Anatomical-Based Adaptive RT: It Begins Here!

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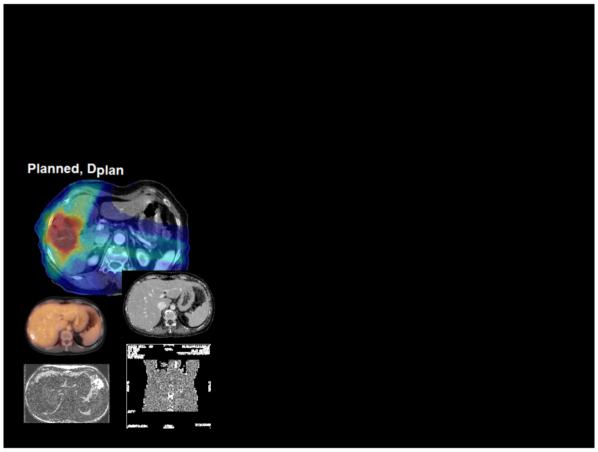
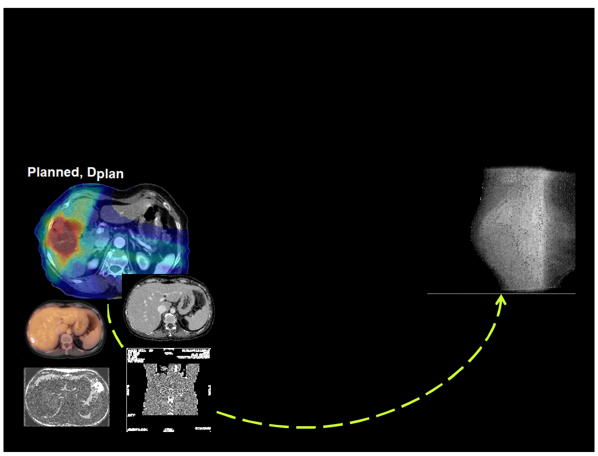
Disclosure

- Research Grants:
  - RaySearch Laboratories
  - Elekta Oncology Systems
  - Philips Medical Systems
- Member, IMPAC Physics Advisory Board
- The presenter has financial interest in the Morfeus deformable registration technology presented through a licensing agreement with RaySearch Laboratories

Acknowledgments

- Lei Dong (Scripps Proton Therapy Center)
- Emily Heath (Ryerson University)
- Sasa Mutic (Washington University, St. Louis)
- Jan-Jakob Sonke (Netherlands Cancer Institute)
- Stephen Breen (Princess Margaret Hospital)
- James Stewart, Karen Lim, Young-Bin Cho (Princess Margaret Hospital)
- Henrik Rehbinder, Anna Lundin (RaySearch Laboratories)


Planned, Dplan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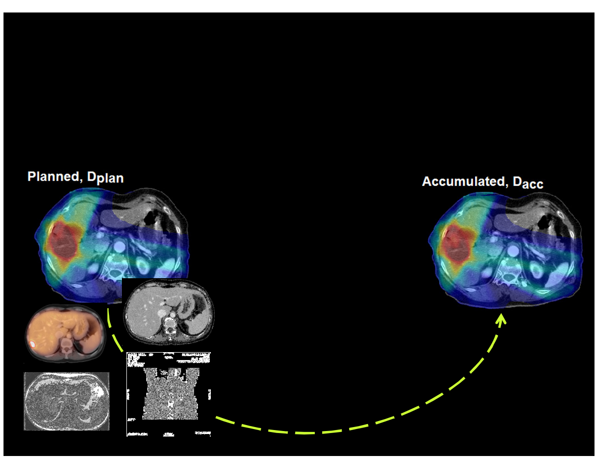
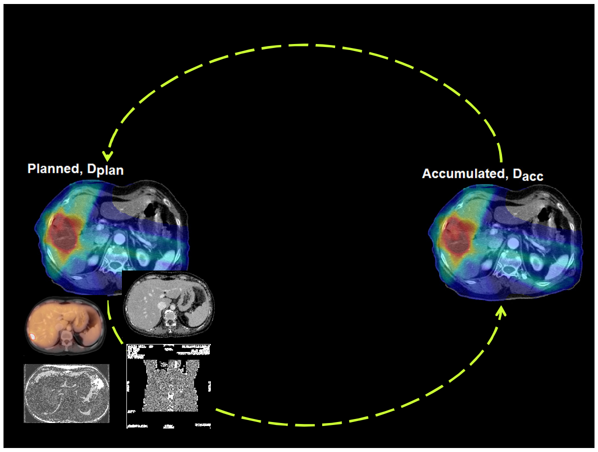
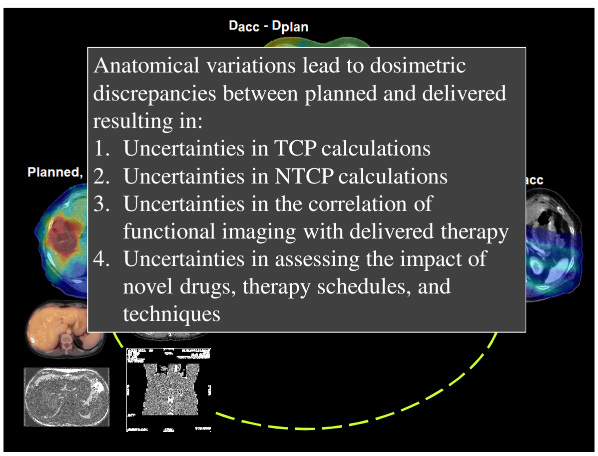

Planned, Dplan
Accumulated, Dacc





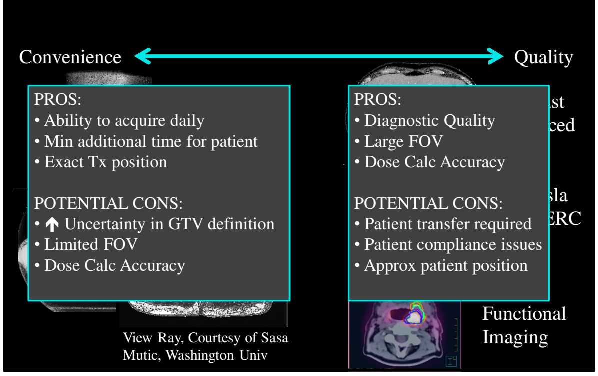
Objectives

- 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



2. (Auto) Segmentation

- Combined with Deformable Registration
  - Register 2 images ➔ 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

1. Kashani, Med Phs, 2008; 2. Brock IJROBP, 2009

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

Phys Med Biol. 2009 Oct 21;54(20):6239-50
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

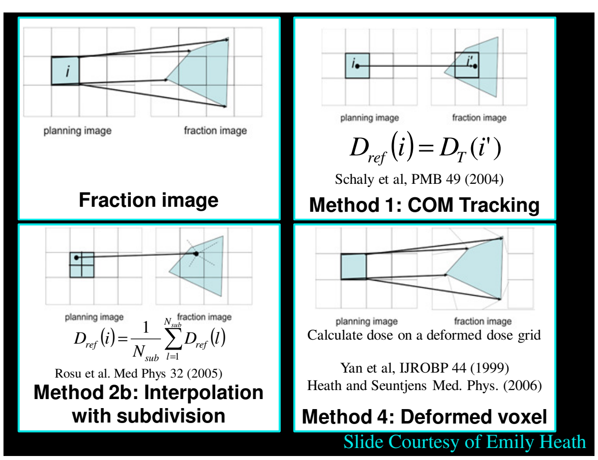
The use of megavoltage CT (MVCT) images for dose recomputations

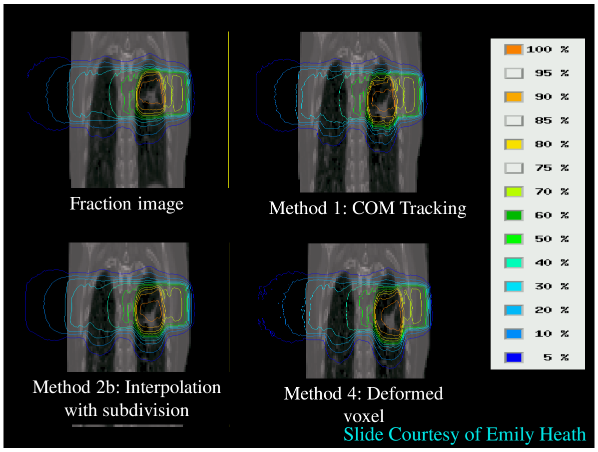
Phys Med Biol. 2005 Sep 21;50(18):4259-7
Langen KM, et al

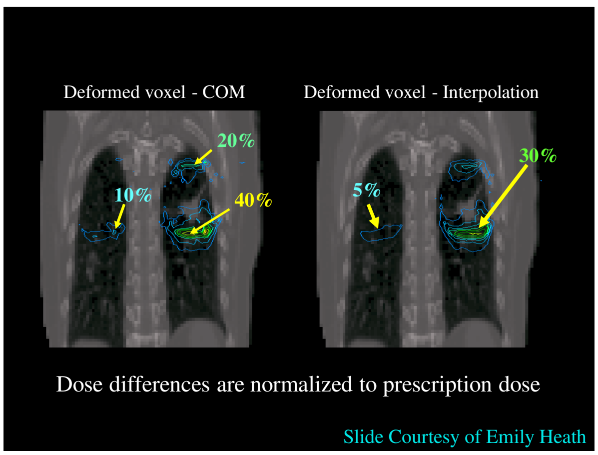
- Tested the stability of the MVCT numbers
  - Variation of calibration with spatial arrangement of the phantom, time and MVCT acquisition parameters
- Two calibration curves that represent the largest variations were applied to six clinical MVCT images for recalculations to test for dosimetric uncertainties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

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?







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

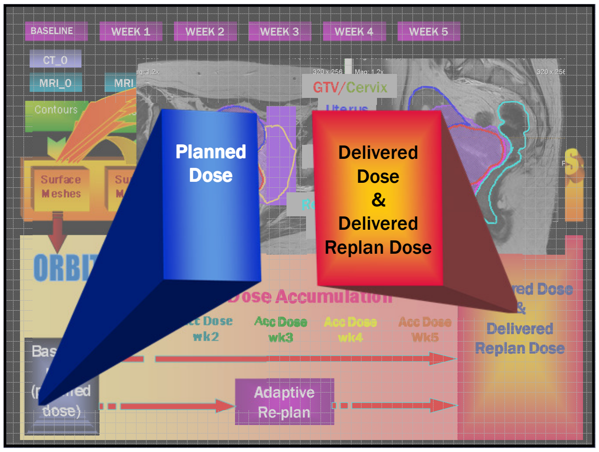
Classes of Anatomical Response

- 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 23% 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

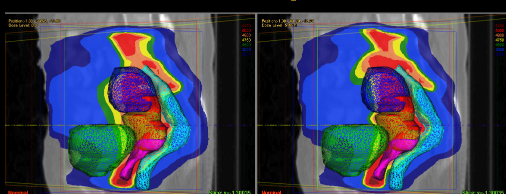
Dose: 48 Gy



Example of nominal dose grid with changing geometry

Baseline Organ Geometry — "Planned" dose distribution

Baseline Organ Geometry — *Updated* dose distribution



Planned Dose — Delivered Dose

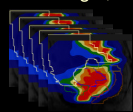
SUMMARY

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

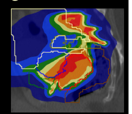
Planning Scenarios

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

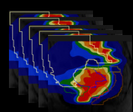
Criteria:
- D98% GTV > 50 Gy
- D98% CTV > 49 Gy
- D98% PTV > 47.5 Gy
- OARs subject to RTOG 0418 protocol

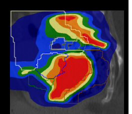


25 Fractions



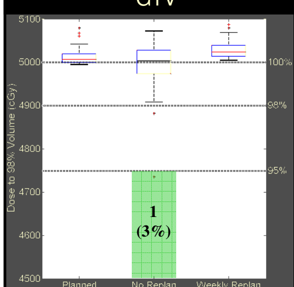
2) Automatic weekly replan with pre-treatment optimization function



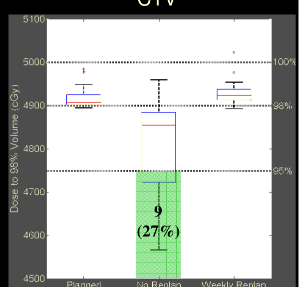


Results – Target Coverage: 3 mm Margin, IGRT

GTV



CTV



Retrospective studies evaluating automated weekly replanning for cervix cancer indicate that

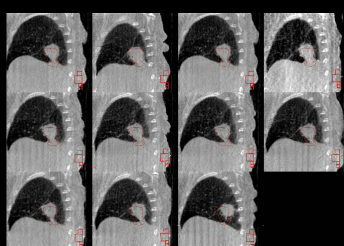
10%	1.	Intra-fraction motion is so large that it dominates any potential dosimetric impact adaptive planning for anatomical changes.
27%	2.	Weekly replanning can enable acceptable target coverage while maintaining organ-at-risk sparing with 3 mm PTV plans.
23%	3.	Anatomical response is very predictable 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 site.
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
- Reference: Stewart J, Lim K, Kelly V, Xie J, Brock KK, Moseley J, Cho YB, Fyles A, Lundin A, Rehbinder H, Löf J, Jaffray D, Milosevic M., Automated weekly replanning for intensity-modulated radiotherapy of cervix cancer. Int J Radiat Oncol Biol Phys. 2010 Oct 1;78(2):350-8.

Lung Cancer

Movie courtesy of Jan-Jakbo Sonke



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

ELSEVIER

Seminars in RADIATION ONCOLOGY

Adaptive Radiotherapy for Lung Cancer

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

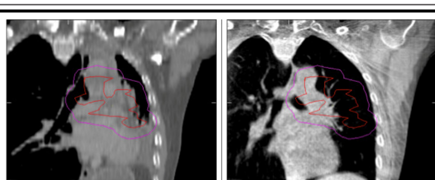
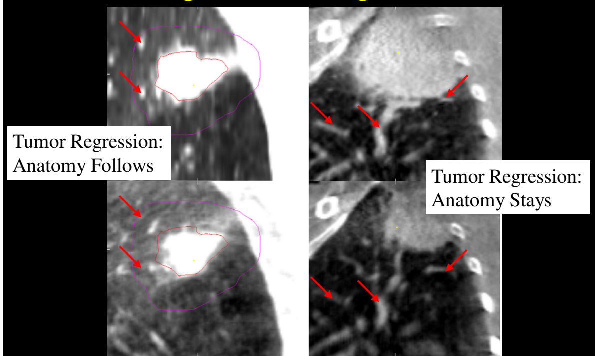


Figure 7 Example of progressive anatomical changes requiring plan adaptation depicting the planning CT (left) and first week CBCT (right) aligned on the bony anatomy. Pretreatment GTV (red) and PTV (purple) delineations are overlaid on both scans. Due to shrinkage of the tumor the atelectasis (seen on the planning CT scan) dissolved and a shift of mediastinal structures to the normal position occurred (seen on the CBCT scan). As a consequence, the dose distribution changed, the dense tissue of the collapsed lung dissolved, the tumor, and subcarinal lymph node moved outside the PTV and excessive irradiation of normal lung tissue occurred.

Lung Tumor Regression



Lung cancer tumor regression has been demonstrated by several groups, however, adapting to this regression may not be straightforward because

13%	1. Microscopic disease may still exist even when the visible tumor has regressed
20%	2. It is impossible to model lung tumor regression
20%	3. Air in the lungs make it impossible to perform meaningful dose calculations
30%	4. Breathing motion introduces uncertainty that cannot be accounted for
17%	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
- References: Sonke JJ, Belderbos J., Adaptive radiotherapy for lung cancer., Semin Radiat Oncol. 2010 Apr;20(2):94-106.
- Badawi AM, Weiss E, Sleeman WC, Hugo GD, PMB, 57(2):395-413, 2012.

IJROBP Vol. 81, No. 4, pp. e275–e282, 2011

CLINICAL INVESTIGATION Lung

ADAPTIVE RADIOTHERAPY FOR LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER DOES NOT UNDERDOSE THE MICROSCOPIC DISEASE AND HAS THE POTENTIAL TO INCREASE TUMOR CONTROL

Matthias Guckenberger, M.D.,*†‡ Anne Richter, M.Sc.,* Juergen Wilbert, Ph.D.,* Michael Flentje, M.D.,* and Mike Partridge, Ph.D.§

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.

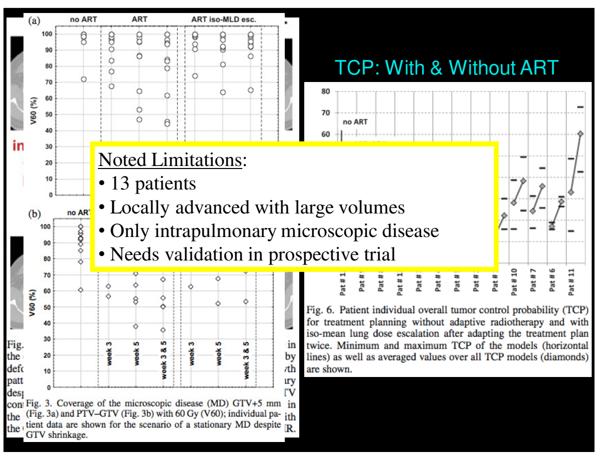


Fig. 3. Coverage of the microscopic disease (MD) GTV+5 mm (Fig. 3a) and PTV–GTV (Fig. 3b) with 60 Gy (V60); individual patient data are shown for the scenario of a stationary MD despite GTV shrinkage.

Fig. 6. Patient individual overall tumor control probability (TCP) for treatment planning without adaptive radiotherapy and with iso-mean lung dose escalation after adapting the treatment plan twice. Minimum and maximum TCP of the models (horizontal lines) as well as averaged values over all TCP models (diamonds) are shown.

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

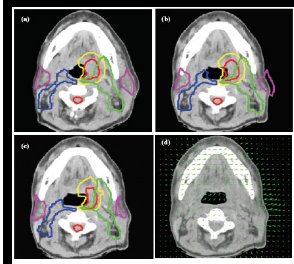
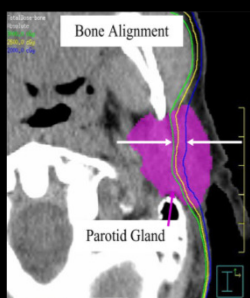


Figure 9. Autocontouring on head-and-neck images. (a) One slice of the planning CT with physician-drawn contour overlaid. (b) Corresponding slice on daily CT with planning contours directly overlaid. (c) Daily CT with deformed planning contours obtained by deformable registration algorithm. (d) Daily CT with displacement overlaid (scaled).

- 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

Clinical Investigation: Head and Neck Cancer

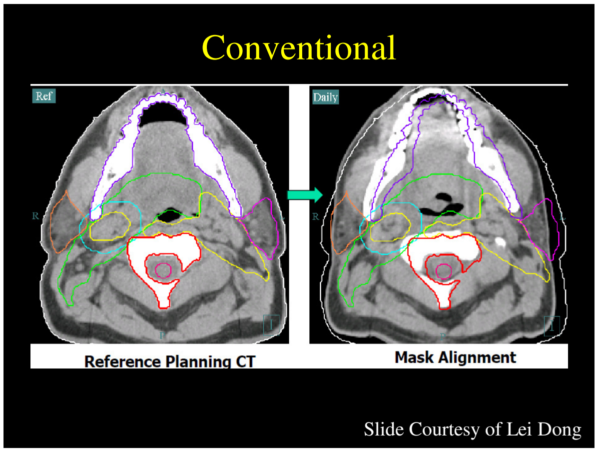
IJROBP 83 (3), pg. 986-993

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

David L. Schwartz, M.D.,*,†,‡ Adam S. Garden, M.D.,‡ Jimmy Thomas, M.D.,‡ Yipei Chen, B.S.,§ Yongbin Zhang, M.S.,§ Jan Lewin, Ph.D.,‖ Mark S. Chambers, D.M.D.,‖ and Lei Dong, Ph.D.§

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 replan- ning. 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.


Conventional
Ref
Daily
Reference Planning CT
Mask Alignment
Slide Courtesy of Lei Dong

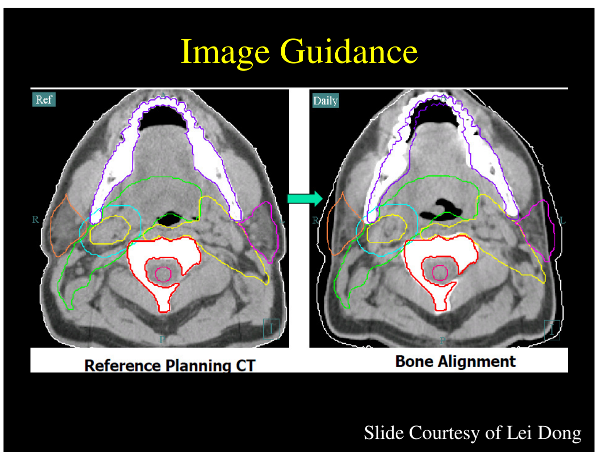
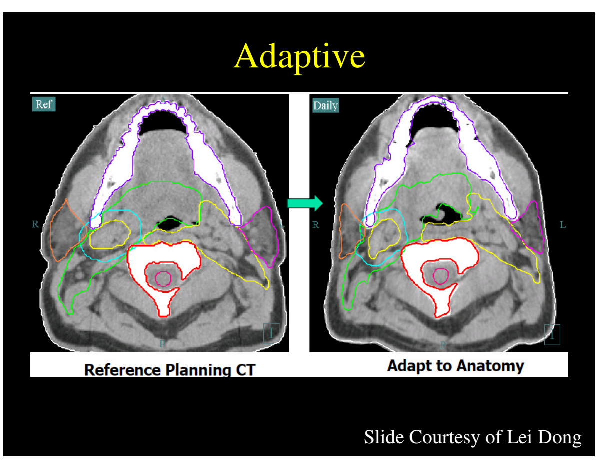


Image Guidance
Ref
Daily
Reference Planning CT
Bone Alignment
Slide Courtesy of Lei Dong


Adaptive
Ref
Daily
Reference Planning CT
Adapt to Anatomy
Slide Courtesy of Lei Dong

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

Fig. 3. Timing of adaptive radiotherapy (ART) replanning. Distribution of the triggering fraction for replanning is plotted for both first and second ART events.

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

17%	1. Will likely results 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

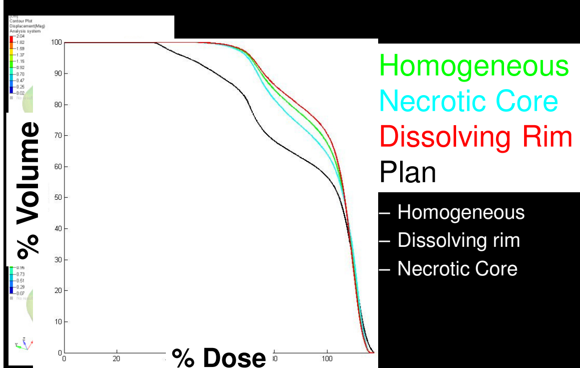
Can provide dosimetric benefit with only one or two mid-treatment replanning event

- Answer: 3
- Reference: Schwartz DL, Garden AS, Thomas J, Chen Y, Zhang Y, Lewin J, Chambers MS, Dong L., Adaptive Radiotherapy for Head-and-Neck Cancer: Initial Clinical Outcomes From a Prospective Trial. Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):986-93

Shrinking Volume: Is Tissue Response Modeled Correctly?

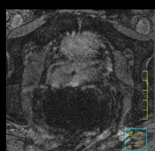
- How do we model the reduction?
- Does it have dosimetric consequences?
- What volume to we use for the DVH?

Modeling Volume Reduction

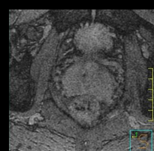


Relative Anatomical Changes

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



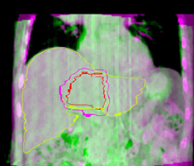
2 MR images obtained of the same prostate cancer patient at the start of Tx and mid-way through Tx



Motion Changes

- Breathing motion effects 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