Dr.ssa Debora Beldì

S.C.D.U. Radioterapia
A.O.U. "Maggiore della Carità"
Università del Piemonte Orientale "A. Avogadro"
NOVARA

XXIII CONGRESSO
AIRO

Giardini Naxos - Taormina, 26 - 29 ottobre

IL RUOLO DELLA IORT NEL TRATTAMENTO MULTIMODALE DEL CARCINOMA PROSTATICO AD ALTO RISCHIO DI RECIDIVA

Beldi D., Apicella G., Ferrara E., Mones E., Marchioro G., Volpe A., Terrone C., Krengli M.

BACKGROUND: *Il tumore della prostata*

BASSO-INTERMEDIO RISCHIO: DFS a 5 anni 80-92%, DSF a 10 anni 76-92%

ALTO RISCHIO o LOCALMENTE AVANZATO:

- **EBRT+/-OT** (studi con FU di 10 aa)
  - ∞ **RTOG 9202** (T2c-4 N0-1 M0) (Horwitz, *JCO* 2008)
    DFS 22.5%; bDFS 48.1 % a 10 aa
  - ∞ **EORTC 22863** (T1-2 M0 pd, T3-4 N0-1 M0) (Bolla, Lancet Oncol 2010)
    DFS 47.7% a 10aa
  - ∞ **TROG 9601** (T2b-4 N0 M0) (Denham, Lancet 2011)
    DFS 36%; bDFS 47.2% a 10 aa

- **PROSTATECTOMIA RADICALE senza EBRT adiuvante:**

Table 2 – Series investigating radical prostatectomy in men with high–risk prostate cancer†

Study	Cases, no.	Median follow-up	BCR-free survival at 5 yr, %	BCR-free survival at 10 yr, %	PCa-specific survival at 5 yr, %	PCa-specific survival at 10 yr, %	PCa-specific survival at 15 yr, %	Overall survival at 5 yr, %	Overall survival at 10 yr, %
Stephenson et al. [36]	1962	48 mo	–	–	–	92	81	–	–
Eggener et al. [38]	1326*	56*1 and 96*2 mo	–	–	–	72	89	–	–
Nguyen et al. [25]	110*4 and 206*5	44 mo	45*4 and 52*5	35*4 and n/a*5	–	–	–	–	–
Yossepowitch et al. [40]	957	4.3 yr	68	59	–	–	–	–	–
Spahn et al. [42]	712*3	77 mo	64.8	51.9	89.8	84.5	–	73.6	58
Ward et al. [49]	1179	2.4 yr	47.4	35.7	–	–	–	–	–
Mattei et al. [51]	188	60 mo	71	–	–	–	–	–	–
Zwergel et al. [41]	275*3	42 mo	–	**45.4%**	93	83	71	87	70

Bastian P. Eur Urol, 2012

RADIOBIOLOGIA

CLINICAL INVESTIGATION **Genitourinary Cancer**

DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: α/β = 1.4 (0.9–2.2) GY

RAYMOND MIRALBELL, M.D.,*† STEPHEN A. ROBERTS, PH.D.,‡ EDUARDO ZUBIZARRETA, M.D.,§ AND JOLYON H. HENDRY, PH.D.‖

ANTICANCER RESEARCH *33*: 1009-1012 (2013)

Is the α/β Ratio for Prostate Tumours Really Low and Does It Vary with the Level of Risk at Diagnosis?

JACK F. FOWLER[1], IULIANA TOMA-DASU[2] and ALEXANDRU DASU[3]

Alta sensibilità alle alte dosi/frazione:
(razionale x singola dose e ipofrazionamento)

Potenziale vantaggio su controllo locale

IN LETTERATURA

Author	#	Patients' selection	Surgical approach	IORT Energy / Dose	EBRT
Takahashi 1985	14	Stage B2-D2	Perineal No RP	10-14 MeV / 28-35 Gy (single dose) 20-25 Gy combined with EBRT	50 Gy to pelvic lymph nodes
Abe 1991	21	Stage B2-D2	Perineal No RP	8-14 MeV / 28-35 Gy (single dose) or 20-25 Gy combined with EBRT	50 Gy to pelvic lymph nodes
Higashi 1998	35	Stage B-C	Perineal/retropubic No RP	25-30 Gy	30 Gy, 2 Gy/fx
Kato 1998	54	Stage B2-D1	Perineal/retropubic No RP	25-30 Gy	30 Gy, 2 Gy/fx
Orecchia 2007 IEO- Mi	11	Interm.- high risk	Retropubic IORT-RP	8-10 MeV / 12 Gy	45 Gy, 1.8 Gy/fx
Saracino 2008 Regina Elena-Roma	34	Interm. risk	Retropubic RP-IORT	7-9 MeV / 16-22 Gy	no
Rocco 2009 IEO- Mi	33	Interm.- high risk	Retropubic IORT-RP	8-10 MeV / 12 Gy	45 Gy, 1.8 Gy/fx
Krengli 2010 Novara	38	Interm.- high risk	Retropubic IORT-RP	9-12 MeV / 10-12 Gy	46-50 Gy, 2 Gy/fx

CASISTICA

Dal settembre 2005 a Agosto 2013: **88 pz Ca prostata ad alto-altissimo rischio**

Caratteristiche dei pazienti	N = 88
Età mediana (min-max), anni	68 (52-76)
iPSA mediano (min-max), ng/ml	14.6 (2.0-63.9)
PSA post-operatorio mediano	0.06 ng/ml

Criteri di inclusione

Almeno 2 dei seguenti:
PSA tot > 10 ng/ml
Gleason Score ≥ 7
Stadio clinico ≥ cT2c
Positività > 2/3 prelievi bioptici
Probabilità di malattia organo confinata < 25% (Nomograms of MSKCC)

Sono stati esclusi pz con:

- Età >76 aa
- IBD
- Probabilità di malattia organo confinata > 25% (Kattan nomograms MSKCC)

CASISTICA

GS Bioptico mediano → 8

Range (4-10)

GS Patologico mediano → 9

Range (6-10)

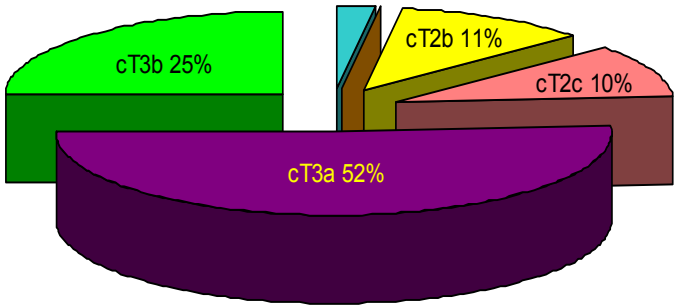
Stadio clinico

cT3: 77%

cT1c 2%

cT2a 0%

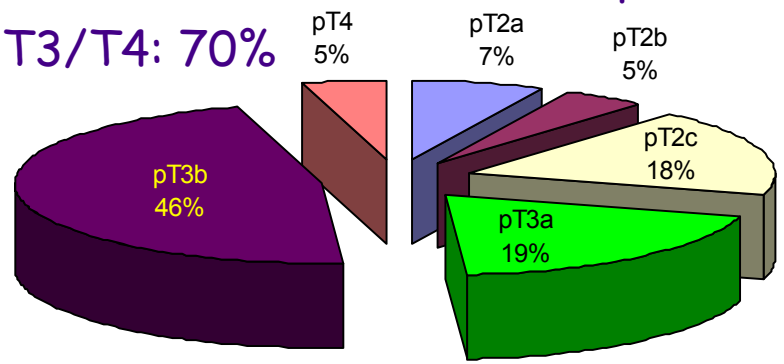
cT2: 21%



Stadio patologico

pT2: 30%

pT3/T4: 70%

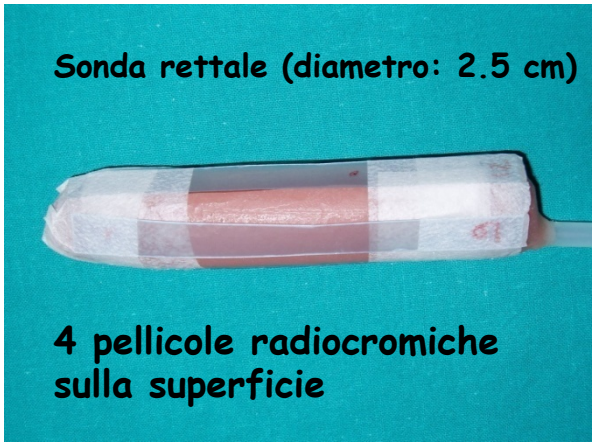


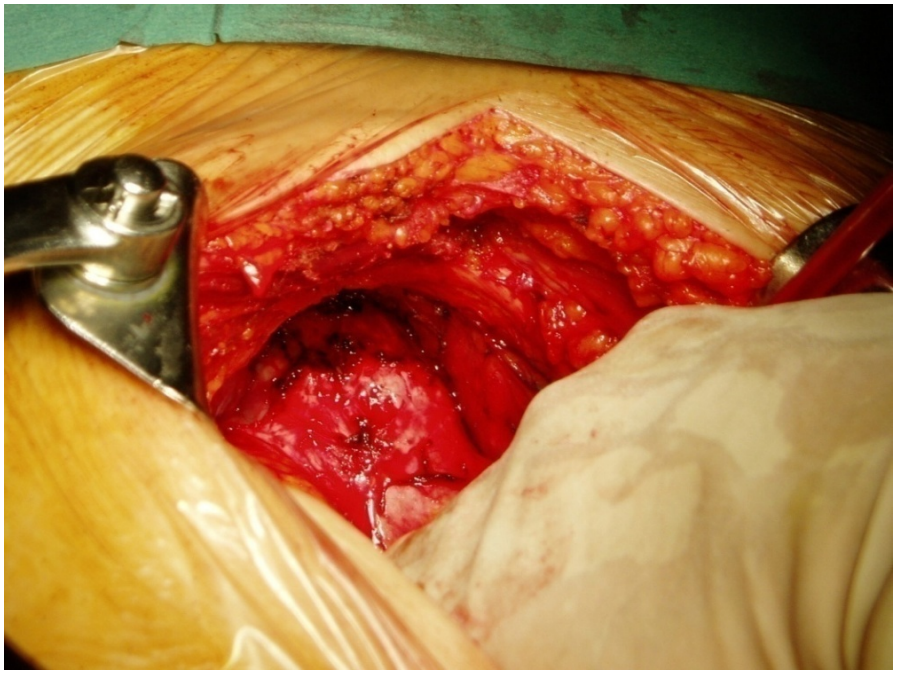
Margini Chirurgici POSITIVI: **55/88 pz (62,5%)**

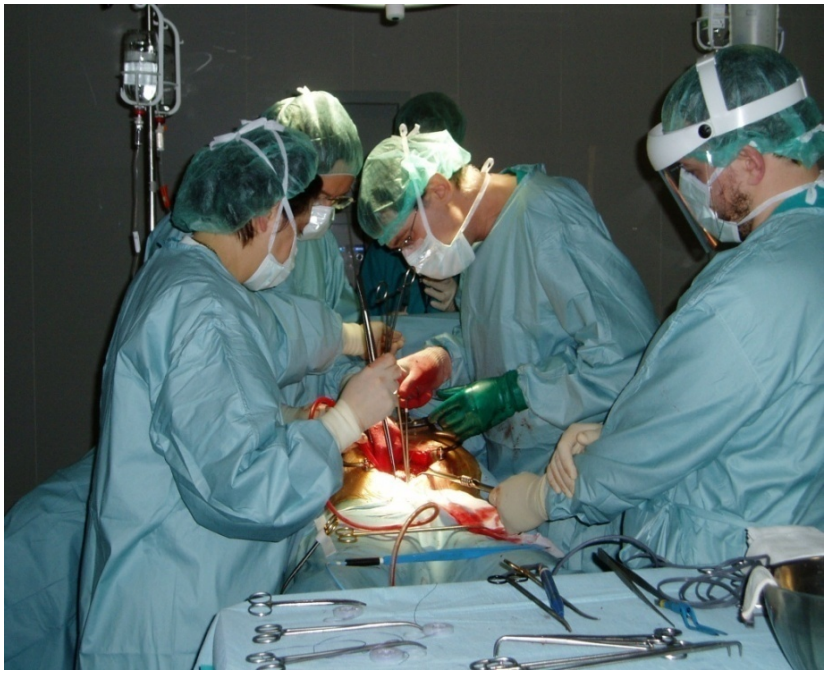
pN+ **25/88 (28,4%)**

METODICA

1. Induzione della anestesia generale
2. Inserimento della **sonda rettale per la dosimetria in vivo**
3. Esposizione dell'apice prostatico



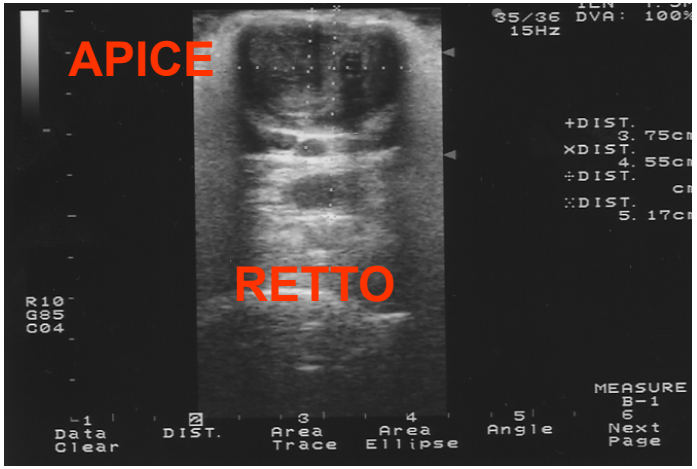




ECOGRAFIA INTRAOPERATORIA

4. Ecografia intraoperatoria:

ANTERIORE CAUDALE

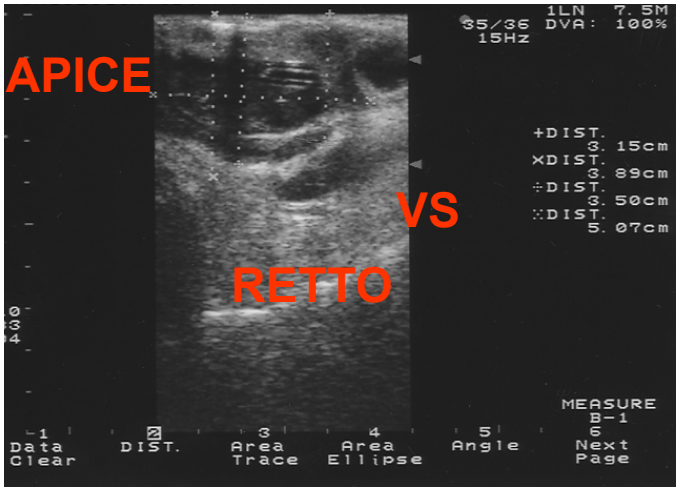


Valutazione:

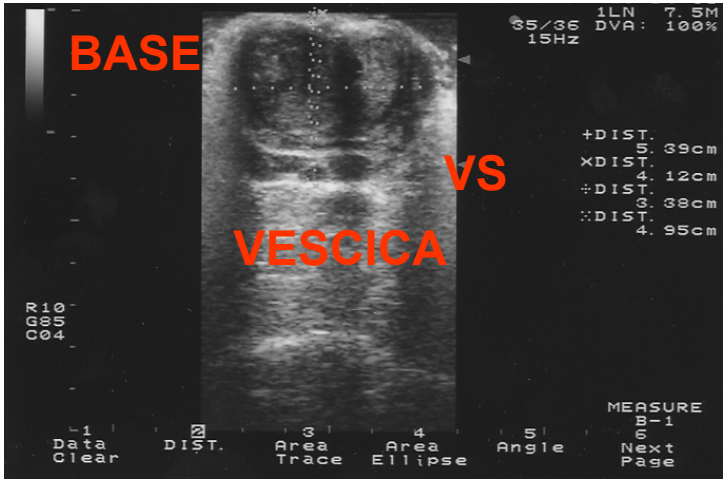
a. diametro antero-posteriore della ghiandola
(valore medio: **3,2 cm**)

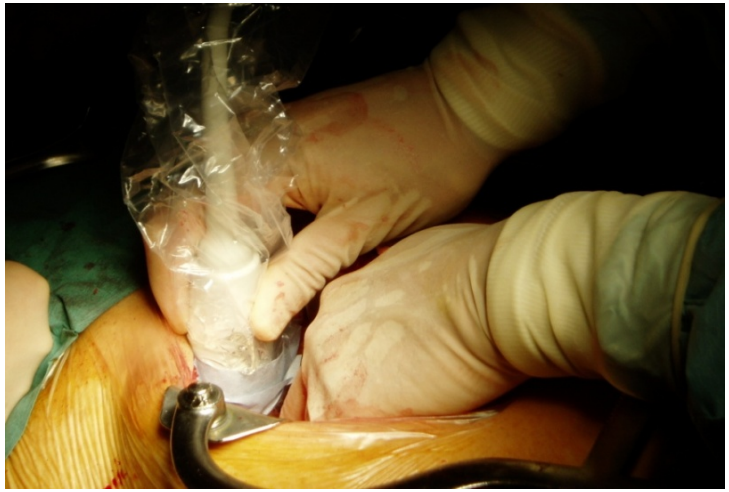
b. distanza sup. prostatica-parete anteriore del retto
(valore medio: **3,6 cm**)

SAGITTALE



ANTERIORE CRANIALE



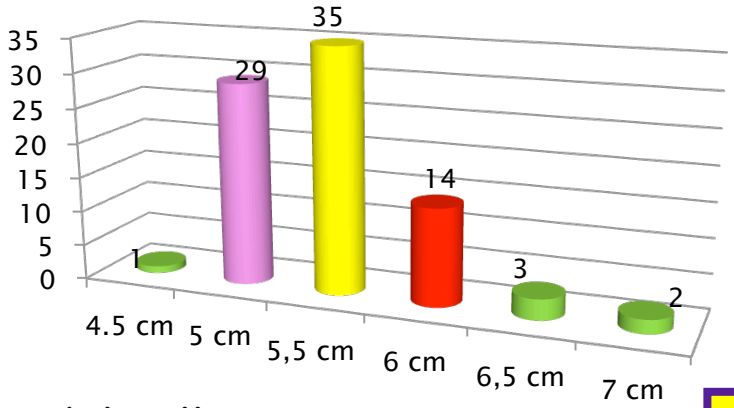


METODICA

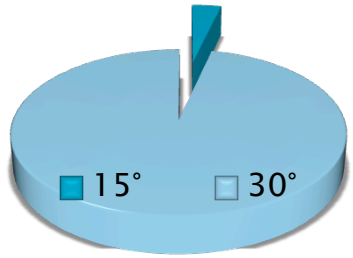
5. Scelta di:

- Energia elettroni 9 (50%) o 12 (50%) MeV – Mobetron, Intraop

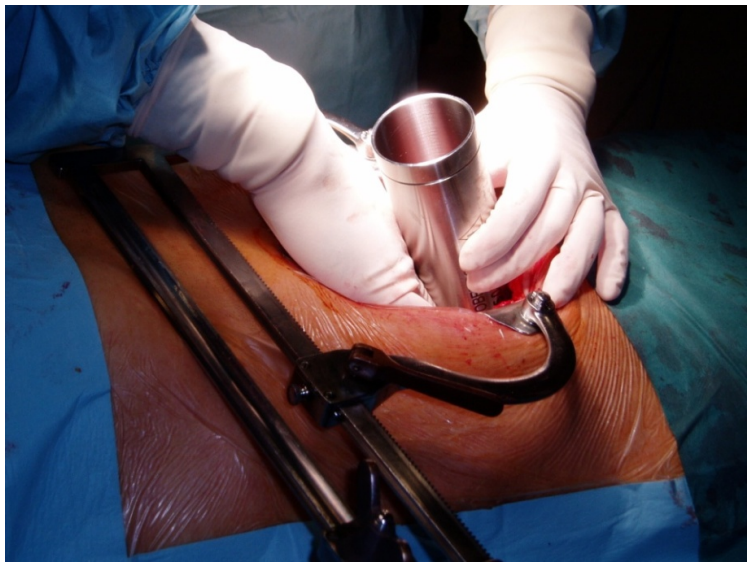
•Diametro collimatore



Angolo Collimatore



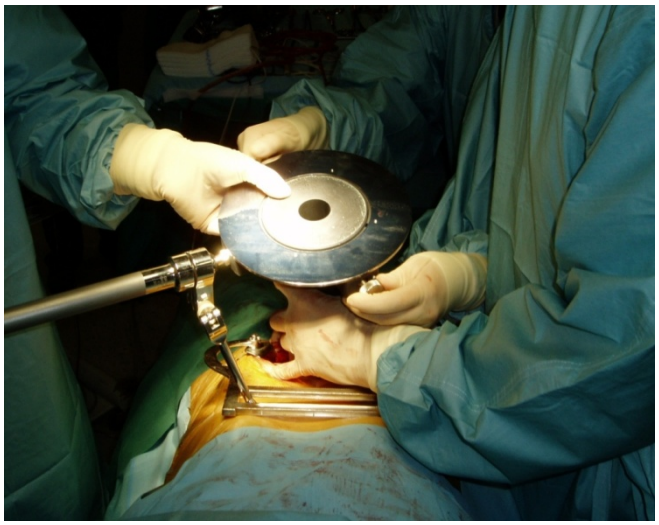
6. Posizionamento del collimatore



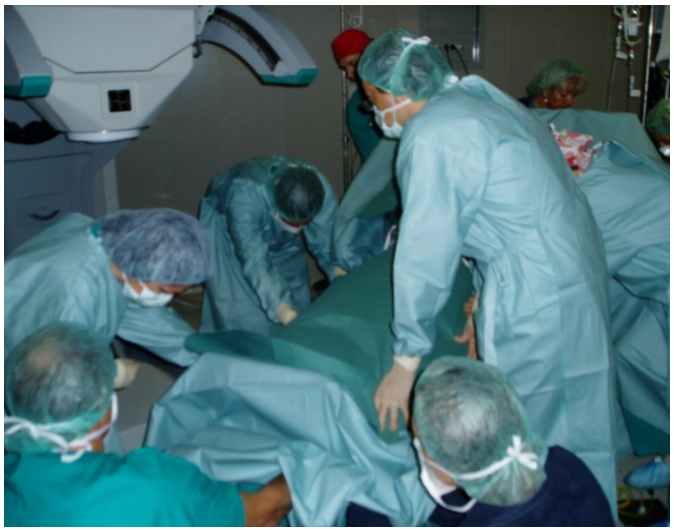
VOLUME TARGET:
loggia prostatica con 5-10 mm di margine

METODICA

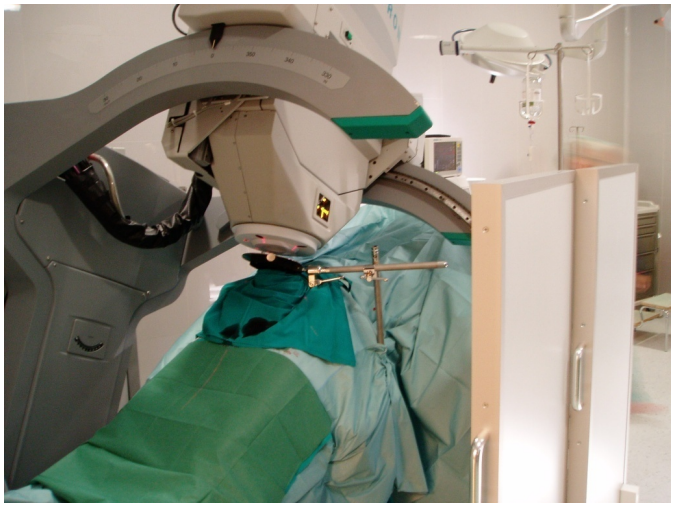
7. Il collimatore viene fissato al lettino operatorio



8. Il lettino operatorio viene posizionato sotto l'acceleratore



9. Soft docking

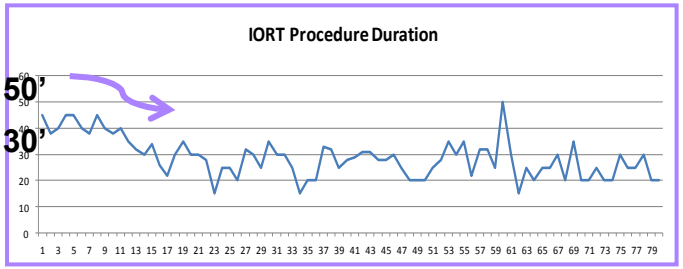


10. Fase di irradiazione

DOSE: 12 Gy - Boost anticipato

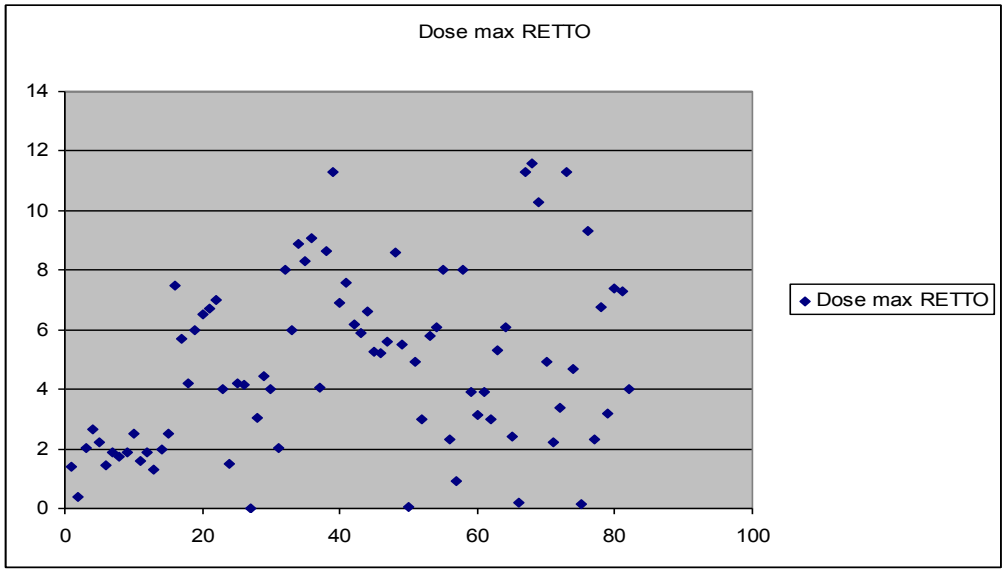
11. Si procede infine con la prostatectomia radicale + LAD

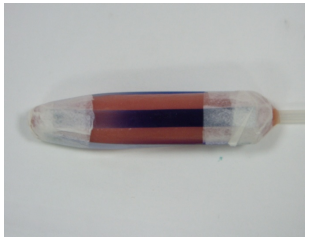
METODICA

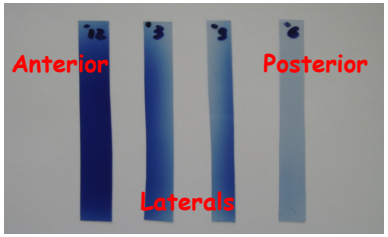


Mediana tempo IORT 30 min (15-50 min)
Mediana tempo totale della procedura RP + IORT 240 min (range 150-360)

DOSIMETRIA RETTALE IN VIVO (82 pz)







Dose media parete rettale: **4.32 Gy** (range: 0.06-11.3 Gy)

MORBIDITA' DELLA PROCEDURA RP + IORT

Non si sono verificate complicanze maggiori;

71.6 % (63/88): necessaria trasfusione ematica

Complicanze minori in 27/88 pz (30.6%):

- Linfocele sintomatico 11.3%
- Ematoma 3.4%
- Occlusione anastomosi vescico-uretrale 4.5%

Non tossicità acuta rettale connessi alla IORT

Ad **1 anno di FU il 64,7%** dei pz è **continente** 57/88.

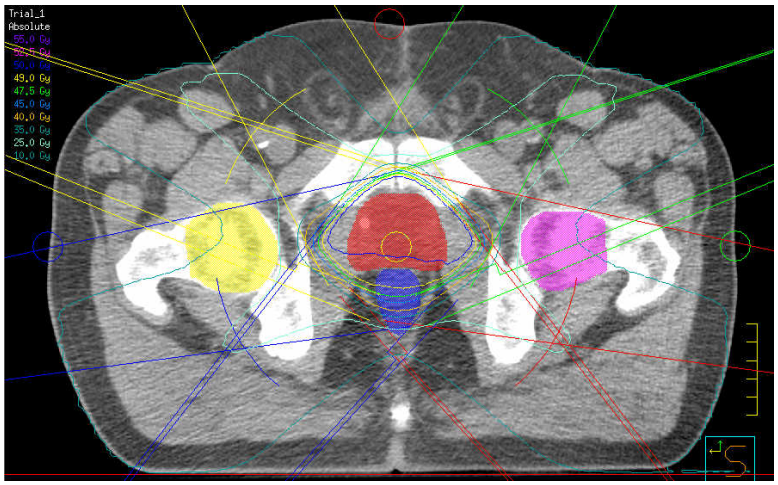
Incidenza di complicanze perioperatorie **sovrapponibile** a quella riportata per interventi di prostatectomia radicale per tumori localmente avanzati *

*Gontero , Eur Urol 2007;51:922-929
* Rocco B,. *BJU Int* 2009;104:1624–30

EBRT ADIUVANTE

Indicazioni: su loggia prostatica

a. Stadio ≥ pT3a
b. Margini chirurgici positivi (R1)



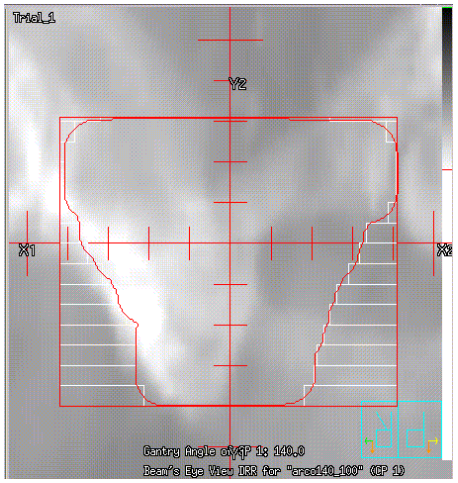
69/88 **(78.4%)** candidati

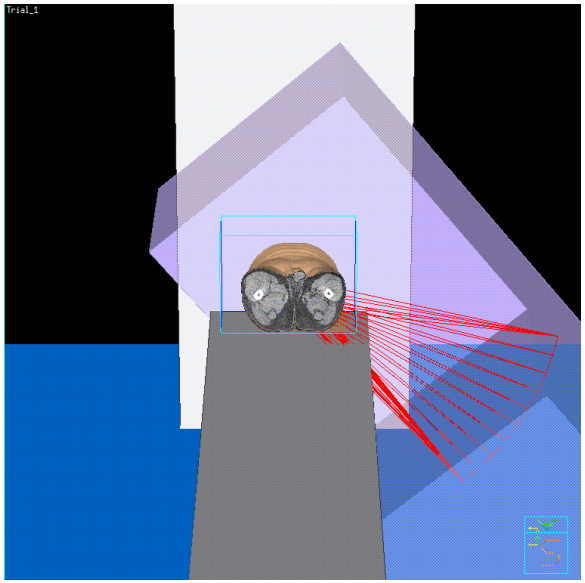
DOSE: **50 Gy** (2Gy/fr)

Intervallo di tempo RP + IORT→ EBRT:

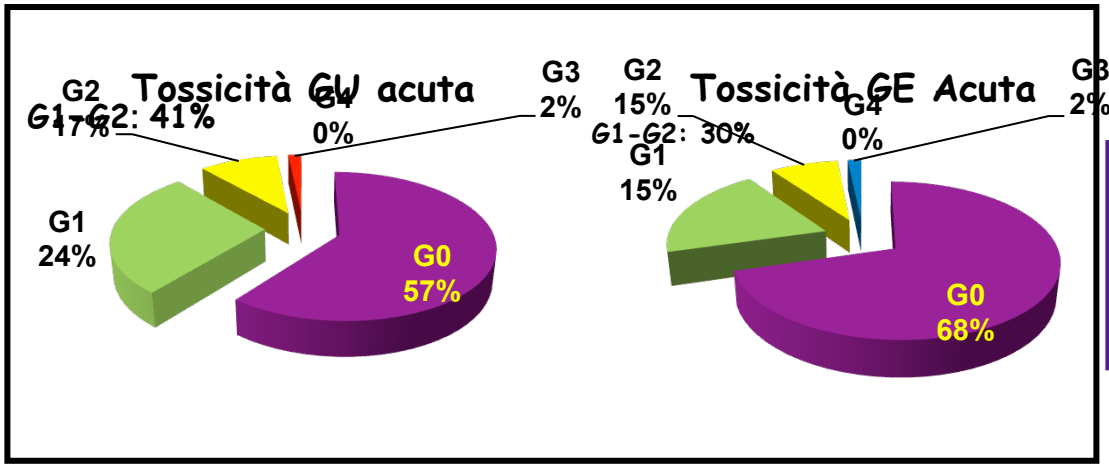
3-4 mesi

Ormonoterapia adiuvante:
57/88 (64.7%) pz





TOSSICITA'



CONFRONTO (from Valicenti R. IJROBP, 2013)

Table 1 Acute toxicity effects of RT after prostatectomy (ranges based on RTOG or CTCAE grading system)

Study arm type	Genitourinary		Gastrointestinal	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Adjuvant	10.5%-26%	2.0%-8.0%	22.0%-25.0%	0.0%-2.0%

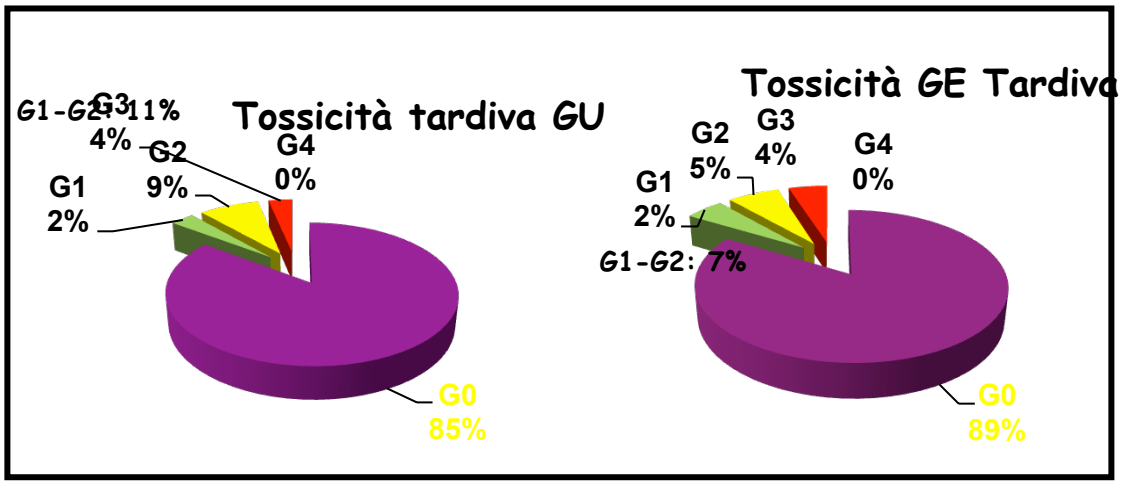


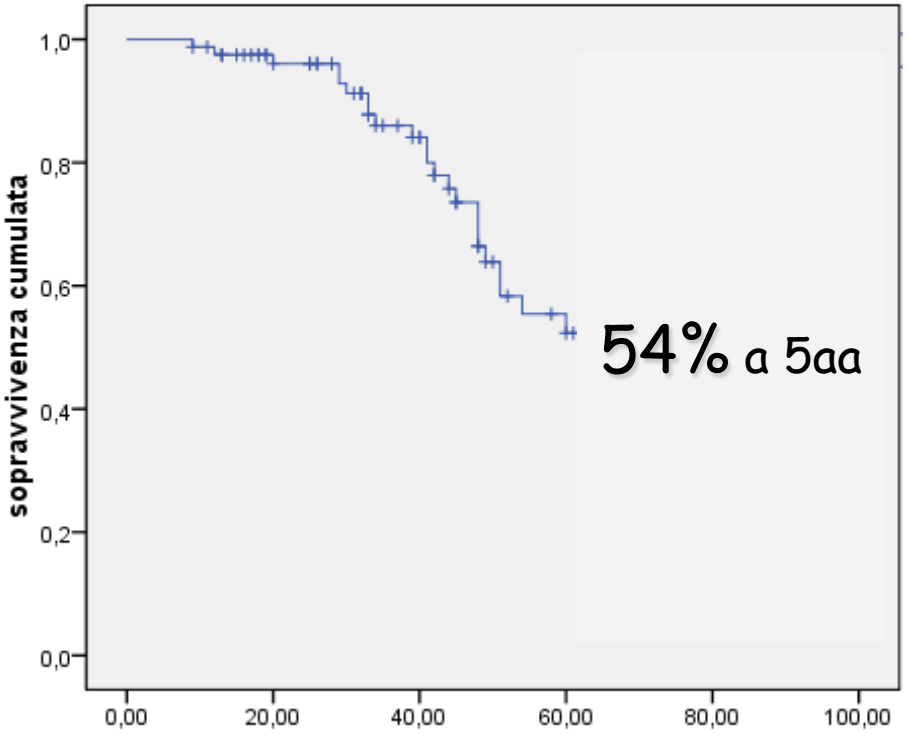
Table 2 Late toxicity effects of RT after prostatectomy (ranges based on RTOG/EORTC or CTCAE grading system)

Study arm type	Genitourinary		Gastrointestinal	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Adjuvant	2.0%-22.0%	0.0%-10.6%	1.0%-12.7%	0.0%-6.7%

Sopravvivenza libera da recidiva biochimica

Recidiva Biochimica:
PSA ≥ 0,2 ng/ml

Mediana di FU **48 mesi**
24/88 recidive



Sede	N° (%)
Recidiva biochimica	16/88 (18%)
Recidiva linfonodale	4/88 (4%)
Progressione ossea	2/88 (2%)
Progressione polmonare	1/88 (1%)
Progressione encefalica	1/88 (1%)
Nessuna recidiva in loggia prostatica	

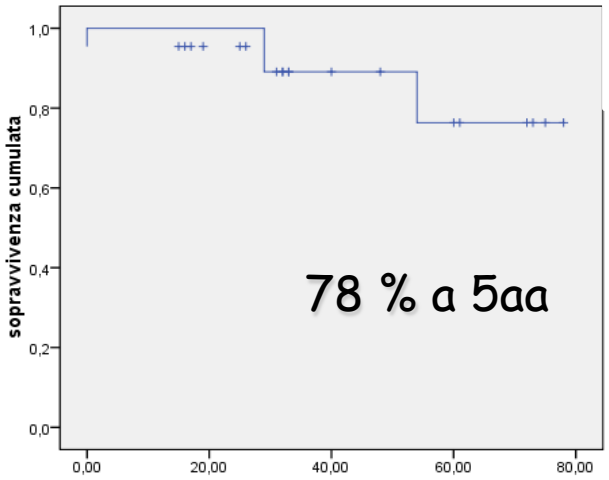
RECIDIVA LOCOREGIONALE:

	RT adiuvante	No RT
EORTC 22911	8,4%	17,3% p<0,05
SWOG 8794	8%	22%

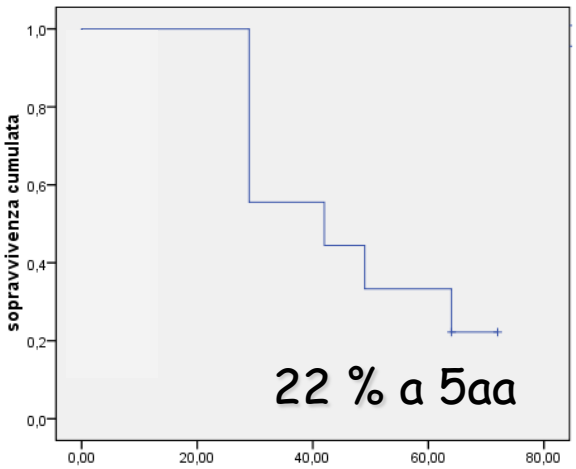
Valicenti R. IJROBP, 2013

Sopravvivenza libera da recidiva biochimica

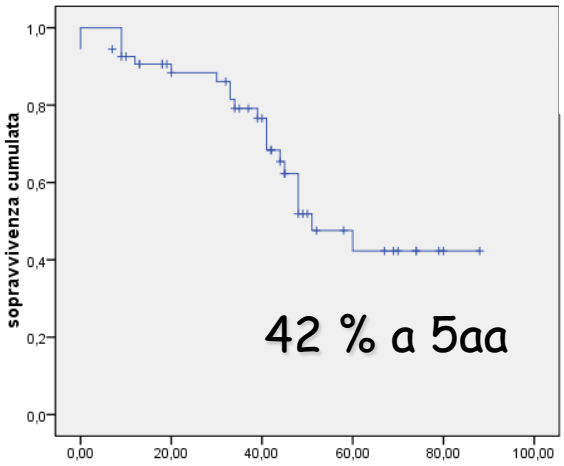
Pz HIGH RISK (NCCN)



Pz con N1



Pz VERY HIGH RISK (NCCN)



CONCLUSIONI

∞ I dati radiobiologici (basso α/β) sembrano supportare l'erogazione di alte dosi per frazione.

∞ Associazione RP + IORT **risulta fattibile**, senza rilevante tossicità rettale.

∞ Limiti: tempo di FU

∞ Tematiche aperte:

- selezione dei pazienti: quali pz beneficiano di IORT?
- IORT come singolo trattamento o come boost?
- In caso di EBRT adiuvante quale frazionamento utilizzare? Ipofrazionamento?


GRAZIE PER L' ATTENZIONE

Associazione
Italiana
Radioterapia
Oncologica

BACKGROUND: *Il tumore della prostata*

CME ASTRO

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Guidelines

Adjuvant and Salvage Radiation Therapy After Prostatectomy: American Society for Radiation Oncology/American Urological Association Guidelines

Richard K. Valicenti, MD, MBA,* Ian Thompson Jr., MD,† Peter Albertsen, MD, MS,‡ Brian J. Davis, MD, PhD,§ S. Larry Goldenberg, MD,‖ J. Stuart Wolf, MD,¶ Oliver Sartor, MD,# Eric Klein, MD,** Carol Hahn, MD,†† Jeff Michalski, MD, MBA,‡‡ Mack Roach III, MD,§§ and Martha M. Faraday, PhD‖‖

Int J Radiation Oncol Biol Phys, Vol. 86, No. 5, pp. 822–828, 2013

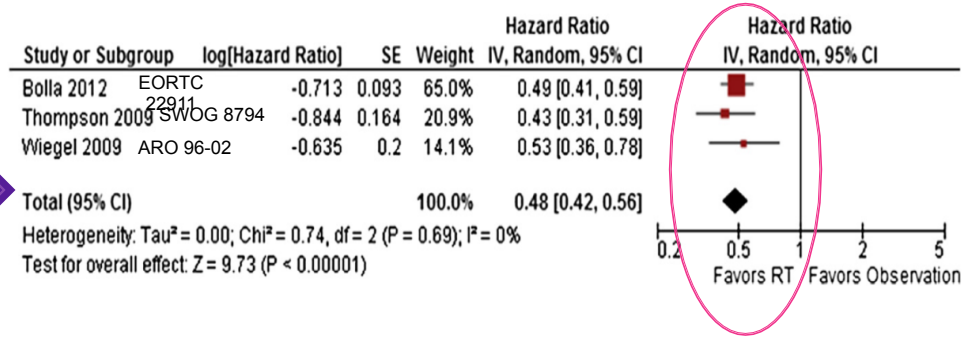
Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: A systematic review and meta-analysis

Scott C. Morgan[a,b], Tricia S. Waldron[c,*], Libni Eapen[a,b], Linda A. Mayhew[c], Eric Winquist[d,e], Himu Lukka[c,f,g], on behalf of the Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care[1]

Radiotherapy and Oncology 88 (2008) 1–9

Trials randomizzati su Radioterapia adiuvante in presenza di fattori di rischio:
T3a/b e R+

Vantaggio su bRFS



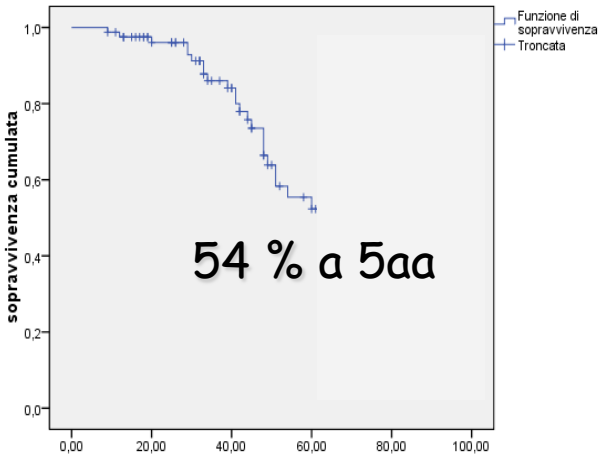
SEDI DI RECIDIVA

- **Anastomosi uretro-vescicale: 66%**
- **Collo vescicale: 16%**
- **Area retrotrigonale: 13%**
- **altre: 5%**

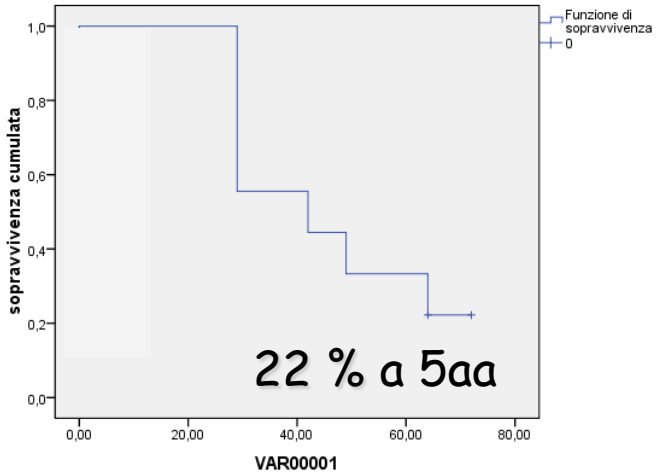
RECIDIVA LOCOREGIONALE:

	RT	No RT
EORTC 22911	8,4%	17,3% p<0,05
SWOG 8794	8%	22%

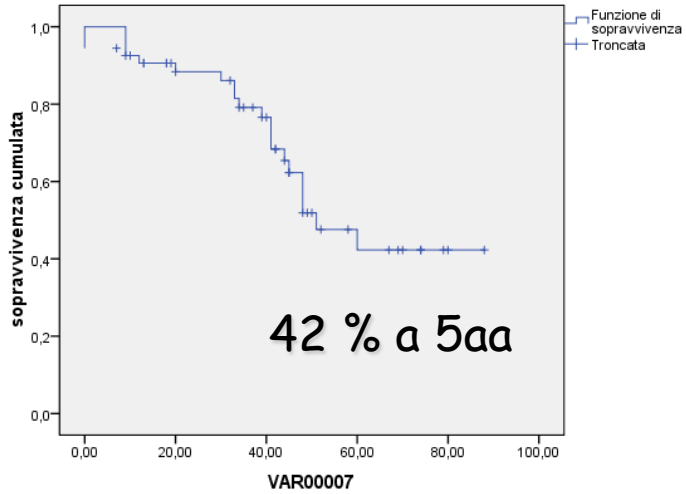
Biochimical Free Survival



Pz con N1



Pz VERY HIGH RISK (NCCN)



Pz HIGH RISK (NCCN)