WORKSHOP

Controversie nelle strategie terapeutiche del carcinoma prostatico localizzato ad alto rischio

Intensificazione mediante BT: CONS

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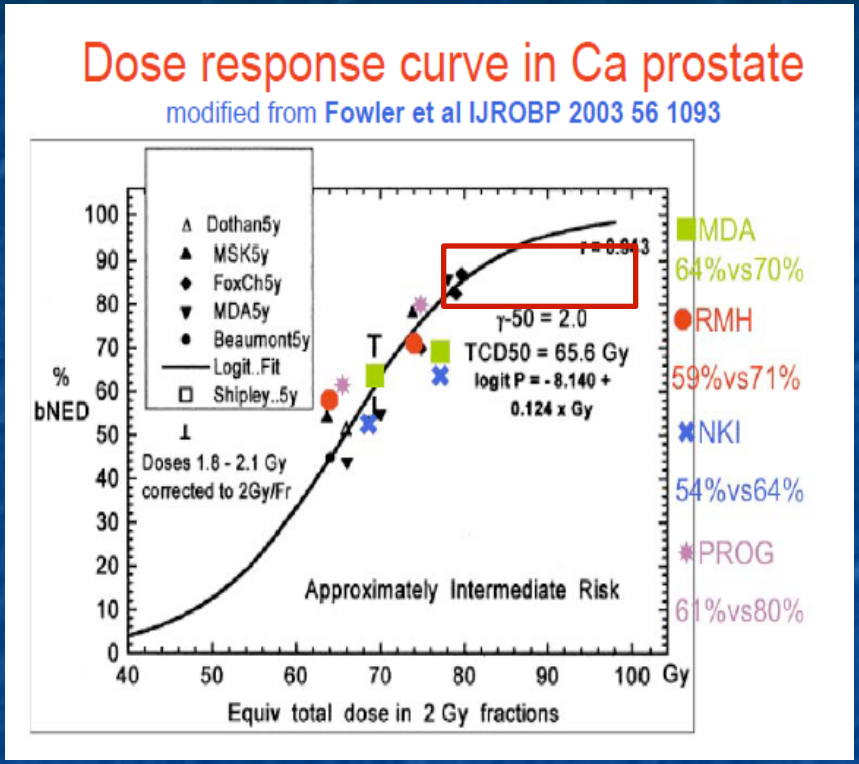
HDR-BT in high risk prostate cancer

- Dose escalation improves clinical results
- Patients with intermediate to high risk prostate cancer can benefit from dose escalation
- Local failure may be the predominant mode of failure in these pts
- BT is an alternative method of delivering highly conformal RT
- Role of pelvic RT and AD

What about the “rigth” level of dose-escalation?



Current state of the evidence for high dose CFRT from RCT

- Evidence that high-dose CFRT
  - Improves PSA control
  - Improves freedom from failure
  - Increases late bowel effects
  - Prolongs time to start of hormone therapy
- Lack of evidence (as yet) for effect on
  - Local and distant failure
  - Survival (death by all causes)
  - Survival (prostate cancer deaths)

Schultz RI and Kagan R , IJROBP ,2011

Btw 10 and 20% of high risk pts developed MTS after RT…
Questions about the effectivness of dose escalation and about the skewing of results by incipient MTS…
The escalation of dose to specifically achieve FFbF is questionable.

How to best deliver higher dose of Rt without significantly increasing normal tissue toxicities?

HDR-BT boost as alternative means of precise dose delivery

- Physical and dosimetric advantages (steep dose gradient/ (optimization of dose distribution)
- Flexibility for dose intensity modulation and conformality (selective dosing inside the CTV)
- No interfx or intrafx motion or set-up errors
- Short period of treatment
- Larger dose per fraction to increase therapeutic window (> control while limiting chronic toxicity)

How to best deliver higher dose of Rt without significantly increasing normal tissue toxicities?

HDR-BT boost as alternative means of precise dose delivery

- Volumetric disadvantages
- Anatomic interference
- More inhomogeneous target coverage (high-dose region in the central part of the PTV)
- Invasive procedure (pain, analgesics,etc)
- In-patient procedure (anesthesia) with significant time, resources and technical expertise required
- Learning curve longer than EBRT

Patient selection criteria for a curative combined TEMPORARY BT and EBRT treatment

Inclusion criteria	Stages T1b–T3b
	Any Gleason score
	Any iPSA without distant metastases
Exclusion criteria	Volume > 60 cm^3
	TURP within 6 months
	Infiltration of the external sphincter of the bladder neck
	Significant urinary obstructive symptoms
	Pubic arch interference
	Rectum-prostate distance on TRUS < 5 mm
	Lithotomy position or anaesthesia not possible

GEC-ESTRO-EAU, 2005

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

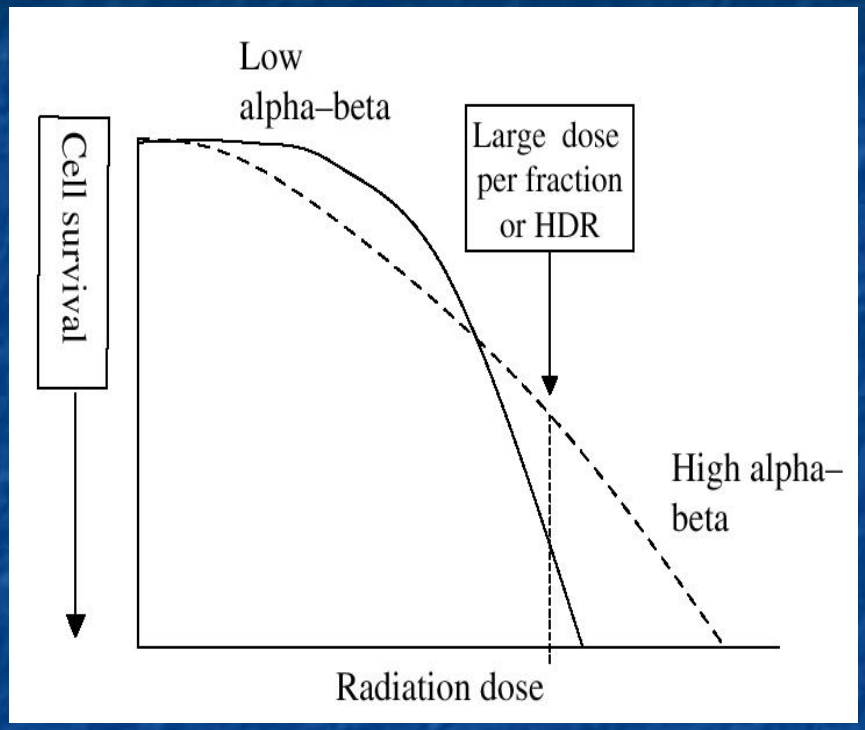
P-EBRT	BED (α/β ratio of 1.2)	HDR	BED (α/β ratio of 1.2)	Total BED	Total BED (α/β ratio of 3.0)
23 x 2 Gy = 46 Gy	122.67	5.5 Gy x 3	92.13	215	123
23 x 2 Gy = 46 Gy	122.67	6.0 Gy x 3	108.00	231	131
23 x 2 Gy = 46 Gy	122.67	6.5 Gy x 3	125.13	248	138
23 x 2 Gy = 46 Gy	122.67	8.25 Gy x 2	129.94	253	139
23 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

High risk pts have significant risk of ECE+ and/or VS+: not optimal dose from P-EBRT

- **DIFFICULT COVERAGE OF:**
  - **SEMINAL VESICLES**
  - **APEX**
  - **LARGE MIDDLE LOBE**

What about radiobiologic advantages of HDR ?

- A high dose per fx results in lower cell survival for tissues with a lower a/b ratio (for prostate is ~1.2-1.5) and relative sparing of normal tissues



The large variation in HDR brachytherapy prescription between institutions results in an even wider range of biologically equivalent dose delivered

Morton G, Clinical Oncology 2005

HDR-BT boost is a precise hypofx RT…..but

Radiobiology

a/b: ??? 1.2 to 15.4/Gy

- evidence of very low a/b from HDR data …
- but they `forgot` some issues (hypoxia)…
  (Nahum et al IJROBP, 2003)
- …or they were not talking about the cancer population (heterogeneity)
- *a/b is unknown, but it appears now unjustified to go for a schedule that works only if a/b is low (or where the D is too low)*

Growth rate: usually slow (even in "high risk'"?)

Reoxigenation ?, redistribution ? (not in LQ model)

Role of SF2 (hypoxia linked) and n^ of clonogenic cells

VOLUME 23 · NUMBER 6 · FEBRUARY 20 2005

JOURNAL OF CLINICAL ONCOLOGY

Randomized Trial Comparing Iridium Implant Plus External-Beam Radiation Therapy With External-Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate

Jinka R. Sathya, Ian R. Davis, Jim A. Julian, Qing Guo, Dean Daya, Ian S. Dayes, Himu R. Lukka, and Mark Levine

Better results in bRFS and biopsy proven LC

Radiotherapy and Oncology 84 (2007) 114–120
www.thegreenjournal.com

Phase III randomised trial

High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial

Peter J. Hoskin*, Kate Motohashi, Peter Bownes, Linda Bryant, Peter Ostler

Mount Vernon Cancer Centre, Northwood, UK

Better bRFS ,less acute rectal tox and improved QoL

Hsu IC et al, IJROBP,78,751-758,2011 : phase II- RTOG 0321
EBRT 45 Gy/25 frs + HDR-BT 19 Gy/2 frs
late 3+ GU or GI tox at 18 mo : 2.5 %

CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 2, pp. 363–370, 2011

DOSE ESCALATION IMPROVES CANCER-RELATED EVENTS AT 10 YEARS FOR INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER PATIENTS TREATED WITH HYPOFRACTIONATED HIGH-DOSE-RATE BOOST AND EXTERNAL BEAM RADIOTHERAPY

ALVARO A. MARTINEZ, M.D., F.A.C.R.,* JOSE GONZALEZ, M.D.,* HONG YE, M.S.,* MIHAI GHILEZAN, M.D., PH.D.,* SUGANDH SHETTY, M.D.,* KENNETH KERNEN, M.D.,† GARY GUSTAFSON, M.D.,* DANIEL KRAUSS, M.D.,* FRANK VICINI, M.D.,* AND LARRY KESTIN, M.D.*

*Radiation Oncology Department and †Urology Department, William Beaumont Hospital, Royal Oak, Michigan

BRACHYTHERAPY

Brachytherapy 9 (2010) 15–22

External beam radiotherapy plus high-dose-rate brachytherapy for treatment of locally advanced prostate cancer: The initial experience of the Catalan Institute of Oncology

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Alfredo Polo[3], Evelyn Martinez[2], Ana Boladeras[2], Ferran Ferrer[2], Pietro Gabriele[1],
Luis Linares[4]

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[4]*East Jefferson General Hospital, New Or*

ELSEVIER

HDR-BT boost for intermediate / high risk pts

Reference	Centre	HDR per fraction (Gy) × number of fractions	Number of catheter insertions	External-beam dose (Gy)	Comments
Kovacs and Galalae [20]	Kiel	15 × 2	2	50 (40 Gy to prostate)	15 Gy to peripheral zone; 10 Gy to prostate. HDR brachytherapy during EBRT
Martinez *et al.* [21]	William Beaumont	5.5 × 3 11.5 × 2	3 2	46	Sequential dose escalation protocol. HDR brachytherapy during first 3 weeks of EBRT
Borghede *et al.* [22]	Goteborg	10 × 2	2	50	15 Gy to tumour; 10 Gy to prostate. HDR brachytherapy sandwiched between EBRT
Mate *et al.* [17]	Seattle	3–4 × 4	1	50.4	3–4 Gy minimal dose; 6–7 Gy to peripheral zone. HDR brachytherapy before EBRT
Deger *et al.* [23]	Berlin	10 × 2 9 × 2	2	40–50.4	HDR brachytherapy before EBRT
Syed *et al.* [16]	Long Beach	5 × 3 5.5 × 4 6.5 × 4	1	39.6–45	HDR brachytherapy either before or after EBRT
Pellizzon *et al.* [24]	Sao Paulo	4 × 4 5 × 4	1	45	HDR brachytherapy after EBRT
Demanes *et al.* [25]	Oakland	6 × 4	2	36	Two insertions 1 week apart; HDR either before or after EBRT
Martin *et al.* [26]	Offenbach	5–7 × 4	4	39.6–45	Transrectal technique using four needles; 2 weeks between each implant; HDR brachytherapy before EBRT
Curran *et al.* [27]	Burlington	6 × 3	1	50	HDR brachytherapy before EBRT
Hiratsuka *et al.* [28]	Kawasaki	5.5 × 3 5.5 × 4	1	45 41.8	HDR brachytherapy during EBRT (after 20 Gy)
Chiang *et al.* [29]	Kaohsiung	4.2 × 3	2	50.4–54	HDR brachytherapy before EBRT

Morton G , Clin.Oncol. 2005

Two different approaches to HDR fx have evolved:

- ¬ separate catheter insertions for each HDR fraction
- ¬ a single insertion followed by 2-4 frs over 1-2 days

HDR-BT boost in high risk prostate cancer

- HDR –BT allows the delivery of very high BEDs.
- Multiple , single institutions have published studies using a wide range of fractionation and implant schedules and variable schedules of EBRT showing promise in bc and toxicity grade 3+,GU= up to 8%, GI=up to 4%.
- A mature not RCT monoinstitutional dose escalated study shows the treatment to be well tolerated with favorable clinical results (better LC, decreased b and c failures, decreased MTS).
- A prospective multiinstitutional trial resulted in acceptable levels of Aes.
- RCTs documented advantages from HDR-BT boost but vs not contemporary EBRT practices.

HDR-BT boost in high risk prostate cancer

- Overall treatment time of combined treatment varies generally btw 5-8 wks related to EBRT and BT regimens and timing.
- Crude rates of urethral strictures range btw 0-14% and incontinence rate is btw 0- 6.3%
- Data regarding dose volume histograms and or dosimetric predictors (specially for the urethra) have been less consistently reported.
- Lack of robust informations related to the impact on IPSS, QoL, sexual bother and function
- Quality assurance process is developing

Compararison of 3 radiotherapy modality on biochemical control and OS for the treatment of prostate cancer REVIEW , Pieters BR et al, ReO,2009

Materials and methods

A systematic search was performed resulting in 40 articles to be used. Data were extracted on biochemical control and overall survival at 3, 5, and 8 years and other time points mentioned in the articles.

Conclusion

The combination of external beam radiotherapy and HDR-BT results in a superior biochemical control and overall survival ….

Comment

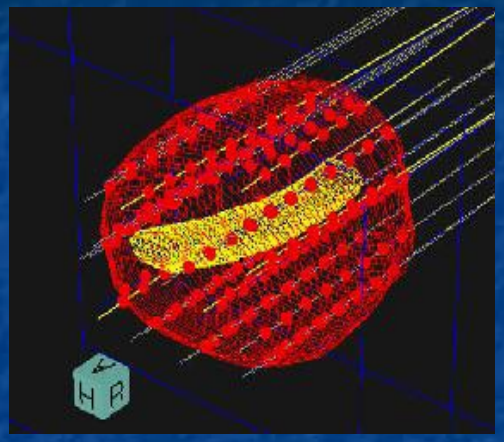
data from risks groups were not used

iPSA, cT, HT were not balanced

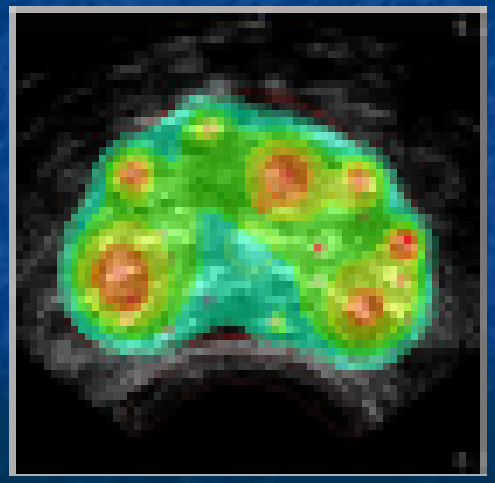
Different PSA relapse definition

HDR-BT in high risk prostate cancer

1. Volume evaluation (2-4 weeks before)
2. Intraoperative planning
3. Needles ± seeds implantation
4. TRUS / CT/ MRI-based planning
5. Treatment delivery



- Need of specific equipment
- Specialized multidisciplinary team
- Need of adequate learning curve
- Time consuming
- Costs ?



How to best deliver higher dose of Rt without significantly increasing normal tissue toxicities?

HDR-BT boost as alternative means of precise dose delivery

-Flexibility for dose intensity modulation and conformality

But importance of optimal seed position and dwell time/real time dose distribution for IMBT/IGBT

-No interfraction or intrafraction motion or set-up errors

But prostate edema and perineum swelling, damage due to implant itself, needle migration and catheter / gland movement btw frs

-Short period of treatment

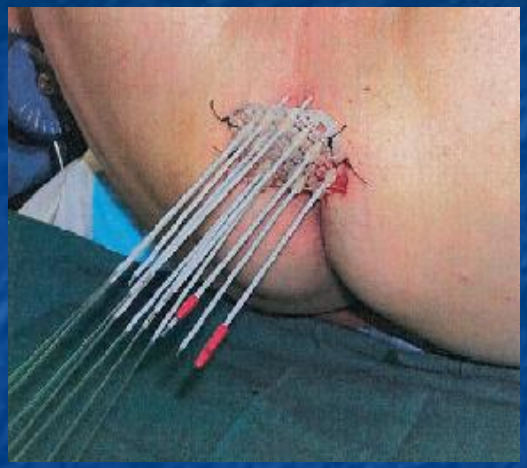
But overall treatment time may be 6-8 wks with hospital admission

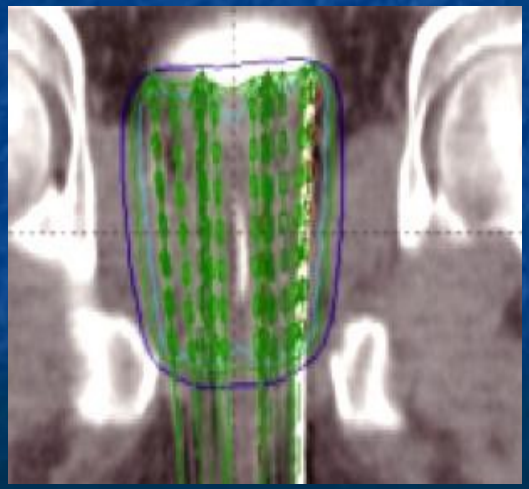
-Larger dose per fraction to increase therapeutic window
(improving control while limiting chronic toxicity)

But with larger dose/fraction may be disadvantageous for OARS if geometry is not optimized

Pt's point of you

- Hospital admission
- Invasive procedure
- Anhestesia
- Pain, analgesics
- Discomfort for lithotomy position,catheter, etc
- Toxixity (urethra)
- Impact of QoL?

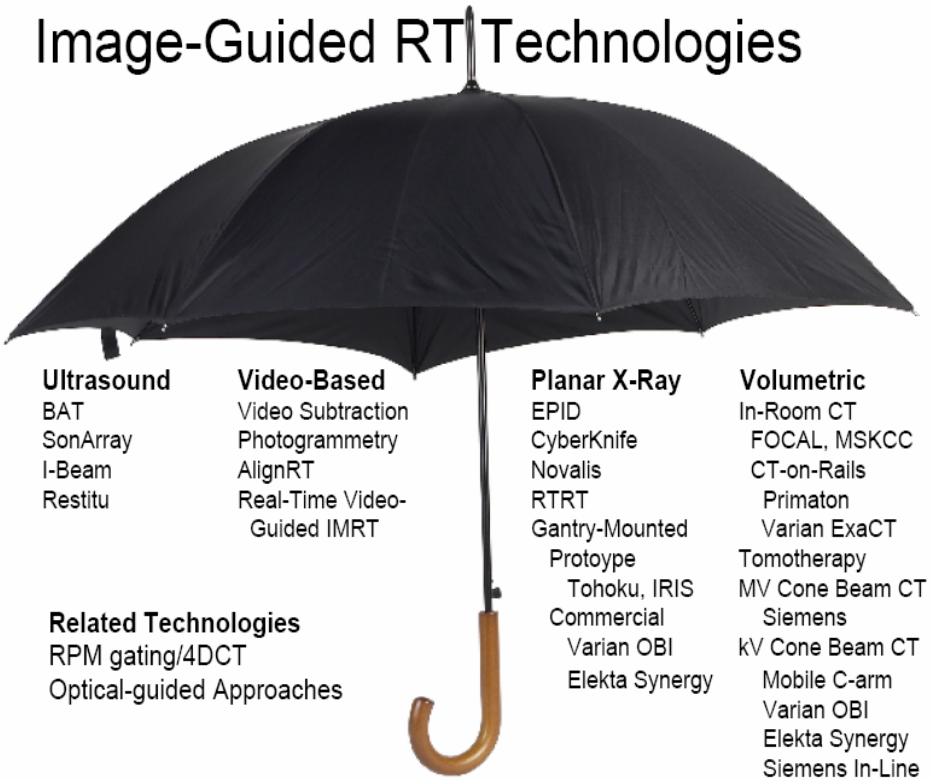




Is 2 always better than 1 ?

Role of counseling

Image-Guided RT Technologies



Ultrasound
BAT
SonArray
I-Beam
Restitu

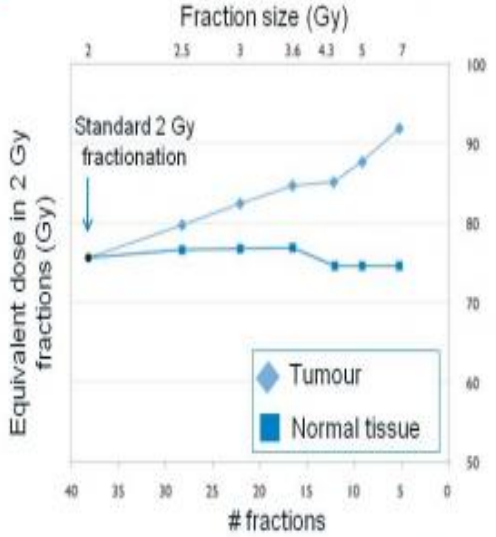
Video-Based
Video Subtraction
Photogrammetry
AlignRT
Real-Time Video-Guided IMRT

Related Technologies
RPM gating/4DCT
Optical-guided Approaches

Planar X-Ray
EPID
CyberKnife
Novalis
RTRT
Gantry-Mounted
Protoype
Tohoku, IRIS
Commercial
Varian OBI
Elekta Synergy

Volumetric
In-Room CT
FOCAL, MSKCC
CT-on-Rails
Primaton
Varian ExaCT
Tomotherapy
MV Cone Beam CT
Siemens
kV Cone Beam CT
Mobile C-arm
Varian OBI
Elekta Synergy
Siemens In-Line

Theoretic advantage of hypofractionation in PCa



» **Increasing** the **fraction size** (and **decreasing** the **number of fractions**) will translate in a better tumour control probability without increasing normal tissue toxicity

Adapted from Ritter M. Cancer J 2009; 15:1-6

IMRT - IGRT - Stereotassica
SIB - Frazionamenti alterati

RADIOTERAPIA ADATTATIVA

HYPOFRACTIONATED BOOST TO THE DOMINANT TUMOR REGION WITH INTENSITY MODULATED STEREOTACTIC RADIOTHERAPY FOR PROSTATE CANCER: A SEQUENTIAL DOSE ESCALATION PILOT STUDY

RAYMOND MIRALBELL, M.D.,*† MERITXELL MOLLÀ, M.D.,* MICHEL ROUZAUD, D.SC.,† ALBERTO HIDALGO, M.D.,‡ JOSÉ IGNACIO TOSCAS, M.D.,* JOAN LOZANO, M.D.,* SERGI SANZ, B.SC.,§ CARMEN ARES, M.D.,† SANDRA JORCANO, M.D.,* DOLORS LINERO, D.SC.,* AND LLUÍS ESCUDÉ, D.SC.*

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64 Gy/32 frs or 64,4 Gy/35 frs on P+VS -50.4 Gy/28 frs pelvis

IMRT boost: 2 frs w 5 up to 8 Gy

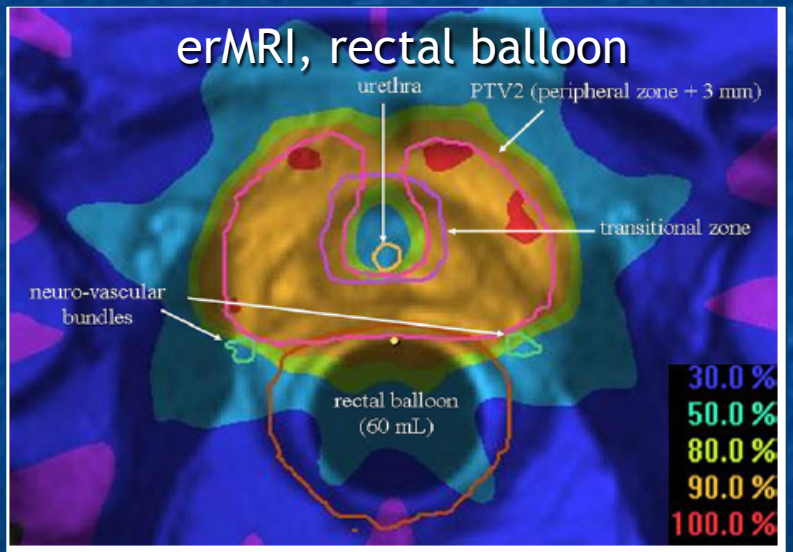


Fig. 1. Dose distribution in the axial plane of an endorectal magnetic resonance image through the center of CTV2 (boost volume limited to the prostatic peripheral zone or dominant tumor-bearing region). The urethra, prostatic transitional zone, neurovascular plexus, and the rectum with an inflated balloon are also displayed. Isodose contours are represented by different colour bands; corresponding values are displayed in the lower-right corner.

STEREOTACTIC BODY RADIOTHERAPY AS MONOTHERAPY OR POST–EXTERNAL BEAM RADIOTHERAPY BOOST FOR PROSTATE CANCER: TECHNIQUE, EARLY TOXICITY, AND PSA RESPONSE

SIAVASH JABBARI, M.D.,* VIVIAN K. WEINBERG, PH.D.,† TANIA KAPREALIAN, M.D.,* I-CHOW HSU, M.D.,* LIJUN MA, PH.D.,* CYNTHIA CHUANG, PH.D.,* MARTINA DESCOVICH, PH.D.,* STEPHEN SHIAO, M.D., PH.D.,* KATSUTO SHINOHARA, M.D.,† MACK ROACH, III, M.D.,*† AND ALEXANDER R. GOTTSCHALK, M.D.,PH.D.*

Departments of *Radiation Oncology, †Urology, and ‡Biostatistics and Computational Biology Core, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California

45-50.4 Gy/25-28 frs on whole pelvis with IMRT ; CK-SBRT boost: 19 Gy in 2 frs seeking to replicate HDR-BT's dosimetry

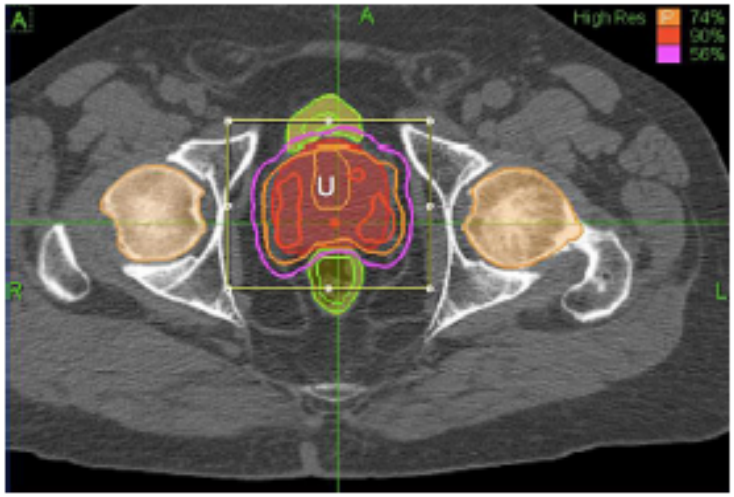


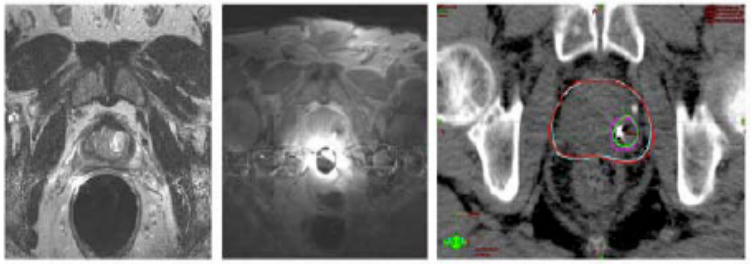
Fig. 3. Sample stereotactic body radiotherapy (SBRT) dosimetric plan. The dose delivered for SBRT boost was 19 Gy in 2 fractions prescribed to the 74% isodose line. The 90% isodose line represent 120% of the prescription dose (22.8 Gy), and the 56% isodose line represents 75% of the prescription dose (14.25 Gy). The urethra (U) was defined by T2 axial MRI images on a 3T scanner. The V75% for bladder and rectum was <2 cc. The V120% for the urethra was <10%.

IMRT BOOSTING TECHNIQUE

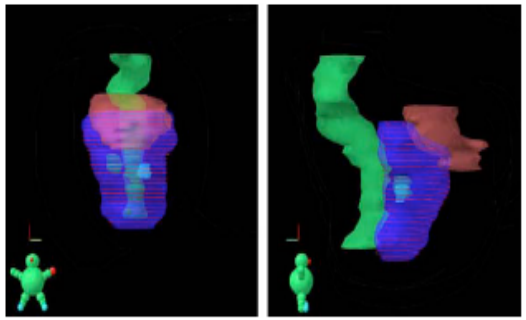
The DIL concept , the SIB technique

Simultaneous integrated boost of biopsy proven, MRI defined dominant intra-prostatic lesions to 95 Gray with IMRT: early results of a phase I NCI study

Singh Rad Oncol 2007 2 1-6



DCE MRI , guided biopsy and planning scan with fiducial



N=4

75.6Gy (42 F) to prostate with 94.5 Gy (SIB) to 2 DIL

INTENSITY-MODULATED RADIOTHERAPY AS PRIMARY THERAPY FOR PROSTATE CANCER: REPORT ON ACUTE TOXICITY AFTER DOSE ESCALATION WITH SIMULTANEOUS INTEGRATED BOOST TO INTRAPROSTATIC LESION

Fonteyne IJROBP 2008 72 799-807

- No. 230 2002-7
- Prostate Dose (median) 78Gy SIB to DIL 80 Gy
- DIL in 50%
- Gd 3 GI 0%
- Gd 3 GU 7%

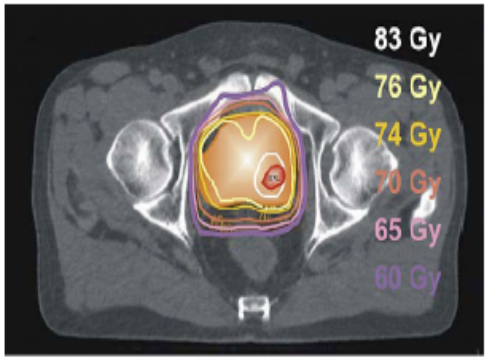


Fig. 2. Example of dose distribution with simultaneous integrated boost ≤83 Gy to intraprostatic lesion.

IMRT boost methods deliver substantially different physical dose distribution

Conclusions

- Dose escalation by combining EBRT with BT:

  - may have an important role for the radical treatment of high risk localised prostate cancer
  - provides optimal conformal radiation dose delivery
  - is an alternative method for dose-escalation with radiobiological (caution) and physical advantages but pts discomforts and need of specific equipement and espertise (but if you have , use it)
  - lack of high level of evidence BT boost is superior to EBRT
  - crucial role of counseling "… the **best** treatment choice is one made by an informed patient who is comfortable with, and committed to, **whichever he chooses**…"