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Brachytherapy in the Image-guided IMRT Era

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(Radiumhemmet, Stockholm: 1945)

Outline
BT in IG-IMRT Era

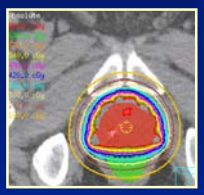
- Evolution of medical practices: a Darwinian struggle
- Brachytherapy (BT) vs IMRT
  - Geometric uncertainty
- The future: integrated BT-IMRT
- Scientific/Clinical Challenges

Dynamics of a Successful Therapeutic Modality

- 1910-1940s: BT is sole RT modality for giving curative doses to deep tumors
  - 1930s: 80,000 procedures/y. 100 Gy doses common
- Competitive Threats to BT: Example 1950s
  - Rigid Radium needles ⇒ radiation hazards and steep learning curve
  - Competition: MV EB and improved surgical techniques
  - Solution: manual afterloading, flexible catheters, and ^{192}Ir seeds
- Exploiting technological opportunity to address clinical needs ⇒ BT retains competitive edge
- Future competitor ??: Image-Guided IMRT

BT: High Doses with Acceptable Toxicity

- HDR BTx-EB Kiel-Beaumont-Seattle Experience
  - Intermediate risk prostate Ca
  - TRUS-guided HDR interstitial BTx
    - 2 x (9-11.5 Gy) to prostate
  - EB: 40-50 Gy whole pelvis

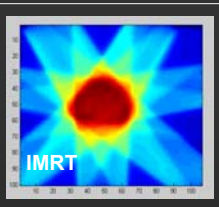


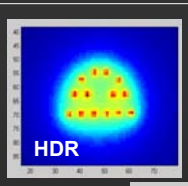
- Equivalent doses ($NTD_{1.8Gy}$) for $\alpha/\beta = 3$
  - Prostate: 90 – 116 Gy
  - Peripheral zone: 150 Gy
  - 5 year results: bNED = 88%, G3 toxicities = 3-4%
- Highest reported EB-only $NTD_{1.8Gy}$ = 86 Gy

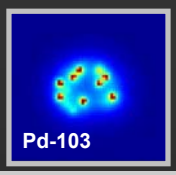
Brachytherapy (BT) vs. External Beam (EB)

- Observation: BT can deliver higher doses to CTV/GTV than EB for same toxicity level
- Possible Explanations
  - LDR = hyperfractionation ⇒ ⇑ normal tissue repair
  - BT is inherently more conformal than even best IMRT or 3DCRT
  - BT has superior geometric targeting accuracy: ⇓ PTV margin is needed to assure CTV coverage
  - BT central hotspots confer biological advantage

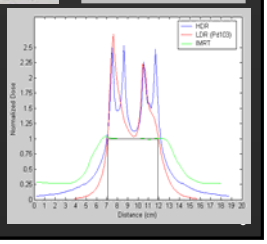
BTX vs. IMRT Transverse Plane Conformality







- Dose 1 cm outside CTV
  - IMRT: 57%
  - HDR: 37%
  - Pd-103: 25%
- IMRT: 5-fold more normal tissue receives dose >75% of prescribed dose



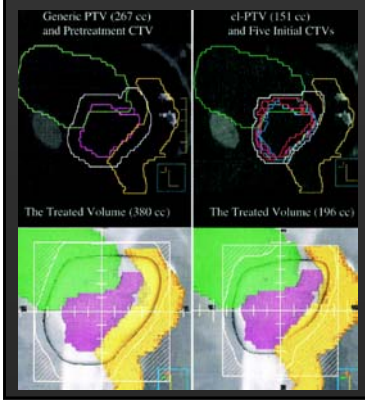
Why use BT in the IMRT era?

- IMRT can support dose conformality and normal tissue avoidance comparable to to BT
  - Noninvasive
  - Not limited to surgically accessible target volumes
  - Can treat extended target volumes
  - Better CTV dose homogeneity
  - Less deformation of pre-treatment anatomy
- If Image-Guided Adaptive Radiation Therapy (IGART) improves targeting accuracy, why use BT?

IMRT: Geometric Uncertainty

- IMRT Setup and internal tissue motion errors
  - Interfraction systematic: errors persisting during entire RT course
  - Interfraction Random: Fx-to-Fx fluctuations
  - Intrafraction motion: breathing
- Error magnitude
  - Prostate:
    - » $\sigma, \Sigma \approx$ 2-3 mm
    - » 25%-35% of patients have errors > 5 mm
    - » 11 mm PTV margins are needed to achieve adequate CTV coverage for 90% of patients
  - Cervical Cancer: 15 mm margins
  - NSCLC: > 20 mm margins

Adaptive Radiation Therapy: Yan et al.



- 5 Serial CT's during 1st week
- New PTV
- Single off-line correction for tissue motion & setup error
- Mean PTV reduction: 24%

Normal Tissue Sparing and Image-guided IMRT

- Prostate: PTV Margins required
  - Conventional RT: 11 mm
  - Offline setup correction: 9.3 mm
  - Offline correction: setup+organ motion: 7.5 mm
    - » Beaumont-style ART
  - Online setup 8.4 mm
  - Online setup + offline organ 6.0 mm
  - Online setup + organ motion 3-4 mm
- Other sites: cervix and lung require larger PTV margins: 15-20 mm

Permanent Prostate Implants

Planned (TRUS) vs delivered (Post Op CT) seed locations

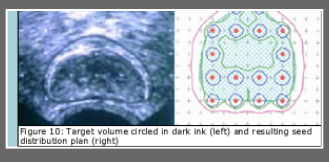
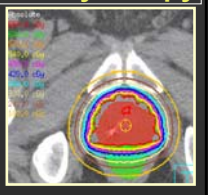


Figure 10: Target volume circled in dark ink (left) and resulting seed distribution plan (right)

- Available data (Roberson 97, Tascherau 99) $\Rightarrow \sigma \approx 3$ mm/axis
  - Systematic vs. random not clearly measured
  - Confounding factors: prostate edema and CT vs. TRUS discrepancies
- 3-4 mm random seed errors dose $\Rightarrow$ error < 5%
- HDR stainless steel needle delivery error ≈ 2-3 mm

HDR TRUS Guided Interstitial Brachytherapy



- Geometric uncertainty
  - Needles guided by intraoperative imaging, not external landmarks
  - Systematic needle offset unlikely
  - As tissue moves, sources move $\Rightarrow$ $\Sigma_{ME} \approx 0$
  - ICRU 58: PTV margins not recommended: PTV = CTV
- Largest uncertainty
  - TRUS probe removal & interfraction patient repositioning errors
  - Solution: image with CT and reoptimize before each fraction
  - Compensate for needle positioning error by introp optimization: Final planned dose ≈ HDR delivered dose

Single-Fx HDR vs. IMRT vs. IGART

- **Observation:** HDR BT can give far larger doses than IMRT for given level of complications
- **Explanatory hypothesis:** No PTV margin ⇒ bladder/rectal dose avoidance
- **Method:** Use BED and gEUD/EUD outcome models to compare equivalent treatments
  - IMRT with 10 mm margins: D_{98} = 9 x 2.2 Gy
  - Idealized IGART- no margins: D_{98} = 9 x 2.2 Gy
  - HDR with no margins: D_{98} = 1 x 9 Gy

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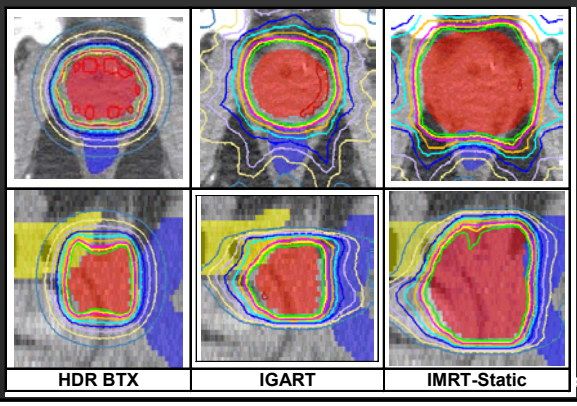
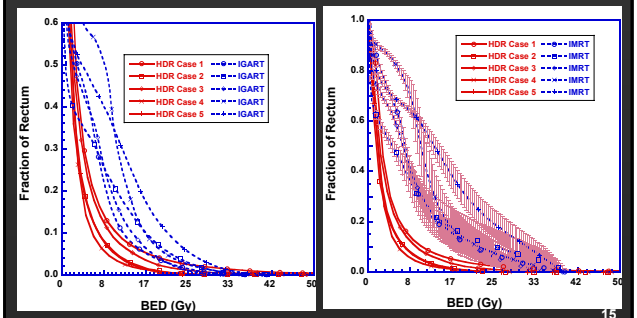
Case 2: Iso-BED (100% = prescribed)



Late Rectal BED-Volume Histograms
HDR vs. IGART and HDR vs IMRT-U



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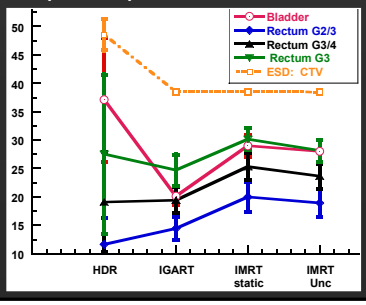
Mean gEUD and EUD

- HDR Tumor EUD: 26% Larger than IMRT or IGART
- G2/3 rectal (a = 4.4): HDR < IGART < IMRT
- G3/4 rectal (a = 8.3): HDR ≈ IGART < IMRT
- Bladder (a = 7.7): IGART< IMRT < HDR



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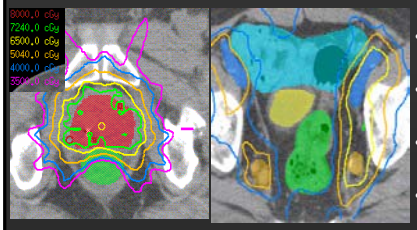
Integrated BT-IMRT

- HDR BT Therapeutic ratio > IMRT
  - Explanation: superior BT targeting accuracy ⇒ smaller margins
  - BT competitive with best achievable IGART
- Prostate: Combined IG-IMRT and IG-BT
  - IG-IMRT: Escalate dose to +/elective PLNs
  - BT: Escalate primary tumor dose
  - Escalated dose/fraction exploits low α/β ratio
  - Further gains: plan IMRT to compensate for HDR hot and cold spots
- Cervix: IG-IMRT to boost intracavitary BT GTV coldspots and to avoid BT normal tissue hotspots

VCU IMRT Dose Escalation protocol

Intermediate Risk Prostate Cancer



- 1 x 6 Gy HDR prostate only
- 28 IMRT Fx's to PLN and prostate
- Online EPID setup to Au markers
- 5 mm PTV margins

- CTV (Prostate + 5 mm): 61 Gy ($NTD_{1.8Gy}$ = 77 Gy)
- Elective PLN : 50 Gy ($NTD_{1.8Gy}$ = 50 Gy)
- 30 patients: No G2/3 toxicity observed yet

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Technical Challenges: Integrated BT-IMRT

- Few quantitative studies of BT geometric errors
  - Serial imaging, contour delineation, real-time planning
- Improved compensation for BT-induced organ deformation and tissue displacement
  - Validation/development of robust deformable image registration
- Planning issues
  - Accuracy of BED and other isoeffective doses to account for fractionation effects
  - Cumulative BED (IMRT + EB) planning and managing residual geometric uncertainty

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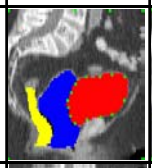
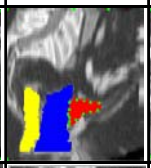
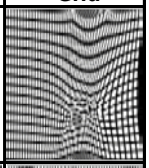
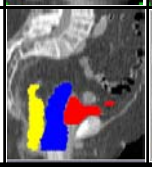
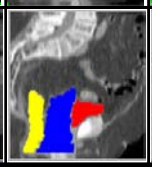
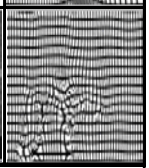
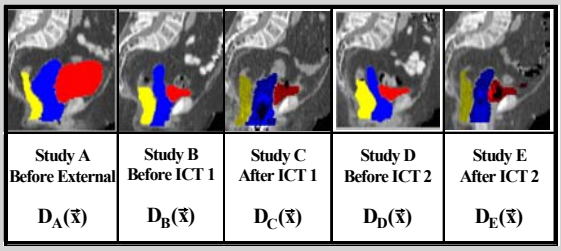
Results: Patient 2

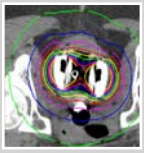
	Template T_i	Deformed T_i	Target T_C ICT 1	Deformed Grid
A to C				
E to C				

Dose Matrix Deformation

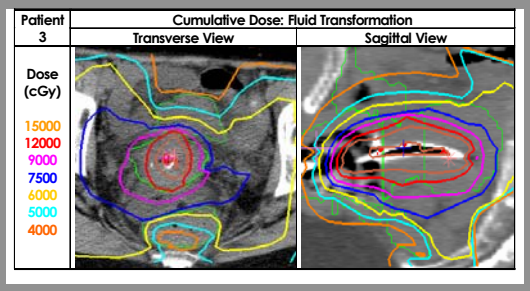


Study A Before External	Study B Before ICT 1	Study C After ICT 1	Study D Before ICT 2	Study E After ICT 2
$D_A(\vec{x})$	$D_B(\vec{x})$	$D_C(\vec{x})$	$D_D(\vec{x})$	$D_E(\vec{x})$

$$D_{tot}(\vec{x}) = D_C(\vec{x}) + \sum_{i \in \{A,B,D,E\}} D_i\left(\vec{h}_{iC}(\vec{x})\right)$$



Patient 3: Cumulative Dose Fluid Transform



Linear-Quadratic Model

Biologically Effective Dose =

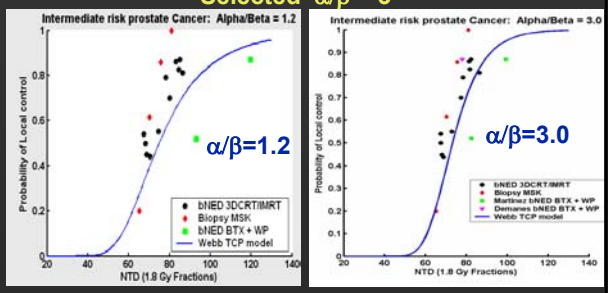
$$BED = D_{tot}\left(1 + \frac{d}{(\alpha/\beta)}\right)$$

D_{tot} = Physical dose, d = fraction size

- (α/β) thought to be 1.2 – 3 Gy
  - Fowler/Brenner: permanent implants vs. 3DCRT outcome data
  - Brenner/Thames: Martinez HDR-WP outcome data
    - » 23 x 2 Gy WP + BTX from 3 x 5.5 Gy to 2 x 11.5 Gy
- LQ permits addition of BTx + IMRT

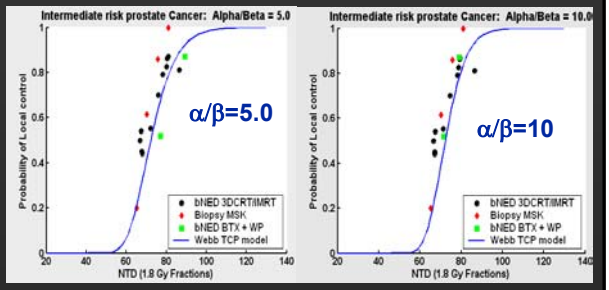
bNED Dose Response vs α/β

Selected α/β = 3



- 5 Year bNED rates
  - BT: Martinez (IJROBP 53: 316) Demanes (IJROBP 61: 1306);
  - 3D CRT: Fowler (IJROBP 50: 1021); Levegrun/Bx MSK: (IJROBP 51 1064); Zelefsky/86 Gy

bNED Dose Response vs α/β



- lower α/β values ⇒
  - ⇑ discordance between IMRT+BTx and IMRT trials
  - ⇑ relative importance of BTx relative to IMRT
- 1.5-3.0 α/β range ⇒ 10% uncertainty in total NTD

Conclusions

- BT: important therapeutic tool for 100 years
  - Competing modalities: Market favors those who perform basic research to retain competitive advantage
- Image-guided IMRT vs HDR BT PTV margins
  - Real-time replanning on Tx position CT images: better than feasible IGART??
- Solutions
  - Measure geometric uncertainty of BT vs EB
  - Develop BT techniques that exploit ⇓ uncertainty
  - Exploit complementary strengths of BT and IGART via integrated planning