Image-Guided and Adaptive Radiation Therapy

Perspectives

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IGRT Today

Myriad of in-room technologies focusing on improving setup and target localization

Four major categories based on imaging approach
– Video
– Ultrasound
– Planar
– Volumetric
Image-Guided RT Technologies

Ultrasound
- BAT
- SonArray
- I-Beam
- Restitu

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

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

Volumetric
- In-Room CT
- FOCAL, CT-on-Rails
- Primaton
- Varian ExaCT
- Tomotherapy
- MV Cone Beam CT
- kV Cone Beam CT
- MR-Cobalt
- MR-Linac

Related Technologies
- RPM gating/4DCT
- Optical-guided Approaches
- Calypso
Not New

Cobalt-60 unit with in-room kV imaging
Karolinska University (1957)
Integrated Cobalt-kV imaging unit
Princess Margaret Hospital (1959)

Integrated Cobalt-kV imaging unit
NKI Amsterdam (1960)
Early IGRT Technologies

“Patient Repositioning and Motion Detection Using a Video Cancellation System”

Connor WG, Boone ML, Veomett R, Hicks J, Miller RC, Mayer E, Sheeley N.

International Journal Radiation Oncology Biology Physics
1:147:1975
Other Modalities

- Subsequently both ultrasound and planar imaging techniques (EPID)
- More recently volumetric approaches
In-Room IGRT Modalities Today
Makes one go absolutely crazy....
1600 radiation oncologists surveyed

Great majority (94%) use some form of in-room IGRT in their patients

Majority use it only infrequently or rarely

Predominantly prostate, head/neck, CNS and lung

Simpson et al. Cancer 2010;116;3953
## Table 3. Proportions of Radiation Oncologists Using In-Room Image-Guided Radiation Therapy to Treat Various Disease Sites

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>No. of Users (% of All Users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary</td>
<td>328 (91.1)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>267 (74.2)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>259 (71.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>241 (66.9)</td>
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<tr>
<td>Gastrointestinal</td>
<td>216 (60)</td>
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<tr>
<td>Gynecologic</td>
<td>209 (58.1)</td>
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<tr>
<td>Palliative</td>
<td>164 (45.5)</td>
</tr>
<tr>
<td>Breast</td>
<td>160 (44.4)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>144 (40)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>86 (23.9)</td>
</tr>
</tbody>
</table>

Simpson et al. Cancer 2010;116;3953
Simpson et al. Cancer 2010;116;3953
Cumulative Adoption

Simpson et al. Cancer 2010;116;3953
Concept of IGRT is actually much broader

Use of modern imaging modalities, especially those incorporating functional or biological information, to augment target delineation
IGRT

Variety of sophisticated imaging approaches have used to augment target delineation

Most attention focused on Positron Emission Tomography (PET)

Also Magnetic Resonance Imaging (MRI), functional MRI (fMRI), MR Spectroscopy (MRS), and Single Photon Emission Computed Tomography (SPECT)
Image-Guided Treatment Planning

- Increasing interest in using PET and MRI techniques to improve how RT is planned
- Improves our ability to accurately target the tumor

Leong et al. Radiother Oncol 2006;78:254
5 Prostate Cancer Pts
MR Spectroscopy (MRS) $[^1\text{H-}\text{Spectroscopy}]$
Feasibility of identifying intraprostatic lesions
Safely dose escalate to 90 Gy
80 low-intermediate risk prostate cancer pts
Prostascint-guided brachytherapy
Regions of ↑uptake escalated to 150%
144 Gy \(^{125}\text{I}\) and 115 Gy \(^{103}\text{Pd}\)
4-year biochemical FFS 97.4%
T2* Pulse Echo MRI
“Fat Fraction”

Used to differentiate between red and yellow marrow

Loren Mell MD
ASCO Young Investigator Award
1600 radiation oncologists surveyed

Great majority (95%) have used advanced imaging to augment targeting of tumor

Majority use it only infrequently or rarely

Predominantly PET (76%) and MRI (72%)

Predominantly lung, brain and head/neck tumors

Simpson et al. JACR 2009;6:876
### Table 3. Prevalence of image-guided target delineation use by disease site

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<thead>
<tr>
<th>Disease Site</th>
<th>Number of Users (% of All Users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>286 (79.0)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>289 (79.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>72 (19.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>302 (83.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>193 (53.3)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>159 (43.9)</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>166 (45.9)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>52 (14.4)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>203 (56.1)</td>
</tr>
<tr>
<td>Palliative</td>
<td>94 (26.0)</td>
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</tbody>
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Simpson et al. JACR 2009;6:876
IGRT Survey

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Simpson et al. JACR 2009;6:876
IGRT of Tomorrow

- Will broader even further to include image guided adaptation
- Adapt to changes in the tumor (and patient) detected by imaging during the treatment
- Transform the RT process from a static to a dynamic process
Adapt to What Changes?

Morphologic
– Changes in size and/or shape of tumors and normal tissues

Functional
– Changes in physiology and biology
Adaptive IGRT

- Morphologic changes are particularly interesting

- Significant impact on the treatment plan
  - $\uparrow$ tumor size $\rightarrow$ $\downarrow$ target coverage $\rightarrow$ $\downarrow$ LC
  - $\downarrow$ tumor size $\rightarrow$ $\uparrow$ normal tissue dose $\rightarrow$ $\uparrow$ toxicity
  - $\Delta$ shape $\rightarrow$ $\downarrow$ target coverage and $\uparrow$ normal tissue dose $\rightarrow$ $\uparrow$ toxicity and $\downarrow$ LC

- Adapting to changes may allow us to alter our dose up and/or down
Morphologic Changes

And such changes are potentially detected with novel in-room imaging (MVCT, CBCT, etc)

Opens the door for potentially adapting to them on-line
Adaptive IGRT

- Different rationale exists for functional changes
- Functional imaging may identify changes supporting the use of higher doses
- Changes may also be identified which allow dose de-escalation reducing the risk of toxicities
- Functional changes in normal tissues may signal the need to adapt treatment plan avoiding potential toxicities
Adaptive IGRT

Discussions of adaptive IGRT quickly turn to the technical issues involved

Purpose here is to review some of the morphologic changes that occur and which may form a basis for adaptive IGRT
Conventional Wisdom

Morphologic changes are not common and occur only in a few tumor sites
Reality

Morphologic changes are common and occur in the great majority of tumor sites.
Morphologic Changes
Most brain tumors have long been thought to change little at all during treatment.

Recent evidence with serial MRI during RT has questioned this belief.
19 high grade gliomas treated with 3DCRT
T1- and T2-weighted and FLAIR imaging
Imaged prior to RT, weeks 1 and 3 and post-RT
Changes at week 3:
- 2 pts >50% decrease in GTV
- 12 pts slight rim enhancement or cystic changes
- 3 pts increased GTV
Median increase in GTV: 11.7 cc (9.8-21.3 cc)
Decrease V-95% of the PTV
No analysis of dosimetric consequences

Fig. 1. Grade 3 anaplastic oligoastrocytoma with tumor response Week 3 MRI during radiotherapy.
Fig. 4. Grade 4 glioblastoma multiforme with tumor progression at Week 1 MRI (Pre-Tx MRI was performed 1 week before initiation of RT).
Head and Neck Cancers

- Morphologic changes well known in these tumors
- Long been commonplace to re-simulate patients with significant changes including weight loss
- Increased available of in-room images increased our awareness of these changes and their impact on treatment
14 locally advanced pts imaged using CT-on-rails
3 scans per week
Overall 69.5% shrinkage in GTV
Average GTV reduction = 0.2 cc/day
Median percentage shrinkage = 1.8%/day
Head and Neck Cancers

- Serial imaging during RT also reveals changes in parotid glands
- Glands decrease in volume
- Move medially into high dose volumes
Evaluation of geometric changes of parotid glands during head and neck cancer radiotherapy using daily MVCT and automatic deformable registration

Choonik Lee, Katja M. Langen, Weiguo Lu, Jason Haimerl, Eric Schnarr, Kenneth J. Ruchala, Gustavo H. Olivera, Sanford L. Meeks, Patrick A. Kupelian, Thomas D. Shellenberger, Rafael R. Mañon

*Department of Radiation Oncology, M.D. Anderson Cancer Center Orlando, FL, USA, †TomoTherapy, Inc. Madison, WI, USA, ‡Department of Head and Neck Surgery, M.D. Anderson Cancer Center Orlando, Orlando, FL, USA, §Department of Head and Neck Surgery, The University of Texas, M.D. Anderson Cancer Center, TX, USA

- 10 pts treated with daily MVCT setup using helical tomotherapy
- Average parotid gland volume decrease = 21.3%
- Median rate 0.7%/day

Lee et al. Radiother Oncol 2008;89:81
Parotid Displacement

- Mean displacement = 5.3 mm
- Average shift = 0.22 mm per day
- Due to weight loss and regression of bulky nodes
Dosimetric Consequences

- Tumor regression, parotid shrinkage and displacement and weight loss all result in higher than planned parotid doses

- Higher doses result also in other normal tissues including the spinal cord
13 patients replanned midway through treatment due to tumor regression and weight loss

- No re-planning → ↓target coverage and ↑normal tissue dose
  - V95% of the PTV reduced in 92% of patients
  - Spinal cord max increased in all 13 patients
  - Brainstem max increased in 85%

- Re-planning ↑target coverage and normal tissue sparing

Lung Cancer

- Morphologic changes well known in these tumors
- Long been commonplace to re-simulate patients with changes seen on portal films
- Increased available of in-room images increased our awareness of these changes and their impact on treatment
22 stage I-III lung cancer patients

Pre and mid-treatment CT (30 and 50 Gy)

Mean GTV reduction
  - On first scan: 24.7%
  - On second scan: 44.3%

Largest reduction occurred in majority of patients by the first scan (30 Gy)

Pre-Treatment

30 Gy

50 Gy
Sometimes tumor volumes increase

21 lung cancer patients
Repeat 4DCT after 15 fractions
Mean reduction in internal target volume (ITV) = 34 cc
Mean overall PTV reduction = 55.6 cc
6/21 patients had a larger ITV
% increase of 6%, 21% and 47%

Does Adapting to Changes Help?

Results are Mixed
17 lung cancer patients

- Daily MVCT using helical tomotherapy
- Mean GTV decrease: -0.79%/day
- Adapting re-planning beneficial in some but not all pts

Two groups benefited:
  - Patients with a global linear decrease
  - Patients with an initial plateau then rapid decrease

No benefit in 24% of patients with variable or no clear GTV decrease

Gastrointestinal Cancers

- Limited data assessing morphologic changes occurring during treatment in GI tumors
- No data on the dosimetric consequences of these changes
15 locally advanced rectal cancer pts
MRI pre-RT, after 10 fractions and post-RT
Significant reductions in tumor volumes at each point
  – Pre-treatment tumor volume = 27.1 cc
  – After 10 fractions = 13.4 cc
  – Post-treatment = 6.7 cc

Breast Cancer

Another tumor site in which little or no changes are thought to occur.
Most likely due to the preponderance of early stage patients treated with adjuvant RT.
However, even in those women, a variety of morphologic changes occur during RT.
30 early stage breast cancer pts

Conventional CT pre-RT and at 40 Gy

95% had significant reductions in the lumpectomy volume

Mean volume pre-RT = 32.1 cc

Mean volume at 40 Gy = 25.1 cc

Overall mean reduction of 22.5%

No change in the overall breast volume (0.11% reduction)

Would adapting help?

Nichols et al.
ASTRO 2009

- 40 early stage breast cancer patients
- CT pre-RT and again at 37.8-41.4 Gy
- In women with >35% reduction in lumpectomy cavity, replanning significantly reduced the V90% volume of the boost sparing more breast tissue
- Mean difference 119 cc
- 25/40 patients had clinically significant changes in boost plans: 13 lower electron energy, 11 smaller cone

Genitourinary (GU) Cancers

- Lots of data published regarding morphologic changes in prostate and bladder cancer patients
- Majority demonstrate that clinically significant morphologic changes occur during RT
- Important since many think that the prostate moves but deforms little
25 early stage prostate cancer patients
All with implanted fiducial markers
Serial MRI scans (pre-RT and randomly during treatment)
Prostate volume decreased by 0.5%/fraction
Fiducial markers in-migrated by 0.05 mm/fraction
Significant deformations occurred particularly in patients with a history of a TURP

Significant deformations in prostate volume in a patient with a prior TURP
Do these changes matter? Would adapting to them help?

On-line re-optimization of prostate IMRT plans for adaptive radiation therapy*

Q Jackie Wu¹, Danthai Thongphiew¹,², Zhiheng Wang¹, Boonyanit Mathayomchan², Vira Chankong², Sua Yoo¹, W Robert Lee¹ and Fang-Fang Yin¹

- Daily CBCT imaging of early stage prostate cancer
- Overall volume of prostate changed little
- Large deformations noted anterior portion of the prostate and in the seminal vesicles
- Underdosage of the target tissues
- Re-planning improved target coverage and conformity index
- Improved rectal sparing, no benefit in bladder sparing

Such large deformations can not be addressed by translational corrections alone
21 bladder cancer patients
Partial bladder definitive irradiation
Serial conventional CT imaging
Mean GTV decrease by 40 cc (range 4-100 cc)
Overall decrease 0.09 cc/day
But no change in 6 and increase in 1 patient
Also GTV markedly changed in shape during treatment

Pos et al. Int J Radiat Oncol Biol Phys 2006;64:862
Do these changes matter?

- 65% of patients had part of the CTV outside the planning CT-based PTV at least once during RT
- Incomplete coverage of the bladder volume occurred most commonly along the cranial aspect of the bladder
- In only 71% of patients did the GTV receive 95% of the prescribed dose on the weekly scans
Gynecologic Cancers

No debate that gynecologic tumors, particularly cervical cancer, shrink and deform during treatment.

Many authors have demonstrated this using serial CT, MRI and more recently in-room imaging.
14 intact cervical cancer patients
MRI pre-RT and again at 30 Gy mid-treatment
Mean volume pre-RT = 71 cc
Mean volume at 30 Gy = 39 cc

60 intact cervical cancer patients

MRI pre-RT, at 2-2.5 weeks, at 4-5 weeks and post-RT

Median volumes

- Pre-RT 54 cc
- 2-2.5 weeks 31 cc
- 4-4.5 weeks 7 cc
- Post-RT 0 cc

Gynecologic Cancers

Huh et al. evaluated 66 cervical cancer pts with serial MRI scans

Significant deformations seen in the cervix, uterus and normal tissues

Changes most pronounced in younger women (< age 60)

Huh et al. Radiother Oncol 2004;71:73
Do These Changes Matter?

Results are Mixed
20 locally advanced cervical cancer patients
Weekly MRI scans
MRI plan generated based on pre-RT MRI + 5 mm margins cast onto weekly MRI scans
Mean GTV D-98 decreased (5017 to 4987 cGy)
Mean CTV D-98 decreased (4920 to 4865 cGy)
Accumulated GTV dose >95% in all patients
Accumulated CTV dose >95% in all but 1 patient (uterus changed from retroverted to anteverted during RT)

Other results less favorable

Mell et al. (UCSD)
Red Journal (in press)

- 10 cervical cancer patients with daily CBCT
- CTV based on pre-RT imaging cast onto daily CBCT and modified to account for regression and deformation
- Using a 5 mm expansion, the percentage of fractions not covered by the prescription dose was 95.4%
- Even with generous margins (2 cm), the % fractions not covered by the prescription dose was 20%
Would adapting help?

Explored re-planning mid-way through treatment
Re-planning improved sparing of the rectum
In patients with > 20 cc GTV regression, re-planning improved sparing of the bowel as well

But what about the rest of treatment?

A new treatment plan may be beneficial on one day but may be worse on subsequent days.
Lawson et al. (UCSD)  
ASTRO 2009

- 10 cervical cancer patients with daily CBCT
- 2 IMRT plans were generated
  - initial IMRT plan based on the planning CT
  - Adaptive IMRT plan based on the CBCT at 30 Gy
- Non-adaptive approach used on the initial plan
- Adaptive approach switched to the adaptive plan at 30 Gy
- Adaptive approach improved CTV V100 and conformity index compared to the non-adaptive approach
- Also better bladder and small bowel sparing
- Mixed results in terms of rectal sparing
  - 4 improved, 3 no improvement, 3 worse
Bone Marrow Imaging:
MRI IDEAL Fat Fraction Maps

Pre-Treatment

Mid-Treatment

Post-Treatment
Lymphomas

One of the most radiosensitive tumors

Long been commonplace to resimulate patients with significant regression to spare normal tissues
Lymphoma

Renaud et al.
Can J Urol 2009;16:4639

- Bulky abdominal non-Hodgkin’s lymphoma patient
- Treated on helical tomotherapy with daily MVCT
- During treatment, GTV shrank by 50.6%
- Re-planning midway through treatment would have reduced the dose to all surrounding normal tissues including the kidneys, liver, spinal cord and bowel
- Mean liver and spinal cord doses could have been reduced by 3.8 and 4 Gy, respectively
10 craniopharyngioma patients
Median age 8.4 years
Weekly MRI scans
Maximum GTV reduction 28.4% (4.1 cc)
Re-planning based on weekly scans improved the tumor control probability from 90.8% to 85.7%
No improvements seen in the normal tissue complication probabilities and sparing of normal structures
Adaptive IGRT

Data shown literally only scratch the surface of the myriad of morphologic changes that are known to occur during RT.

Many other tumors have not yet been evaluated during treatment.

Seems changes are being found wherever and whenever one looks.
Adaptive IGRT

Question quickly turning from do changes occur to should we adapt to them

Only way to answer whether adaptive IGRT helps or hurts our patients is to perform carefully designed prospective clinical trials
## Adaptive IGRT Protocols

<table>
<thead>
<tr>
<th>Site</th>
<th>Prospective Protocols</th>
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</thead>
<tbody>
<tr>
<td>CNS</td>
<td>-</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>+</td>
</tr>
<tr>
<td>Lung</td>
<td>+</td>
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<tr>
<td>Breast</td>
<td>+</td>
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<td>GI</td>
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UCSD Center for Advanced Radiotherapy Technologies (CART)
Thank-you for your attention