Brachytherapy in the Image-guided IMRT Era

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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/yr. 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 Iridium 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_{1.8 Gy}) 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_{1.8 Gy} = 86 Gy

(Radiumhemmet, Stockholm: 1945)
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 conformity and normal tissue avoidance comparable 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:
    » σ, Σ = 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

- 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 $\approx$ 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 $\Rightarrow \Sigma_{\text{MC}} \approx 0$
  - 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 $\approx$ 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: $D_{98} = 9 \times 2.2 \text{ Gy}$
  - Idealized IGART- no margins: $D_{98} = 9 \times 2.2 \text{ Gy}$
  - HDR with no margins: $D_{98} = 1 \times 9 \text{ Gy}$

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

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

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 $\approx$ IGART < IMRT
- Bladder ($a = 7.7$): IGART < IMRT < HDR
Conclusions: Prostate

• HDR BTx + IMRT: improved therapeutic ratio
  – BTx: smaller geometric uncertainty than current IMRT
  – BTx: may have therapeutic ratio competitive with best practical IGART

• Current clinical data: BTx + EB tolerable dose escalation much larger than IMRT alone

• Problems
  – LQ parameter uncertainty ⇒ 10% uncertainty in equivalent IMRT dose escalation
  – Deformable image registration needed to reduce registration uncertainties to 2 mm

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

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

Results: Patient 2

<table>
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<th>Template T_i</th>
<th>Deformed T_i</th>
<th>Target T_c ICT 1</th>
<th>Deformed Grid</th>
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<tr>
<td>A to C</td>
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<td>E to C</td>
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**Dose Matrix Deformation**

\[
D_{\text{tot}}(x) = D_C(x) + \sum_{i \in \{A, B, D, E\}} D_i \left( \tilde{R}_{IC}(x) \right)
\]

**Linear-Quadratic Model**

Biologically Effective Dose =

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

- \((\alpha/\beta)\) 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

**Patient 3: Cumulative Dose Fluid Transform**

**bNED Dose Response vs \(\alpha/\beta\)**

- Selected \(\alpha/\beta = 3\)

- 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); Zaloudek/Bx Gy
**bNED Dose Response vs $\alpha/\beta$**

- lower $\alpha/\beta$ values ⇒
  - ↑ discordance between IMRT+BTx and IMRT trials
  - ↑ relative importance of BTx relative to IMRT
- 1.5-3.0 $\alpha/\beta$ 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