Imaging For Clinical Trials and Adaptive Radiation Therapy (ART) Clinical Trials: A Physician’s Perspective

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Outline

Overview imaging in clinical trial
- Clinical trial decision
- Post-treatment response assessment
- As a biomarker to predict long-term outcome

Imaging for adaptive RT trial
- Motivation of ART: during-RT changes in tumor and normal tissue
- Process of ART and Imaging for ART
- A clinical trial of Biological imaging guided ART (BigART)

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Imaging for Clinical Trial Decision

- Imaging is essential for almost all diseases in oncology.
- Advanced imaging like PET functional imaging has been used as the state of art modality for cancer diagnosis and management.
- Imaging is needed for work-up or care for almost all solid tumors enrolling in clinical trial decision.

Imaging for Clinical Trial Conduct

- Imaging are study variables associated with trial outcome:
  - Disease, tumor location, size, stage and comorbid considerations.
- Imaging for trial endpoint assessment:
  - Treatment response.
  - Local tumor control and distant disease spread.

Imaging Modality for Response Assessment

- 2D X-ray, ultrasounds…
- CT is applicable for most conditions.
- MRI or PET functional imaging depending on the organs of origin and tumor types:
  - MRI for brain, liver, pancreas.
  - PET for head and neck, cervical cancer, lymphoma…
  - Lung.

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CT Imaging Response Assessment

WHO Criteria: AxB cm²

Response Evaluation Criteria in Solid Tumors (RECIST) Criteria:
A cm only

The WHO criteria were introduced in 1979 and use bidimensional measurements of target lesions.

RECIST, introduced in 2000 and revised in 2009, use unidimensional measurements of the longest diameters of target lesions.

Nichino M et al, Academic Radiology, 2011

Assessing Tumor Response

World Health Organization (WHO)
- Partial Response (PR) > 50% decrease in sum of products
- Progressive Disease (PD) > 25% increase

Response Evaluation Criteria in Solid Tumors (RECIST)
- Partial Response (PR) > 30% decrease in longest diameter
- Progressive Disease (PD) > 20% increase in diameter

From Wahl, RSNA

Assessing Tumor Response

RECIST 1.1
- Progressive Disease > 20% increase in diameter but also a 5 mm absolute increase now required
- Maximum lesions to determine response reduced to 5
- Maximum lesions per organ reduced to 2
- Assessment of lymph nodes now incorporated: nodes with short axis > 15 mm can be target lesions
- Interpretation of FDG-PET assessment now included


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CT Volume Measurement May Be Better

Challenge of CT Assessing Response

PET To Assess Treatment Response
Post-RT PET to Assess Pathology Response and Tumor Control

From a cohort of 56 resected patients, s/p chemo (N0-1) or chemoRT (N2), PET & CT within 1 month

Reduction of FDG activity has a linear correlation with non-viable tumor.

PET to Assess Pathology Response

PET is a more accurate predictor than the change of size on CT scan, irrespective of cell type of lung cancer

Cerfolio et al, ATS, 2004

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Post-RT PET Response and Overall Survival

PET and CT responses were identical in only 40% patients (weighted Kappa of 0.35) (Mac Manus et al, JCO, 2003).

PET and CT performed at 70 days post 60 Gy RT

PET after ChemoRT to Predict Survival

34 patients, 33 had both chemo and RT
RT=65-68 Gy, 1.5 Gy/d in 19 patients, 22 Gy, 2 Gy/d in 14 patients. One patient with initial stage T3 pN0 M0 disease received preoperative irradiation without chemotherapy (48.6 Gy) (Hellwig et al, 2004).

Post ChemoRT PET Predicts Survival

88 patients, 73 with chemoRT, 15 with RT alone (Mac Manus et al, 2005).

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Post-RT PET Response Predict Failure Pattern

HR of local failure for PMR pts: 2.15, P=0.009
HR of distant failure for PMR pts: 2.05, P=0.041

CMR (complete metabolic response) had lower local and distant failure.

Mac Manus et al, Lung Cancer, 2005
CMR Pts

PMR Pts

HR of local failure for PMR pts: 2.15, P=0.009
HR of distant failure for PMR pts: 2.05, P=0.041

Mac Manus et al, Lung Cancer, 2005
CMR Pts

PMR Pts

PERCIST

Complete metabolic response: SUL normalization of all lesions to less than the mean of their SUV and equal to normal surrounding tissue.

Partial metabolic response: SUL decrease in the SUL peak verification with follow-up study if anatomic criteria indicate disease progression.

Progressive metabolic disease: 1.5% increase to the SUV peak. 75% increase in TCG of the 5 most active lesions. Visible increase in extent of FDG uptake. Verification with follow-up study if anatomic criteria indicate complete or partial response.

No change or resolution: neither partial nor progressive disease.

PET and Assessment of Cancer Therapy

FDG-PET As a Biomarker for Cancer Treatment

PET and Assessment of Cancer Therapy

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FDG Activity Change After Chemo

FDG Uptake May Be A Surrogate for EGFR Mutation

| Table 6 - Relationship between EGFR mutation and 18F-FDG uptake in adenoma |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 18F-FDG uptake              | High (n=16)                 | Low (n=71)                  | p Value                     |
| EGFR Mutant                 | 2                           | 14                          | 0.003                        |
| Kaira et al, Respiratory Investigation, 2014; 52 (2) 121-128. |

Tumor Responses on CT, PET (FDG), PET (H20) and MRI

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The Greater Role of Imaging in RT Trial

More than RT decision post RT monitoring

- RT planning: simulation, target definition, conform radiation to the target and normal tissue sparing
- RT delivery: position/localization the patient, and monitor the changes in anatomy, density and biology during the course of RT

Why ART?

Motivation of ART: during-RT changes in tumor and normal tissue

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Changes During RT

- Patient changes: weight, shape, thickness
- Tumor changes: size, shape, texture, function...
- Organs at risk: organ fullness (stomach), function (atelectasis), fluid collection (pleural effusion)...
- Location and spacial relationships between tumor and normal tissue

Changes in Head and Neck Cancer on CT

Changes in CT Tumor Volumes in H&N

Gross tumor volumes decreased at a median rate of 0.2 cm³ or 1.8% of initial volume/treatment day.

Barker et al, Red Journal, 2004

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Changes in Tumor Location in H&N

Barker et al., Red Journal, 2004

Changes of Rectum in Prostate RT

ART Slideshare from Mayur Mayank

Changes of Rectal Volume During RT

Ratio of rectal volume during radiotherapy course over rectal volume on simulation CT scan for during RT course.

Frank et al., Red Journal, 2008

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Changes of Bladder Volume During RT

Ratio of bladder volume during radiotherapy course over bladder volume on simulation CT scan for during RT course.


Changes of Prostate and SV During RT

Prostate and seminal vesicle (SV) anteroposterior (AP) random variability by change in rectal filling (data from all patients combined).


Misses of Prostate and SV During RT

Frequency of prostate and seminal vesicle (SV) misses as function of margin size (internal organ variation only).


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Tumor Shrinks During RT Measured by CBCT

Ramsey et al, 2006
Integrating clinical trial and ART, Kong AAPM 2017

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Metabolic Tumor Volume Shrinks More

50 pts, 88 tumors
NSCLC

CT-GTV During RT (40% reduction)
PET-GTV During RT (30% reduction)

70% PET volume reduction

Summary Changes During RT
both tumor and normal tissues

- Set-up errors
- Target and organ motion
- Anatomic changes in location and size
- Biologic functional changes

Without ART, one may miss the tumor or harm the patients by over dosing the normal tissues.

What is (ART)?
Role of Advanced Imaging.

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What Is ART?

- It is not just IGRT
- It uses IGRT for guidance and takes motion into consideration
- ART applies adaptive plan to patient-specific changes that are unaccounted for in initial plan.

ART Original Concept (2D)

- Traditionally, “Adaptive radiation therapy is a closed-loop radiation treatment process where the treatment plan can be modified using a systematic feedback of measurements.”… EPID
- By adjusting the patients’ position and MLC shapes, the mean systematic error was 4 mm with a range of 2 to 7 mm before adjustment. It was reduced to 0.5 mm with a range of 0.2 to 1.4 mm after adjustment.
- By decreasing margin, dose may be escalated safely.

Advanced Image Guided ART: Evolving ART Concept

- 2D-E PID guided ART to individually adapt the PTV margin
- 3D-CBCT, CT-on-rail, MVCT guided ART for offline, online replanning
- 4D: 4D online MRI guided ART for online/realtime adoption
- 5D: Biological, functional imaging guided ART—BigART
Earlier Process of Adaptive RT

Set-up Errors

Brabbins et al., Red Journal, 2005

Current ART Process

Online: physicist, therapist, physician
Real time: physicist, therapist, physician
Offline: dosimetrist, physicist and physician

Olson: Suitable for progressive change and we need response to RT

Fraction: Physical Changes

Essential Components for Modern ART

- Modern pretreatment imaging
- Real time imaging to detect the changes
- Evaluation the changes in tumor and OARs
- Precise image registration (deformable)
- Model based segmentation, automatic re-contouring (ideally)
- Accurate dose computation (deformable)
- Rapid automatic treatment planning (ideally)
Biology Guided Adaptive Radiation Therapy (BigART)

- Adaptation of RT in time and space
- Based on biological and anatomic features
- Combined consideration of tumor and normal tissue

PET Guided BigART Improves Tumor Control

- UMCC2007123
  - ART escalated doses to 86Gy while kept lung NTCP at 17.2%
  - 82% 2-year tumor control, versus
    - 34% historical control from UM
    - 65% from RTOG617
- Mature results also show a potential to improve survival

An ART Clinical Trial in NSCLC: BigART

Leaning from RTOG1106

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Motivation of the Study: Tumor Changes on PET-CT

Example of Tumor Changes on PET-CT

Advantages of during-PET ART

- Tumor dose can be escalated by 19% more if the lung normal tissue complication probability (NTCP) is kept same.
- Lung NTCP could be decreased by 18% if the tumor dose is unchanged.

Example:
- Pt # Mr. B, keep lung NTCP unchanged (this case was 9%)
- Re-simulation at 40 Gy, start boost RT at 50 Gy
- GTV reduced by 50%
- Total dose escalated by 11 Gy
- Code dose decreased by 12 Gy

Kong et al, JCO, 2007

Feng (Kong), Red Journal, 2009

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UMCC 2007-123

Using FDG-PET Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with NSCLC

PET and CT based conformal therapy, 2.2-2.85 Gy daily, to 17.2% NTCP for lung

CT restimulation and PET-CT during RT (at 40-50 Gy)

Reg plan based on during-RT PET target, keeping lung NTCP 17.2%

PET and CT based conformal therapy, 2.2-2.85 Gy daily, to 17.2% NTCP for lung

Adaptive plan individualized to each tumor

NSCLC Unresectable Inoperable Stage II-III

PET and CT based conformal therapy

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Original Dose In ART Arm

<table>
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<th>Fraction</th>
<th>Dose</th>
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</table>

Treatment Targets

30 daily fractions, 2.2-4.25 Gy daily fractions

2.2-2.85 Gy/Fx

2.4-4.25 Gy/Fx

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RTOG1106: BiGART in NSCLC

The Primary Endpoint: 2 year local-regional tumor control rate
*1:2 randomization, stratified by MLD > vs < 14 Gy; GTV > vs < 200cc, and squamous vs nonsquamous ca.

Control arm:
- RTOG 0617 arm
- Uniform dose RT

Experimental arm:
- Individualized adaptive RT

The Primary Endpoint: 2 year local-regional tumor control rate

1) Doses to OARs are strictly limited
2) Lower prescription dose and greater dose heterogeneity to reach the dose limits of OARs

Mandates of Imaging Radiation Technology
- 3DCRT/IMRT
- PET scanner must be ACRIN credentialed
- Precise imaging registration (rigid) is mandatory
- 4DCT motion assessment is essential
- IGRT is mandatory for adaptive phase of RT
- PET metabolic target was the primary target for ART
- PET based adaptive design is essential

This is the first RTOG trial in stage III NSCLC requiring all of these modern technologies for daily fractionated RT

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Credentialing Requirements

- ACRIN credentialing
  - Institution
  - PET scanner
- RTOG credentialing:
  - IGRT and imaging registration
  - IMRT if you would like to use
  - Motion management
  - Dry-run case for target, OARs, imaging registration and RT planning

http://atc.wustl.edu/protocols/rtog/1106/1106.html

Can Everybody Do BigART?

Preparation of RTOG1106 ART Trial

Three dry run planning studies were performed through 12-14 centers.

RTOG1106 Dry-Run Case #1

60 years old female with T4 N2 M0 stage IIIB NSCLC of the right lower/middle lobe, a patient treated at UMCC2007123
Uniform plan on pre-treatment PET-CT

Adaptive plan on during-treatment PET-CT

Higher dose to residual active tumor!!

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### Dosimetric Effect of the Adaptive Plan Doses of PTV and OARs for Case #1

<table>
<thead>
<tr>
<th>Plan Bs</th>
<th>Mean Lung Dose (Gy)</th>
<th>LUNG V20 (%)</th>
<th>ESOPH Max (Gy)</th>
<th>ESOPH Mean (Gy)</th>
<th>ESOPH V65 (%)</th>
<th>CORD Max (Gy)</th>
<th>HEART V40 (%)</th>
<th>HEART V65 (%)</th>
<th>BRACH Max</th>
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<tr>
<td>Plan As</td>
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<td></td>
<td>9.99</td>
<td>-1.70</td>
<td>1.36</td>
<td>-3.69</td>
<td>14.32</td>
<td>-0.93</td>
<td>-6.57</td>
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<tr>
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<td>25.35</td>
<td>-1.70</td>
<td>1.36</td>
<td>-3.69</td>
<td>14.32</td>
<td>-0.93</td>
<td>-6.57</td>
<td></td>
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</tr>
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</table>

### Members Participated 1st Case

- University of Michigan/AAVA: Feng-Ming Kong MD PhD, Cassandra Brooks CMD, Tim Ritter PhD
- Case Western University Hospital: Michael Godley MD, Jason Salski PhD
- Thomas Jefferson Hospital: Maria Sanci-Morrone MD, Ying Xue PhD, Janny Kueh RTT, MBn
- Cleveland Clinic: Gregory Vajda MD, Nicole Vossel CMD, Donna Malton, CMD
- Stanford University: Billy Lee MD, Peter Marks PhD
- Medical College of Wisconsin: Elizabeth Faller MD, Bo-Tao PhD, Dan Selove MD
- Penn State Hershey Cancer Center: John Varlotta MD, Javiera Kragiat CMD
- McGill Hospital: Sheng Fu MD, Emily Mann PhD
- Moffitt Cancer Center: Timothy Spilka MD, Mark Rosen CMD, Mary-Lou Dufresne CMD
- Princess Margaret Hospital: Alexander Sun MD, Jane Higgins CMD
- University of Texas Medical Branch: Luczac Saab MD, A J Grubski CMD
- Peking Union Medical College: Luhua Wang MD, Bo Chen MD
- MD Anderson Cancer Center: Masashi Kenami MD, David Miller CMD
- Washington University at St Louis: Jeffrey Hickey, MD, Lindsay Aupperle, MB

### Changes in Normal Tissue

- Baseline 0 Gy 0 Day
- 46 Gy 39 days
- 50 Gy 42 days

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Global Pulmonary Function During-RT

- Mean % predicted
- Absolute value

Radiation Induced Changes in Diffusion

Individual Differences in DLCO responding to RT

- 47% patients remain +10% of baseline level.
- 20% patients improved (more than 10% elevation).
- 30% patients decreased (more than 10% reduction).

V-Defect Score During- & Post-RT

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V/Q SPECT of Central and Peripheral Tumors

V/Q SPECT Lung Function Map

Q Changes During- and Post-RT

After 12 months, Q reduced in most cases for functioning lung (red), unchanged in defect lung (green).

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After 12 months, V reduced in most cases for functioning lung (red), unchanged in defect lung (green).

Lung V/Q SPECT to Guide Adaptive RT

The mean lung dose to the functioning lung reduced by 2 Gy.

Ten Haken et al. 2009

Advanced Imaging in ART: BigART

Locally advanced NSCLC for Example

Basel on

PET and CT based biological strategy

To normal tissue and host immune function based BigART

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- Dick Fraass

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- David Jerama
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- Lon Marsh

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- Xuwei Cai
- Jingbo Wang
- Weili Wang
- Pawinee Mahasittiwat
- Xue Meng
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- Bing Xia
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- Yaping Xu
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- Andrew Chang
- Rishi Reddy
- Jules Lin

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- Michele Castle
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- Kate Ersting
- Kate Hurffman

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- Dean Brenner
- Kemp Cease

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- Kevin Flaherty
- Jeffrey Curtis

Pathologists:
- Jeffrey Myers
- Lindsay Schmidt

Lab Scientists:
- David Lehman
- David Beers

INFORMATION

INFORMATION

Thank you!!!

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Sam #1: Which of the following is true for FDG-PET during the course of fractionated radiotherapy?
- Should not be performed as there will be radiation inflammation to cause confounding effects
- Can be performed during the course of RT, but with significant noise from normal lung
- Has limited role on adaptive treatment
- *Can guide adaptive treatment to escalate RT dose without increasing doses to normal tissue

Kong et al, JCO, 2017
Feng (Kong) et al, Red Journal, 2017

Sam #2: Lung V/Q SPECT-CT
- V/Q SPECT can be used to map lung function during the course of fractionated radiation therapy. Which of the following is correct?
  - A. Can be easily registered retrospectively without a CT scan
  - B. Changes little during the course of fractionated RT in vast majority of patients
  - C. Changes on V/Q SPECT during the course of radiation may have significant impact on functional dosimetry
  - D. V/Q SPECT has not been done clinically during the course of radiation therapy, the changes are unknown to radiation oncology community


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