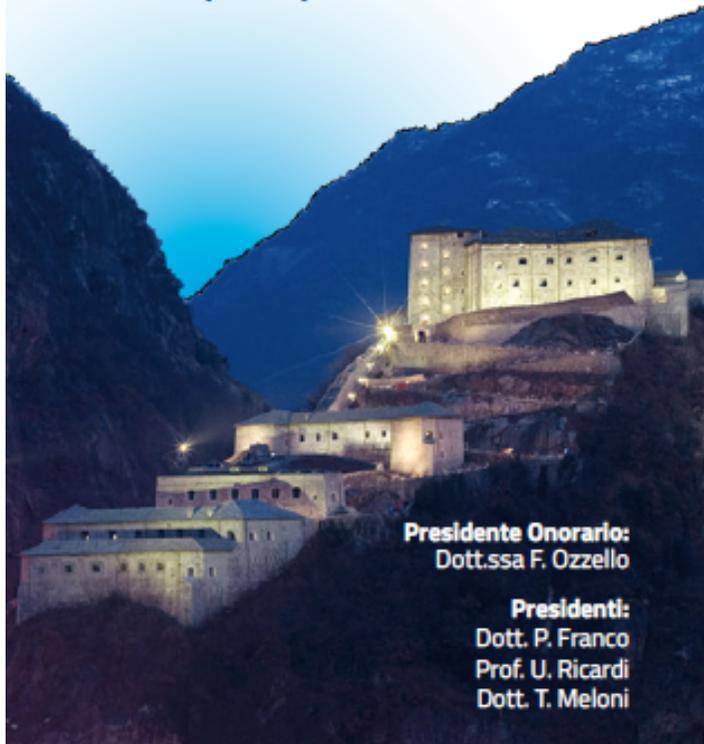




Associazione
Italiana
Radioterapia
Oncologica

IV CONGRESSO AIRO PIEMONTE/VALLE D'AOSTA/LIGURIA

Il carcinoma prostatico:
tra multidisciplinarietà e
nuove prospettive



Presidente Onorario:
Dott.ssa F. Ozzello

Presidenti:
Dott. P. Franco
Prof. U. Ricardi
Dott. T. Meloni

FORTE DI BARD • VALLE D'AOSTA
14 dicembre **2013**

Nuovi approcci radioterapici al carcinoma prostatico:

La radioterapia intraoperatoria

Marco Krenagli

Cattedra di Radioterapia
Università degli Studi del Piemonte Orientale

“A. Avogadro”

SCDU Radioterapia
AOU Maggiore della Carità



BACKGROUND: *il tumore della prostata localmente avanzato*

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**

BACKGROUND: *Il tumore della prostata localmente avanzato*

- PROSTATECTOMIA RADICALE senza EBRT adiuvante:

- Bastian P. Eur Urol, 2012

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 | – | – |
| Eggerer 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 |

- Carver, The Journal of Urology 2006:
→ LR (Local Recurrence) 48% dei pz ad un FU medio di 6 aa

BACKGROUND: *Il tumore della prostata localmente avanzato*

- PROSTATECTOMIA RADICALE + EBRT adiuvante



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

International Journal of Radiation Oncology
biology • physics
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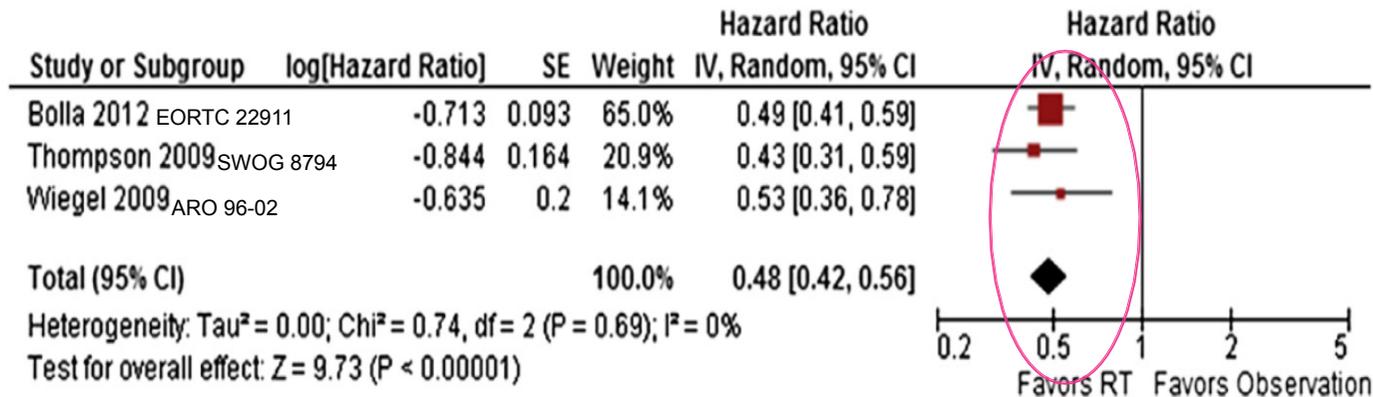
Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: A systematic review and meta-analysis

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 Care¹

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



RECIDIVA LOCOREGIONALE

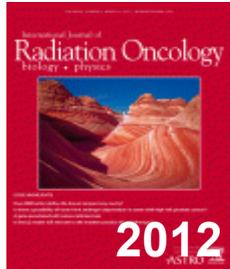
SEDI

- 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% |

RADIOBIOLOGIA



CLINICAL INVESTIGATION

Genitourinary Cancer

DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: $\alpha/\beta = 1.4$ (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. FOWLER¹, IULIANA TOMA-DASU² and ALEXANDRU DASU³

Alfa/beta: 1.55

**Basso $\alpha/\beta \rightarrow$ sensibilità alle alte dosi/frazione:
razionale x singola dose e ipofrazionamento**



Potenziale vantaggio sul controllo locale

Il razionale dell' utilizzo della IORT

Outcome insoddisfacente
con Tx standard nel Tumore
ad Alto rischio

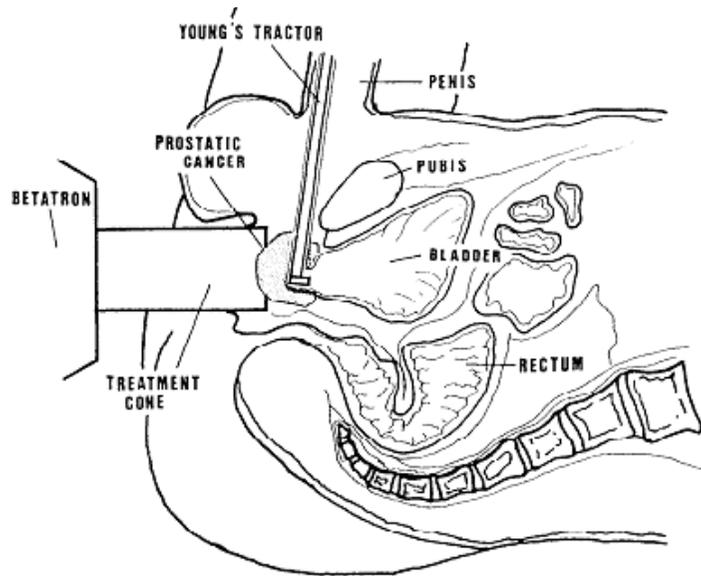
Tumore della Prostata: **BASSO**
rapporto α/β → **Buona Risposta**
alle **ALTE DOSI** per Frazione

IORT:

- A. Erogazione di una **alta dose** in una **singola frazione** su un' area chirurgicamente definita
- B. Minima esposizione dei tessuti circostanti (dislocati e/o protetti)
- C. **Incremento dell' effetto radiobiologico** di una singola dose elevata di radiazioni
(una singola dose di IORT =1,5-2,5 volte la stessa dose totale di EBRT frazionata)
- D. **Eliminazione foci microscopici di neoplasia** → riduce il rischio di malattia residua nel sito
chirurgico
→ blocca il ripopolamento cellulare nel tempo che
intercorre tra la chirurgia e l' avvio della RT
adiuvante

In letteratura: STUDI STORICI

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INTRAOPERATIVE RADIOTHERAPY IN THE DEFINITIVE TREATMENT OF LOCALIZED CARCINOMA OF THE PROSTATE

MASAJI TAKAHASHI, M.D.,* KENICHIRO OKADA, M.D.,† YUHTA SHIBAMOTO, M.D.,*
MITSUYUKI ABE, M.D.* AND OSAMU YOSHIDA, M.D.‡

Kyoto University School of Medicine, Sakyoku, Kyoto 606, Japan

Posizione litotomica
Accesso perineale
No RP
IORT come Boost,
seguita da EBRT

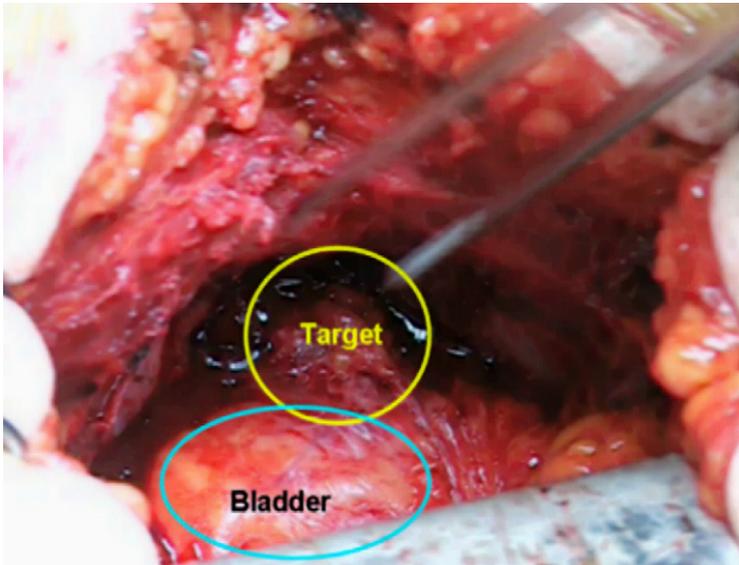
● Original Contribution

INTRAOPERATIVE RADIOTHERAPY: THE JAPANESE EXPERIENCE

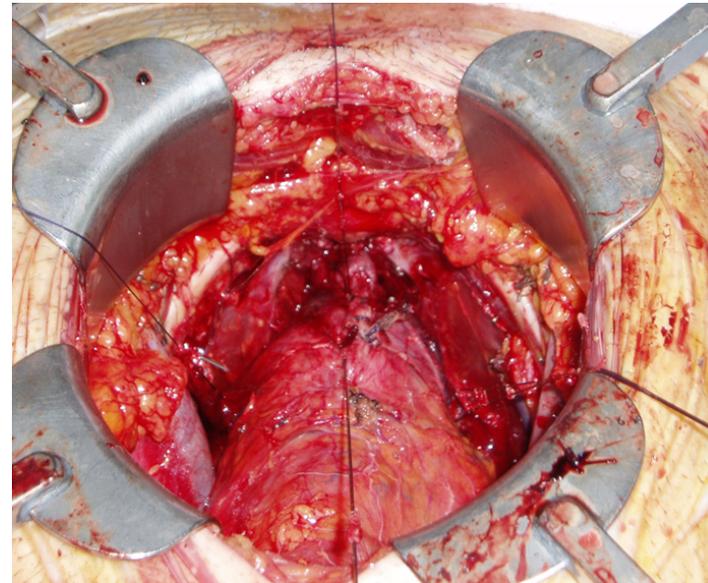
MITSUYUKI ABE, M.D. AND MASAJI TAKAHASHI, M.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 7, pp. 863-868
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Intermediate and High risk, locally advanced



- Italian series : (Saracino, 2008)



(courtesy of R. Orecchia)

- Inst. Regina Elena, Rome (after prostate removal)
- EIO, Milan; UH of Novara (before prostate removal)

In letteratura: tumori prostata localmente avanzati trattati con IORT

| 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 | 11 | Interm.-high risk | Retropubic IORT-RP | 8-10 MeV / 12 Gy | 45 Gy, 1.8 Gy/fx |
| Saracino 2008 | 34 | Interm. risk | Retropubic RP-IORT | 7-9 MeV / 16-22 Gy (dose escalation) | no |
| Rocco 2009 | 33 | Interm.-high risk | Retropubic IORT-RP | 8-10 MeV / 12 Gy | 45 Gy, 1.8 Gy/fx |
| Krengli 2010 | 38 | Interm.-high risk | Retropubic IORT-RP | 9-12 MeV / 10-12 Gy | 46-50 Gy, 2 Gy/fx |

In letteratura: tumori prostata localmente avanzati trattati con IORT

| Author | Local control and F/U | Survival | Toxicity |
|----------------|-----------------------|---|--|
| Takahashi 1985 | 82% (4-140 mos) | - | Delayed wound healing of perineal incision No severe IORT related |
| Abe 1991 | 81% @ 5 yrs | 72% OS @ 5 years | 100% early hematuria 10% early pollakiuria 1 chronic cystitis, 1 late urethral stricture |
| Higashi 1998 | - | 92% (stage B), 87% (stage C) OS @ 5 years | No critical cystitis, proctitis, anal bleeding |
| Kato 1998 | 83% @ 5 yrs | 89% DSS, 74% BRFS @ 5 yrs | 20% early rectal G3-G4 (without rectal spacer) 7% early rectal G3 (with rectal spacer) |
| Orecchia 2007 | - | - | Peri-operative. 1 lymphocele, 3 anastomotic leakage |
| Saracino 2008 | 91% (19-59 mos) | 77% BRFS @ 3 years | No urinary or rectal toxicity ≥G1 |
| Rocco 2009 | - | 97% BRFS @ 2 yrs, 100% OS (3-24 months) | GU: 17% G≥2 (early), 7% G≥2 (late) GI: 10% G≥2 (early), 0% G≥2 (late) |
| Krengli 2010 | 98% (6-46 mos) | 82% BRFS, 100% OS (6-46 months) | Peri-operative: lymphocele 16%, hematoma 6%; After EBRT: 11% G2 early rectal G2 11%, early urinary G2 4%; bladder neck stricture 7% |



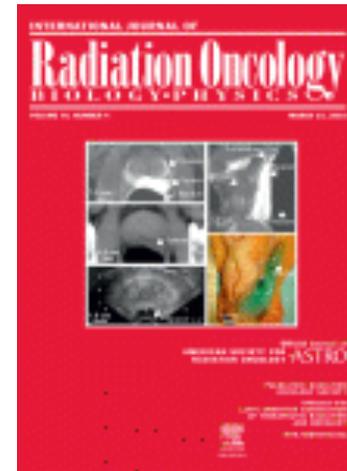
CLINICAL INVESTIGATION

Prostate

**INTRAOPERATIVE RADIOTHERAPY DURING RADICAL PROSTATECTOMY FOR
LOCALLY ADVANCED PROSTATE CANCER: TECHNICAL AND DOSIMETRIC
ASPECTS**

MARCO KRENGLI, M.D.,* CARLO TERRONE, M.D.,† ANDREA BALLARÈ, M.D.,* GIANFRANCO LOI, PH.D.,‡
ROBERTO TARABUZZI, M.D.,† GIAN SILVIO MARCHIORO, M.D.,† DEBORA BELDI, M.D.,*
ELEONORA MONES, PH.D.,‡ CESARE BOLCHINI, R.T.,* ALESSANDRO VOLPE, M.D.,† AND BRUNO FREA, M.D.§

Departments of *Radiotherapy, †Urology, ‡Medical Physics, University Hospital Maggiore della Carità, Novara, Italy; and §Department
of Urology, Hospital S. Maria della Misericordia, Udine, Italy



**May intra-operative radiotherapy have a role in the treatment
of prostate cancer?**

Marco Krengli ^{a,*}, Carlo Terrone ^b, Barbara Alicja Jereczek-Fossa ^c, Debora Beldi ^d,
Roberto Orecchia ^e

^a Department of Radiotherapy, University Hospital Maggiore della Carità and University of Piemonte Orientale, Corso Mazzini 18 - 28100 Novara, Italy

^b Department of Urology, University Hospital Maggiore della Carità and University of Piemonte Orientale, Corso Mazzini 18 - 28100 Novara, Italy

^c Department of Radiotherapy, European Institute of Oncology and University of Milan, Via Ripamonti 435 - 20141 Milan, Italy

^d Department of Radiotherapy, University Hospital Maggiore della Carità, Corso Mazzini 18 - 28100 Novara, Italy

^e Department of Radiotherapy, European Institute of Oncology, University of Milan and CNAO Foundation, Via Ripamonti 435 - 20141 Milan, Italy



IORT nel tumore prostata: Casistica



CRITERI di INCLUSIONE



Almeno 2 dei seguenti:

PSA tot > 10 ng/ml

Gleason Score \geq 7

Stadio clinico \geq cT2c

Positività > 2/3 prelievi biotici

Probabilità di malattia organo confinata < 25% (Nomograms of MSKCC)

Dal settembre 2005 a Agosto 2013: **88 pz Ca prostata ad alto-altissimo rischio¹**

| Caratteristiche dei pazienti | N = 88 |
|-------------------------------|---------------|
| Età mediana (min-max), anni | 68 (52-76) |
| iPSA mediano (min-max), ng/ml | 14.4 (2.0-80) |
| PSA post-operatorio mediano | 0.06 ng/ml |

IORT nel tumore prostata: Casistica

**Stadiazione prechirurgica:
TC +/- RM pelvi, scintigrafia ossea**

Consenso informato specifico

Discussione multidisciplinare con staff dedicato



**Oncologo Radioterapista
Chirurgo
Fisico Sanitario
Tecnico di Radiologia
Infermiere di Sala
Anestesista**

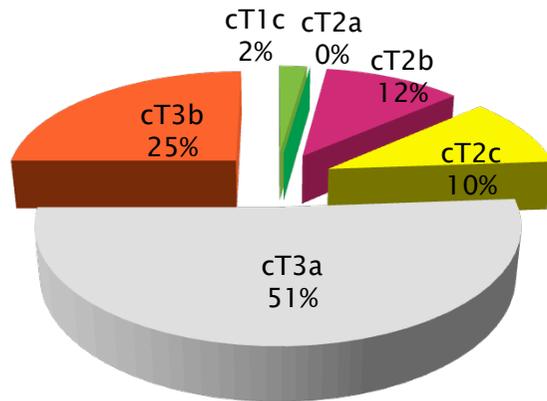
CASISTICA

GS Bioptico mediano → 8
Range (4-10)

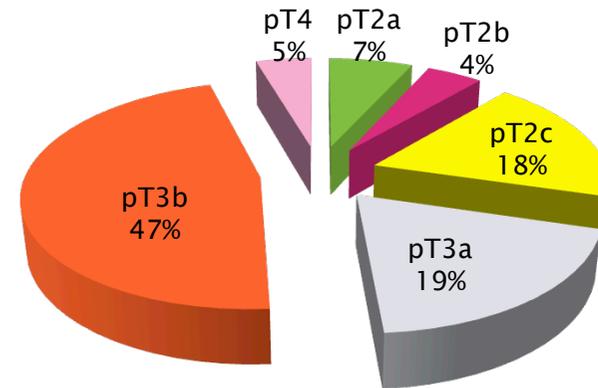


GS Patologico mediano → 9
Range (6-10)

Stadio clinico cT3: 76%
cT2: 22%



Stadio patologico pT3/4: 71%
pT2: 22%

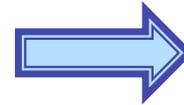


R+: 55/88 (62.5%)

pN+: 25/88 (28.4%)

METODICA

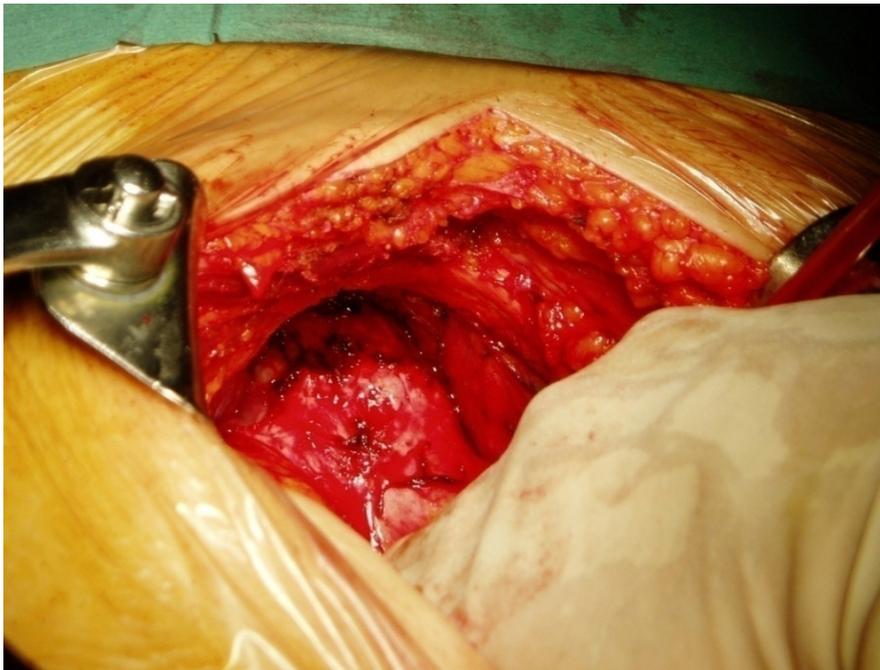
1. Induzione della anestesia generale
2. Inserimento della **sonda rettale**
per la dosimetria in vivo
3. Esposizione dell' apice prostatico



Sonda rettale (diametro: 2.5 cm)



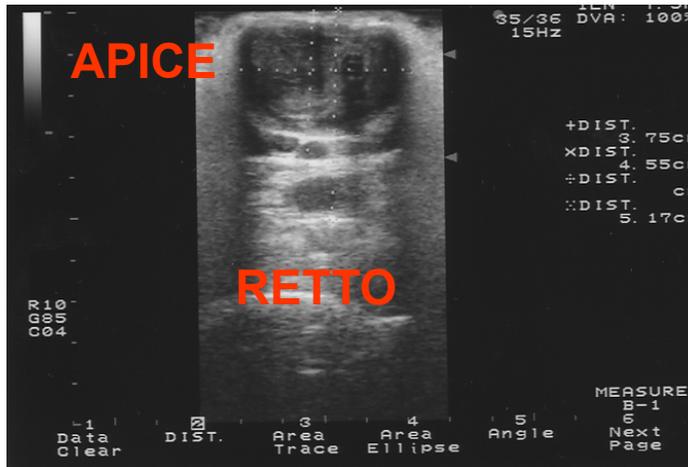
4 pellicole radiocromiche
sulla superficie



METODICA

4. Ecografia intraoperatoria:

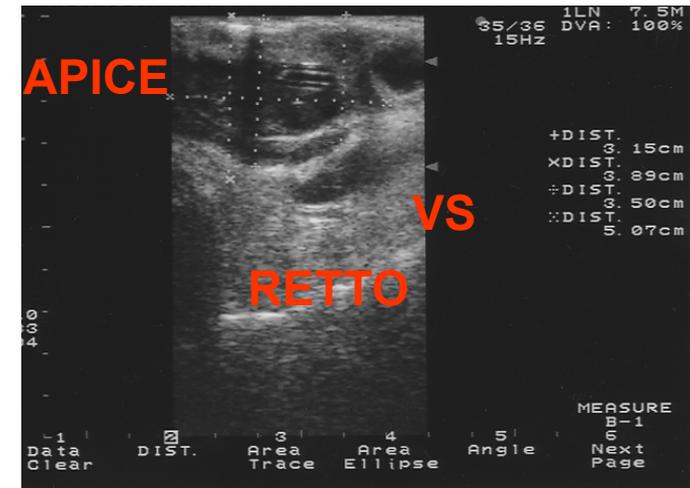
ANTERIORE CAUDALE



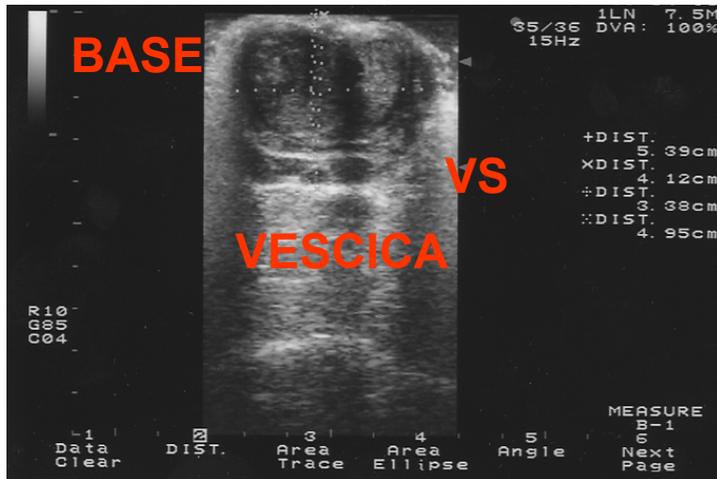
Valutazione:
a. diametro antero-posteriore della ghiandola (valore medio: **3.2 cm**)

b. distanza sup. prostatica-parete anteriore del retto (valore medio: **3.6 cm**)

SAGITTALE



ANTERIORE CRANIALE

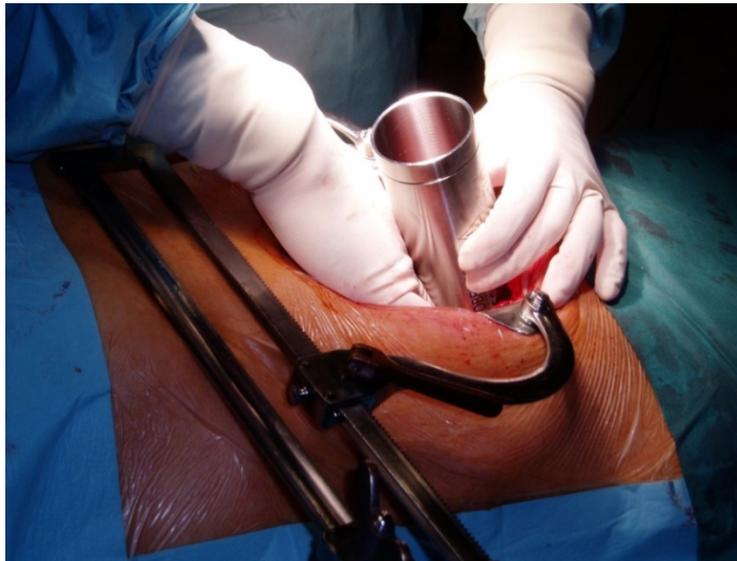


METODICA

5. Scelta di:

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

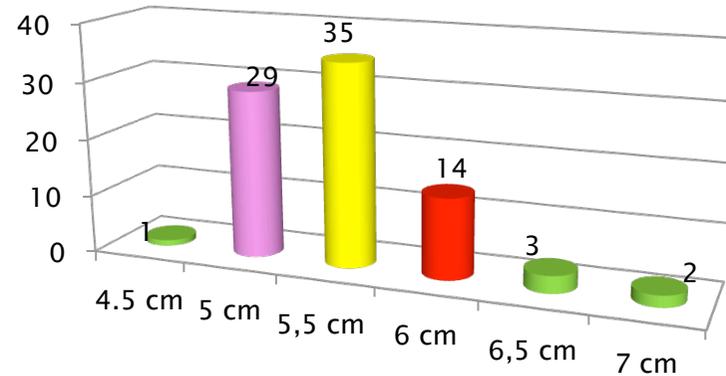
11. Si procede infine con la prostatectomia radicale + LAD

METODICA: aspetti tecnici



Mobile Linac: Mobetron, Intraop
Energy: 9 MeV (50%) - 12 MeV (50%)
Target Dose: 12 Gy (90% isodose)

Diametro collimatore



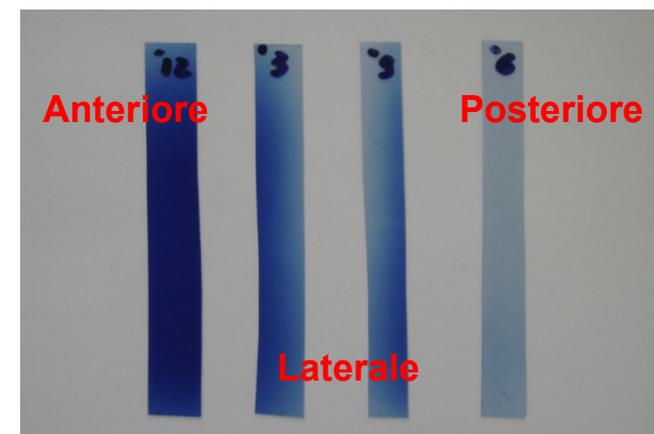
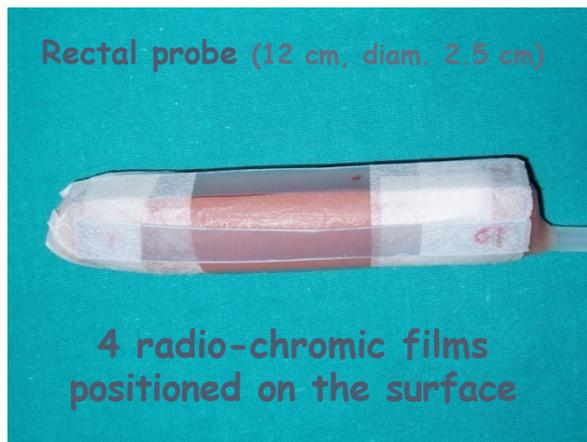
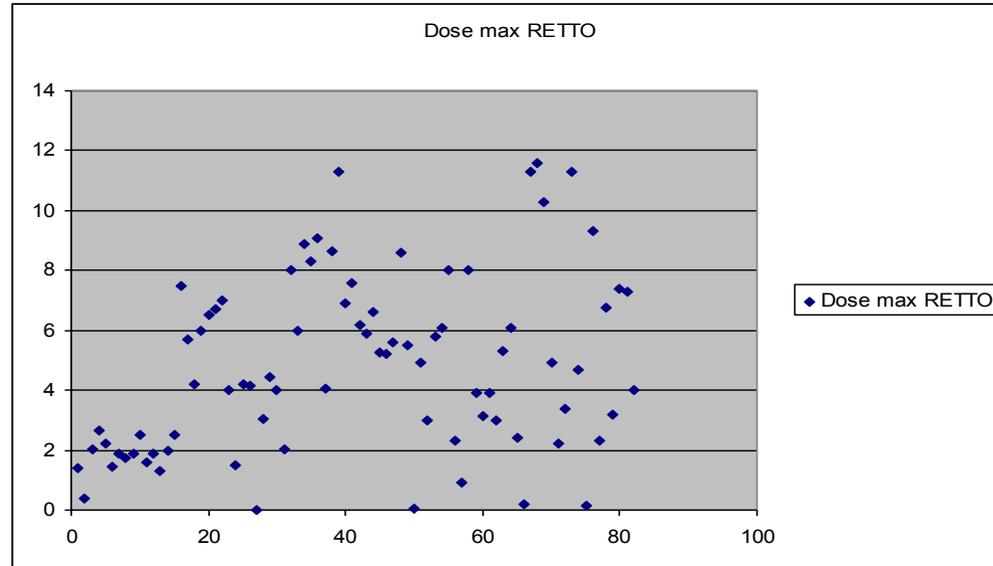
Angolo collimatore: 30° (96%); 15° (4%)

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



DOSIMETRIA RETTALE

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



MORBIDITA' RP + IORT

Non si sono verificate complicanze maggiori;

71.6 % (63/88): necessaria trasfusione ematica

Complicanze minori in 26/88 pz (29.5 %):

- Linfocele sintomatico 8/88 (9%)
- Ematoma 2/88 (2.3%)
- Occlusione anastomosi vescico-uretrale 4/88 (4.5%)
- Fistole 5/88 (5.7%)
- Altro (8%)

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

- Stadio \geq pT3a
- Margini chirurgici positivi (R1)

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

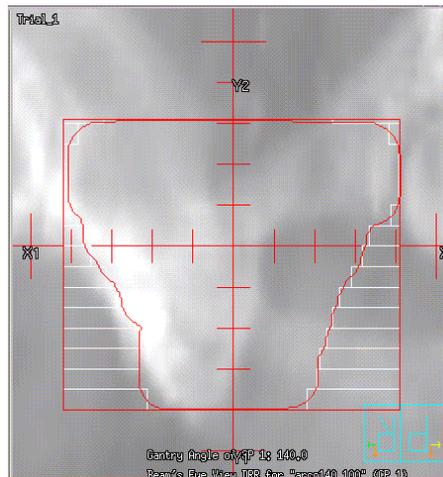
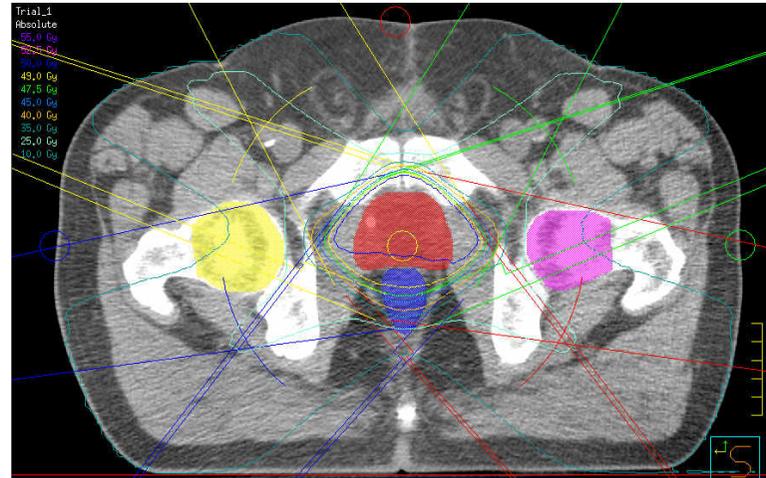
DOSE: **50 Gy** (2Gy/fr)

Intervallo di tempo RP + IORT \rightarrow EBRT:

3-4 mesi

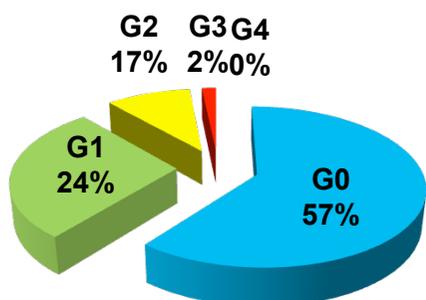
Ormonoterapia adiuvante:

57/88 (64.7%) pz

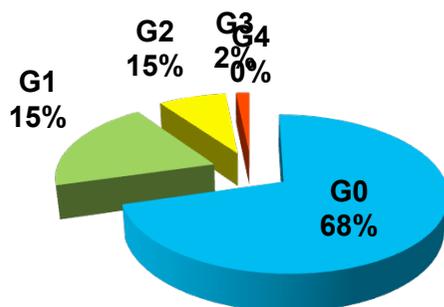


EBRT ADIUVANTE: tossicità

Tossicità GU acuta



Tossicità GI Acuta

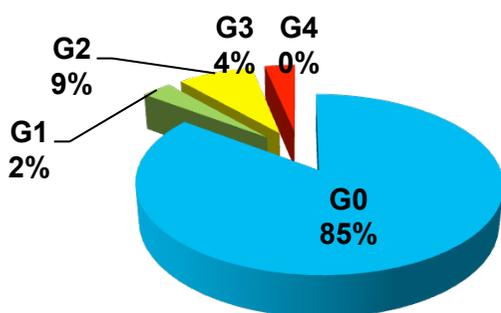


CONFRONTO (from Valicenti R. IJROBP, 2013)

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% |

Tossicità tardiva GU



Tossicità GI Tardiva

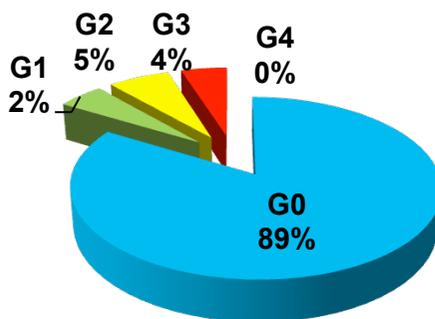


Table 2 Late toxicity effects of RT after prostatectomy (ranges based on RTOG/EORTC or CTCAE grading system)

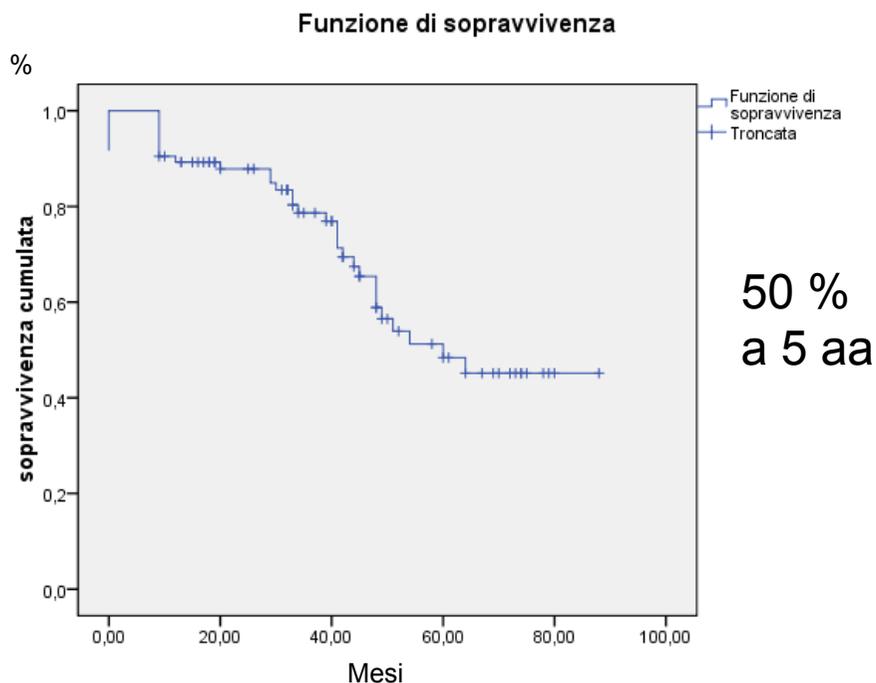
| Study arm type | Genitourinary | | Gastrointestinal | |
|----------------|---------------|------------|------------------|------------|
| | Grades 1-2 | Grades 3-4 | Grades 1-2 | Grades 3-4 |
| Adjuvant | 2.0%-22.0% | 0.0%-10.6% | 1.0%-12.7% | 0.0%-6.7% |

Sopravvivenza libera da Recidiva biochimica

Recidiva Biochimica: PSA \geq 0,2 ng/ml

Mediana di FU **48 mesi**
(range 10-89)

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 | |

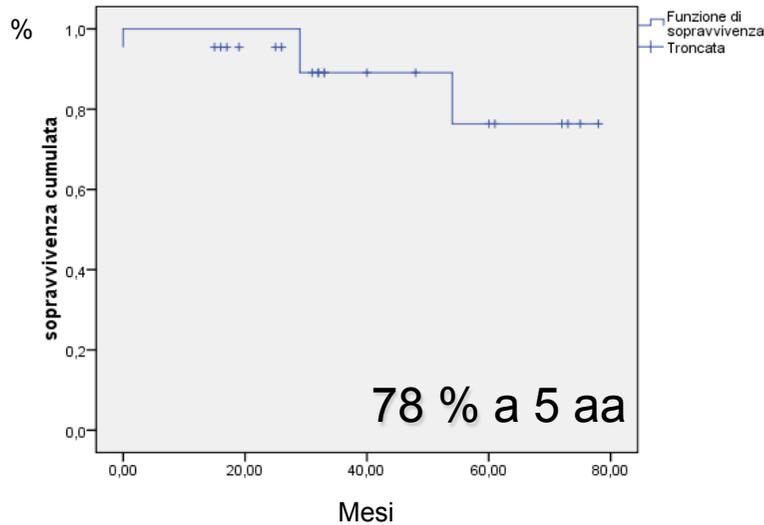
RECIDIVA LOCOREGIONALE:

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

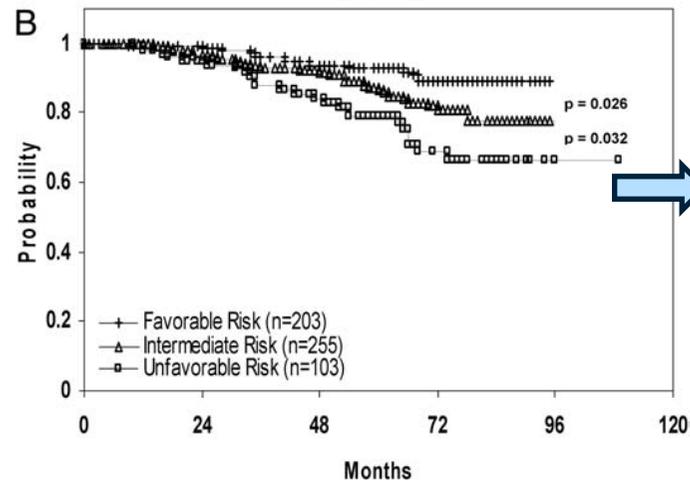
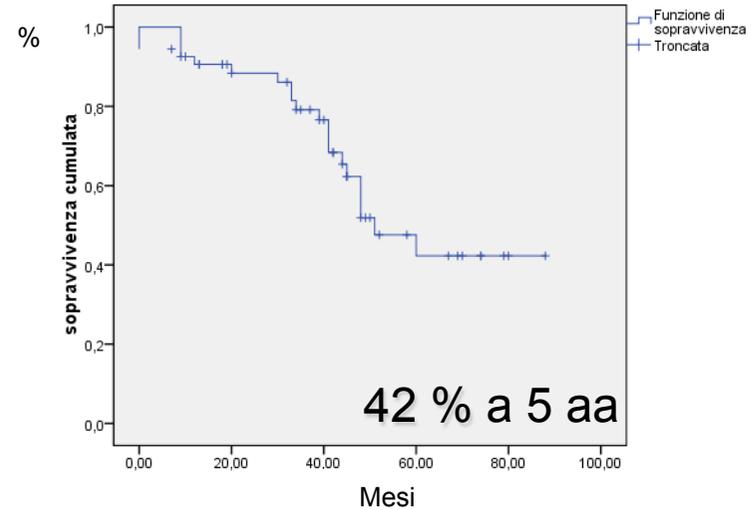
Valicenti R. IJROBP, 2013

BFS: stratificazione in base a classi di rischio cliniche

Pz HIGH RISK (NCCN)



Pz VERY HIGH RISK (NCCN)



PSA relapse-free survival per pz unfavorable risk (NCCN) sottoposti a EBRT + HT: 67% a 8aa. (Houston definition for biochemical relapse) ¹

¹ Zelefsky, The Journal of Urology 2006

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?



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Thanks !