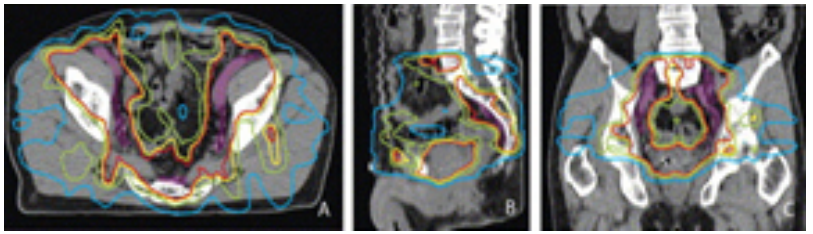
Controversie nelle strategie terapeutiche del carcinoma prostatico localizzato ad alto rischio

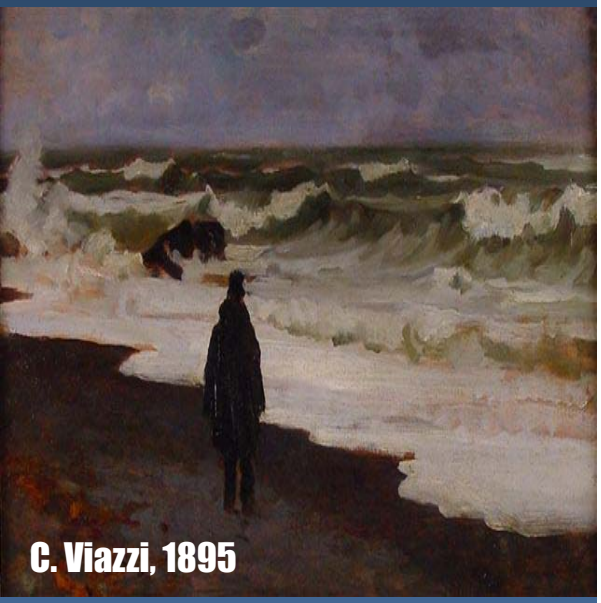
Irradiazione pelvica: Pros



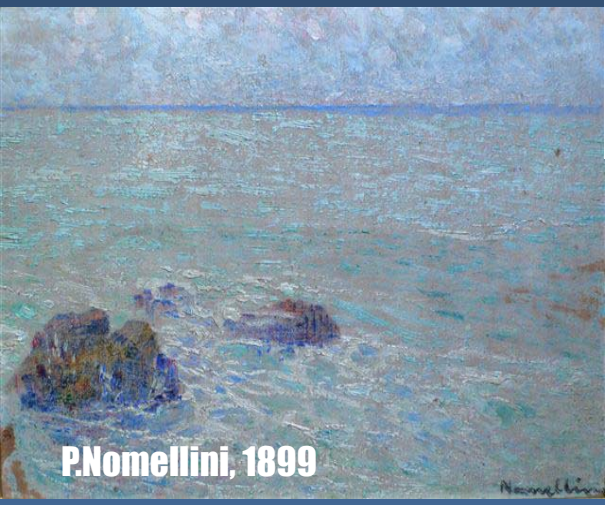
Paola Franzone

Sistema Sanitario Regionale Piemonte
Azienda Ospedaliera Nazionale
SS. ANTONIO e BIAGIO
e CESARE ARRIGO
Alessandria

IL PROBLEMA


C. Viazzi, 1895

- Pazienti affetti da neoplasia prostatica con fattori prognostici sfavorevoli (elevati PSA, stadio clinico e grading) hanno un rischio aumentato di avere malattia extraprostatica.
- Solo l'androgeno-deprivazione, ha, in questi casi, migliorato la sopravvivenza.
- La Radioterapia esterna prostatica, anche con dose escalation, è limitata dall'eventuale presenza di malattia pelvica oltre la sede irradiata.
- La Radioterapia pelvica potrebbe migliorare l'outcome di quei pazienti con localizzazioni linfonodali macro o microscopiche.



Guidelines on Prostate Cancer

A. Heidenreich (chairman), M. Bolla, S. Joniau, M.D. Mason, V. Matveev, N. Mottet, H-P. Schmid, T.H. van der Kwast, T. Wiegel, F. Zattoni

European Association of Urology

	LE
In localised prostate cancer T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention. There is fairly strong evidence that low-, intermediate- and high-risk patients benefit from dose escalation	2
For patients in the high-risk group, short-term ADT prior to and during radiotherapy results in increased overall survival, but three years of adjuvant ADT are better according to the results of EORTC 22961	2a
Transperineal interstitial brachytherapy with permanent implants is an option for patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS	2b
Immediate post-operative external irradiation after RP for patients with pathological tumour stage T3 N0 M0 improves overall survival, biochemical and clinical disease-free survival with the highest impact in cases of positive margins (R1)	1
An alternative option is to give radiation at the time of biochemical failure, but before PSA rises above 0.5 ng/mL	3
In locally advanced prostate cancer T3-4 N0 M0, overall survival is improved by concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external beam irradiation for patients with a WHO 0-2 performance status.	1
For a subset of patients with T2c-T3 N0-x and a Gleason score of 2-6, short-term ADT before and during radiotherapy may favourably influence overall survival	1b
In very high-risk prostate cancer, c-pN1 M0 with no severe co-morbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment improve overall survival, disease-specific failure, metastatic failure and biochemical control	2b

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 4.2011 Prostate Cancer

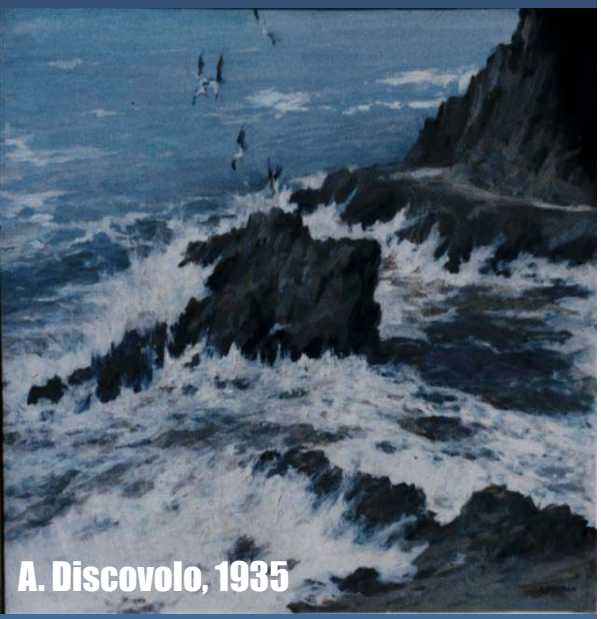
NCCN Guidelines Index
Prostate Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

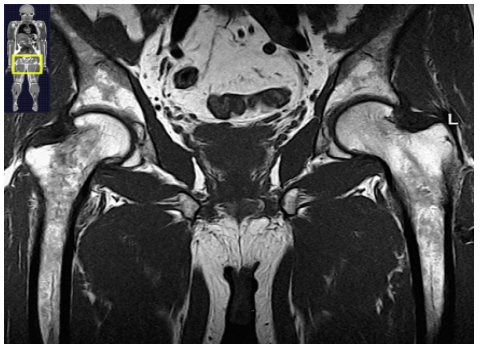
External Beam Radiotherapy:

- 3D conformal and IMRT (intensity modulated radiation therapy) techniques should be employed. Image guided radiation therapy (IGRT) is required if dose ≥ 78 Gy.
- Doses of 75.6-79 Gy in conventional 36-41 fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses between 78-80+ Gy provide improved PSA-assessed disease control.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 y (category 1).
- Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques such as IGRT using CT, ultrasound implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.

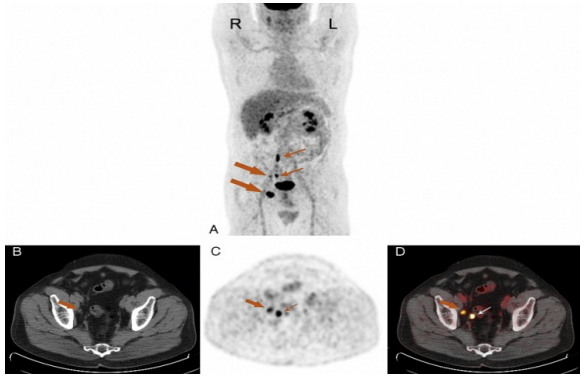
Stadiazione linfonodale mediante imaging



TC ed RM : scarsa sensibilità (criterio volumetrico insufficiente)

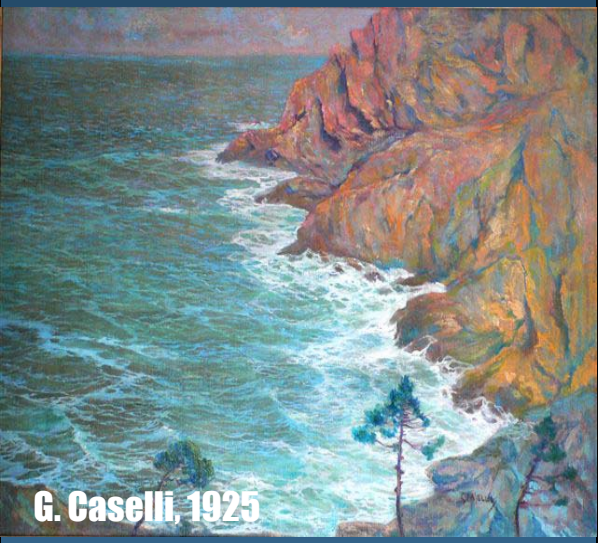


PET con Colina: promettente, soprattutto nel setting postoperatorio in associazione al PSA



Identificazione del linfonodo sentinella mediante linfoscintigrafia, SPECT/CT o SPECT/RM

Mattei, 2008: PLND dovrebbe includere le regioni iliache esterne, otturatorie ed iliache comuni.


G. Caselli, 1925

Stadiazione linfonodale chirurgica

STUDER, J Urol 2002:

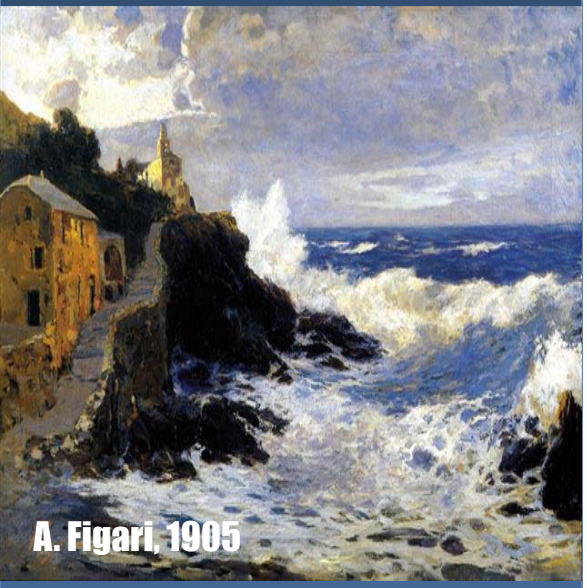
Il riscontro di metastasi linfonodali solitarie aumenta marcatamente quando viene eseguita una PLND.
Circa metà delle metastasi possono non essere rinvenute se si esegue una linfoadenectomia solo otturatoria.
Dopo PR il PSA relapse è di circa il 30% e in parte può essere dovuto a metastasi linfonodali non diagnosticate.

BRIGANTI, Urology 2007:

La probabilità di rinvenire linfonodi positivi è proporzionale al numero di linfonodi asportati: 2-10 (5.6%), 10-14 (8.6%), 15-19 (10.2%), 20-40 (17.6%)
In analisi multivariata il numero di linfonodi asportati è il maggior predittore di interessamento linfonodale ($p<0.001$)

I nomogrammi derivati da serie chirurgiche potrebbero sottostimare la vera incidenza di linfonodi positivi.

Studi retrospettivi di WPRT



Radioterapia esterna

5 Studi, più di 2500 pazienti, prevalentemente con rischio linfonodale >15%

WPRT vs PORT con o senza HT,

- 4 Studi: miglioramento di PSA control-rate
- 1 Studio: anche migliore cause-specific survival.
- Nello Studio negativo l'irradiazione pelvica non arrivava a L5-S1

Radioterapia postoperatoria

2 Studi, più di 400 pazienti con linfonodi positivi o ricaduti.

- 2 Studi: miglioramento PSA-control-rate
- 1 Studio: anche migliore cause-specific survival

Studi prospettici

RTOG 85-31, 92-02, 86-10, EORTC 22863:

- nella malattia ad alto rischio insieme a long term HT era prevista anche WPRT.

Trial RTOG 94-13, 1300 pazienti:

- NHT + WPRT impattava significativamente su PFS e OS in pazienti a rischio intermedio ed alto (>15% rischio N + sec. nomogramma).

Table 2. Progression-free survival*

Treatment arm	*n*	*p**
WPRT + NHT	198/320	0.065
PORT + NHT	210/316	
WPRT + AHT	220/319	
PORT + AHT	199/320	
Pairwise comparison		
WPRT + NHT vs.		
PORT + NHT		0.066
WPRT + AHT		0.022
PORT + AHT		0.75
PORT + NHT vs.		
WPRT + AHT		0.69
PORT + AHT		0.15
WPRT + AHT vs.		
PORT + AHT		0.057

Abbreviations as in Table 1.
* *p* value is from the Log–rank for comparing progression-free survival curves.

Table 3. Overall survival

Treatment arm	*n*	*p*
WPRT + NHT	104/320	0.027*
PORT + NHT	99/316	
WPRT + AHT	130/319	
PORT + AHT	101/320	
Pairwise comparison		*p* value†
WPRT + NHT vs.		
PORT + NHT		0.9629
WPRT + AHT		0.019
PORT + AHT		0.80
PORT + NHT vs.		
WPRT + AHT		0.019
PORT + AHT		0.86
WPRT + AHT vs.		
PORT + AHT		0.01

Abbreviations as in Table 1.
* Log–rank test for comparing overall survival curves.
† *p* value is from the log rank for comparing overall survival curves.

RTOG 94-13


A.Beniscelli, 1920

- Il maggior beneficio si otteneva per Gleason 7-10 e PSA < 30 ng e Gleason < 7 con PSA>30 ng. (Altri avevano un rischio o troppo basso di essere N+ oppure erano a rischio di malattia oltre la pelvi).

- Subset NHT+ WPRT, NHT+ minipelvic RT, NHT+ PORT: DFS a 7 anni del 40%, 35% , 27% rispettivamente.

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 3, pp. 646–655, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.04.003

CLINICAL INVESTIGATION **Prostate**

AN UPDATE OF THE PHASE III TRIAL COMPARING WHOLE PELVIC TO PROSTATE ONLY RADIOTHERAPY AND NEOADJUVANT TO ADJUVANT TOTAL ANDROGEN SUPPRESSION: UPDATED ANALYSIS OF RTOG 94-13, WITH EMPHASIS ON UNEXPECTED HORMONE/RADIATION INTERACTIONS

COLLEEN A. LAWTON, M.D.,* MICHELLE DESILVIO, PH.D.,† MACK ROACH III, M.D.,‡ VALERY UHL, M.D.,§

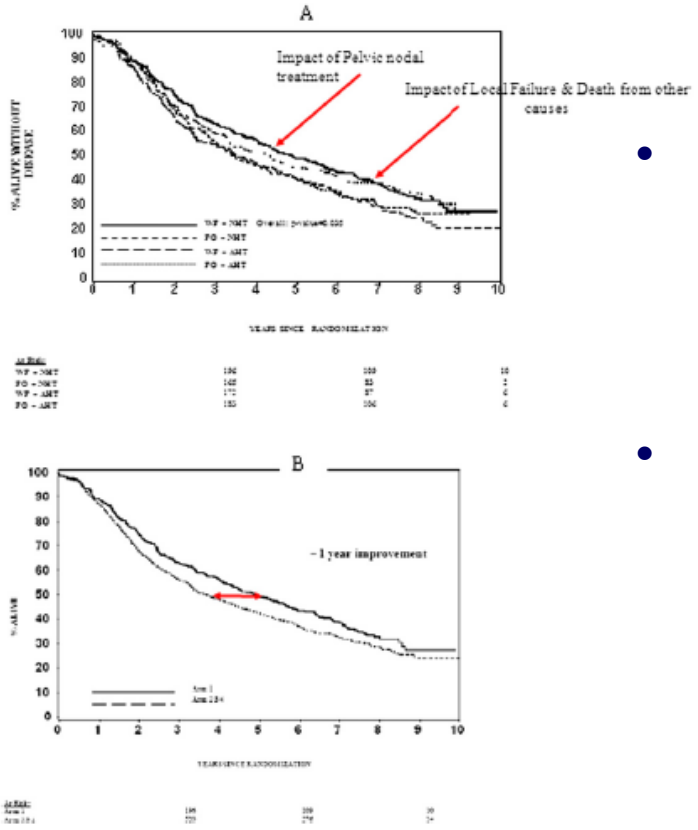


Fig. 3. (A) Progression-free survival in all arms per Radiation Therapy Oncology Group-9413 protocol definition (includes death from any cause). (B) Progression-free survival in whole pelvic radiotherapy (WPRT) + neoadjuvant hormone therapy (NHT) vs. arms prostate only radiotherapy (PORT) + NHT, WPRT + AHT (Adjuvant hormonal therapy) and, PORT + AHT (update by Lawton and colleagues) (60).

- **Con l'allungarsi del follow-up le morti non dovute a cancro della prostata superano gli eventi cancro-relati**
- **Comparsa di recidive locali (dose alla prostata non più di 70 Gy) che confondono il beneficio della WPRT**

Studi prospettici

Trial Getug-01, 444 pazienti

PFS e OS simile nei 2 bracci

(WPRT vs PORT più o meno HT)

- HT in numero non quantizzato di pazienti
- Solo 45% dei pazienti con rischio linfonodale>15%
- WPRT non arrivava a L5-S1
- PFS definita secondo i criteri ASTRO e non secondo i criteri Phoenix

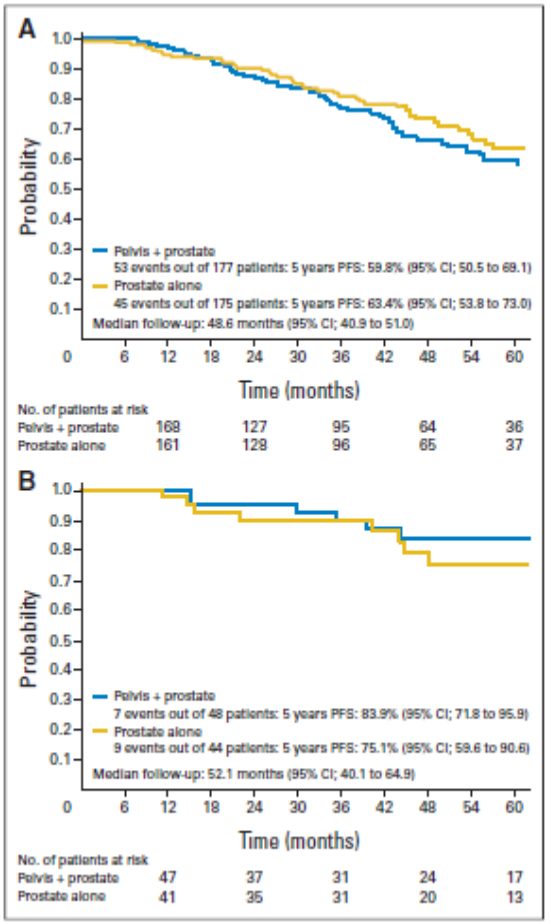
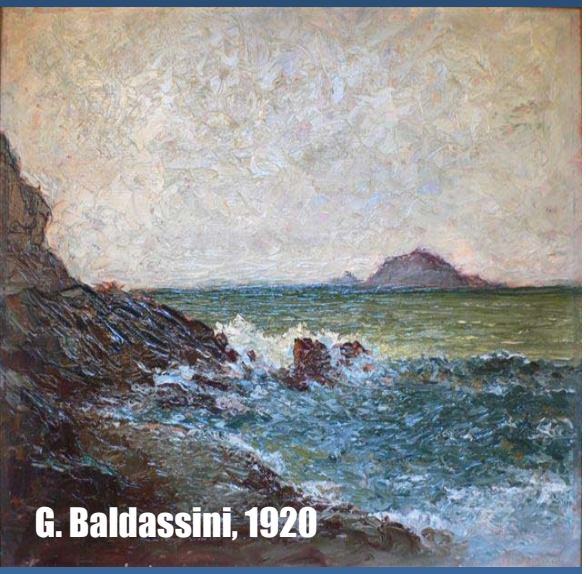


Fig 2. Progression-free survival (PFS) according to the stratified groups. (A) High-risk group. (B) Low-risk group.



RTOG 0924

Treatment Schema

STRATIFY	REGISTER	RANDOMIZE
1. Risk Group: "Favorable" High or "Unfavorable" Intermediate Risk: 1.GS=7-10 and T1c-T2b and PSA < 50 ng/ml or 2.GS=6, T2c-T4 or > 50% biopsies + & PSA <50 or 3.GS=6, PSA > 20 ng/ml and T1c-T2b		**Arm 1:** NADT + Prostate & SV **vs** **Arm 2:** NADT + Whole-Pelvic RT
2. Type of RT Boost: IMRT vs Brachytherapy (HDR + PPI)		
3. Duration of Androgen Deprivation Therapy Short Term vs Long Term ADT		

Fig. 4. Radiation Therapy Oncology Group 0924 schema. This study will evaluate the potential benefit of WPRT in patients with intermediate- risk prostate cancer and multiple adverse features or favorable high-risk disease. The primary endpoint is cause specific survival. GS = Gleason score; RT = radiotherapy; IMRT = intensity-modulated radiotherapy, HDR = high dose rate; PPI = permanent prostatic implant, NADT = neoadjuvant anti-androgen therapy; SV = seminal vesicles; WPRT = whole pelvic radiotherapy.

RTOG 0534

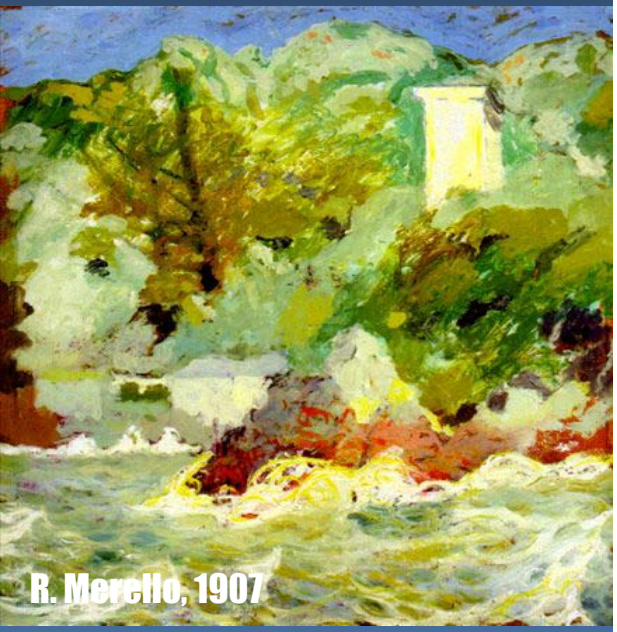
A Phase III Trial of Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) in Prostate Cancer Patients with a Rising PSA After Radical Prostatectomy

SCHEMA (1/8/09) (3/24/10)

	SV Involvement		
	1. No		
S	2. Yes	**R**	**Arm 1: PBRT Alone**
T		**A**	PBRT 64.8-70.2 Gy
R	**Prostatectomy Gleason Score**	**N**	
A	1. Gleason ≤ 7	**D**	
T	2. Gleason 8-9	**O**	**Arm 2: PBRT + NC-STAD**
I		**M**	PBRT 64.8-70.2 Gy + NC-STAD for 4-6 months,
F	**Pre-Radiotherapy PSA**	**I**	beginning 2 months before RT
Y	1. PSA ≥ 0.1 and ≤ 1.0 ng/mL	**Z**	
	2. PSA > 1.0 and < 2.0ng/mL	**E**	
			Arm 3: PLNRT + PBRT + NC-STAD
	Pathology Stage		PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy,
	1. pT2 and margin negative		NC-STAD for 4-6 months,
	2. All others		beginning 2 months before RT

SV = seminal vesicle; RT = radiotherapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; NC-STAD = neoadjuvant and concurrent short term androgen deprivation

Tossicità



RTOG 9413

Tossicità acuta G3 più evidente nei bracci con NHT indipendentemente da WPRT o PORT

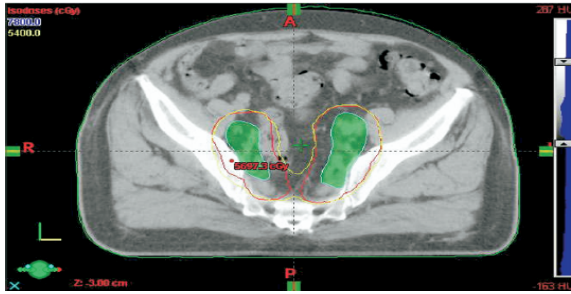
Tossicità tardiva G3 non statisticamente differente

Table 7. Acute and Late GU and GI RT Toxicity (Grade ≥ 3)*

	Whole-pelvis RT + Boost (n = 643)		Prostate-only RT (n = 640)		
	No. Toxicities	%	No. Toxicities	%	P†
Acute					
GU	22	3	28	4	.39
GI	14	2	5	1	.06

	Whole-pelvis RT + Boost (n = 641)			Prostate-only RT (n = 638)			
	No. Toxicities	1 Year, %	2 Years, %	No. Toxicities	1 Year, %	2 Years, %	P‡
Late							
GU	16	1.7	2.0	15	1.4	2.0	.85
GI	12	1.5	1.7	5	0.3	0.6	.09

IMRT- IGRT -WPRT



- Riduce la tossicità agli OAR (. V45 tenue ridotta del 60%, V45 retto ridotta del 90% rispetto a 3DCRT - Ashman, 2005)

- Particolare risparmio degli OAR in caso di dose escalation (78 Gy alla prostata e 54 Gy ai linfonodi rispetto a EBRT 72 Gy alla prostata e 50 Gy ai linfonodi – Liu, 2007)

Chung, 2009

Table 5. Acute rectal toxicities as scored by RTOG and CTCAE criteria between NUH (IMRT) and UCSF (IG-IMRT)

	RTOG grade			CTCAE grade		
Toxicity	0	1	2	0	1	2
Rectal						
IMRT	1 (10)	1 (10)	8 (80)	1 (10)	4 (40)	5 (50)
IG-IMRT	6 (40)	7 (47)	2 (13)	6 (40)	8 (53)	1 (7)
Bladder						
IMRT	1 (10)	3 (30)	6 (60)	2 (20)	4 (40)	4 (40)
IG-IMRT	0 (0)	13 (87)	2 (13)	0 (0)	14 (93)	1 (7)

Abbreviations: RTOG = Radiation Therapy Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; other abbreviations as in Table 1.

Irradiazione dei linfonodi pelvici in Piemonte-Valle d'Aosta

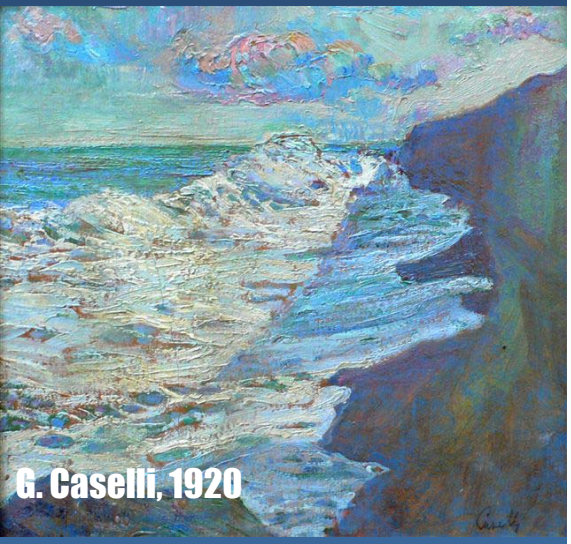
Dipartimento "Rete Oncologica del Piemonte e della Valle d'Aosta"

"Neoplasie Urologiche"
Carcinoma della Prostata

Torino, 10 novembre 2011

Aula Infernotti
A.O.U. San Giovanni Battista Torino
Presidio San Giovanni Antica Sede - Via Cavour, 31 - Torino

Coordinatori dell'Evento
Dott. Oscar Bertetto
Dott.ssa Monica Viale



Pazienti sottoposti a Radioterapia esclusiva anche sui linfonodi pelvici:

- Biennio 2004-2005: 17.8% (in 4 Centri su 7)
- Biennio 2009-2010: 10.4% (in 7 Centri su 10)

Pazienti sottoposti a Radioterapia postoperatoria anche sui linfonodi pelvici:

- Biennio 2004-2005: 12.9% (in 5 Centri su 7)
- Biennio 2009-2010: 9.2% (in 8 Centri/10)

Criteri decisionali:

- RT esclusiva: Rischio N+ >15% sec. Nomogrammi (3 Centri), Alti/altissimi rischi (3 Centri), N+ clinico (1 Centro)
- RT postoperatoria: pN+ (5 Centri), pN+ o linfoadenectomia insufficiente in PSA>10 o Gleason>5, Nomogrammi, N+ alla PET con Colina


grazie per l'attenzione!!!