L’IGRT
IN TOMOTERAPIA:
Aspetti Clinici e Fisici

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Istituto Scientifico S. Raffaele- Milano

Napoli, 8-9 Giugno 2007
Reduce the uncertainty of microscopic extension

Precise localization of the tumor and/or target volume and sensitive structures

Reduce the uncertainty in the set-up and identify and reduce organ motion

**IMAGING**

Reduction of safety margins

REDUCTION of COLLATERAL DAMAGE to OAR

**IGRT**

High selectivity in radiation dose administration

INCREASE of RADIATION DOSE and DOSE per FRACTION

**IMPROVEMENT IN LOCAL CONTROL**
Terminology

**Image-Guided Radiation Therapy (IGRT)**

Use images to position patients

- Portal images
- EPID
- KV X Rays
- Ultrasound
- CT-based

**Image-Guided Radiation Therapy (IGRT) with TomoTherapy**

- Megavoltage CT (MVCT) based
Helical tomotherapy: a dedicated image-guided IMRT system

TomoTherapy Hi*Art II

from: W. Kalender, Computed Tomography: Fundamentals, System Technology, Image Quality, Applications
Patient Image: Prostate

Diagnostic (Kv) CT  

Tomotherapy (MV) CT
Patient Image: Prostate

Diagnostic (Kv) CT

Tomotherapy (MV) CT
Patient Image: Head and Neck

Diagnostic (Kv) CT  
Tomotherapy (MV) CT
Dental Filling

TomoCT  kVCT
MVCT Imaging Characteristics

- Uniformity is comparable to diagnostic CT scanners while noise is worse
- MVCT numbers are consistent – suitable for dose calculations
- Spatial resolution using 512x512 matrix is ~1.5 mm
- Dose: ~1.1 cGy for 5-mm slice width and pitch of 1; dose decreases with “looser” pitch
- Energy ~ 3.48 MV
  - Slightly softer than treatment beam → smaller spot size, improved penumbra & contrast resolution

- **Image Quality is acceptable for patient alignment and is also acceptable for delineation of many soft tissue structures.**

Meeks et al., *Med Phys* 32(8):2673, 2005
IMAGE GUIDED RADIOTHERAPY (IGRT)

TARGET LOCALIZATION

CLINICAL APPLICATIONS
Effect of Rectal Distention
Interfraction Variability

Simulation CT

Intraprostatic markers

Prostate/Rectum Interface
Effect of Rectal Distention

Interfraction Variability

Megavoltage CT at treatment
Image Registration CT to TomoCT
Coronal ALIGNED
Transverse INITIAL
ANATOMIC VARIATIONS: clinical impact

MDACC study

Biochemical Control by Rectal Distension
For Intermediate Risk Patients:

- CSA ≤ 11.2 cm²
  - 28% at 5 years
  - = 16 Gy

- CSA > 11.2 cm²

Biochemical Control by Rectal Distension
For High Risk Patients:

- CSA ≤ 11.2 cm²
  - 34% at 5 years
  - = 18 Gy

- CSA > 11.2 cm²

DE CREVOISIER JROBP 2005-2007
DAILY DOSE RECALCULATION

Challenge:
Cumulate doses in an anatomically meaningful way

Rectal daily DVHs from recalculation on daily MV CTs

Treatment Plan DVH

Daily DVHs

Langen et al. ASTRO 2004.
MV-CT : RECTAL DISTENTION
MV-CT : RECTAL EVACUATION
60 pts median follow up: 25 months (15-37 m)

ACUTE TOXICITY RESULTS

<table>
<thead>
<tr>
<th>RTOG</th>
<th>GU</th>
<th>LGI</th>
<th>UGI 29/60</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>25</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>G1</td>
<td>21</td>
<td>18</td>
<td>12(5)</td>
</tr>
<tr>
<td>G2</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
60 pts median follow up: 25 months (22-37 months)

**LATE TOXICITY RESULTS**

<table>
<thead>
<tr>
<th>RTOG</th>
<th>GU</th>
<th>LGI</th>
<th>UGI 29/60</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>35</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>G1</td>
<td>15</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>G2</td>
<td>7</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>G3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- GU
- LGI (rectum)
- UGI

The chart shows the distribution of toxicity levels G0, G1, G2, and G3 for GU, LGI, and UGI.
Prostate Adjuvant treatment
RECTAL ACUTE TOXICITY
Comparison TOMO vs 3DCRT
Prostate Adjuvant treatment

GI LATE TOXICITY *
COMPARISON TOMO vs 3DCRT

*cumulative

3DCRT – 153 pts
TOMO – 50 pts
Clinical Applications: Head and Neck
Type of alignment: bone
basale

Inizio RT
<table>
<thead>
<tr>
<th>Protocol</th>
<th>IG%</th>
<th>Error &gt;3 mm</th>
<th>Error &gt;5 mm</th>
<th>Error &gt;10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: No imaging</td>
<td>0%</td>
<td>72%±3%</td>
<td>37%±2%</td>
<td>4%±1%</td>
</tr>
<tr>
<td>B1: Initial fraction only</td>
<td>3%</td>
<td>79%±3%</td>
<td>47%±2%</td>
<td>8%±1%</td>
</tr>
<tr>
<td>B3: Mean of initial three fractions</td>
<td>9%</td>
<td>63%±3%</td>
<td>31%±2%</td>
<td>1%±0.5%</td>
</tr>
<tr>
<td>B5: Mean of initial five fractions</td>
<td>15%</td>
<td>53%±3%</td>
<td>26%±2%</td>
<td>1%±0.5%</td>
</tr>
<tr>
<td>B7: Mean of initial seven fractions</td>
<td>21%</td>
<td>33%±3%</td>
<td>26%±2%</td>
<td>1%±0.5%</td>
</tr>
<tr>
<td>C: Weekly imaging, 3-mm threshold</td>
<td>20%</td>
<td>60%±3%</td>
<td>31%±2%</td>
<td>2%±0.5%</td>
</tr>
<tr>
<td>D: First five fractions + weekly imaging, patient-specific threshold</td>
<td>31%</td>
<td>50%±2%</td>
<td>27%±2%</td>
<td>4%±1%</td>
</tr>
<tr>
<td>E: Imaging every other fraction, running mean</td>
<td>50%</td>
<td>29%±2%</td>
<td>11%±1%</td>
<td>0.5%±0.3%</td>
</tr>
</tbody>
</table>

Frequencies of residual errors observed with different protocols exceeding 3, 5, and 10 mm

“Protocols that use IG for 0–50% of all treatments have three-dimensional residual setup errors of 5 mm in 47–11% of all treatment. The acceptability of the reduced setup accuracy and precision that is caused by infrequent use of IG depends on treatment margins and the proximity of sensitive structures. If target structures are in close proximity to critical sensitive structures, IG should be used daily”.

Tomotherapy toxicity profile

Acute toxicity in 45 pts

Late toxicity in 25 pts > 6 mts f-up
Clinical Applications: Lung
Type of alignment: bone, trachoea, tumor
34.2 Gy

TC basale

MV-CT
GA, 66 yrs NSCLC

Baseline

PET/CT

MVCT/kVCT

Tomotherapy plan

50 Gy

HSR Milan
GA, 66 yrs NSCLC

50 Gy

MVCT/kVCT

60 Gy

Tomotherapy plan

Initial plan
Riposizionamento manuale:

criteri

reperi ossei

isodosi

HSR, Milano
VOLUMI SULLE 6 MV-CTs * CONSECUTIVE

MV-CT 1  MV-CT 2  MV-CT 3

MV-CT 4  MV-CT 5  MV-CT 6

* Finestra per la visualizzazione del parenchima
COMPARAZIONE TRA I VOLUMI

\[ \Delta \left( \Sigma \text{MV-CT} / 4D-\text{ITV} \right) \]

\[ \Delta \left( \Sigma \text{MV-CT} / 4D-\text{PTV} \right) \]
## RISULTATI

<table>
<thead>
<tr>
<th>Lesione</th>
<th>MEDIA±DS</th>
<th>Σ MVCT</th>
<th>4D ITV</th>
<th>4D PTV</th>
<th>Δ(Σ MVCT/ITV)</th>
<th>Δ(Σ MVCT/PTV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.7±1.68</td>
<td>33.67</td>
<td>37.29</td>
<td>83.59</td>
<td>4.55</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>3.13±0.38</td>
<td>5.70</td>
<td>3.63</td>
<td>14.37</td>
<td>2.70</td>
<td>0.45</td>
</tr>
<tr>
<td>3</td>
<td>1.76±0.76</td>
<td>4.48</td>
<td>2.79</td>
<td>14.82</td>
<td>2.34</td>
<td>0.66</td>
</tr>
<tr>
<td>4</td>
<td>10.17±1.88</td>
<td>17.65</td>
<td>11.52</td>
<td>29.96</td>
<td>7.16</td>
<td>0.19</td>
</tr>
<tr>
<td>5</td>
<td>0.87±0.05</td>
<td>2.16</td>
<td>2.19</td>
<td>10.94</td>
<td>0.78</td>
<td>0.07</td>
</tr>
<tr>
<td>6</td>
<td>6.28±1.41</td>
<td>15.28</td>
<td>12.95</td>
<td>33.74</td>
<td>6.04</td>
<td>0.55</td>
</tr>
<tr>
<td>7</td>
<td>2.10±0.36</td>
<td>3.13</td>
<td>3.13</td>
<td>14.18</td>
<td>1.43</td>
<td>0.07</td>
</tr>
<tr>
<td>8</td>
<td>1.56±0.5</td>
<td>3.27</td>
<td>5.55</td>
<td>21.66</td>
<td>0.42</td>
<td>0.00</td>
</tr>
<tr>
<td>9</td>
<td>5.62±1.72</td>
<td>9.54</td>
<td>15.51</td>
<td>43.66</td>
<td>1.18</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>2.81±0.34</td>
<td>6.32</td>
<td>8.76</td>
<td>28.13</td>
<td>2.02</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>MEDIA</td>
<td>10.12</td>
<td>9.88</td>
<td>29.51</td>
<td>2.86</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>DS</td>
<td>9.79</td>
<td>11.81</td>
<td>21.68</td>
<td>2.30</td>
<td>0.26</td>
</tr>
</tbody>
</table>
CONCLUSIONI

• Buona riproducibilità tra Σ MV-CT e 4D-PTV

• La maggiore discordanza tra Σ MV-CT e 4D-ITV potrebbe essere dovuta a:
  - al tipo di coregistrazione semiautomatico
  - al differente spessore delle slices MV-CT e 4D-PET/TC
  - al diverso potere di risoluzione delle immagini MV-CT rispetto a quelle 4D-PET/TC
  - alla variabilità inter/intra-osservatore
  - alle impostazioni di visualizzazione utilizzate

• Sono necessari ulteriori studi per validare questi dati e la relativa metodologia di confronto delle immagini.
A two step procedure:
- a fully automatic registration based on bony anatomy
- matching adjusted through direct visualization (overlapping of the 12th costo-vertebral joints and of inter vertebral spaces; aorta, vena cava, and the origins of their main vessels, etc)
Difference between “bone” and “operator” matching

- 12Pts, 180 daily MVCT
- For the three main axes, the deviation between bone matching and the final direct visualization

<table>
<thead>
<tr>
<th></th>
<th>LR</th>
<th>CC</th>
<th>AP</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3 mm</td>
<td>6.8%</td>
<td>9.6%</td>
<td>3.4%</td>
<td>19.2%</td>
</tr>
<tr>
<td>≥ 5 mm</td>
<td>3.4%</td>
<td>4.5%</td>
<td>2.3%</td>
<td>9.0%</td>
</tr>
<tr>
<td>≥ 7 mm</td>
<td>2.3%</td>
<td>4.0%</td>
<td>1.1%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Max shift</td>
<td>10mm</td>
<td>7mm</td>
<td>5mm</td>
<td>13mm</td>
</tr>
</tbody>
</table>
Potential New Clinical Opportunities:

Re-treatment for patients not eligible for radiation therapy before TomoTherapy due to cord tolerance
Prostate TOMO: Image-guidance
Image guidance through MVCT (TOMOSIB)

- On-line daily correction, normal mode
- No margin reduction compared to 3DCRT (8mm/8mm/10mm for LR/AP/CC)
- Two step matching: 1) automatic bone matching: registration of data (set-up error); 2) fine adjustment by the physician, based on direct visualization of the prostate: registration of data (organ motion)
Rectal emptying procedures: pre-MVCT

- Variable rectal filling is the main cause of prostate motion (Van Herk 2001)
- Rectum full at the planning scan is a strong predictor of lack of LC due to geographical miss (De Crevoisier 2005, Heemsbergen 2007)

- Patients instructed to emptying the rectum (rectal enema)
- Rescan planning CT if rectum full
Emptying procedures: post-MVCT

- In case of large rectum, there is the possibility of significant deformation of prostate and seminal vesicles.
- In this case, the assessment of the shift may be uncertain, due to different impact on SV, caudal, central, cranial portions of the prostate.

- After MVCT, in case of very large rectum, the physician may operate procedures to emptying the rectum (rectal catheter and/or sending the patient to toilet).
- Second MVCT to verify the effectiveness of the procedure and then treat.
Patients data analysis
(Fiorino et al. IJROBP 2008)

• 21 low risk pts (Tomo SIB protocols, no pelvis)
• Data of 522 fractions available
• Bone matching (BM) data
• Direct visualization (DV) adjustment: analysis of the differences between DV and BM
• Analysis of impact of post-MVCT procedures (17/21 pts, 410 fractions)
Example of postMVCT emptying procedure
# Large shifts (PA direction)

<table>
<thead>
<tr>
<th>Without post-MVCT procedures</th>
<th>Deviations from</th>
<th>≥3 mm 20/410 (4.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone matching</td>
<td>≥ 5 mm 9/410 (2.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 7 mm 3/410 (0.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>With post-MVCT procedures</th>
<th>Deviations from</th>
<th>≥3 mm 11/410 (2.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone matching</td>
<td>≥ 5 mm 3/410 (0.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 7 mm 0/410 (0.0%)</td>
</tr>
</tbody>
</table>
## Prostate motion relative to bone match

<table>
<thead>
<tr>
<th></th>
<th>X(mm)-LL</th>
<th>Y(mm)-CC</th>
<th>Z(mm)-AP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Diff</strong></td>
<td>0.01</td>
<td>-0.08</td>
<td>-0.20</td>
</tr>
<tr>
<td><strong>Systematic (1SD)</strong></td>
<td>0.10</td>
<td>0.20</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Random (1SD)</strong></td>
<td>0.40</td>
<td>0.60</td>
<td>1.30</td>
</tr>
</tbody>
</table>

**Without post-MVCT procedures**

<table>
<thead>
<tr>
<th></th>
<th>X(mm)-LL</th>
<th>Y(mm)-CC</th>
<th>Z(mm)-AP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Diff</strong></td>
<td>0.02</td>
<td>-0.08</td>
<td>-0.06</td>
</tr>
<tr>
<td><strong>Systematic (1SD)</strong></td>
<td>0.10</td>
<td>0.20</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Random (1SD)</strong></td>
<td>0.42</td>
<td>0.60</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**With post-MVCT procedures**

DON'T USE (ONLY) THESE VALUES FOR CALCULATING MARGINS !!!!!!!
Uncertainty in prostate localization

- Automatic Bone matching accuracy
- Consistency in direct prostate visualization among different operators
- Direct prostate visualization vs contour-based or markers
Automatic bone match accuracy

Scan Acquisition: KVCT: 3mm; MVCT: Normal (z= 4 mm) Planned Shift: 10 mm → 1 mm

<table>
<thead>
<tr>
<th>Measured vs Applied shift</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>0.6 ± 0.3 mm</td>
</tr>
<tr>
<td>y</td>
<td>0.8 ± 0.6 mm</td>
</tr>
<tr>
<td>z</td>
<td>0.8 ± 0.5 mm</td>
</tr>
</tbody>
</table>

3D Distance between markers

1.3 ± 1.2 mm (0 - 4mm)

Phantom Study
Maggiulli et al
ESTRO 2006
Inter-observer variability of direct prostate visualization

- 7 observers routinely performing “prostate match”
- 10 sample MVCTs of 5 patients
- Blind match (bone before, direct visualization adjustment after)

<table>
<thead>
<tr>
<th></th>
<th>mean (max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD (LL) mm</td>
<td>0.29 (max 0.6)</td>
</tr>
<tr>
<td>SD (CC) mm</td>
<td>0.48 (max 1.1)</td>
</tr>
<tr>
<td>SD (PA) mm</td>
<td>0.78 (max 1.6)</td>
</tr>
<tr>
<td>SD (degree)</td>
<td>0.08 (max 0.3)</td>
</tr>
</tbody>
</table>

Fiorino et al. IJROBP 2008
Direct visualization vs markers vs contour based

• Prostate better visualized on axial MVCT

• More accurate shift assessment in PA and LR direction compared to CC

• A posteriori contour-based match introduces “large” drawing uncertainties, especially at the cranial and caudal edges (Song 2006, Langen 2006)
  
  - Ratios of average P and SV volumes of 1.1 and 1.2 respectively.
  - On average the local delineation variability (interobserver and intraobserver) in terms of standard deviation increased by 0.32 cm. from KVCT to MVCT

  - Largest increase in target localization uncertainty is in the Y direction (CC) that also exhibits the greatest prostate motion

• Direct visualization reported to be quite consistent with marker-based assessment when physicians match the images (Langen 2006)
Direct visualization vs intra-prostatic calcifications (IPC)

- 20 MVCT of 5 pts with IPC: blinded, single observer DV match vs. IPC match

- **DV vs intra-prostatic calcifications match**: underestimate of DV if shift < 3 mm

- For PA direction:
  \[ \Delta_{(IPC-DV)} = 1.2 \text{ mm (SD =1.2 mm)} \]
Some take-home message

- Rectal emptying procedures (also without IGRT!) drastically reduces the impact of prostate motion.

- Be careful with other uncertainties (intrinsic limits of your IGRT system, intra-fraction motion, contouring, shape deformation...). "Safe" margins: 8-10 mm without IGRT; 5-6 mm with daily IGRT !!!!!!!!!!!
Adaptive Radiation Therapy (ART):
• Use information from images to change subsequent treatments
  - Change margin based on observed setup/organ motion
  - Use images to evaluate dosimetry (dose-guided, dose compensation…)

Adaptive Radiation Therapy (ART) with TomoTherapy:
• Using MVCT images to evaluate dosimetry on daily basis
Adaptive Radiation Therapy (ART) with TomoTherapy

Acquire MVCT

↓

Recalculate dose distribution on MVCT

↓

Add dose distribution to calculate cumulative dose

↓

Compare with plan

↓

Adapt plan
DVH Recalculation

Plan DVH

39 “true” DVHs
PET/CT PLANNED “ADAPTIVE” TOMOTHERAPY

Baseline  
50 Gy  
4 weeks post-TT

TT plan 1  
TT plan 2

HSR Milan
10 patients with NSCLC, treated with Helical Tomotherapy.

Average 27 scans per patient.

Average 1.2% shrinkage per day:
Range 0.6-2.3% shrinkage per day.

kVCT vs. end-of-treatment MVCT
Dosimetric consequence?
Observation of tumor regression

Observation of parotid shrinkage and migration

Barker et al., IJROBP, 59, pp 960, 2004
ADAPTIVE RADIOTHERAPY
CLINICAL STRATEGY?

**Off-line**
- Sim / Plan
- Image Treatment
- Patient leaves Off-line new plan
- New Treatment
- Next fraction

**On-line**
- Sim / Plan
- Image Treatment
- Patient stays On-line new plan
- New Treatment
- Same fraction

FREQUENCY?
- Daily?
- Weekly?
- Daily first week?
- Dose trigger points?
CONCLUSION

• IMRT is an advanced form of conformal radiotherapy permitting the safe delivery of effective radiation doses, improving cure rates and limiting toxicity

• IGRT includes a multitude of imaging modalities that need to be evaluated individually

• The advent of MVCT imaging in radiotherapy departments allows the localization, verification and positioning of the patient with greater confidence

• CT based solutions provide the most anatomic information, and allows dose guided radiotherapy and ultimately “true” adaptive radiotherapy

• Ultimate solution for motion awaits the development of real time imaging and treatment delivery