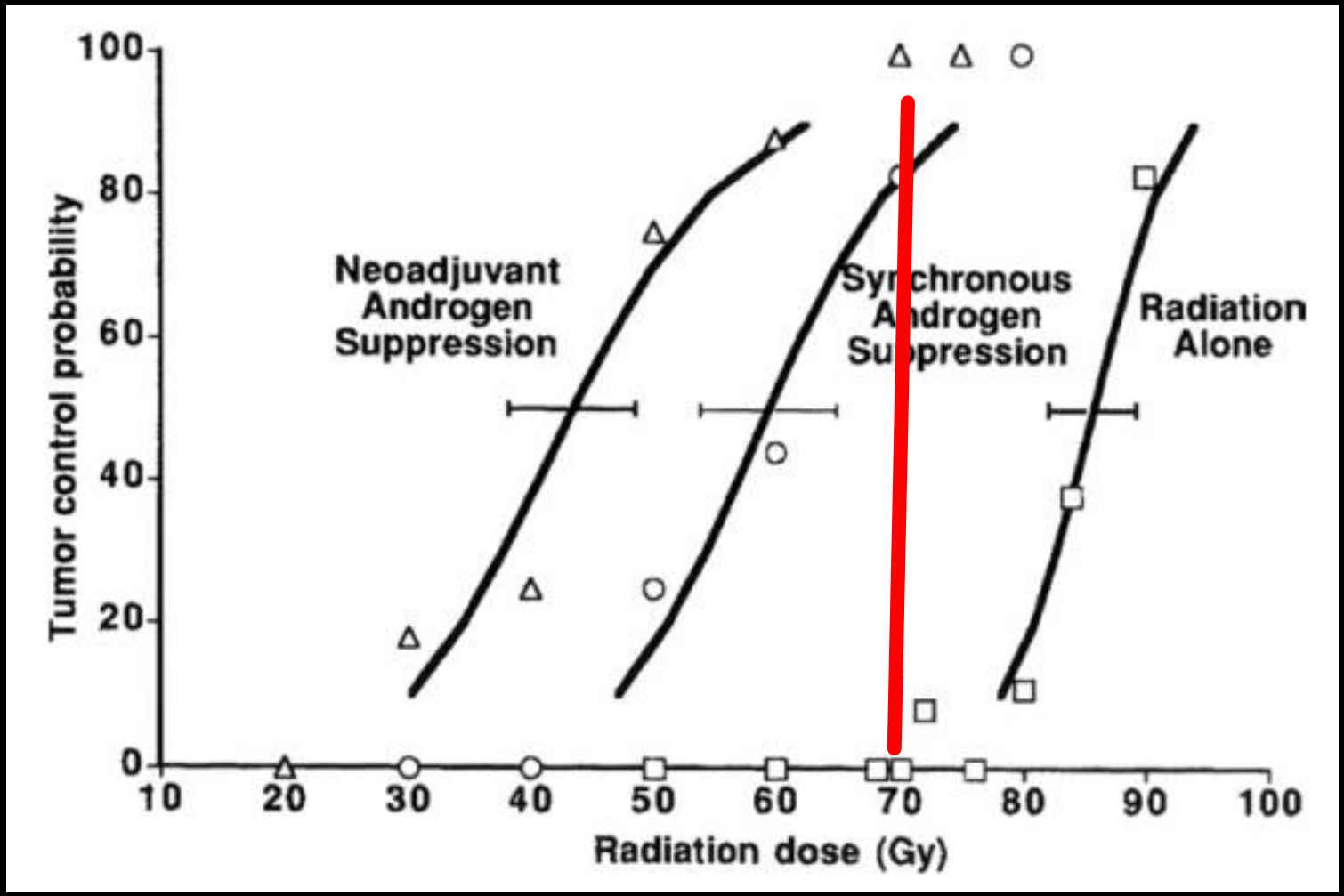
Urologic Oncology 26 (2008) 522–529

Br J Urol Int 2010;105:8–13

Cancer Discov 3(11):1245-1253, 2013.

Cancer Discov 3(11):1254-1271, 2013.

Evidenze sui Razionali: radiobiologico



N Engl J Med 1995;333:1757–63

Cancer Res 1997;57:1054–7

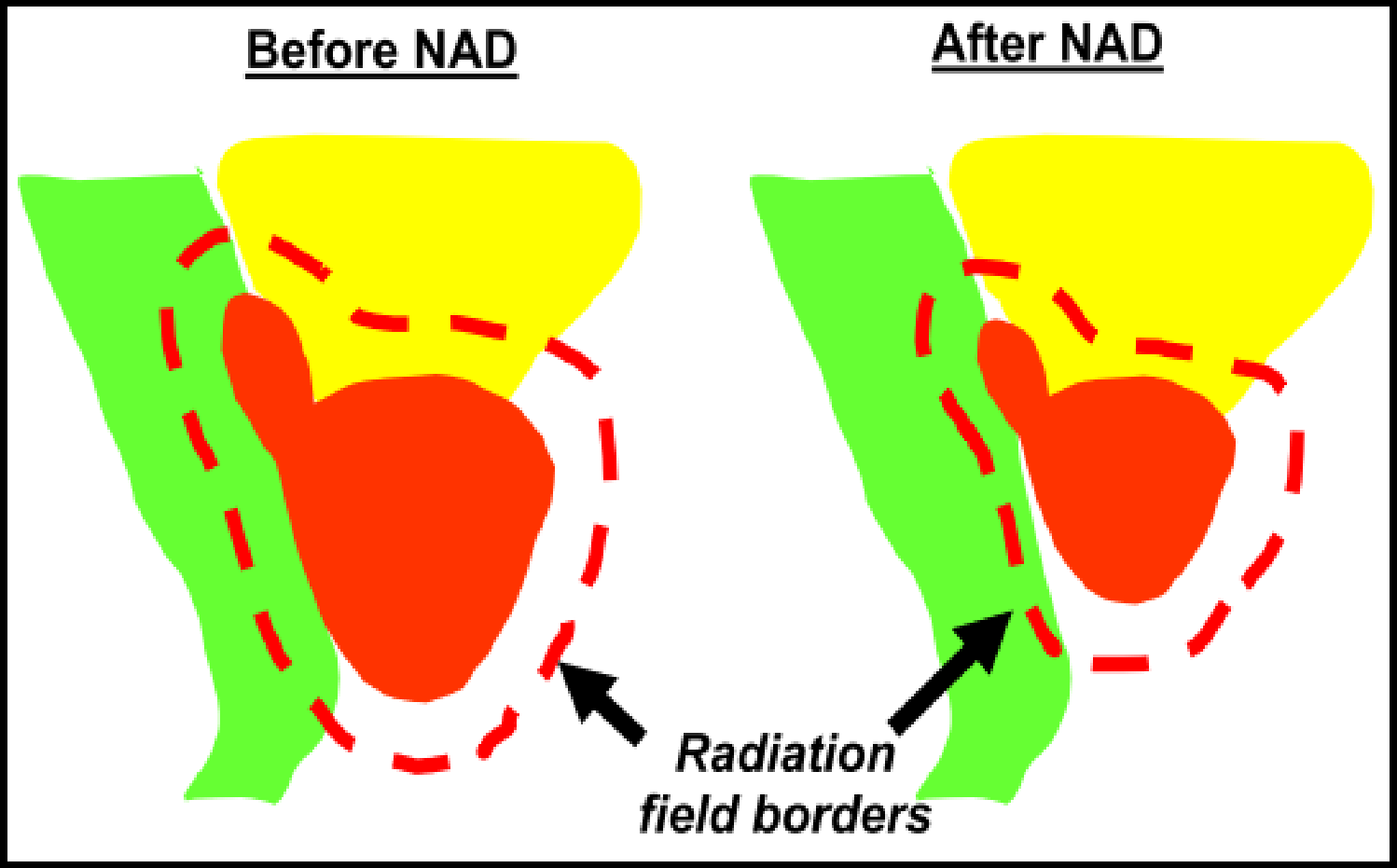
IJROBP 1997;38:1067–70

Urology 1997;49:74–83

IJROBP 1997;38(5):1071–7

Nature 2001;7:987–9

Evidenze sui Razionali: tecnica e DVH

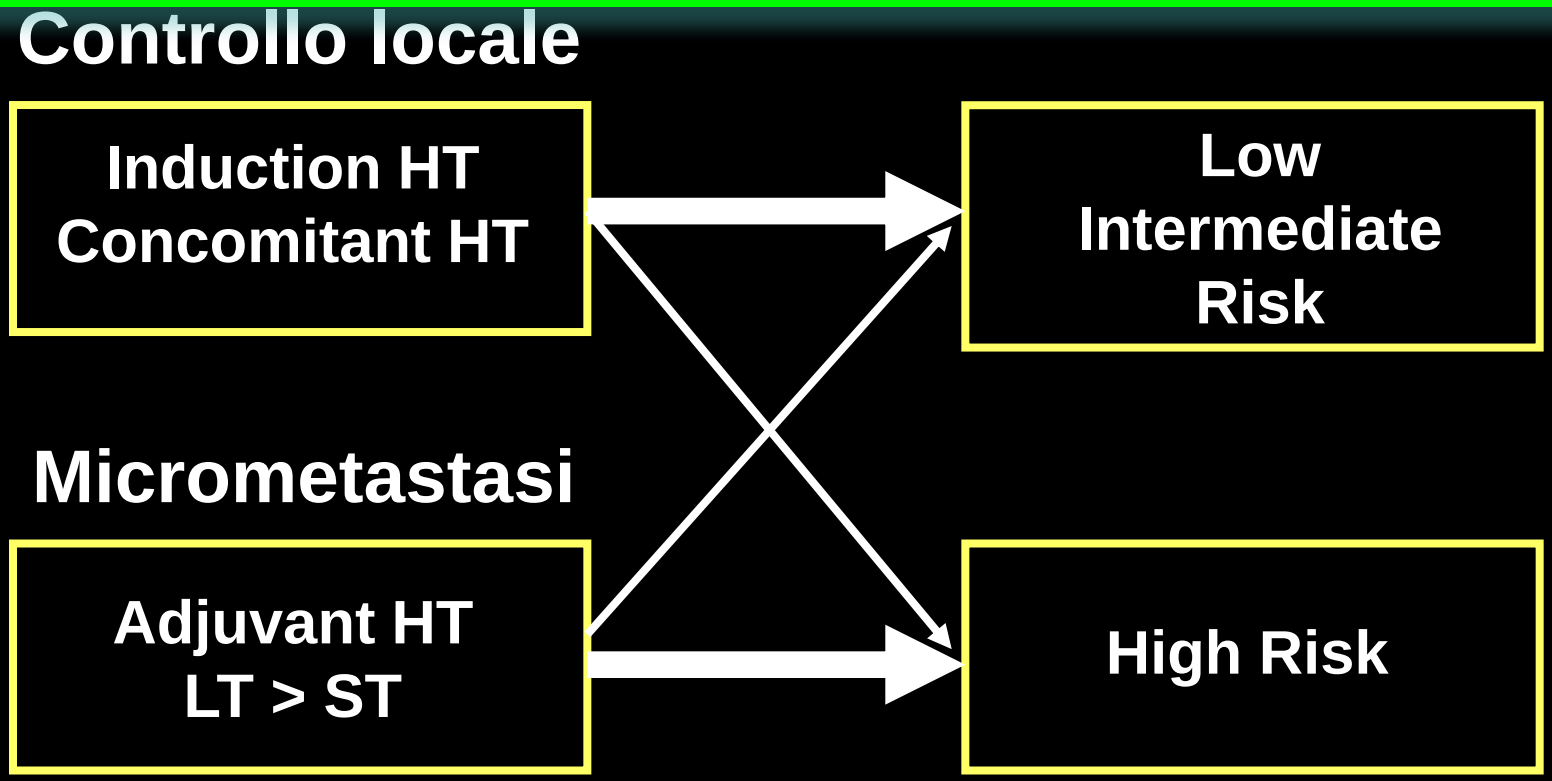


1. DownSizing con riduzione del CTV
2. Minore Organ Motion e minor overlapping su OaR per una maggiore precisione balistica

Evidenze sui Razionali: clinico

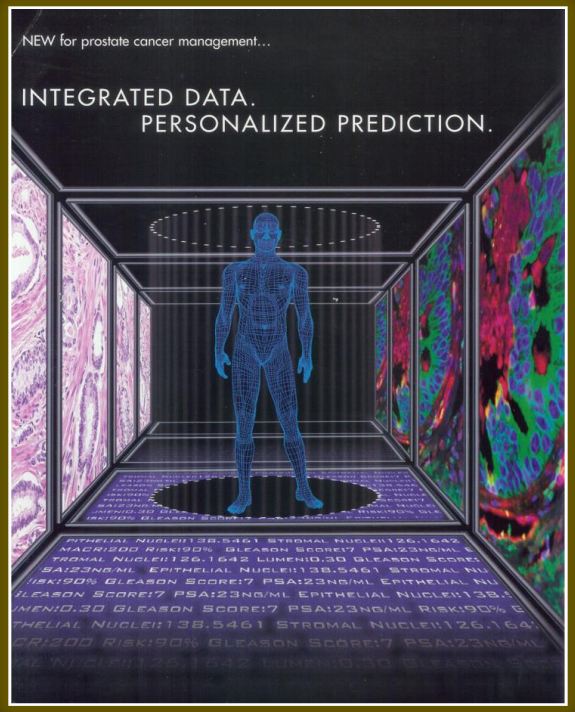
1. Maggiore efficacia e/o minore tossicità
2. Cooperazione Spaziale per il miglior controllo locoregionale e sistemico

Miglior Indice Terapeutico



Evidenze sui Razionali: prognostico

1. Sopravvivenza libera da deficit funzionali, da malattia biochimica, clinica e da terapia (Qualità di Vita)
2. Sopravvivenza Causa Specifica e Globale (Quantità di Vita)



Metagramma di predizione personalizzata:
Quod Vitam e Quod Valetudinem

Cancer 2009;115:3107–11

Evidenze dagli studi randomizzati

Author, year	Patients	Study design	Conclusions	Comments
EORTC 22863 (Bolla 2002)	415 pts, high-risk : T3-4 (89%) or T1-2 WHO 3	RT vs. RT + CAAD (3 years)	LC, DFS, OS advantage with AD	Pelvis 50 Gy + 20 Gy prostate boost
RTOG 8531 (Pilepich 2005)	977 pts, high-risk: T3 (15%) or T1-2, N+ or pT3 and (+) margin or (+) SV	RT (AD at failure) vs. RT + AAD indefinite	LC, DFS, DM, OS advantage with AD for GS 8-10	Pelvis 44-46 Gy + prostate boost of 20-25 Gy (prostate bed only to 60-65 Gy in postop RT). Pre-PSA study
RTOG 8610 (Pilepich 2001)	456 pts, high-risk: bulky T2b, T3-4, N+ allowed	RT vs. RT + NCAD (4 months)	OS advantage with AD for GS < 7	Pelvis 44-46 Gy + prostate boost of 20-25 Gy. Pre-PSA study
RTOG 9202 (Hanks 2003)	1554 pts, high-risk: T2c-4, PSA < 150 ng/ml, N+ allowed	RT + NCAD (4 months) vs. RT + NCAD (4 months) + AAD (24 months)	DFS, OS advantage with 24 month AAD for GS 8-10	Pelvis 4-46 Gy + prostate boost of 20-25 Gy
RTOG 9413 (Roach 2003)	1323 pts, intermediate to high risk: T2c-4 GS $\geq$ 6 or risk of N+ > 15%, PSA < 100 ng/ml	WP + NCAD (4 months) vs WP + AAD (4 months) vs PO + NCAD (4 months) vs PO + AAD (4 months)	PFS advantage with NCAD + WP	2x2 factorial design to study the impact of AD timing and RT field size

Author, year	Patients	Study design	Conclusions	Comments
L-101 (Laverdiere 2004, 1997)	161 pts, Intermediate and high-risk: T2-3	RT vs. NCAD (3 months) + RT vs. NCAD (5 months) + RT + AAD (5 months)	BC advantage with any form of AD over RT alone	
L-200 (Laverdiere 2004)	325 pts, Intermediate and high-risk: T2-3	NCAD (5 months) + RT vs NCAD (5 months) +RT + AAD (5 months)	No BC difference between arms	
BWH (D'Amico 2004)	206 pts, intermediate-high-risk:: T1b-2b, GS $\geq$ 7, PSA 10-40 ng/ml	RT vs RT + NCAAD (6 months)	PFS, CSS, OS advantage with AD	
Granfors (Granfors 2006)	91 pts, Intermediate-high risk: T1-4, pN0-3, WHO 1-3	RT vs. bilateral orchiectomy 4 weeks before RT	Study halted due to strong PFS and OS benefit with orchiectomy	No OS difference for node negative tumors
CUOG (Crook 2009)	378 all risk pts	NCAD (3 months) + RT vs NCAD (8 months) + RT	No difference in outcomes	Significant DFS benefit with longer NCAD in high-risk pts
TROG 96.01 (Denham 2011)	818 pts, Intermediate-high risk: cT2b-T4 N0	RT alone vs. NCAD (3 months) + RT vs. NCAD (6 months) + RT	BC, LC, DFS, DM, CSS advantage with longer NCAD	Low dose RT in both arms. Benefit more evident in high risk pts
Sacramento (Jones 2011)	Low and intermediate-risk 1979 pts	RT alove vs NCAD (4 months) + RT	Better OS with ADT in intermediate, but not in low risk	

Evidenze e linee guida

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Prostate Cancer

Risk Class	Definition	ADT+RT
Low risk	T1-2a, GS≤6, PSA ≤10	None
Intermediate Risk	T2b-c, GS=7, PSA=10-20	Neoadj/conc (4-6 mo)
High risk	T3a, GS≥8, PSA>20	Long term neoad/conc/adj (2-3years)
Very High risk	T3b, T4	
Metastatic N1 M0	Any T N+, M0	

Evidenze e linee guida: EAU 2015

	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**

Risk Group	RT Recommandations	LE	GR
in all risk groups of non-metastatic PCa	EBRT should be offered	2a	A
In low-risk PCa	Intensity-modulated radiotherapy with escalated dose (74-78Gy) and <u>without ADT</u> is an alternative to brachytherapy	1a	A

Risk Group	RT Recommandations	LE	GR
intermediate-risk	Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months). For patients unsuitable for ADT (comorbidities or sexual health preservation), the recommended treatment is IMRT at an escalated dose (76-80 Gy) or a combination of IMRT and brachytherapy.	1b	A
high-risk localized	It mandatory to use a combined modality approach, consisting of dose-escalated IMRT to 76-78 Gy including the pelvic lymph nodes in combination with long-term ADT (2-3 yr). The duration of ADT has to take into account WHO Performance Status, comorbidities, and poor prognostic factors (> T2c, GPS 8-10, and PSA > 20 ng/mL).	1b	A
Locally advanced cN0	RT must be given in combination with long-term ADT (2-3 yr)	1a	A
cN+	Pelvic external irradiation can be given in combination with immediate long-term ADT.	2b	B

Short-course ADT and intermediate risk disease

Author/year	N° pts	N° In Risk	Median Fup	ADT	RT dose	Endpoint	Results
Jones (2011)	2028	1068	9,1	0 vs 4 months	66,6 Gy	OS	Increased OS, bPFS, CSS
Denham (2011)	818	130	10,6	0 vs 3 vs 6 ms	66Gy	CSS,LC	Increased OS, CSS
D'Amico (2008)	206	80	7,6	0 vs 6 ms	74Gy	bPFS	Increased OS, CSS

LE: 1b GR: A

Pazienti eterogenei + Dose totale: 65-74Gy
Possibile effetto migliorativo dato da % prevalente di alto rischio e dose totale ≤74Gy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 14, 2011 VOL. 365 NO. 2

Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer

Christopher U. Jones, M.D., Daniel Hunt, Ph.D., David G. McGowan, M.B., Ch.B., Mahul B. Amin, M.D., Michael P. Chetner, M.D., Deborah W. Bruner, R.N., Ph.D., Mark H. Leibenhaut, M.D., Siraj M. Husain, M.D., Marvin Rotman, M.D., Luis Souhami, M.D., Howard M. Sandler, M.D., and William U. Shipley, M.D.

RTOG 94-08: October 94-April 01; 2028 randomized patients

Prostate adenoca

T1b-T2b

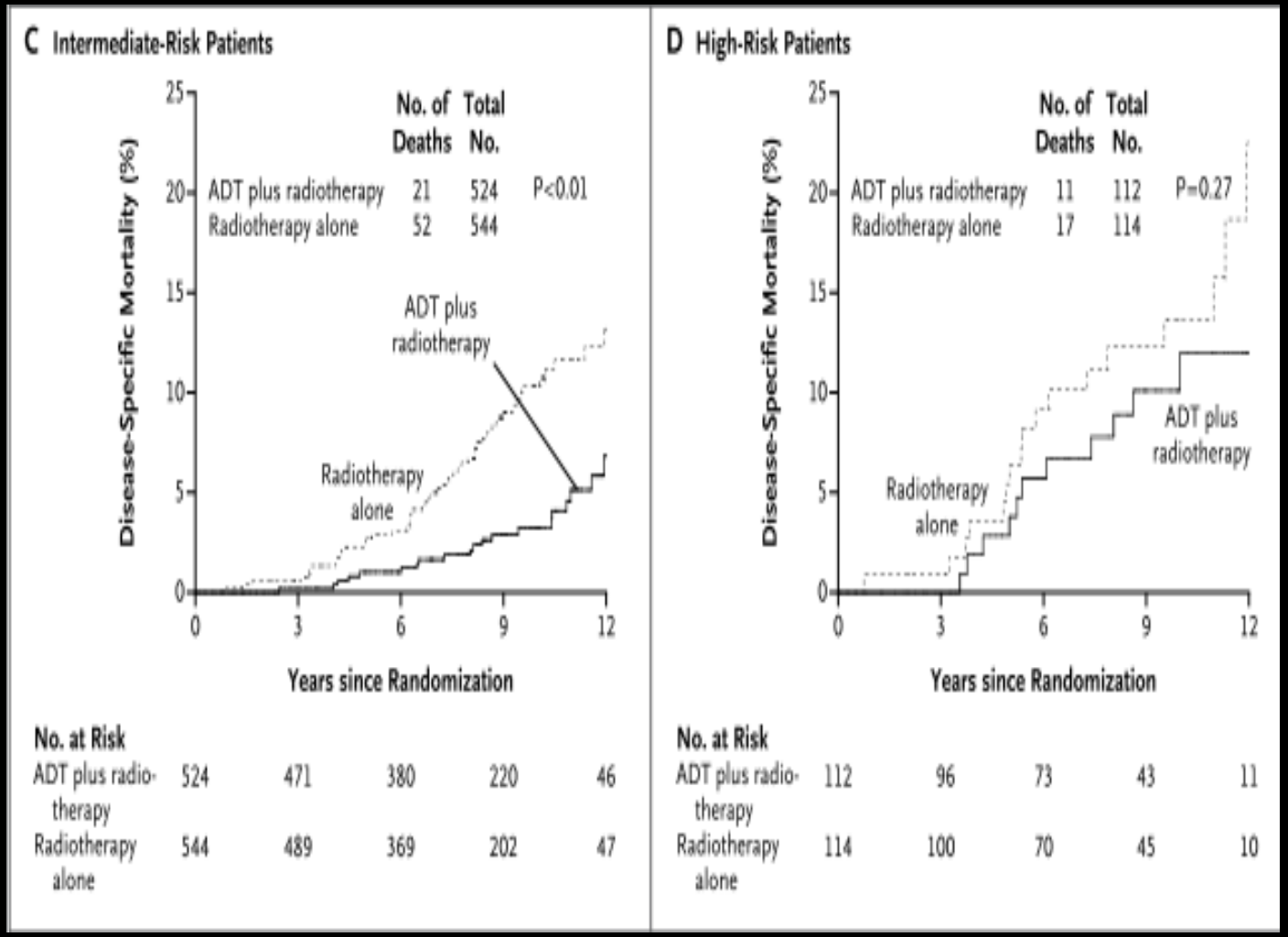
PSA<20 ng/ml

4 mo
Neoadjuvant
LHRH analogue*

→ Same RT + ADT

RT alone 66.6 Gy

Jones CU, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365(2):107–118



Sopravvivenza globale rischio intermedio e alto

Mortalità cancro specifica per rischio intermedio e alto

Median Follow up: 9.1 yrs

10 year Biochemical Control : 74 vs 59% (p=0.001)

10 year Cause Specific Survival: 96 vs 92% (p=0.001)

10 year Overall Survival: 62 vs 57% (p=0.03)

Short-course ADT in intermediate risk and RT Dose escalation

Non disponibili studi randomizzati
Studio GETUG 14 chiuso per insuff. reclutamento
In corso: studi randomizzati: RTOG 0815 e GICOR 17 NCT00936390, EORTC 22991, NCT00021450, NCT00104741

Studio Retrospettivo del MDACC: Int J Radiation Oncol Biol Phys, Vol. 85, No. 3, pp. 693 - 699, 2013

Studio Retrospettivo del MSKCC: Int J Radiation Oncol Biol Phys, Vol. 85, No. 4, pp. 1012-1017, 2013

Clinical Investigation: Genitourinary Cancer

Is Androgen Deprivation Therapy Necessary in All Intermediate-Risk Prostate Cancer Patients Treated in the Dose Escalation Era?

Katherine O. Castle, MD, Karen E. Hoffman, MD, MHSc, MPH, Lawrence B. Levy, MS, Andrew K. Lee, MD, MPH, Seungtaek Choi, MD, Quynh N. Nguyen, MD, Steven J. Frank, MD, Thomas J. Pugh, MD, Sean E. McGuire, MD, PhD, and Deborah A. Kuban, MD

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Based on recursive partitioning analysis, intermediate-risk patients treated with RT alone were divided into 3 prognostic groups:
(1) 188 favorable patients: GS 6, T2b or GS 3+4, T1c;
(2) 71 marginal patients: GS 3+4, T2a-b;
(3) 68 unfavorable patients: GS 4+3 or T2c disease.

…not all intermediate-risk patients benefit from the addition of androgen deprivation to high-dose radiation.
While prospective randomized studies accrue, available information must be weighed against tumor characteristics, patient comorbidities, and the side effect profile of combination therapy.

Int J Radiation Oncol Biol Phys, Vol. 85, No. 3, pp. 693 - 699, 2013

Clinical Investigation: Genitourinary Cancer

Short-term Androgen-Deprivation Therapy Improves Prostate Cancer-Specific Mortality in Intermediate-Risk Prostate Cancer Patients Undergoing Dose-Escalated External Beam Radiation Therapy

Zachary S. Zumsteg, MD,* Daniel E. Spratt, MD,* Xin Pei, PhD,* Yoshiya Yamada, MD,* Abraham Kalikstein, BS,* Deborah Kuk, MS,† Zhigang Zhang, PhD,† and Michael J. Zelefsky, MD*

*Departments of *Radiation Oncology and †Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York*

Using multivariate analysis, **ADT was an even stronger predictor of improved PSA-RFS (P<.001), DM (P<.002), and PCSM (P<.004). Gleason score (4+3) and >50% positive biopsy cores were other independent predictors of PCSM.**

…the significant heterogeneity of the intermediate-risk subgroup …. future prospective trials are necessary to further refine the clinical and biologic characteristics that predict benefit from the combined use of ADT and dose-escalated RT.

Int J Radiation Oncol Biol Phys, Vol. 85, No. 4, pp. 1012-1017, 2013

Platinum Priority – Prostate Cancer

Editorial by Anthony V. D'Amico on pp. 903–904 of this issue

A New Risk Classification System for Therapeutic Decision Making with Intermediate-risk Prostate Cancer Patients Undergoing Dose-escalated External-beam Radiation Therapy

Zachary S. Zumsteg[a], Daniel E. Spratt[a], Isaac Pei[a], Zhigang Zhang[b], Yoshiya Yamada[a], Marisa Kollmeier[a], Michael J. Zelefsky[a,]*

[a] Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [b] Department of Epidemiology-Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

1024 patients treated with EBRT ≥ 81 Gy

Favorable	Unfavorable
One intermediate risk factor	**Multiple** intermediate risk factors
Gleason score **3+4**	Gleason score **4+3**
<50% positive biopsy cores	**≥50%** positive biopsy cores

Zumsteg ZS JW et al, Eur Urol 2013

Personalizing the Management of Men with Intermediate-risk Prostate Cancer

Anthony V. D'Amico *

Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA

New treatment algorithm in men with unfavorable intermediate-risk PCa who are planning to undergo RT:

1. Obtain a 3T multiparametric MRI in men with biopsy GS 7 UIR PCa and assess whether areas suspicious for GS 8–10 PCa exist.

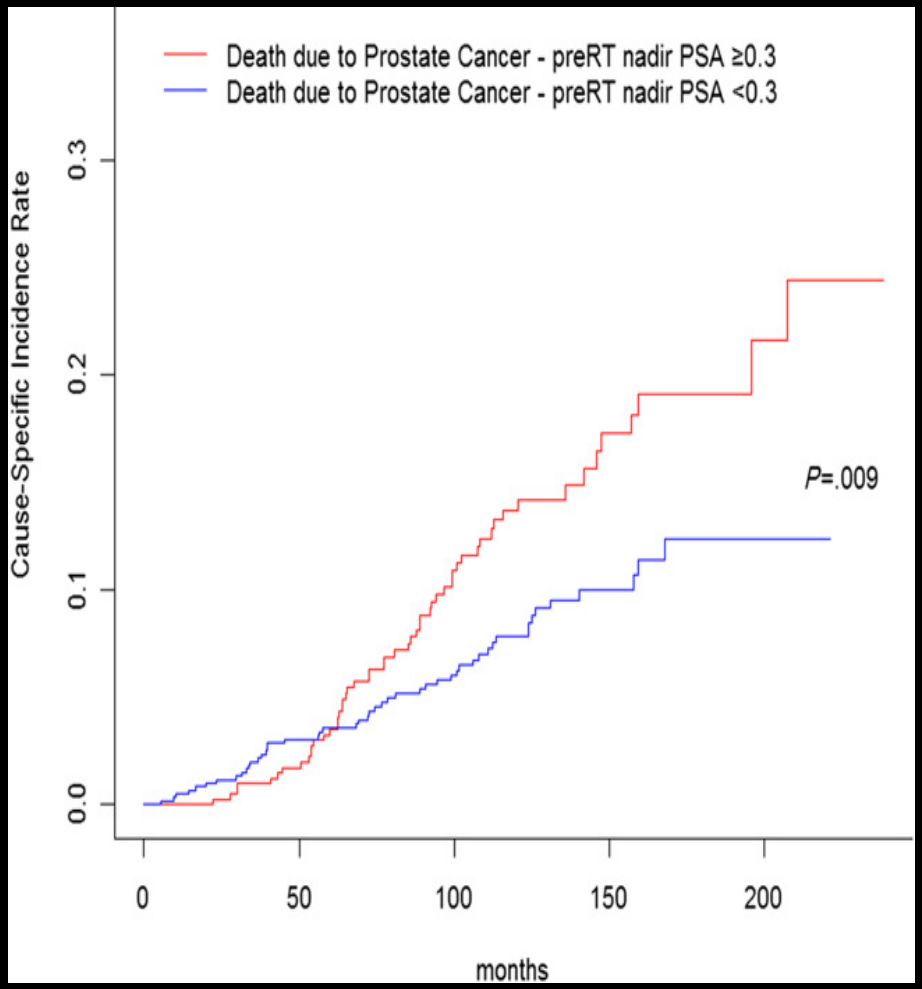
2. If suspicious areas are noted, then biopsy those areas using an MRI/TRUS fusion platform or take additional cores from the suspicious areas using a TRUS-based approach.

3. If the biopsy is negative for GS 8–10 PCa, then treat with RT and 6 mo of AST.

4. If the biopsy is positive for GS 8–10 PCa, then treat with RT and 28–36 mo of AST.

EUROPEANUROLOGY64(2013)903–904

Biochemical Response to Androgen Deprivation Therapy Before External Beam Radiation Therapy Predicts Long-Term Prostate Cancer Survival Outcomes



Pre-RT nadir PSA values of

0.3 ng/mL

after neoadjuvant ADT were associated with

improved long-term biochemical tumor control, reduction in distant metastases, and prostate cancer-related death.

Zelefsky Int J Radiation Oncol Biol Phys, 2013

Short ADT and intermediate risk disease

1) Stratificare i pazienti secondo nomogrammi (MSKCC) o fattori di rischio clinici (MDACC):

Malattia Favorable → RT High Dose

Malattia Sfavorevole → RT + Neo/Conc ADT

2) Monitorare PSA e testosterone

Long-course ADT and high risk disease

- RTOG 85-31 : Adjuvant
- EORTC 22863 : Concomitant and adjuvant
- RTOG 86-10 : Neo adjuvant and concomitant
- RTOG 92-02 : Neo adjuvant concomitant and adjuvant
- RTOG 94-13 : Neo adjuvant and concomitant
- TTROG 96-01 : Neo adjuvant and concomitant
- EORTC 22961 : Short term vs long term

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

Meta-Analysis of Randomized Trials

Emilio Bria, MD[1]; Federica Cuppone, MD[1]; Diana Giannarelli, PhD[2]; Michele Milella, MD[1]; Enzo Maria Ruggeri, MD[3]; Isabella Sperduti, PhD[2]; Paola Pinnarò, MD[1]; Edmondo Terzoli, MD[1]; Francesco Cognetti, MD[1]; and Paolo Carlini, MD[1]

Seven trials (4387 patients)

Hormone suppression significantly decreased

1. **biochemical failure** (RR, 0.76; 95% CI, 0.70-0.82; P < .0001)
2. **Local and distant relapse**, by 36% and 28%, without differences in toxicity

Hormone suppression significantly improved

1. **clinical progression-free survival** (RR, 0.81; 95% CI 0.71-0.93; P<.002), with absolute differences of 10% and 7.7%.
2. **cancer-specific survival** (RR, 0.76; 95% CI, 0.69- 0.83; P < .0001)
3. **OS** (P < .0001) with absolute differences of 5.5% and 4.9%.

CONCLUSIONS: Hormone suppression plus radiotherapy significantly decreases recurrence and mortality of patients with localized prostate cancer, without affecting toxicity.

LE: 1a GR: A

Cancer 2009;115:3446–56

Studi randomizzati: OT ± RTE

Trial /Year	TNM	N° pts	ADT	RT	Effects on OS
SPCGF-7/ SFUO-3 (2009)	T1b-2 Grade 2-3, T3 N0 M0	880	LHRH agonist for 3 mo plus continuous Flutamide	70 Gy 3D-CRT vs. no RT	Significantly better survival with combined treatment (HR 0.68, 95% CI 0.52-0.89, p = 0.04).
Mottet (2012)	T3-4 N0 M0	273 264	LHRH agonist for 3 yrs	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-years OS 71.4% vs 71.5%.
NCIC CTG PR.3/ MRC PRO7/ SWOG (2015)	T3-4 (88%), PSA > 20 ng/ mL (64%), GLS 8-10 (36%) N0 M0	1205	Continuous LHRH agonist	65-70Gy 3D-CRT vs. no RT	10-years OS = 49% vs 55% favouring combined treatment (HR = 0.7, p < 0.001).

LE: 2b GR: A

Sasse et al. BMC Cancer 2012, 12:54
http://www.biomedcentral.com/1471-2407/12/54

BMC Cancer

RESEARCH ARTICLE Open Access

Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review

André D Sasse[1*], Elisa Sasse[2], Albertina M Carvalho[3] and Ligia T Macedo[1]

Sasse et al. BMC Cancer 2012, 12:54

Review Article

Current Trends for the Use of Androgen Deprivation Therapy in Conjunction With Radiotherapy for Patients With Unfavorable Intermediate-Risk, High-Risk, Localized, and Locally Advanced Prostate Cancer

Mack Roach III, MD[1,2]

Cancer 2014;120:1620–9

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

Rolando M. D'Angelillo[a,*], Pierfrancesco Franco[b], Berardino De Bari[c], Alba Fiorentino[d], Stefano Arcangeli[e], Filippo Alongi[d]

[a] Radiation Oncology Campus Bio-Medico University, Rome Italy
[b] Department of Oncology, Radiation Oncology, University of Turin School of Medicine, Turin, Italy
[c] Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois – CHUV, Lausanne Switzerland
[d] Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, Negrar-Verona, Italy
[e] Radiation Oncology, Azienda Ospedaliera S. Camillo-Forlanini, Rome, Italy

Critical Reviews in Oncology/Hematology 93 (2015) 136–148

BJC

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

Keywords: EBRT; prostate cancer; network meta-analysis

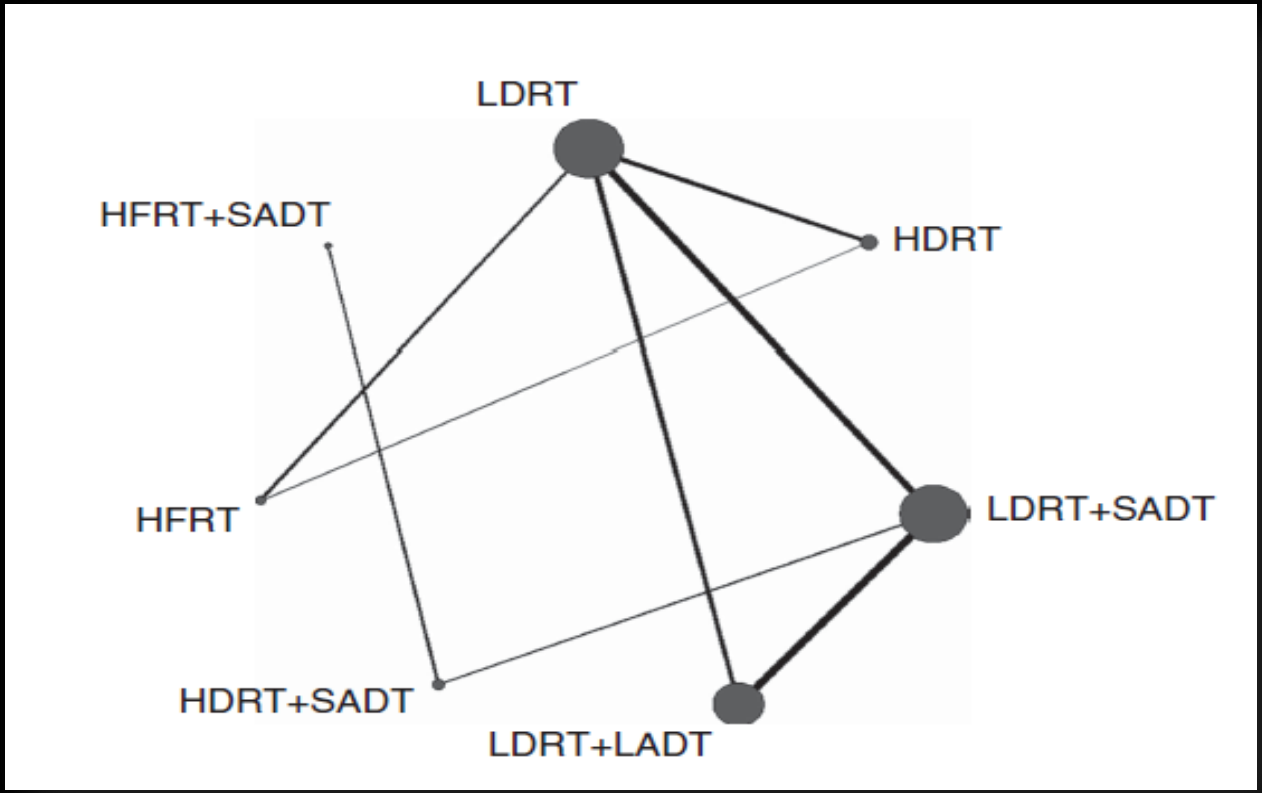
Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

Z Zhu[1], J Zhang[1], Y Liu[1], M Chen[1], P Guo[2] and K Li[*,1]

Network meta-analisi di efficacia e tossicità su 27 Studi randomizzati con 7 schemi di RT±OT

	OM				BF				CSM			
	OR	95% CI	P	I^2	OR	95% CI	P	I^2	OR	95% CI	P	I^2
HDRT vs LDRT	0.91	0.72–1.14	0.395	0	0.61	**0.49–0.76**	**0.000**	0	0.92	0.67–1.26	0.586	0
LDRT + SADT vs LDRT	0.77	**0.66–0.90**	**0.001**	0	0.48	**0.41–0.57**	**0.000**	0	0.51	**0.38–0.67**	**0.000**	0
LDRT + LADT vs LDRT	0.65	**0.48–0.87**	**0.004**	28.20%	-	-	-	-	0.56	**0.38–0.83**	**0.004**	44.20%
LDRT + LADT vs LDRT + SADT	0.86	0.71–1.06	0.160	30.90%	0.65	**0.44–0.96**	**0.030**	*82.60%*	0.71	**0.53–0.95**	**0.023**	21.60%
HDRT + SADT vs LDRT + SADT	1.1	0.72–1.69	0.671		0.64	**0.48–0.83**	**0.001**	0	0.62	0.21–1.81	0.383	43.80%
HFRT vs LDRT	0.86	0.62–1.20	0.380	0	0.84	0.67–1.07	0.151	0	0.67	0.34–1.34	0.257	0
HFRT vs HDRT	0.94	0.06–15.42	0.962		0.61	0.10–3.82	0.595		-	-	-	-
HFRT + SADT vs HDRT + SADT	0.43	0.17–1.12	0.083		0.63	0.28–1.40	0.258		0.28	0.06–1.37	0.144	

According to the network meta-analysis for treating localised or locally advanced prostate cancer …….



The most efficacious regimen is… **HFRT + Short ADT**

The higher toxic regimen is…… **HFRT + Short ADT**

Evidence Based RT+ADT

Per i pazienti con neoplasia prostatica clinicamente localizzata o localmente avanzata, a rischio intermedio sfavorevole fino ad alto rischio, la RT radicale combinata con l'OT migliora il controllo biochimico, clinico, la Sopravvivenza Globale e Cancro Specifica

LE: 1a- 2b GR: A-B

Le molteplici variabili prognostiche, la frequente morbilità associate, le diverse aspettative dei pazienti portano, nella pratica clinica, all'applicazione della…..

Prognosis Guided RT

- Bilancio funzionale basale
- Bilancio di comorbidità
- Approfondire l'I²RT per il preplanning, planning and delivery (IGRT)
- Condivisione degli algoritmi prognostici, produzione del metagramma perdonalizzato
- Flessibilità su dosi, tecniche, volumi, integrazioni OT finalizzate alle aspettative concordate
- Monitoraggio biochimico, clinico del trattamento OT+RT

Personalized RT

R^7 paradigm:
To the **Right patient and tumor**, the **Right intervention**, for the **Right reason**, at the **Right location**, at the **Right time**, with the **Right outcome**, monitored in **Real time**

Clinical Investigation

What Aspects of Personal Care Are Most Important to Patients Undergoing Radiation Therapy for Prostate Cancer?

Kimberley A. Foley, MSc,*,† Deb Feldman-Stewart, PhD,*,‡ Patti A. Groome, PhD,*,† Michael D. Brundage, FRCPC,*,†,‡,§ Siobhan McArdle, MSc,§ David Wallace, MSc,*,† Yingwei Peng, PhD,*,†,‖ and William J. Mackillop, FRCPC*,†,‡,§

*Cancer Care and Epidemiology, Queen's Cancer Research Institute; †Department of Public Health Sciences and ‡Department of Oncology, Queen's University; §Cancer Centre of Southeastern Ontario; and ‖Department of Mathematics and Statistics, Queen's University, Kingston, Ontario, Canada

Many different elements of personal care are important to patients undergoing radiation therapy for prostate cancer, but the 3 aspects of care that most believe are most important are these:

1. **the perceived competence of their caregivers,**
2. **the empathy and respectfulness of their caregivers,**
3. **the adequacy of information sharing.**

Int J Radiation Oncol Biol Phys, Vol. 94, No. 2, pp. 280-288, 2016

Non ho conflitti d'interesse, ma…….

W W W

l'AIRO TriVeneto

signor.marco@aoud.sanita.fvg.it