Anatomical-Based Adaptive RT: It Begins Here!

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Anatomical variations lead to dosimetric discrepancies between planned and delivered resulting in:
1. Uncertainties in TCP calculations
2. Uncertainties in NTCP calculations
3. Uncertainties in the correlation of functional imaging with delivered therapy
4. Uncertainties in assessing the impact of novel drugs, therapy schedules, and techniques

Objectives
• Understand the need for anatomy-based adaptation and methods to safely implement this into the clinic.
• Recognize the need for physiological-based adaptation and methods to safely implement this into the clinic
• Appreciate the radioiological limitations and concerns associated with dose summation and adaptation
• Describe the clinical implications of dose summation and adaptation on individual patient treatments, clinical trials, and outcomes assessment
Tools Needed for Anatomical Based (Dose Accumulation &) Adaptation

1. Images Obtained during Tx
2. (Auto) Segmentation
3. (Deformable) Image Registration
4. Dose Re-calculation & Summation
5. Decision Making Tools
6. Plan Re-Optimization (including delivered dose)

1. Images Obtained during Tx

Convenience

Quality

PROS:
- Ability to acquire daily
- Min additional time for patient
- Exact Tx position

POTENTIAL CONS:
- Uncertainty in GTV definition
- Limited FOV
- Dose Calc Accuracy

View Ray, Courtesy of Sasa Mihic, Washington Univ

2. (Auto) Segmentation

- Combined with Deformable Registration
  - Register 2 images \(\rightarrow\) contours
  - Requires that registration doesn't use contours
- Independent Segmentation
  - Model-based, atlas based, intensity based
3. Deformable Image Registration

- Various DIR algorithms available

DIR becomes even more challenging in Adaptive RT and subsequently more difficult to validate
-- Dramatic changes in tumor/normal tissue volume
-- Non-diagnostic quality images

Requires an understanding of how DIR works!

- Uncertainties must be acknowledged/incorporated into the process


4. Dose Re-calculation & Summation

- How often do you recalculate the dose grid?
  - Can we just use the original dose grid?
  - Probably ok if the patient mass/organ/tumor volume isn’t changing
- What image do you use to re-calc dose?
  - Daily Image
    - CBCT, MVCT, MR
  - Newly acquired CT
  - Deformed CT to match daily image
- How do you sum the dose?

Dose calculation accuracy using cone-beam CT (CBCT) for pelvic adaptive radiotherapy
Guan H, Dong H

- kV CBCT
- Calibration of HU to ED using a mini CT QC phantom
- CBCT and plan-CT for a pelvic phantom were acquired and registered
- Dosimetric difference for 6 MV:
  - largest for the single lateral field plan (max 6.7%)
  - less for the 3D conformal plan (max 3.3%)
  - least for the IMRT plan (max 2.5%).
- Differences for 18 MV were 1-2% less
The use of megavoltage CT (MVCT) images for dose recomputations
Phys Med Biol. 2005 Sep 21;50(18):4259-7
Langen KM, et al

- Tested the stability of the MVCT numbers
  - Variation of calibration with spatial arrangement of the phantom, time and MVCT acquisition parameters
- Two calibration curves that represent the largest variations were applied to six clinical MVCT images for recalculations to test for dosimetric uncertainties
- Largest difference in any of the dosimetric endpoints was 3.1% but more typically the dosimetric endpoints varied by less than 2%

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Slide Courtesy of Emily Heath
4. Decision Making Tools

- Adapt too often
  - Introduce more uncertainty?
  - Use too many resources/increase cost?
  - Chase daily fluctuations?
- Adapt too late
  - Miss the opportunity to improve Tx?
5. Plan Re-Optimization (including delivered dose)

• Simplest Strategy (Naïve):
  – Perform a replan using the same normal tissue constraints and tumor coverage requirements
  – Can be performed without DIR
  – Doesn’t account for deviations in the delivery of the planned dose to date

• Sophisticated Strategy:
  – Optimize new plan taking into account the deviations in the delivered original plan

Classes of Anatomical Response

• Tumor regression
• Normal tissue growth/shrinkage
• Relative anatomy changes (deformation)
• Physiological state/process changes
  – Rectal/bladder filling, breathing motion

Cervix Cancer: Background

• Toxicity concerns exist for neighboring normal tissues
  – Late grades 3 and 4 toxicity can affect up to 20% of locally advanced patients
• Planning studies show IMRT reduces dose to GI structures
• Clinical implementation is challenging
  – Substantial tumor regression
  – Patient specific motion/deformation
• Intra-Fx motion << Inter-Fx motion
  – Cine MR studies

Dose:
- 0 Gy
- 8 Gy
- 20 Gy
- 28 Gy
- 38 Gy
- 48 Gy
Example of nominal dose grid with changing geometry

Baseline Organ Geometry
“Planned” dose distribution

Baseline Organ Geometry
Updated dose distribution

Planned Dose
Delivered Dose

SUMMARY
1. Images Obtained during Tx
   - Weekly MR
2. (Auto) Segmentation
   - Manual Segmentation
3. Deformable Image Registration
   - Contour based similarity metric, linear elastic transformation model
4. Dose Re-calculation & Summation
   - Dose calc on CT, Summation using COM tracking
5. Decision Making Tools
   - Determine the impact of automated weekly replan
6. Plan Re-Optimization (including delivered dose)
   - Naïve
Planning Scenarios

1) IMRT with uniform 3mm PTV margin, no replanning

- D95% GTV > 50 Gy
- D95% CTV > 45 Gy
- D95% PTV > 47.5 Gy
- OTRO 0418 protocol

2) Automatic weekly replan with pre-treatment optimization function

Results – Target Coverage:
3 mm Margin, IGRT

GTV

CTV

Retrospective studies evaluating automated weekly replanning for cervix cancer indicate that

10%

1. Intra-fraction motion is so large that it dominates any potential dosimetric impact adaptive planning for anatomical changes.

27%

2. Weekly replanning can enable acceptable target coverage while maintaining organ-at-risk sparing with 3 mm PTV plans.

29%

3. Anatomical response is very predictable across the patient population and standard replanning can be prescribed for all patients.

37%

4. Anatomical changes are minimal and adaptive replanning is not warranted in this setting.

3%

5. With proper IGRT, cervix patients can be safely treated with no PTV if a single mid-treatment replan is performed.
Weekly replanning can enable acceptable target coverage while maintaining organ-at-risk sparing with 3 mm PTV plans

- Answer: 2

Lung Cancer

- Increase dose → Increase TC
- Increase MLD → Increase toxicity
- Continuous tumor regression is often seen in standard Fx locally advanced NSCLC

Adaptive Radiotherapy for Lung Cancer

Jan-Jakob Sonke, PhD, and José Bellderbos, MD, PhD

Movie courtesy of Jan-Jakbo Sonke
Lung cancer tumor regression has been demonstrated by several groups, however, adapting to this regression may not be straightforward because

1. Microscopic disease may still exist even when the visible tumor has regressed
2. It is impossible to model lung tumor regression
3. Air in the lungs make it impossible to perform meaningful dose calculations
4. Breathing motion introduces uncertainty that cannot be accounted for
5. The voxel resolution on the CT scanner is not adequate to visualize the tumor response

Microscopic disease may still exist even when the visible tumor has regressed

• Answer: 1
Purpose: To evaluate doses to the microscopic disease (MD) in adaptive radiotherapy (ART) for locally advanced non–small-cell lung cancer (NSCLC) and to model tumor control probability (TCP).

Methods and Materials: In a retrospective planning study, 3D conformal Tx plans for 13 patients with locally advanced NSCLC were adapted to shape and volume changes of the GTV once or twice during conventionally Fx RT with total doses of 66 Gy; doses in the ART plans were escalated using an iso-mean lung dose (MLD) approach compared to non-adapted Tx.

Conclusions: Adaptation of radiotherapy to the shrinking GTV did not compromise dose coverage of volumes of suspect microscopic disease and has the potential to increase TCP by >40% compared with radiotherapy planning without ART.

Noted Limitations:
• 13 patients
• Locally advanced with large volumes
• Only intrapulmonary microscopic disease
• Needs validation in prospective trial

Classes of Anatomical Response

• Tumor regression
• Normal tissue growth/shrinkage
• Relative anatomy changes (deformation)
• Physiological state/process changes
  – Rectal/bladder filling, breathing motion
Establish a Deformation Algorithm

- Wang, et al, PMB 2005
- Difference in images (ext) and gradient of image (int) act as forces
- Addition of active force (gradient of moving image)
- Accuracy: 96% voxels < 2 mm for mathematical phantom

Evaluate Potential Impact:
Is what you plan what you get?

- O’Daniel et al. IJROBP 2007
- 11 patients, 2 CTs/week
- Demons Deformable Registration
- Dose calculated on each CT
- DIR mapped each dose distribution back to reference
- Accumulated dose was summed
- Increase in parotid dose: median 1 Gy

Adaptive Radiotherapy for Head-and-Neck Cancer: Initial Clinical Outcomes From a Prospective Trial

Purpose: To present pilot toxicity and survival outcomes for a prospective trial investigating adaptive radiotherapy (ART) for oropharyngeal squamous cell carcinoma.

Conclusion: This is the first prospective evaluation of morbidity and survival outcomes in patients with locally advanced head-and-neck cancer treated with automated adaptive replanning. ART can provide dosimetric benefit with only one or two mid-treatment replanning events. Our preliminary clinical outcomes document functional recovery and preservation of disease control at 1-year follow-up and beyond.
SUMMARY

1. Images Obtained during Tx
   - Daily CT (CT on-rails)

2. (Auto) Segmentation
   - Auto-segmentation via DIR

3. Deformable Image Registration
   - Modified (dual force accelerated) Thirion’s Demons Algorithm

4. Dose Re-calculation & Summation
   - Calculation on Tx Fx CT, no summation

5. Decision Making Tools
   - Replan prompted by changes identified in patient

6. Plan Re-Optimization (including delivered dose)
   - Naïve, empirical adaptive PTV (1 mm)

Replan: Timing and Frequency

1 Replan:
   Mean parotid dose sparing was improved by:
   • 2.8% (p = 0.003) in the contralateral parotid
   • 3.9% (p = 0.002) in the ipsilateral parotid

2 Replans:
   Mean parotid dose sparing was improved by:
   • 3.8% (p = 0.026) for the contralateral parotid
   • 9% (p = 0.001) for the ipsilateral parotid

Initial outcomes from a prospective clinical trial indicate that adaptive radiotherapy for head and neck cancer

17% 1. Will likely result in severe toxicity and should not be performed

20% 2. Will likely result in a dramatic reduction in tumor control and should not be performed

23% 3. Can provide dosimetric benefit with only one or two mid-treatment replanning events

13% 4. Does not provide dosimetric benefit

27% 5. Can provide dosimetric benefit only with daily replanning
Can provide dosimetric benefit with only one or two mid-treatment replanning event

- Answer: 3

Shrinking Volume: Is Tissue Response Modeled Correctly?

- How do we model the reduction?
- Does it have dosimetric consequences?
- What volume to we use for the DVH?

Modeling Volume Reduction

![Graph showing dose vs. volume for Homogeneous, Necrotic Core, Dissolving Rim plans.](image)
**Relative Anatomical Changes**

- Changes in anatomy position and size (i.e. rectal/bladder filling) can require adaptation
- Adapting to these changes may allow for improved therapeutic intent

2 MR images obtained of the same prostate cancer patient at the start of Tx and midway through Tx

**Motion Changes**

- Breathing motion affects many anatomical sites – Liver, lung, pancreas, stomach...
- Changes in breathing motion may impact the delivered therapy and the required margins

Dramatic decrease in breathing motion

Reduced the PTV volume by 23%, Liver Veff by 12%
GTV1 Dmin(0.5cc): 3336 cGy (+12%)
GTV2 Dmin(0.5cc): 3249 cGy (+10%)

**Summary**

- Anatomical changes occur in many sites – Tumor Response, Normal Tissue Changes
- These changes often have dosimetric impact on tumor coverage and normal tissue sparing
  - Reduces the therapeutic ratio
  - Introduces additional uncertainty into clinical trials and outcomes studies
- Dose accumulation in the presence of anatomical changes can reduce dosimetric uncertainties & provide dosimetric QA
- Adapting to these changes can ensure tumor coverage and ability to optimize the therapeutic index
- Understanding, modeling, and accounting for these changes is often necessary before advancing to functional adaptation