Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

«PELVI O NON PELVI, QUESTO È IL DILEMMA» : ANALISI RETROSPETTIVA SULL'IRRADIAZIONE ELETTIVA DELLE STAZIONI LINFONODALI PELVICHE VS RADIOTERAPIA SULLA SOLA LOGGIA PROSTATICA IN PAZIENTI CON CARCINOMA PROSTATICO NON METASTATICO A RISCHIO ALTO E MOLTO ALTO

V. Morelli, E. Ranghetti, P. Ghirardelli, L. Triggiani, M. Maddalo, A. Guerini, G. Pedersoli, N. Singh, S. La Mattina, E. Villa, A. Ravasio, A.M. Guainieri, G. Costantino, D. Tomasini, F. Frassine, L. Costa, L. Pegurri, M. Buglione di Monale e Bastia, V. Vavassori, S.M. Magrini.

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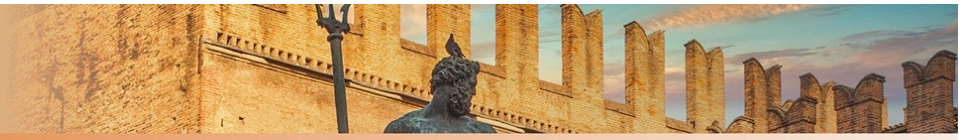


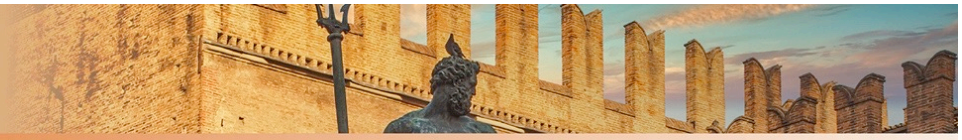
DICHIARAZIONE

Relatore: **VITTORIO MORELLI**

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

«PELVI O NON PELVI, QUESTO È IL DILEMMA»

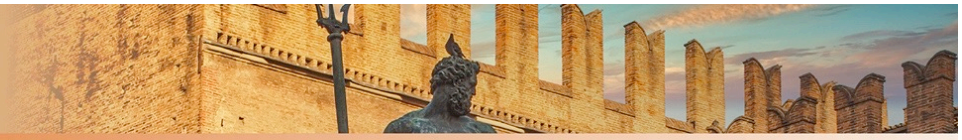


EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on **Prostate Cancer**

European Association of Urology · EANM · SIOG International Society of Geriatric Oncology · European Society of Urogenital Radiology · ESTRO European Society for Radiotherapy & Oncology · EUROPA UOMO The Voice of Men with Prostate Cancer in Europe

6.2.3.2.1 Lymph node irradiation in cN0

There is low level evidence for prophylactic whole-pelvic irradiation as RCTs so far failed to show that patients benefit from prophylactic irradiation (46–50 Gy) of the pelvic LNs in intermediate- and high-risk disease [900-902].



Overview of RCTs evaluating the value of WPRT

	Study design	Number of patients	Lymph node invasion risk	Treatment groups	Primary endpoint	Median follow-up, months
Patients with cN0 disease in the primary setting						
RTOG 9413 trial[1]	RCT	1322	All patients >15% (Roach formula)	2 × 2 design, neoadjuvant hormonal treatment versus adjuvant hormonal treatment and whole pelvis radiotherapy versus prostate-only radiotherapy	Progression-free survival	108
GETUG-01 trial[7]	RCT	446	45% patients >15%	Whole pelvis radiotherapy versus prostate-only radiotherapy, 4–8 months of hormonal treatment	Event-free survival	104
POP-RT trial[11]	RCT	224	All patients >20% (Roach formula), median risk 38%	Whole pelvis radiotherapy versus prostate-only radiotherapy, 24 months of hormonal treatment	Biochemical progression-free survival	68
PIVOTAL trial[3]	RCT	124	All patients ≥30% (Roach formula)	Prostate-only radiotherapy versus whole pelvis radiotherapy, 6–9 months of hormonal treatment	Toxicity, quality of life	24

*De Meerleer G, Berghen C, Briganti A, Vulsteke C, Murray J, Joniau S, Leliveld AM, Cozzarini C, Decaestecker K, Rans K, Fonteyne V, De Hertogh O, Bossi A. Elective nodal radiotherapy in prostate cancer. Lancet Oncol. 2021 Aug;22(8):e348-e357. doi: 10.1016/S1470-2045(21)00242-4. PMID: 34339655.

THE LANCET
Oncology

Volume 19, Issue 11, November 2018, Pages 1504-1515

Articles

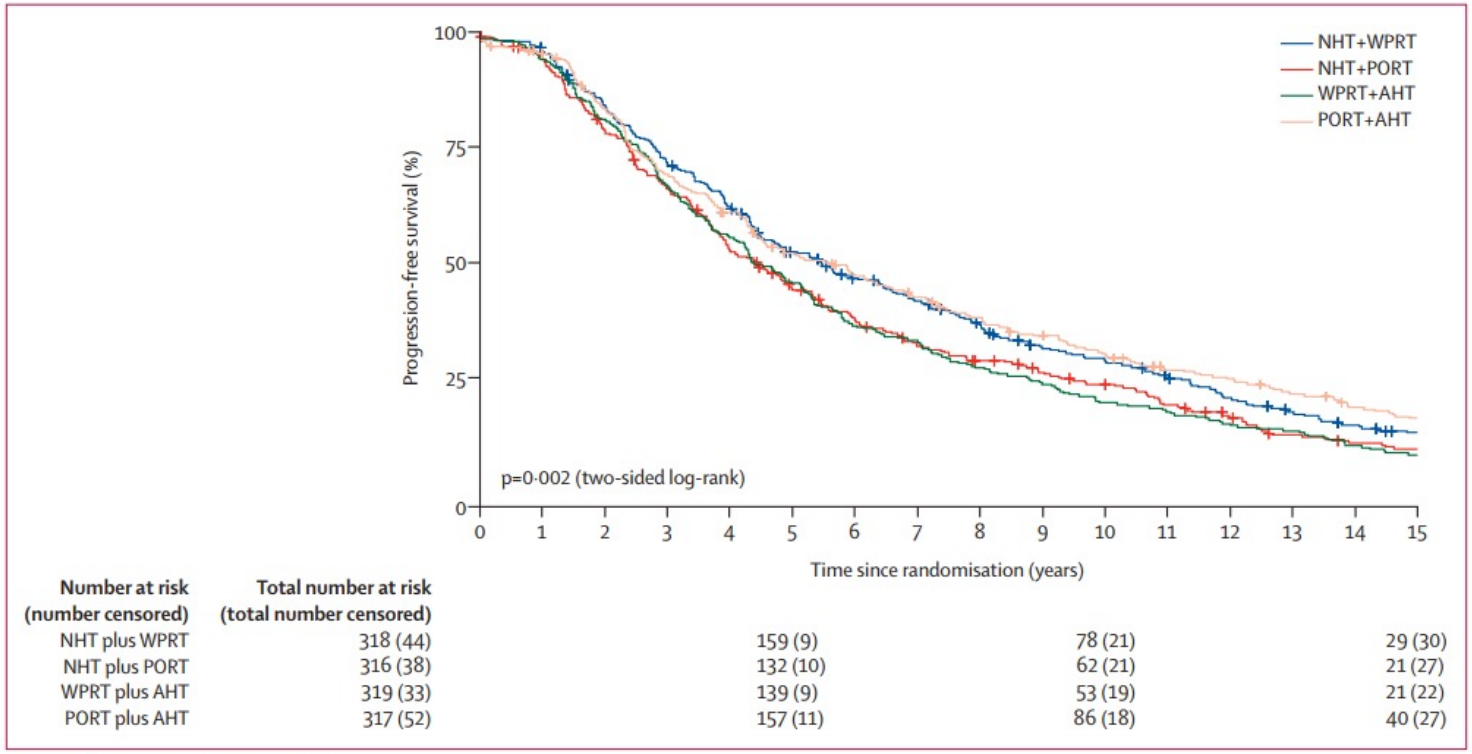
Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial

Prof Mack Roach MD [a], Jennifer Moughan MS [b], Prof Colleen A F Lawton MD [c], Prof Adam P Dicker MD [d], Kenneth L Zeitzer MD [e], Prof Elizabeth M Gore MD [c], Young Kwok MD [f], Michael J Seider MD [g], Prof I-Chow Hsu MD [a], Alan C Hartford MD [h], Prof Eric M Horwitz MD [i], Kosj Yamoah MD [j], Christopher U Jones MD [k], Prof Jeff M Michalski MD [l], Prof W Robert Lee MD [m], Prof Thomas M Pisansky MD [n], Prof Rachel Rabinovitch MD [o], Prof Marvin Rotman MD [p] ... Prof Howard M Sandler MD [u]

1322 pts randomly assigned (1:1:1:1)

- **2 months of neoadjuvant ADT + WPRT**
- **2 months of neoadjuvant ADT + PORT**
- **WPRT + 4 months of adjuvant ADT**
- **PORT + 4 months adjuvant ADT**

- **Primary endpoint: PFS**
- **<u>2x2 factorial design</u>**

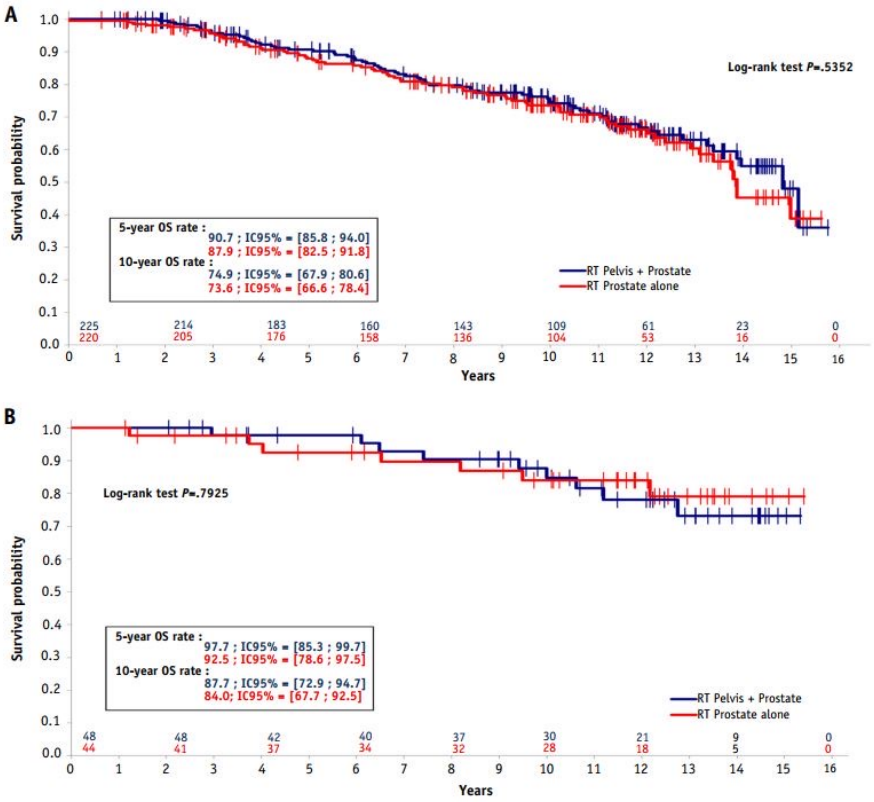


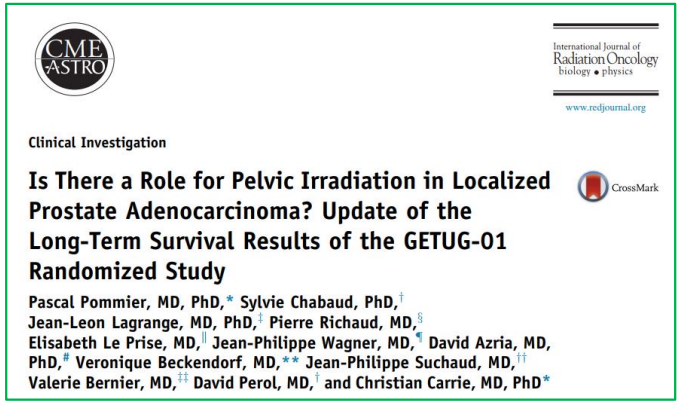
Number at risk (number censored)	Total number at risk (total number censored)			
NHT plus WPRT	318 (44)	159 (9)	78 (21)	29 (30)
NHT plus PORT	316 (38)	132 (10)	62 (21)	21 (27)
WPRT plus AHT	319 (33)	139 (9)	53 (19)	21 (22)
PORT plus AHT	317 (52)	157 (11)	86 (18)	40 (27)

Figure 3: **Progression-free survival**
HR=hazard ratio. AHT=adjuvant hormonal therapy. NHT=neoadjuvant hormonal therapy. PORT=prostate only radiotherapy. WPRT=whole pelvic radiotherapy.

- Dose prescription: prostate (70.2 Gy in 39 fr), pelvis (50.4 Gy in 28 fr)
- Risk of lymph node invasion >15% (Roach formula)
- **Highest progression-free survival (30%) with PORT + ADJ ADT**

Volume 96 • Number 4 • 2016 GETUG-01 trial: long term survival results 763





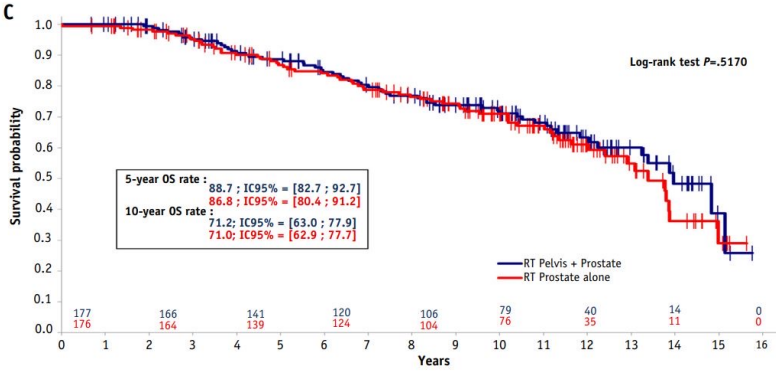
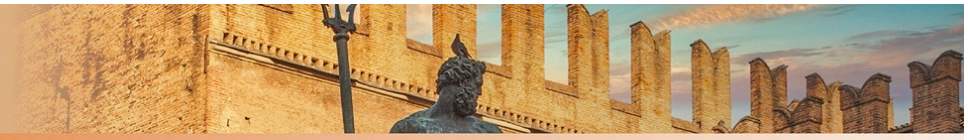


Fig. 1. Overall survival (OS) according to the whole population (A), the stratified low-risk group (B), and the high-risk group (C). *Abbreviations:* IC95% = 95% confidence interval; RT = radiation therapy.



ELSEVIER

Radiotherapy and Oncology
Volume 145, April 2020, Pages 71-80

Original Article

Late toxicity and quality of life with prostate only or whole pelvic radiation therapy in high risk prostate cancer (POP-RT): A randomised trial

Vedang Murthy [a], Priyamvada Maitre [a], Jatin Bhatia [a], Sadhana Kannan [b], Rahul Krishnatry [a], Gagan Prakash [c], Ganesh Bakshi [c], Mahendra Pal [c], Santosh Menon [d], Umesh Mahantshetty [a]

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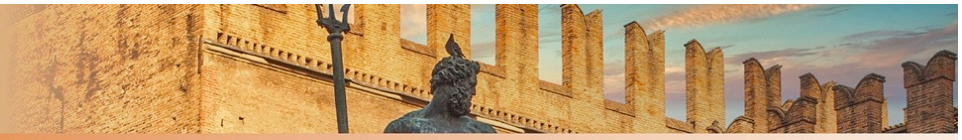
original reports

Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial

Vedang Murthy, MD[1]; Priyamvada Maitre, MD[1]; Sadhana Kannan, MSc[2]; Gitanjali Panigrahi, MSc[1]; Rahul Krishnatry, MD[1]; Ganesh Bakshi, MCh[3]; Gagan Prakash, DNB[3]; Mahendra Pal, DNB[3]; Santosh Menon, MD[4]; Reena Phurailatpam, MSc[5]; Smruti Mokal, MSc[2]; Dipika Chaurasiya, BSc[1]; Palak Popat, DNB[6]; Nilesh Sable, MD[6]; Archi Agarwal, DNB[7]; Venkatesh Rangarajan, DNB[7]; Amit Joshi, DM[8]; Vanita Noronha, DM[8]; Kumar Prabhash, DM[8]; and Umesh Mahantshetty, MD[1]

- 224 patients were enrolled and randomly assigned (1:1) to receive either PORT or WPRT
- Primary endpoints: BFFS;
- Secondary endpoints: DFS, OS, acute and late toxicities, PR-QOL
- Key eligibility criterion: risk of pelvic node involvement of at least 20%, estimated using Roach formula
- After a median follow-up of 68 months, BFFS significantly longer with WPRT than with PORT (95% *vs* 81%; p<0·0001) ;
- DFS (90% with WPRT vs 77% with PORT; p=0.002)
- DMFS (95% vs 88%; p=0.01)



Pelvic or Prostate RT in High-Risk Prostate Cancer

TABLE 3. Comparison With Previous Randomized Trials of Pelvic Radiotherapy

Parameter	RTOG 9413	GETUG-01	POP-RT
T Stage	T2c-T4: 67%	T3: 25.5%	T3b-T4: 46.4%
Estimated pelvic nodal risk	> 35% risk in 24.5%	> 35% risk in 9.8%	Median 38% > 35% risk in 55% > 50% risk in 29%
GS	GS 7-10: 72%	GS 7-10: 50.7% GS 8-10: 10.9%	GS 7-10: 90.2% GS 8-10: 49.1%
Baseline median PSA	22.6 ng/mL	12 ng/mL	28.2 ng/mL
Staging imaging	Chest x-ray, CT pelvis or lymphangiogram, bone scan	CT thorax abdomen and pelvis, bone scan	MRI pelvis, PETCT (F-18 or Ga-68 PSMA) 80% had PSMA PETCT
Pelvic field upper limit	L5-S1	S1-S2	L4-L5 including common iliac nodes
Pelvic dose	50.4 Gy	46 Gy	50 Gy
Prostate dose (biologically effective dose)	70.2 Gy, 1.8 Gy per fraction (112.32 Gy)	66.25-72 Gy, 1.8-2 Gy per fraction (110-122 Gy)	68 Gy, 2.72 Gy per fraction (129.6 Gy)
Radiotherapy technique	Conventional 2-dimensional box fields	Conventional 2-dimensional box fields and 3-dimensional conformal radiotherapy	Image-guided IMRT
ADT	4 months	4-8 months	≥ 24 months

Abbreviations: ADT, androgen deprivation therapy; CT, computed tomography; GS, Gleason score; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; PET, positron emission tomography; POP-RT, prostate-only or whole-pelvic radiation therapy in high-risk prostate cancer; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RTOG, Radiation Therapy Oncology Group.

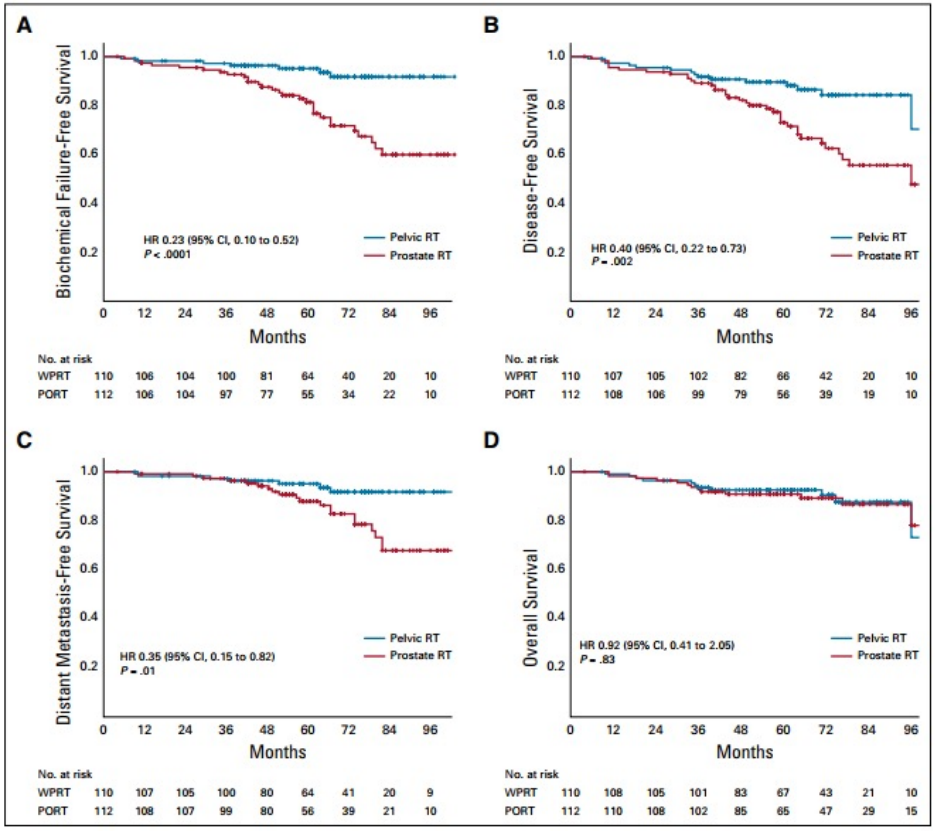


FIG 2. Kaplan-Meier estimates of (A) biochemical failure-free survival, (B) disease-free survival, (C) distant metastasis-free survival, and (D) overall survival. HR, hazard ratio; PORT, prostate-only radiotherapy; RT, radiotherapy; WPRT, whole-pelvic radiotherapy.

TABLE 2. Cumulative Late Toxicity (RTOG)

RTOG Grade	All Patients (N = 222), N (%)	PORT (n = 112), N (%)	WPRT (n = 110), N (%)	*P* (grade 0-1 *v* grade ≥ II)
GU				
0	85 (38.3)	45 (40.2)	40 (36.4)	.02
I	105 (47.3)	57 (50.9)	48 (43.6)	
II	28 (12.6)	8 (7.1)	20 (18.2)	
III	4 (1.8)	2 (1.8)	2 (1.8)	
GI				
0	138 (62.2)	74 (66.1)	64 (58.2)	.28
I	70 (31.5)	33 (29.5)	37 (33.6)	
II	12 (5.4)	5 (4.5)	7 (6.4)	
III	2 (0.9)	0 (0)	2 (1.8)	

Abbreviations: GU, genitourinary; PORT, prostate-only radiotherapy; RTOG, Radiation Therapy Oncology Group; WPRT, whole-pelvic radiotherapy.

Material and methods:

Data of **205 high and very high risk non-metastatic prostate cancer (HR-nmPca) (cN0 and cM0 according to TNM staging)** who underwent normofractionated or hypofractionated RT[1] (**IMRT/VMAT with daily IGRT**) from January 2011 to December 2016 in 2 italian radiation oncology centres were **retrospectively analyzed**.

1: 2.45 – 3.2 Gy / 64 – 73.5 Gy

WPRT group

(Humanitas Gavazzeni – Bergamo)

- **62 pts**

HUMANITAS GAVAZZENI

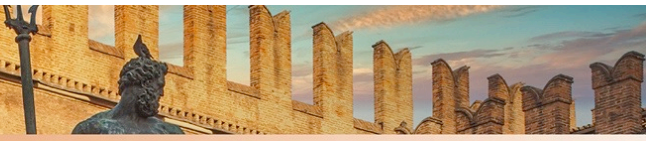
PORT group

(Spedali Civili - Brescia)

- **143 pts**

SPEDALI CIVILI DI BRESCIA
AZIENDA OSPEDALIERA

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili



HR-nmPca cN0 cM0
N = 205

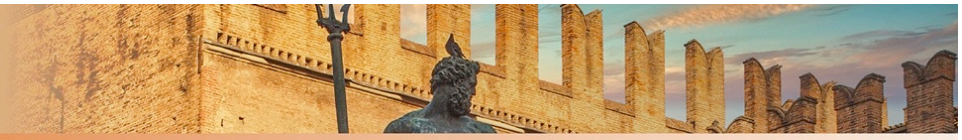
Spedali Civili
(PORT)
N = 143

Humanitas-Gavazzeni
(WPRT)
N = 62

Propensity Score matching 1:1
(Age, ISUP Grade Group, iPSA)

Spedali Civili
(PORT)
N = 61

Gavazzeni
(WPRT)
N = 61



Patients' characteristics

	PORT	WPRT
Number of pts (n° tot 205)	143	62
Age (years)	Mean 72.4 Median 73.7	Mean 72.8 Median 74
iPSA		
• **<10 ng/ml**	69 (48.2%)	35 (56.5%)
• **≥ 10 e < 20 ng/ml**	34 (23.8%)	11 (17.7%)
• **≥ 20 ng/ml**	40 (28%)	16 (25.8%)
ISUP		
• **3+3**	22 (15.4%)	3 (4.8%)
• **3+4**	26 (18.2%)	5 (8.1%)
• **4+3**	12 (8.4%)	8 (12.9%)
• **4+4, 5+3, 3+5**	44 (30.7%)	33 (53.2%)
• **5+5, 4+5, 5+4**	39 (27.3%)	13 (21%)
cT		
• **T1c**	**24 (16.8%)**	**36 (58.1%)**
• **T2a**	**9 (6.3%)**	**1 (1.6%)**
• **T2b**	**5 (3.5%)**	**6 (9.7%)**
• **T2c**	**18 (12.6%)**	**2 (3.2%)**
• **T3a**	**44 (30.7%)**	**6 (9.7%)**
• **T3b**	**34 (23.8%)**	**11 (17.7%)**
• **T4**	**9 (6.3%)**	**0 (0%)**
ADT (adjuvant or concomitant)		
• **Si**	135 (94.4%)	62 (100%)
• **No**	8 (5.6%)	0 (0%)
• **Median**	33	23
• **Mean**	27.56	21.58
RT		
• **Normofractionation (1.8-2 Gy/fr)**	103 (72%)	27 (43.5%)
• **Moderate Hypofractionation (2.3-3.2 Gy/fr)**	40 (28%)	35 (56.5%)

WPRT characteristics

Total dose	Fractionation	N (%)
54 Gy	1,8 Gy/fr	46 (74,19%)
50.4 Gy	1,8 Gy/fr	13 (20,97%)
52.2 Gy	1,8 Gy/fr	2 (3,23%)
46.8 Gy	1,8 Gy/fr	1 (1.61 %)

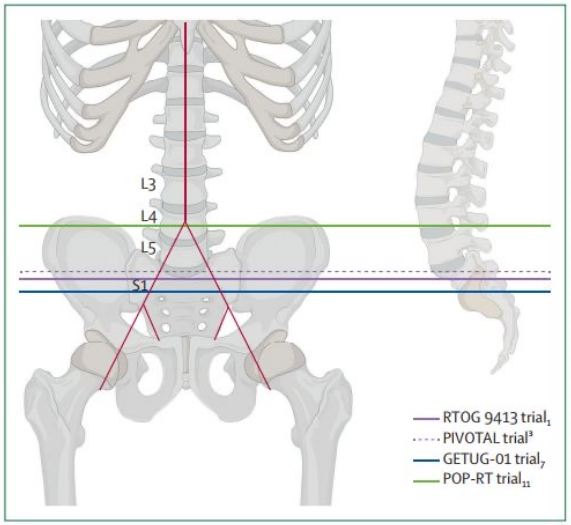


Figure 1: Comparison of radiation treatment upper borders in different randomised trials

*In WPRT arm, pelvic nodal CTV was delineated starting at L4-5 junction to include bilateral common iliac, external iliac, internal iliac, presacral, and obturator nodes

FIGURE IN *De Meerleer G, Berghen C, Briganti A, Vulsteke C, Murray J, Joniau S, Leliveld AM, Cozzarini C, Decaestecker K, Rans K, Fonteyne V, De Hertogh O, Bossi A. Elective nodal radiotherapy in prostate cancer. Lancet Oncol. 2021 Aug;22(8):e348-e357. doi: 10.1016/S1470-2045(21)00242-4. PMID: 34339655.

ELSEVIER
International Journal of Radiation Oncology*Biology*Physics
Volume 109, Issue 1, 1 January 2021, Pages 174-185

Clinical Investigation

NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer

William A. Hall MD *, Eric Paulson PhD *, Brian J. Davis MD, PhD †, Daniel E. Spratt MD ‡, Todd M. Morgan MD §, David Dearnaley FRCR, MD ||, Alison C. Tree FRCR, MD ||, Jason A. Efstathiou MD, DPhil, FACRO, FASTRO ¶, Mukesh Harisinghani MD #, Ashesh B. Jani MD, MSEE, FASTRO **, Mark K. Buyyounouski MD, MS ††, Thomas M. Pisansky MD †, Phuoc T. Tran MD, PhD ‡‡, R. Jeffrey Karnes MD §§, Ronald C. Chen MD, MPH, FASCO, FASTRO ||||, Fabio L. Cury MD ¶¶, Jeff M. Michalski MD, MBA, FASTRO ###, Seth A. Rosenthal MD, FACR, FASTRO *** ... Colleen A.F. Lawton MD, FACR, FASTRO *

EUROPEAN UROLOGY 71 (2017) 37–43
available at www.sciencedirect.com
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European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by Cesare Cozzarini on pp. 44–45 of this issue

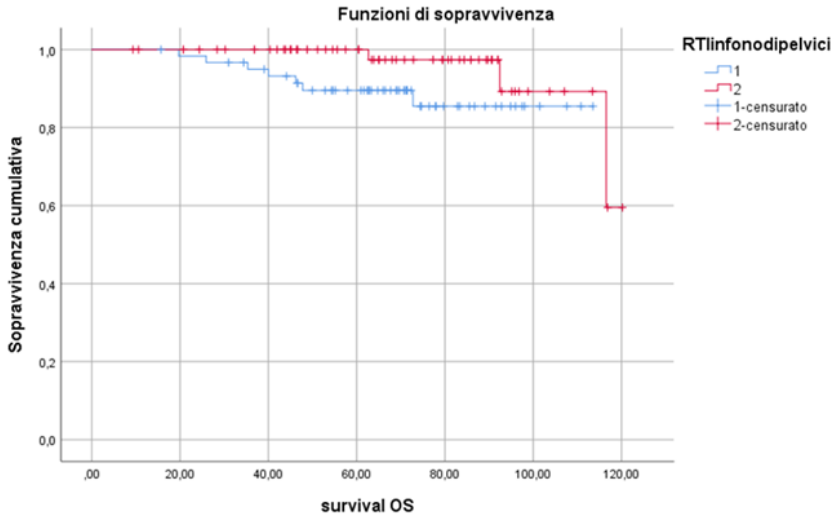
Patterns of Lymph Node Failure after Dose-escalated Radiotherapy: Implications for Extended Pelvic Lymph Node Coverage

Daniel E. Spratt [a,b,†], Hebert A. Vargas [c,†], Zachary S. Zumsteg [a], Jennifer S. Golia Pernicka [c], Joseph R. Osborne [c], Xin Pei [a], Michael J. Zelefsky [a,]*

[a] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [b] Department of Radiation Oncology, University of Michigan, Ann Arbor 48109, USA; [c] Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Results:

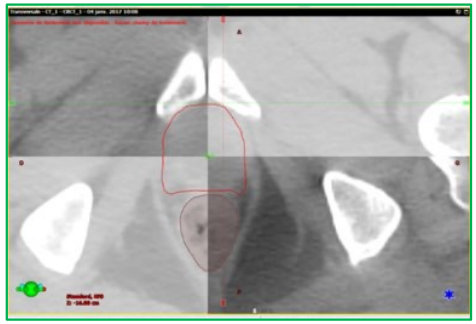
- **Biochemical failure (BF)** occurred in 6 pts in the PORT group (9.83%) and 10 (16.39%) in the WPRT group (p= 0.262).
- **5 years BFFS:** 100.6 months in the PORT group vs 92 months in the WPRT group.
- **Time to mCRPC:** 45.2 months for PORT group vs 43.6 for WPRT group (**p= 0.538**);
- **CSS** was 111.9 for PORT; 117.5 months in WPRT group (**p= 0.995**).
- **OS** was 103.7 months with PORT and 115.3 with WPRT **(p= 0.084**)



Median follow up: 5 years (PORT); 5.5 years (WPRT)

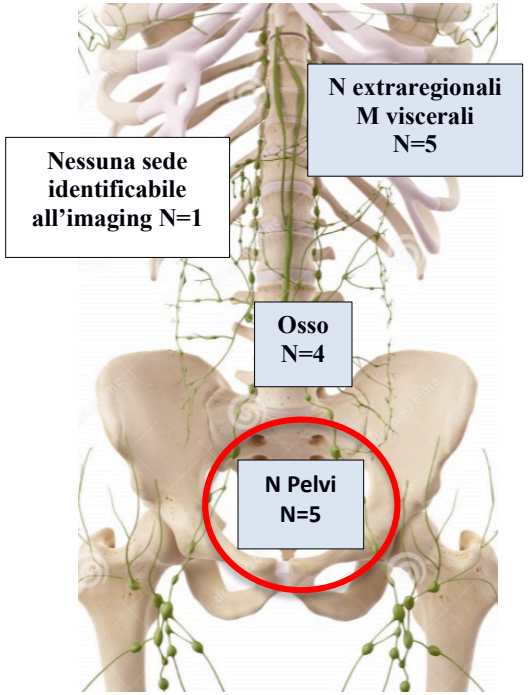
Acute and late toxicity

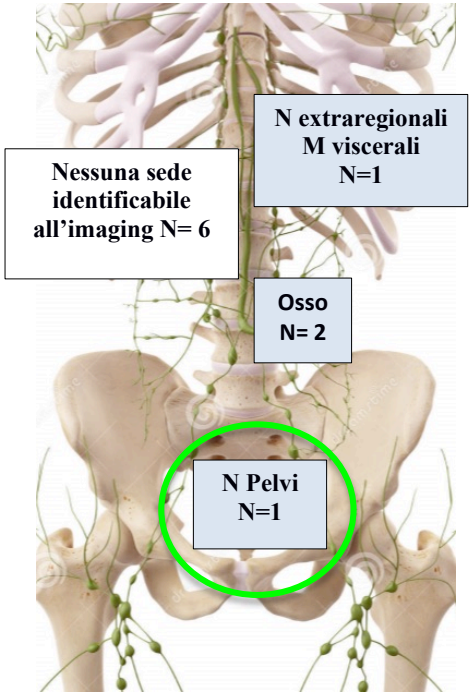
Toxicity G≥3 (CTCAE)	PORT		WPRT	
	Acute	Late	Acute	Late
GU	1 (1.6%)	1 (1.6%)	1 (1.6%)	2 (3.2%)
GI	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)



Clinical sites of recurrence

PORT
N° tot= 6 (9.68%)





WPRT
N° tot= 10 (16.13%)

NB: pelvic lymph node recurrence:
Only 1 patient among those treated with WPRT; 5 cases in PORT group (p= 0.094).

Conclusions

- WPRT did not result into an increase in toxicity, but at the same time it did not improve survival, although the follow-up is still too short.

Future directions:

- Nodal Metastasis-directed therapy or Elective Nodal Radiotherapy at the time of BF (in case of nodal oligorecurrence) may represent viable and effective therapeutic options.
- The integration of PSMA-PET in frontline staging could lead to more accurate treatment decisions.

Main limits of the study

- **Retrospective nature**
- **Sample size**
- **Short follow up**