



WORKSHOP

Controversie nelle strategie terapeutiche del carcinoma prostatico localizzato ad alto rischio

Intensificazione mediante BT: Pros

A. Vavassori

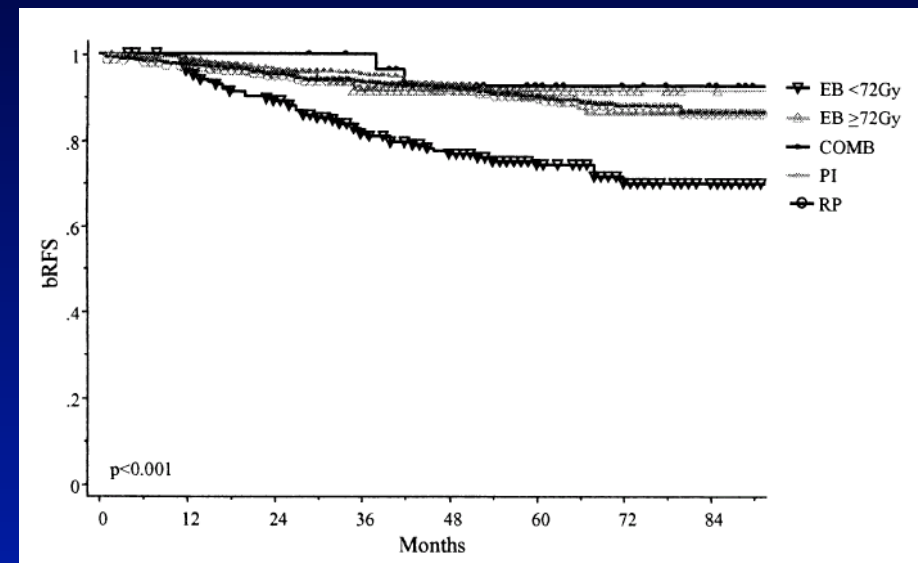
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Introduction

Kupelian: “Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy >72 Gy, permanent seed implantation, or combined seeds/ external beam radiotherapy for stage T1-T2 prostate cancer”, *IJROBP* 2004

2991 pts	# pt.	bNED @ 7 yy
Prostatectomy	1034	76%
3D-CRT < 72 Gy (median 68.4 Gy)	484	48%
3D-CRT ≥ 72 Gy (median 78 Gy)	301	81%
BRT (¹⁰³ Pd or ¹²⁵ I)	950	75%
Comb: RT + BRT	222	77%



“... the **best** treatment choice is one made by an informed patient who is comfortable with, and committed to, **whichever he chooses...**”

Patient selection: ABS/ESTRO

T1c-T2a *and*
G.S. ≤ 6 (7=3+4) *and*
PSAi ≤ 10 ng/ml

**LOW
RISK**

BRT

$> T2a$ *and/or*
G.S. ≥ 7 (4+3) *and/or*
PSAi > 10 ng/ml

1 factor

**INTERMEDIATE
RISK**

2 factors

**HIGH
RISK**

3D-CRT +/- BRT

Patient selection: EBRT + BRT

Febles: "Combining external beam radiotherapy with prostate brachytherapy: issue and rationale", Urology 2004

The combination of EBRT and BRT has been used to improve outcomes in intermediate and high-risk patients

The benefits include:

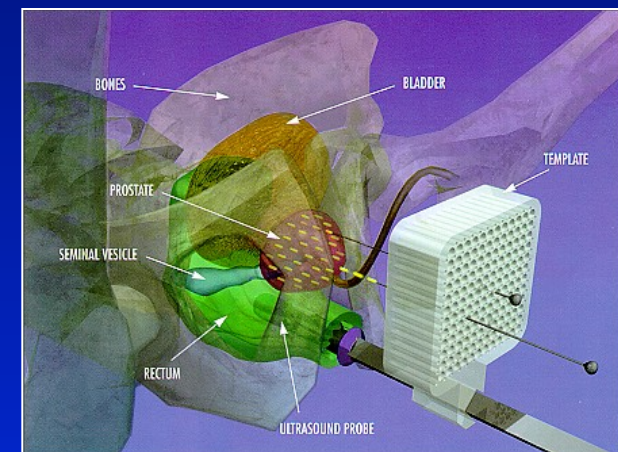
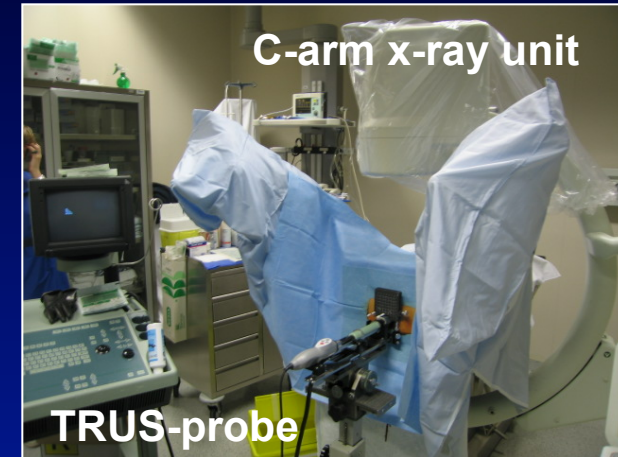
- delivery of a greater radiation dose
- inclusion of extra-capsular disease
- inclusion of seminal vesicle
- coverage of pelvic lymph node, when indicated → IMRT?



TRUS-GUIDED LDR/HDR BRT

Step-by-step technique

1. Volume evaluation (2-4 weeks before)
2. Intraoperative planning (TRUS)
3. Needles \pm seeds implantation (TRUS)
4. TRUS / CT-based planning (HDR)
5. CT-based postimplant dosimetry (LDR)
6. Radioprotection phase (LDR)



TRUS-GUIDED HDR BRT

A wide range of HDR modality and fractionation schemes have been reported in the literature.

Two different approaches to HDR fractionation have evolved:

- separate HDR fractionation for insertion

a single insertion followed by HDR delivered over 1–2 days

BOOST WITH SINGLE FRACTION !!!



EBRT + BRT

Pieters. "Comparison of 3 radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer; a systematic review". Radiother Oncol 2009

A systematic review of observational studies with the data of EBRT, EB+Seeds and EB+TI (1980-2007)

LDR

First author	Year	Number of patients	External beam technique	Target organ external beam	Dose prescribed in BED ₃ (Gy)*
EBSeeds					
Iversen [21]	1989	33	3F	Pelvic Inn	234
Kaye [22]	1995	31	NM	NM	183
Critz [23]	1998	657	Arc, 3D-CRT	Prost, sem ves	183
Ragde [24]	1998	54	4F	Lower pelvic Inn	183
Lederman [25]	2001	348	NM	NM	169-183
Potters [26]	2002	314	4F	Lower pelvic Inn	168-186
Singh [27]	2005	80	3D-CRT	Prost, sem ves	157-161
Jani [28]	2006	54	4F	Prost, sem	169-183
Dattoli [29]	2007	243	NM	Lower pelvic Inn	142-152
Ellis [30]	2007	89	4F	Prost, sem ves	169-185
Sylvester [31]	2007	223	4F	Lower pelvic Inn	169-183
Merrick [32]	2007	204	4F	Pelvic Inn	169
Lee [33]	2007	130	NM	Prost, sem ves	183

HDR

First author	Year	Number of patients	External beam technique	Target organ external beam	Dose prescribed in BED ₃ (Gy)*
EBTI					
Mate [34]	1998	104	Arc, 4F	Prost	105-118
Galalae [5]	2002	144	Arc	Pelvic Inn	139
Pellizzon [35]	2003	108	4F	Prost, sem ves	109-153
Hiratsuka [36]	2004	71	4F	Whole pelvic Inn	119-135
Martin [37]	2004	102	4F	Prost, sem ves	125-146
Åström [38]	2005	214	NM	1988-1993: Pelvic Inn 1993-2000: prost, sem ves	170
Deger [39]	2005	411	4F, 3D-CRT	Low and int risk: prost High risk: prost, sem ves	153-144
Hsu [40]	2005	64	4F, 3D-CRT	Low risk: prost, sem ves Int and high risk: whole pelvic Inn	126
Chin [41]	2006	67	3D-CRT	Low risk: prost Int and high risk: prost, sem ves	134
Izard [42]	2006	165	4F, 3D-CRT	Low risk: prost Int and high risk: prost, sem ves	135
Vargas [6]	2006	197	4F	Whole pelvic Inn	123-188
Yamada [43]	2006	105	3D-CRT	Prost, sem ves	119-151
Hoskin[8]	2007	109	3F, 3D-CRT	Prost	134
Rades [44]	2007	41	4F	Prost, sem ves	153
Phan [45]	2007	309	4F, 3D-CRT, IMRT	Prost, sem ves	126-144
Kälkner [46]	2007	154	3F, 4F	Prost, sem ves	170
Chen [47]	2007	85	3D-CRT, IMRT	Whole pelvic Inn or Prost, sem ves	127



® EBRT vs EBRT+BT

Sathya. "Randomized trial comparing Iridium implant plus EBRT with EBRT alone in node-negative locally advanced cancer of the prostate". JCO 2005

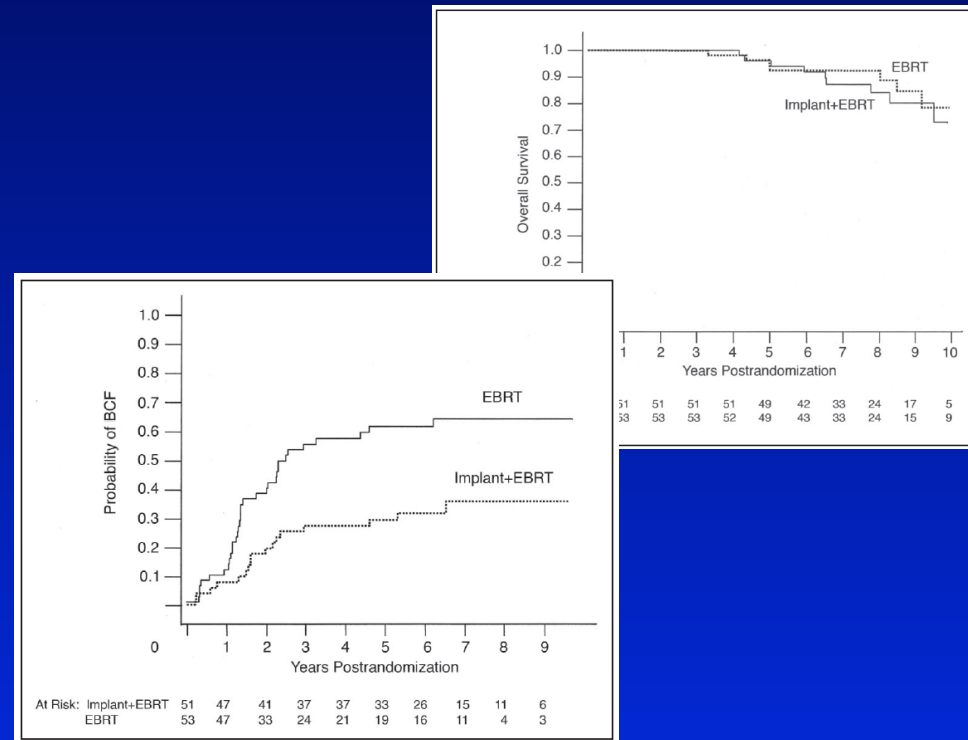
104 patients, T2-3 (1992 – 1997)

- ® 53 EBRT (66 Gy @ 2 Gy)
- ® 51 EBRT (40 Gy @ 2 Gy) + BT (LDR-¹⁹²Ir 35 Gy in 48 h)

Median follow-up 8.2 years

Biochemical or clinical failure:

- EBRT alone = 61%
- EBRT + BT = 29%



® *EBRT vs EBRT+BT*

Hoskin. “HDR BT in combination with EBRT in the radical treatment of prostate cancer:
Hoskin. “HDR BT in combination with EBRT in the radical treatment of prostate cancer:

220 patients, T1-3 (1997 – 2005)

220 patients, T1-3 (1997 – 2005)

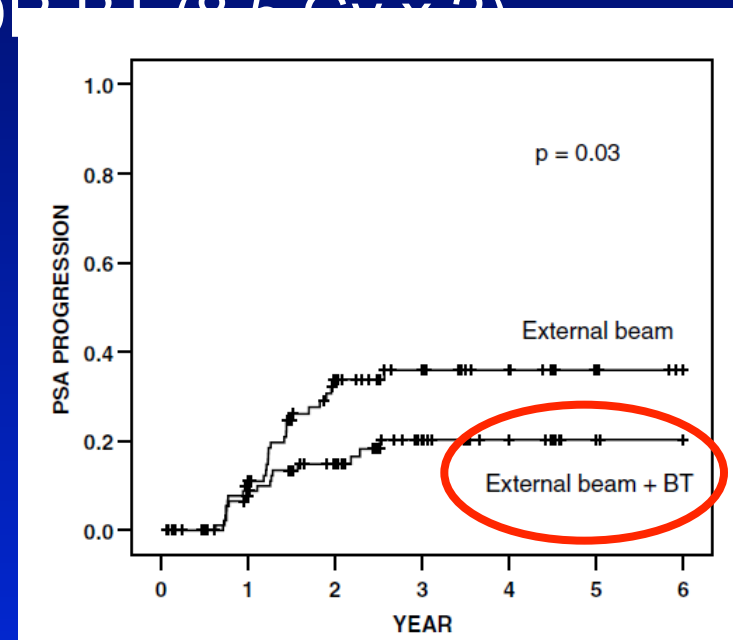
111 EBRT (55 Gy @ 2.75 Gy)

109 EBRT (35.75 Gy @ 2.75 Gy) + HDR BT (9.5 Gy x 2)

Neoadjuvant hormone therapy: 76%

Median follow-up 30 months

No significant difference in late bowel
or bladder toxicity \geq G2



CLINICAL RESULTS

EBRT + BT boost

2011

MARVEL

Sony.Com/Spider-Man



EBRT + LDR-BT

Kubicek. "Combined transperineal implant and external beam radiation for the treatment of prostate cancer: A large patient cohort in the community setting". Brachytherapy 2011

824 patients (1998 – 2004)

EBRT (50.4 Gy @ 1.8 Gy) + BT (¹²⁵I 120 Gy)

Median follow-up 5.5 years

<i>Risk group</i>	OS @ 5-year	bRFS @ 5-year
low	86.1%	85.4%
intermediate	85%	83.2%
high	82.5%	79.6%

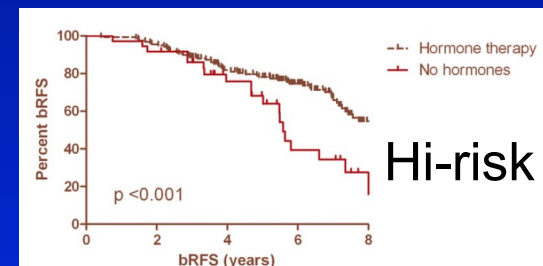
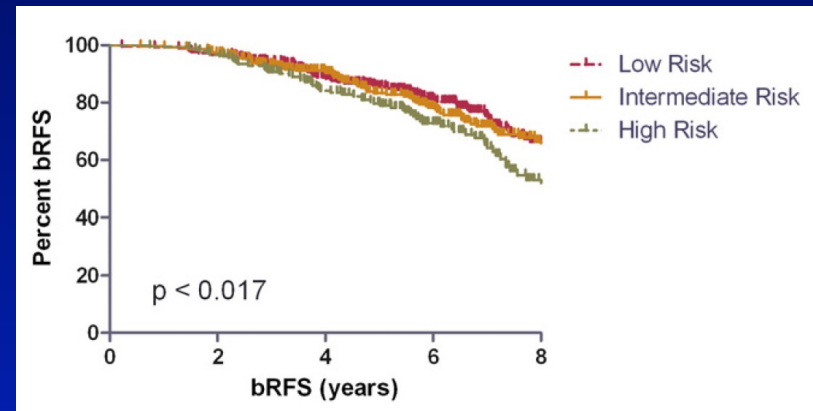


Fig. 3. Biochemical relapse-free survival in high-risk patients.

Neoadjuvant hormone therapy: 71%

EBRT + LDR-BT + DOCETAXEL

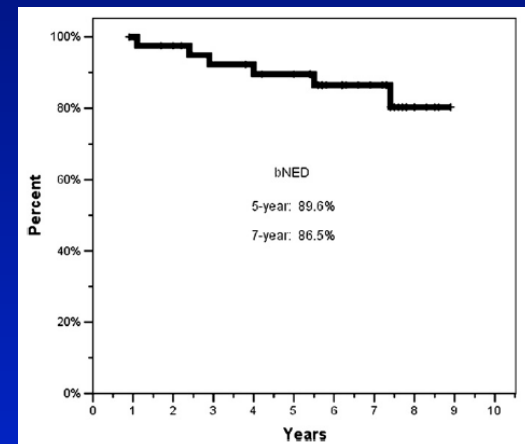
DiBiase. “Long-term results of a prospective, phase II study of long-term androgen ablation, pelvic radiotherapy, BT boost and adjuvant Docetaxel in patients with high-risk prostate cancer”. IJROBP 2011

42 pts with high risk cancer (2000 – 2004)

Week 1 (Day 1)	Week 9	Week 13
Pelvic EBRT 45 Gy (5 weeks) LHRH agonist (2 years) Anti-androgen (4 weeks)	Brachytherapy boost (I-125–108 Gy) or (Pd-103–100 Gy)	Adjuvant docetaxel × 3 cycles (1 cycle = 35 mg/m ² i.v., Days 1, 8, 15 Q 28 days)

Median follow-up = 5.6 years

DFS @ 5-year 89.6%
@ 7-year 86.5%



The 5- and 7-year late Grade 2 GI/GU toxicity was 7.7%

EBRT + HDR-BT

Martinez. "Dose escalation improves cancer-related events at 10 years for intermediate and high-risk prostate cancer patient treated with hypofractionated HDR boost and EBRT". IJROBP 2011

472 pts with intermediate or high risk cancer (1992-2007)

EBRT 46 Gy + HDR-BT

Median follow-up = 8.2 years

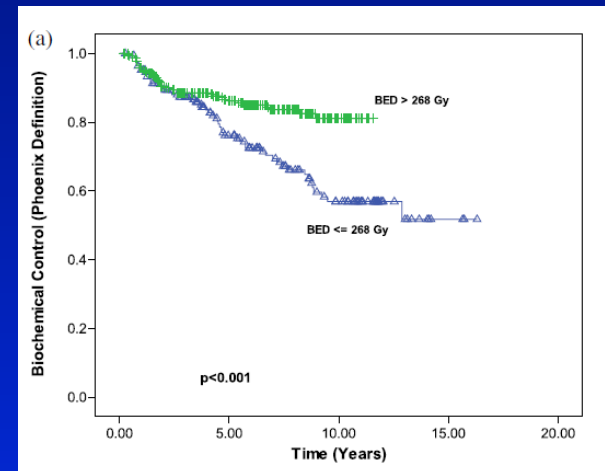
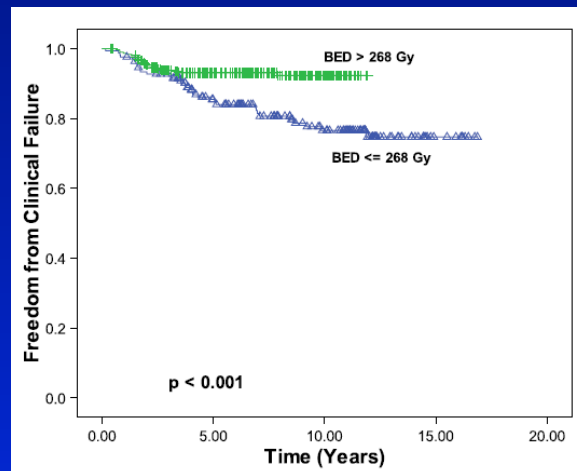
Table 2. Single P-EBRT BED, HDR BED, and total BED

P-EBRT	BED (α/β ratio of 1.2)	HDR	BED (α/β ratio of 1.2)	Total BED	Total BED (α/β ratio of 3.0)
23 x 2 Gy = 46 Gy	122.67	5.5 Gy x 3	92.13	215	123
23 x 2 Gy = 46 Gy	122.67	6.0 Gy x 3	108.00	231	131
23 x 2 Gy = 46 Gy	122.67	6.5 Gy x 3	125.13	248	138
23 x 2 Gy = 46 Gy	122.67	8.25 Gy x 2	129.94	<u>253</u>	139
23 x 2 Gy = 46 Gy	122.67	8.75 Gy x 2	145.10	268	145
23 x 2 Gy = 46 Gy	122.67	9.50 Gy x 2	169.42	292	156
23 x 2 Gy = 46 Gy	122.67	10.50 Gy x 2	204.75	327	171
23 x 2 Gy = 46 Gy	122.67	11.50 Gy x 2	243.42	366	188

EBRT + HDR-BT

Martinez. "Dose escalation improves cancer-related events at 10 years for intermediate and high-risk prostate cancer patient treated with hypofractionated HDR boost and EBRT". IJROBP 2011

<i>Dose level</i>	<i>Clinical failure @ 5-year</i>	<i>bRFS @ 10-year</i>
Low (BED<268 Gy)	23.4%	43.1%
High (BED>268 Gy)	7.7%	18.9%
	$p < 0.001$	$p < 0.001$



HEMI-IRRADIATION BOOST

Schick. "HDR-BT boost to the dominant intra-prostatic tumor region: hemi-irradiation of prostate cancer". The Prostate 2011

77 pts (2000 – 2004) with one lobe involvement

3D-CRT (64 Gy) + HDR-BT (12 – 16 Gy / 2 fr)

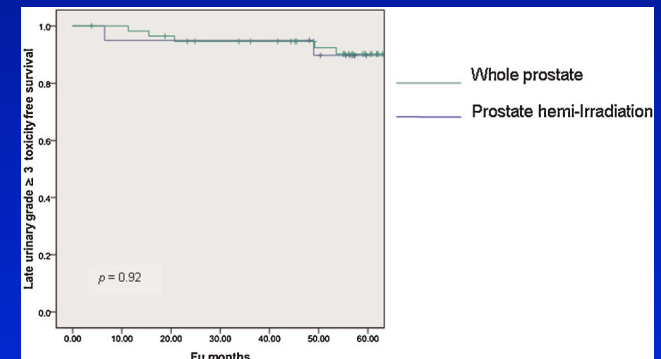
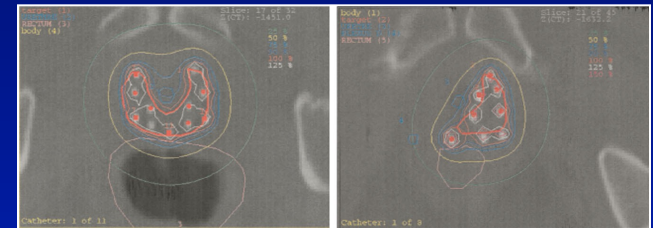
20 pts were boosted to one side of the gland only (MRI-guided)

Median follow-up 69 months

bNED @ 5-year

- unilateral boost 79.7%
- bilateral boost 70.5%

no differences in late rectal toxicity



RETROSPECTIVE STUDY

IMRT+BT boost vs. IMRT alone

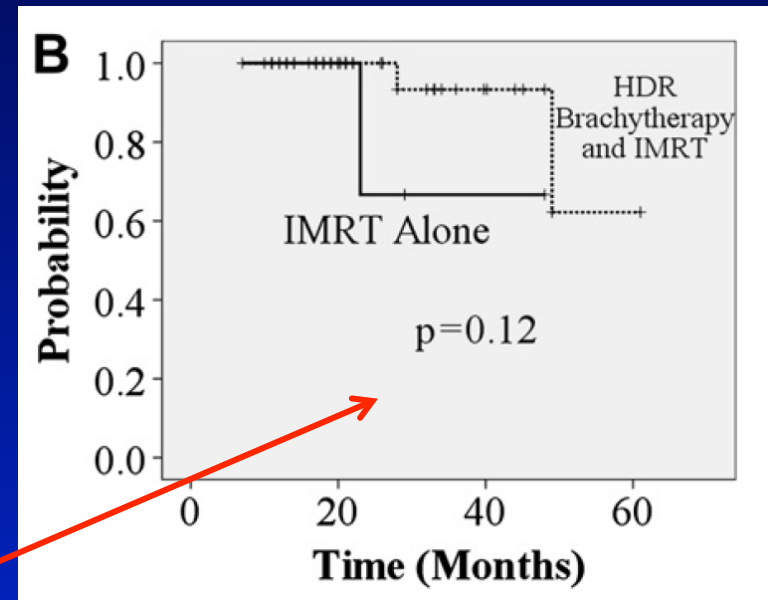


IMRT + HDR-BT vs. IMRT alone

Wilder. "Preliminary results in prostate cancer patients treated with HDR-BRT and IMRT vs. IMRT alone" Brachytherapy 2010

- 240 pts HDR-BT (22 Gy) + IMRT 50.4 Gy (2003-2008)
- 44 pts IMRT 79.2 – 81 Gy
- Median follow-up 2.2 years
- Similar toxicity

	IMRT + BT	IMRT alone
Low	100%	100%
Intermediate	98%	100%
High	93%	67%



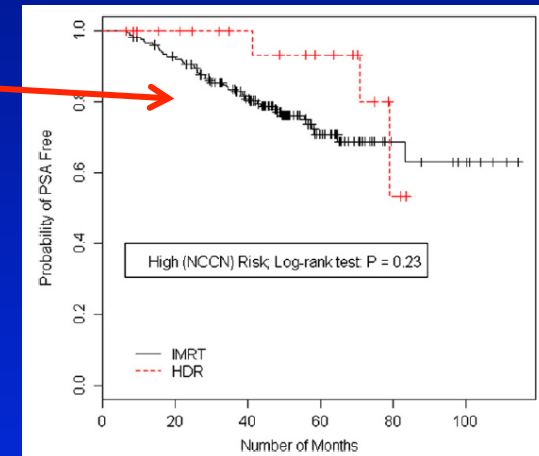
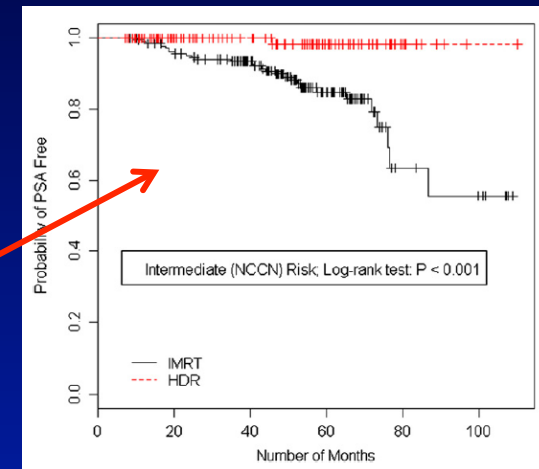
“...we continue to base treatment on physician and patient preference...”

IMRT + HDR-BT vs. IMRT alone

Deutsch. "Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR-BT and IMRT". Brachytherapy 2010

- 160 pts HDR-BT (22 Gy) + IMRT 50.4 Gy (1998-2007)
- 470 pts IMRT 86.4 Gy
- Median follow-up 53 months

	IMRT + BT	IMRT alone
Low	100%	98%
Intermediate	100%	84%
High	93%	71%



“This experience should provide the impetus for an evidence based shift toward greater incorporation of HDR-BT”

DOSIMETRIC STUDY

BT boost vs. EBRT boost



Dosimetry: HDR-BT vs. IMRT

Fatyga "A comparison of HDR BT and IMRT techniques for dose escalation in prostate cancer: a radiobiological modeling study" Med.Phys 2009

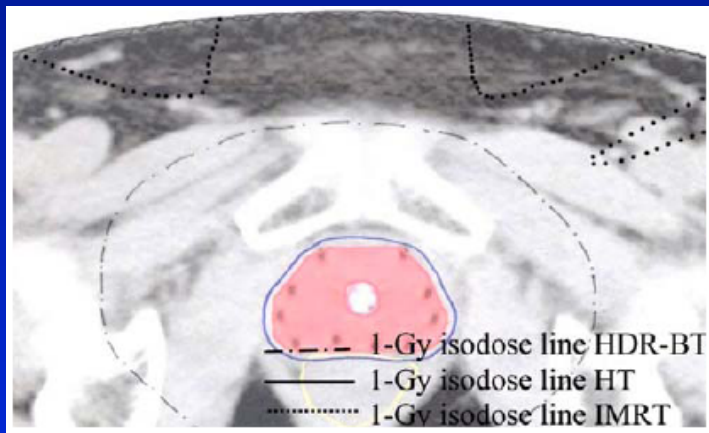
Boost with **7-field IMRT** (2.25 Gy x 9 fr) vs **HDR** (9 Gy)

HDR is significantly $>$ IMRT and \geq IG-IMRT



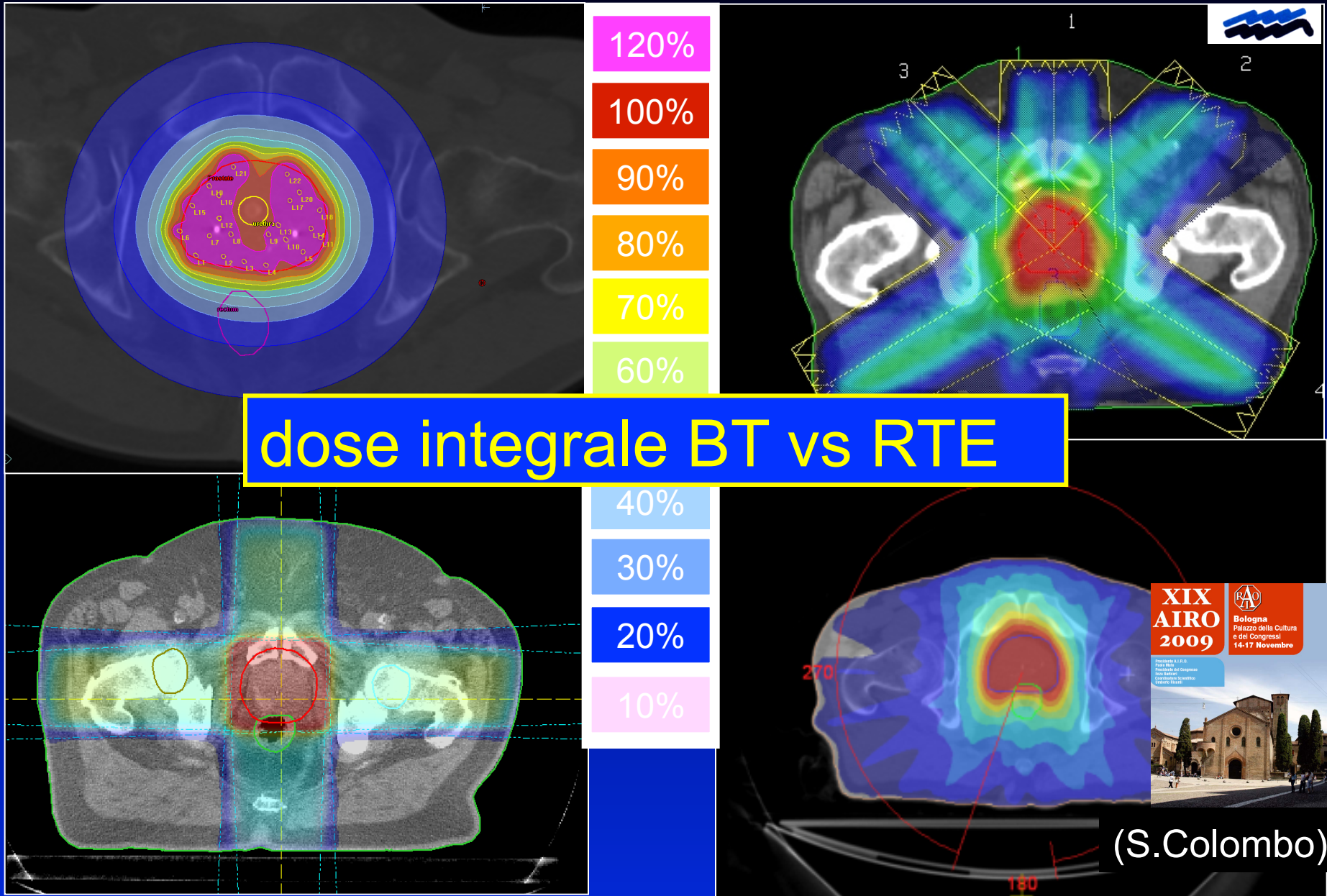
Hermesse "A dosimetric selectivity intercomparison of HDR BT, IMRT and helical tomotherapy in prostate cancer radiotherapy" Strahl.Onkol. 2009

Boost (10 Gy) with **HDR** vs. **5-field IMRT** vs. **Hi-Art**



HDR reduces the volume of healthy tissue receiving a low dose (1 Gy) by a factor 8 or 10 when compared to IMRT and HT

Dosimetry: HDR-BT vs. IMRT



dose integrale BT vs RTE

XIX AIRO 2009
 Bologna
 Palazzo della Cultura
 e dei Congressi
 14-17 Novembre



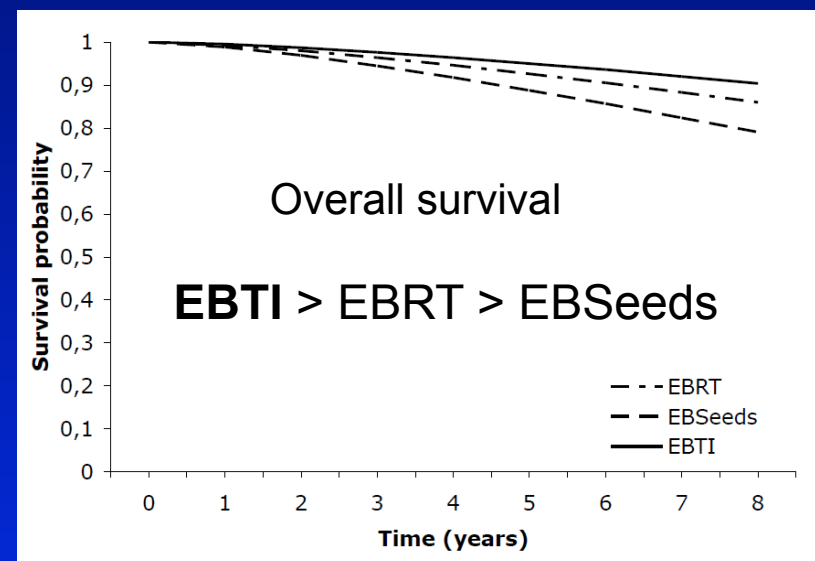
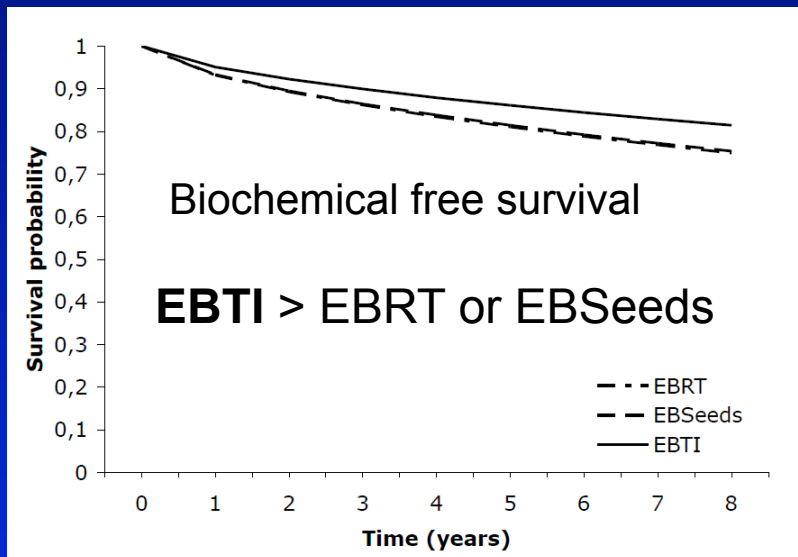
(S. Colomba)

CONCLUSIONS

Dose escalation by combining EBRT + BT:

- may have an important role for the radical treatment of intermediate and poor risk localized prostate cancer
- provides optimal conformal radiation dose delivery
- is equal/superior to EBRT alone

Pieters. "Comparison of 3 radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer; a systematic review". Radiother Oncol 2009



GRAZIE PER L'ATTENZIONE

... e se Vavassori non vi ha convinto,
probabilmente lo farà Vavassori ...

