Clinical Implications Of Dose Summation And Adaptation

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Objectives

1. Understand the need for anatomy-based adaptation and methods to safely implement this in the clinic
2. Recognize the need for physiological-based adaptation and methods to safely implement this into the clinic
3. Appreciate the radiobiological limitations and concerns associated with dose summation, and adaptation
4. Describe the clinical implications of dose summation and adaptation on individual patient treatments, clinical trials, and outcomes assessment.

Important Disclosures

Research grants / Honoraria / Advisory Board:

- Accuray
- Bayer Healthcare
- Elekta
- Varian Medical
- Viewray Inc.
Delivery Techniques
- Standard radiotherapy
- Conformal radiotherapy
  1. 3D RT
  2. IMRT

Localization Techniques
- In-room Guidance:
  - US, X-rays, CT, Optical, RF

Dose Evaluation Techniques
- Dose recalculation
- Dose reconstruction

Localization Techniques
- In-room Guidance:
  - US, X-rays, CT, Optical, RF

Image Guided RT
- Dose-Guided RT
- "True" Adaptive RT

Dose Modification Techniques
- Off-line reoptimization
- On-line reoptimization

Applications of Deformable Registration and Dose Accumulation
- Increasing understanding of variations (anatomic /dosimetric)
- Increasing need for Deformable Registration +/-Dose Accumulation
- Increasing Personalization = Adaptive Radiotherapy
Applications of Deformable Registration and Dose Accumulation

DOCUMENTATION OF “TRUE” DELIVERED DOSES
IMPLICATIONS FOR OUTCOMES ASSESSMENTS

A TYPICAL RADIATION THERAPY COURSE
PRE-TREATMENT EVALUATION

“We’ve found a mass. The good news is we have weapons of mass destruction.”

DESIGN TREATMENT DELIVERY PLAN
TREATMENT PLAN

- Planned Doses
- Single snapshot
- Static Dose/Volume Information
RADIATION THERAPY DELIVERY-TREATMENT COURSE

TREATMENT COURSE: MULTIPLE REPEATS OF PLANNED DELIVERY

POST-TREATMENT EVALUATION

OUTCOMES EVALUATION

Cure / Toxicity
OUTCOMES EVALUATION

OUTCOMES: Cure/Toxicity

PLANNED DOSE? TRUE DOSE?

Toxicity = Quan tec

CLINICAL IMPLICATIONS: TOXICITY EVALUATIONS QUANTEC
(Quantitative Analysis of Normal Tissue Effects in the Clinic)

IJROBP, Vol. 76, No. 3, Supplement
PLAN VS TRUE DOSE - IMPLICATIONS:

Current Practice:
- Study robustness of current RT deliveries
- Better reporting of dose/volume data
- Understand true dose correlations vs outcomes

Future Practice:
- Design of clinical trials: Dose prescriptions
- Reporting of clinical trial results
- Implementation of “true” Adaptive RT


“True” Dose Reporting

Delivery Variations / Adaptive RT – Anatomic Sites

**Head & Neck**
Adaptive radiotherapy of head and neck cancer. Castadot et al. Semin Radial Oncol. 20:84, 2010


**Lung**
Role of Adaptive Radiotherapy During Concomitant Chemoradiotherapy for Lung Cancer: Analysis of Data From A Prospective Clinical Trial. IJROBP. 75(4):1092-7, 2009


**Bladder**

**Cervix**

Clinical Applications:
Observing vs Reacting (Adaptive RT)

**Maintain initial plan integrity:**
Tumor Progression: ~10%
Dosimetric Variations: ~20-30%
Changing anatomy: e.g. Weight loss / Tumor response

**Change plan to benefit from response:**
Change occurring early enough to change plan: ~20%?

**FUTURE CLINICAL TRIALS: AIMS?**
- Maintain integrity: Head/Neck, esophagus, prostate?
- Benefit from response: Lung, Gliomas, GYN?

IMPACT OF ANATOMIC VARIATIONS / ADAPTIVE RT CLINICAL QUESTIONS
- Types of cases and delivery techniques?
- Timing and techniques of dose assessments?
- Magnitude of dosimetric variation vs clinical impact?
- If adaptive, timing of replanning?
- Shrinking margins - Residual microscopic disease?
- Maintaining versus escalating doses?
- Cost effectiveness?
Clinical Scenarios

PLANNED DOSE VS TRUE DOSE

Local Control Assessment vs True Tumor Doses

Tumor progression
Tumor response
Overall anatomic variations

Clinical Contexts:
1. Head & Neck Ca: Toxic treatment
2. Lung Ca: Poor tumor control
Adaptive RT: Clinical Observations
Maintaining the integrity of the initial delivery plan

Tumor progression

Lei Dong, MDACC

UM: 2/14 lung Ca patient progression
Feng et al, IJROBP, 73, 1228, 2009

VU: 1/21 lung Ca patients progression
Spoelstra et al, IJROBP, Vol. 75, 1092, 2009

Head & Neck: Adaptive RT

- Loo et al. Tumour shrinkage and contour change during radiotherapy increase the dose to organs at risk but not the target volumes for head and neck cancer patients treated on the TomoTherapy H&H system. Clin Oncol (R Coll Radiol) 2011;23:40-47.
Head & neck: True Dose Documentation
Yonsei University / Korea:
10 patients with weight loss or neck diameter decrease:
Higher rates of Grade 2 xerostomia
MVCTs were retrospectively contoured, 1 MVCT/week
Doses recalculated based on deformed MVCTs

Head and Neck Ca:
Adaptation with Functional Changes?

Adaptive RT: Impact on dose distribution
Classic CT-based planning Adaptive PET-based planning
SIB-IMRT
30x2.3 Gy
30x1.85 Gy

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P<0.001
Geets, Radiother Oncol 2007;85:105–15
There is evidence that Adaptive Radiotherapy in Head and Neck cancer patients:

1. will not benefit any patient, regardless of any endpoint (dosimetric or clinical).
2. will not benefit patients who show progression during radiotherapy.
3. might benefit a subset of patients who display tumor regression or significant weight loss.
4. should be performed on-line to be truly effective.
5. improves survival in nasopharyngeal cancers.

Lung Ca: Tumor Regression – Anatomic Changes
Kupelian et al., IJROBP, 2005

10 patient with NSCLC, Treated with Helical Tomotherapy
Average 27 scans per patient
Average 1.2% shrinkage per day:
Range 0.6-2.3%

Lung Ca: Functional Changes
TARGETS OF ADAPTATION TO TUMOR RESPONSE

N=23 patients
ST I-III NSCLC
VARYING VOLUMES BUT
STABLE LOCATION:
SUITABLE TARGETS FOR ADAPTATION
FDG-PET scans might provide attractive targets for adaptive radiotherapy in lung cancer because:

1. they mostly display changes in volume but not location.
2. they mostly display changes in location but not volume.
3. FDG-PET scans are routinely obtained throughout a course of radiotherapy.
4. auto-contouring is possible by SUV values on FDG-PET scans.
5. they have been shown to reveal areas of future in-field recurrences.

Clinical Application:
Change plan to benefit from response

LUNG CANCERS

ADAPTIVE RT:
NOT FOR EVERY PATIENT
NOT FOR EVERY TECHNIQUE

N=21 evaluable patients
8% reduction after 30 Gy
Only patient needing replan had progression...

Spoelstra et al, IJROBP, Vol. 75, 1092, 2009
17 lung Ca Cases. RT ~30 fractions.

In 40% of patients in this study, GTV changes were of sufficient magnitude and occurred sufficiently early in the treatment course that one could realistically anticipate that adapted radiotherapy would improve the therapeutic ratio.

If GTV decreases by greater than 30% at any point in the first 20 fractions of treatment, adaptive planning is appropriate to further improve the therapeutic ratio.

Mid-RT PET volumes were used to design boost fields.

N=14 Complete CR in 2 patients
Progression by PET in 2 patients
Mid-RT PET in remaining 10 patients:
Mean decrease in PET volumes: 44% range 10-100%

RT boosts could be designed in the 10/14 patients to increase doses above 100 Gy and reduce normal tissue complication probabilities.

Adaptive RT; Dose Escalation – Lung Ca
University of Wuerzburg, Guckenberger et al. IJROBP, 79, 901, 2011

N=13 patients, advanced NSCLC, weekly CT images
Dose accumulation performed (Surface-based DIR algorithm)
Adaptive plans: Once week 3 / Once in week 5 / Both in weeks 3 then 5

Results:

Safe dose escalation on average from 66 Gy to 74 Gy in all patients
1. Adaptive RT failed in some patients
2. Dose escalation to ~74 Gy was possible in some patients
RADIATION THERAPY ONCOLOGY GROUP
American College of Radiology Imaging Network
RTOG 1106/ACRIN 6697
RANDOMIZED PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE RADIOTHERAPY USING DURING-TREATMENT FDG-PET/CT AND MODERN TECHNOLOGY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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FUTURE CLINICAL TRIALS?
Adaptive RT; Dose Escalation / Lung Ca – RTOG 1106

Personalized RT prescriptions
Table 5.1: Individuated Dose and Fraction Plans for Arm 2 (Based on 14 Gy Ensuring Part)

Keep total 30 fractions:
Largest fraction size allowed: 3.85 Gy
Ablative doses in Locally Advanced Lung Cancer?

An Adaptive RT application

Conventional dose escalation ineffective in advanced lung Ca:
RTOG 0617:
No difference 60 Gy vs 74 Gy

SBRT Boost to Residual Disease
Feddock J et al. IJROBP, 78, S108, 2010
ASTRO 2010

PET-CT one month following conventional CRT
PET positive residual disease (≤7 cm)
An additional 20 Gy in 2 SBRT fractions in 1 week.

N=19.
Median time interval from CRT to SBRT boost: 2 months.
Median follow-up time: 11 months
1 patient experienced grade 3 radiation pneumonitis (5%).

Image-Guided Hypofractionated Radiotherapy with Stereotactic Boost and Chemotherapy for Inoperable Stage II-III Non-Small Cell Lung Cancer

Phase I/II Protocol (UCLA) - PI: Percy Lee

3 WEEK COURSE
Image-Guided Hypofractionated Radiotherapy with Stereotactic Boost and Chemotherapy for Inoperable Stage II-III Non-Small Cell Lung Cancer

Prior to RT
After 40 Gy in 10 Fractions

PLANNED DOSE VS TRUE DOSE

PLANNED DOSE?
TRUE DOSE?

TOXICITY

Toxicity = Quantec

CLINICAL IMPLICATIONS:
TOXICITY EVALUATIONS QUANTEC
(Quantitative Analysis of Normal Tissue Effects in the Clinic)

IJROBP, Vol. 76, No. 3, Supplement
Toxicity Assessment vs True Tumor Doses

Anatomic variations of organs at risk

Clinical Context: Head & Neck Ca

Parotids can get hot in some patients
Deformable registration and dose accumulation on MVCTs
Lee et al. IJROBP 71, 1563-71, 2008

Overdose: Average = 15 %
3 of 10 patients: >10% higher mean parotid dose
7 of 10 patients: <10% (6-8%)

Parotids can get hot in some patients
Deformable registration and dose accumulation on CBCTs

Single case, 33 CBCTs: Deformation, dose accumulation.
Commercially available software
Head & neck: Adaptive

Yonsei University / Korea:
10 patients with weight loss or neck diameter decrease during H&N treatment: higher rates of Grade 2 xerostomia
MVCTs were retrospectively contoured, 1 MVCT/week
Planned Adaptive; recalculate dose based on deformed MVCTs


Adaptive Radiotherapy in Head and Neck Ca


20 head and neck cancer patients:
All treated in 30 fractions
Replan after fraction #15
Start second plan with fraction #20

The two plans were added assuming first 19 fractions identical (plan 1) and last 11 fractions identical (plan 2)

Adaptive Radiotherapy in Head and Neck Ca

- No benefit in patients treated postoperatively.
- In patients treated definitively:
  1. Reduction in mean parotid dose
  2. Reduction in normal tissue volume outside PTV >50 Gy
  3. Patients with the following had the greatest benefit:
     Nasopharyngeal carcinoma patients
     Initial stage T3/4
     Weight loss
     Reduction in lateral neck separation
- Safety of adaptive approach:
  No evidence of in-field or marginal failures

During a course of head and neck radiotherapy, daily parotid doses are expected to:
1. remain constant in all patients, since daily positioning variations do not occur in a face mask.
2. increase in all cases, since parotid glands swell during radiotherapy.
3. increase whenever parotid glands migrate medially due patient weight loss and/or tumor regression.
4. increase in all cases, since all head and neck cancer patients invariably lose weight during treatment.
5. decrease in all cases, since all head and neck cancer patients invariably lose weight during treatment.

Adaptive Dose Painting in Head and Neck Cancer
An Adaptive RT application
21 non-metastatic SCC Head and Neck
3 separate plans

Phase I; 2 dose levels – RT Alone (no chemotherapy)
Median doses:
80.9 Gy to CTV  N=7
85.9 Gy to GTV (smaller)  N=14
ADAPTIVE DOSE PAINTING: LESS TOXICITY?
Duprez F et al. JROBP, 2011; 80; 1045-55.

ACUTE DYSPHAGIA – DOSE GROUP II (Dose 85.9 Gy, Target = GTV)
Few Grade 3
Improvement after 5th week!

Evolution of Adaptive Radiotherapy

Real-Time Radiotherapy

Assessment and adjustments:
- Daily (all fractions)
- On-line
- Intra-fraction variations included
- Deformable registration
- Dose accumulation (inter/intrafraction)
- Real-time adaptation
Complexity of Process: On-line evaluation / adaptive
Deformation / Dose accumulation / CBCTs

Single case, 33 CBCTs: Deformation, dose accumulation.
Commercially available software
165 contours evaluated: 33% good
77% acceptable

~45 minutes to “prepare” each fraction, not counting verification by MD
Off-line an option
On-line would be too inefficient

Real-Time Radiotherapy: In-room MRI
Inter/Intrafraction motion/deformation assessment
In-room MRI / Cobalt IMRT
In-room MRI / Linac

Real-Time Radiotherapy: A necessity for IMPT?
Dose Summation And Adaptation
Conclusions

• Modern in-room imaging techniques enable documentation of anatomic and dosimetric variations throughout treatment courses.

• Deformable registration and dose accumulation allow determination of “true” delivered dose versus planned dose.

• Clinical correlations previously made with “planned” doses should be reassessed with “true” delivered doses.

Dose Summation And Adaptation
Conclusions

• Adaptive Radiotherapy is a process that addresses deforming anatomy, allowing robustness of planned delivery and possibly enabling dose escalation whenever appropriate.

• The proportion of patients benefiting from Adaptive RT still unclear (10-40%)…

• Future design of treatment protocols within or outside of clinical trials should include mechanisms to document “true” delivered doses.

• Tools are still to be refined.

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