INDIANA UNIVERSITY
SCHOOL OF MEDICINE

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

Feng-Ming (Spring) Kong, MD, PhD, FACR
Professor of Radiation Oncology and Medical & Molecular Genetics
Director of Clinical Research, Department of Radiation Oncology
Co-leader of Thoracic Oncology Program
Indiana University School of Medicine

AAPM Annual Meeting, Denver, 8-2-2017

Imaging for clinical trial and ART, Kong AAPM 2017

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)

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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)

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Imaging Modality for Response Assessment

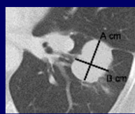
- 2D X-ray, ultrasounds…
- CT is applicable for most conditions
- MRI or PET functional imaging depending on the organs of origin and tumor types
- MRI for brain, liver, pancreas
- PET for head and neck, cervical cancer, lymphoma… lung

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

CT Imaging Response Assessment

WHO Criteria: AxB cm2



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

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

Nichino M et al, Academic Radiology, 2011

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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

Eisenhauer, Therasse, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline. Eur J of Cancer. 2009;45:228-247.

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

CT Volume Measurement May Be Better

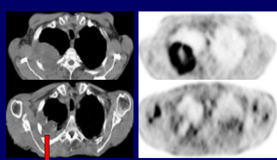
NISHINO ET AL — Academic Radiology, Vol 18, No 1, January 2011

TABLE 2. Intraobserver Agreement for Volume, Uni- and Bidimensional, and CT Attenuation Coefficient Measurements

Types of Measurement	Average Concordance Correlation Coefficient*	Average Mean Relative Difference (%)*	Average Standard Deviation*	Average Trimmed Standard Deviation*	Average Percentage of Observations Inside the Limits (%)*
Volume	0.992 (0.985–0.996)	−5.4 (−9.3, −0.2)	0.148 (0.104–0.220)	0.088 (0.064–0.113)	95.0 (90.5, 98.1)
Longest diameter	0.977 (0.971–0.984)	−3.2 (−6.0, −0.7)	0.110 (0.098–0.117)	0.086 (0.071–0.095)	94.7 (90.5, 98.1)
Longest perpendicular diameter	0.959 (0.946–0.971)	−1.7 (−5.2, 21.3)	0.160 (0.138–0.197)	0.117 (0.100–0.130)	94.3 (90.5, 96.2)
Bidimensional	0.975 (0.959–0.989)	−5.1 (−8.4, 0.3)	0.210 (0.186–0.234)	0.165 (0.141–0.187)	94.7 (92.4, 98.1)
CT attenuation coefficient	0.984 (0.974–0.996)	6.6† (−3.1, 13.7)	26.2† (12.6–33.4)	16.4† (10.1–21.6)	94.5 (90.5, 96.2)

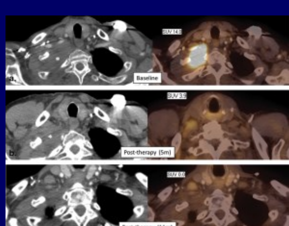
*Numbers in parentheses represent range of each statistical parameter.
†The numbers in these cells are in Hounsfield units (HU).

Challenge of CT Assessing Response

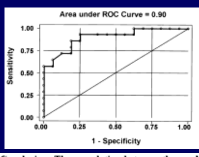


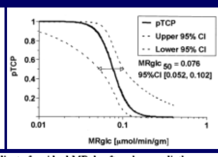
Tumor or scar tissue? PET can be helpful.

PET To Assess Treatment Response



Post-RT PET to Assess Pathology Response and Tumor Control





Conclusion: The correlation between the gradient of residual MRglc after chemoradiotherapy and pTCP is an inverse dose–response relationship. Residual MRglc of 0.076 and ≤0.040 μmol/min/g, representing pTCP 50% and pTCP ≥95%, respectively, may be useful surrogate markers for the tumor response to radiotherapy or chemoradiotherapy in lung cancer. © 2002 Elsevier Science Inc.

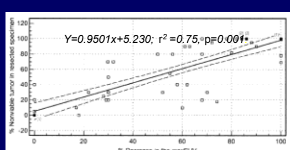
Choi et al, Red Journal, 2002

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

PET to Assess Pathology Response

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.

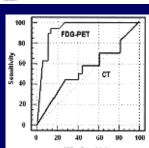
INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

PET to Assess Pathology Response

	Sensitivity		Specificity		Accuracy		PPV		NPV	
	FDG-PET	CT	FDG-PET	CT	FDG-PET	CT	FDG-PET	CT	FDG-PET	CT
≥60%	100%	63%	95%	54%	96%	57%	90%	41%	100%	74%
≥70%	95%	47%	97%	59%	96%	56%	94%	38%	97%	69%
≥80%	90%	47%	100%	63%	96%	57%	100%	27%	95%	70%
≥90%	63%	42%	100%	68%	88%	59%	100%	40%	84%	69%

* All p values are <0.05.



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

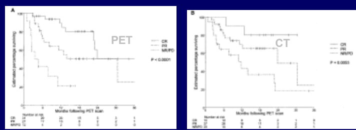
Cerfolio et al, ATS, 2004

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Post-RT PET Response and Overall Survival

73 pts, PET and CT performed at 70 days post 60 Gy RT



PET and CT responses were identical in only 40% patients (weighted Kappa of 0.35).

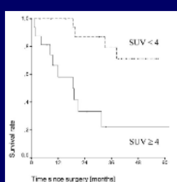
but on multifactor analysis that included the known prognostic factors of CT response, performance status, weight loss, and stage, only PET response was significantly associated with survival duration (P < .0001).

Mac Manus et al, JCO, 2003

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

PET after ChemoRT to Predict Survival



- 34 patients, 33 had both chemo and RT
- RT=(45-68 Gy,1-1.5 Gy/d, in 19 patients; 32 Gy, 2 2 Gy/d, in 14 patients). One patient with initial stage T3 pN0 M0 disease received preoperative irradiation without chemotherapy (48.6 Gy)

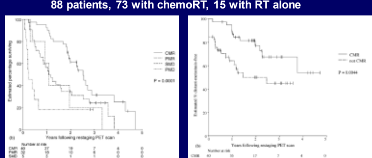
Hellwig et al, 2004

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Post ChemoRT PET Predicts Survival

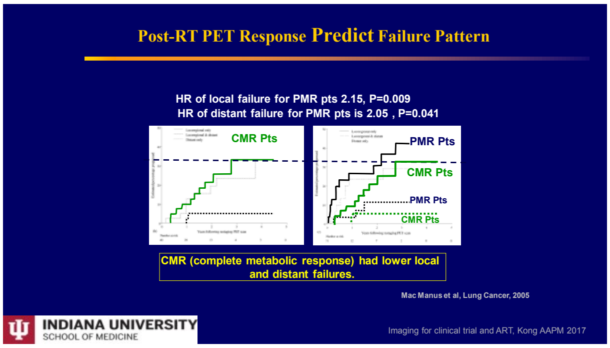
88 patients, 73 with chemoRT, 15 with RT alone

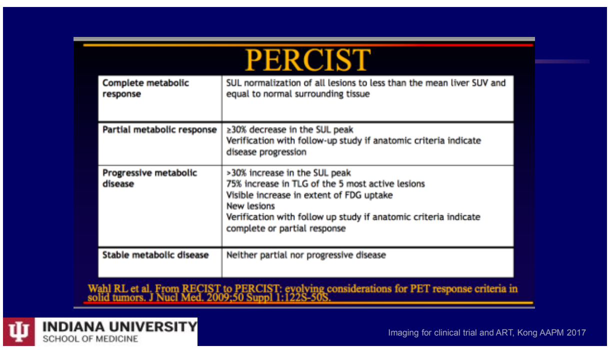


Mac Manus et al, 2005

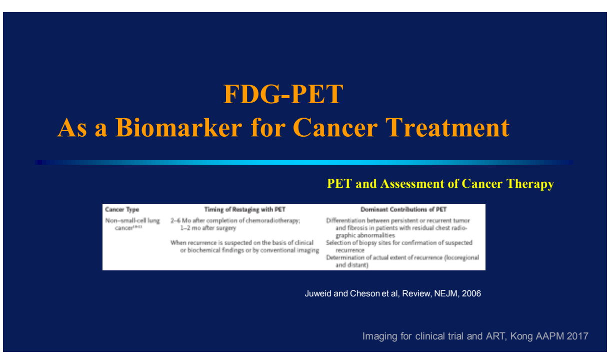
INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017



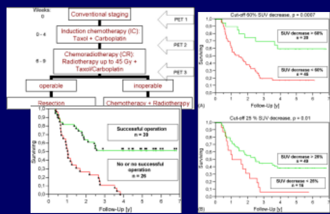


Complete metabolic response	SUL normalization of all lesions to less than the mean liver SUV and equal to normal surrounding tissue
Partial metabolic response	≥30% decrease in the SUL peak Verification with follow-up study if anatomic criteria indicate disease progression
Progressive metabolic disease	>30% increase in the SUL peak 75% increase in TLG of the 5 most active lesions Visible increase in extent of FDG uptake New lesions Verification with follow up study if anatomic criteria indicate complete or partial response
Stable metabolic disease	Neither partial nor progressive disease



Cancer Type	Timing of Restaging with PET	Dominant Contributions of PET
Non–small-cell lung cancer	2–6 Mo after completion of chemoradiotherapy; 1–2 mo after surgery	Differentiation between persistent or recurrent tumor and fibrosis in patients with residual chest radiographic abnormalities
	When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging	Selection of biopsy sites for confirmation of suspected recurrence Determination of actual extent of recurrence (locoregional and distant)

FDG Activity Change After Chemo



Eschmann et al, 2007

PET1 vs PET2

FDG Uptake May Be A Surrogate for EGFR Mutation

Table 4 – Relationship between EGFR mutation and ^{18}F-FDG uptake in adenocar

^{18}F-FDG uptake		Preoperative primary site High ($n = 14$)	Preoperative primary site Low ($n = 21$)	p-Value
EGFR	Mutant	2	14	0.015
	Wild-type	12	9	

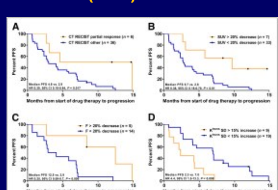
Abbreviation: EGFR, epidermal growth receptor factor.

K Kaira et al, Respiratory Investigation, *2014, 52 (2) 121-128,*

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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



PFS stratified for response after 3 wk of treatment according to CT (A), 18F-FDG PET (B), H215O PET (C), and DCE MRI (D). Adrianus J. de Langen et al. J Nucl Med 2010;52:48-55

JNM

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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)

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Why ART?

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

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

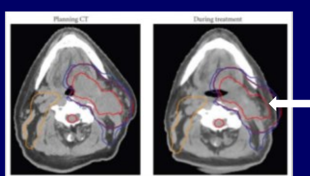
Changes During RT

- 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

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

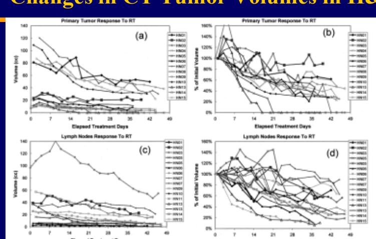
Changes in Head and Neck Cancer on CT



INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Changes in CT Tumor Volumes in H&N

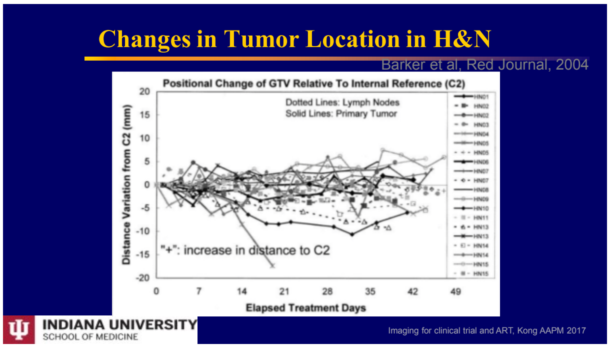


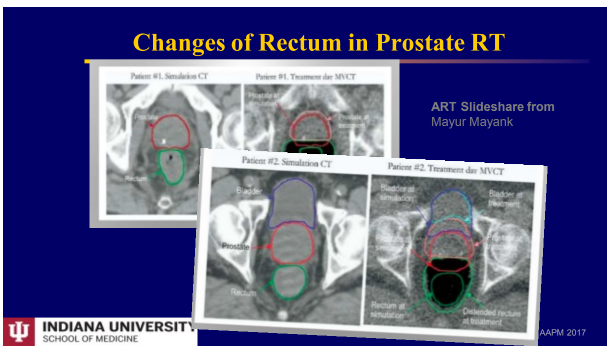
Barker et al, Red Journal, 2004

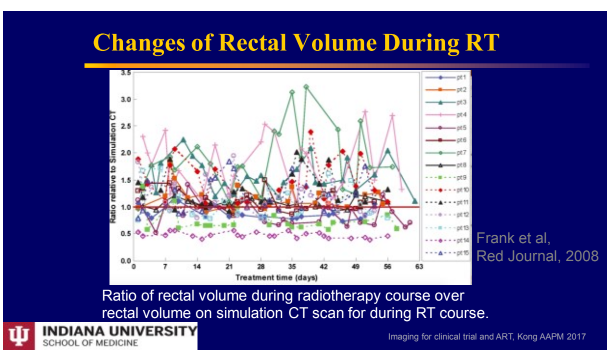
Gross tumor volumes decreased at a median rate of 0.2 cm^3 or 1.8% of initial volume/treatment day.

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

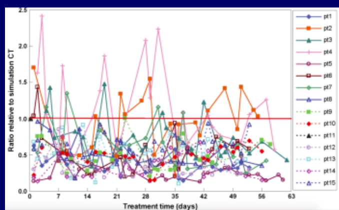
Imaging for clinical trial and ART, Kong AAPM 2017


Changes in Tumor Location in H&N
Barker et al, Red Journal, 2004
Positional Change of GTV Relative To Internal Reference (C2)
Dotted Lines: Lymph Nodes
Solid Lines: Primary Tumor
Distance Variation from C2 (mm)
"+": increase in distance to C2
Elapsed Treatment Days
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017


Changes of Rectum in Prostate RT
ART Slideshare from
Mayur Mayank
Patient #1. Simulation CT
Patient #1. Treatment day MVCT
Patient #2. Simulation CT
Patient #2. Treatment day MVCT
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
AAPM 2017


Changes of Rectal Volume During RT
Ratio relative to Simulation CT
Treatment time (days)
Frank et al,
Red Journal, 2008
Ratio of rectal volume during radiotherapy course over
rectal volume on simulation CT scan for during RT course.
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

Changes of Bladder Volume During RT



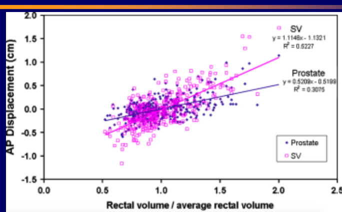
Frank et al, Red Journal, 2007

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

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Changes of Prostate and SV During RT



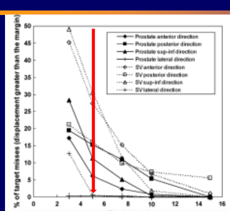
Frank et al, Red Journal, 2007

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

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Misses of Prostate and SV During RT



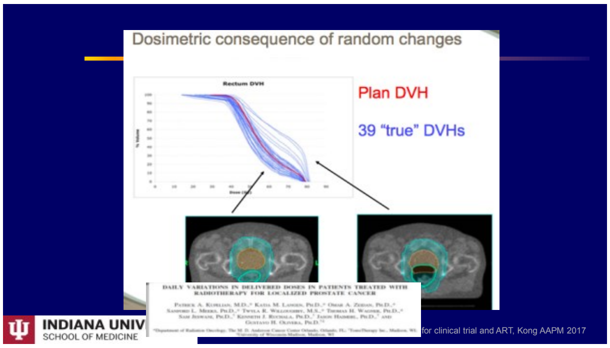
Frequency of prostate and seminal vesicle (SV) misses as function of margin size (internal organ variation only).

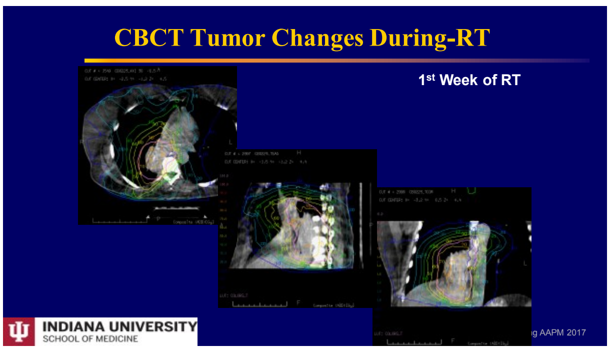
For 5 mm margin, 15% of times had posterior direction miss for both Prostate and SV, 30% of times SV will have misses at anterior and superior/inferior directions, without ART.

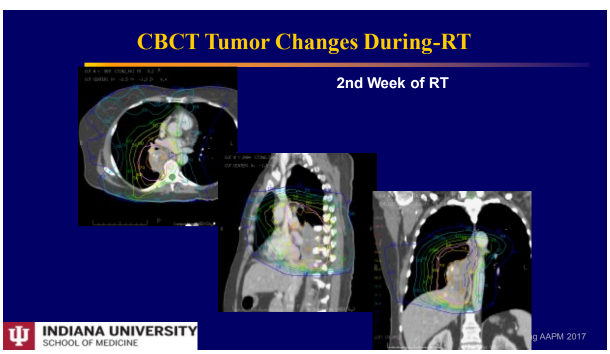
Frank et al, Red Journal, 2007

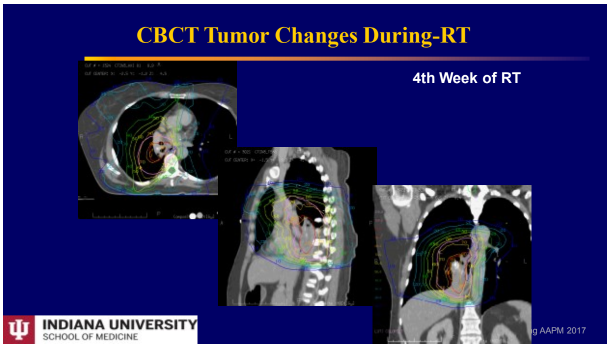
INDIANA UNIVERSITY SCHOOL OF MEDICINE

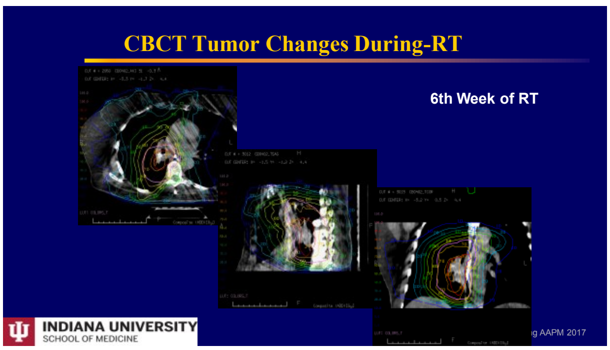
Imaging for clinical trial and ART, Kong AAPM 2017

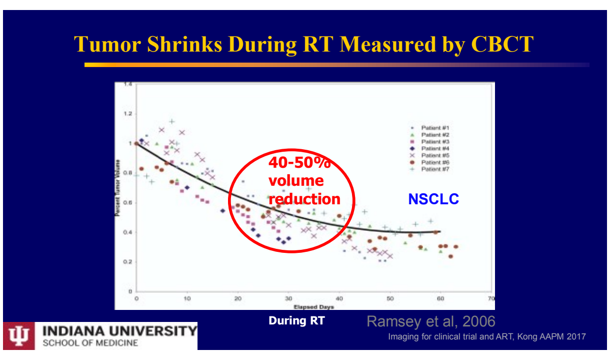

Dosimetric consequence of random changes
Rectum DVH
Plan DVH
39 "true" DVHs
DAILY VARIATIONS IN DELIVERED DOSES IN PATIENTS TREATED WITH RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER
INDIANA UNIV
SCHOOL OF MEDICINE
for clinical trial and ART, Kong AAPM 2017


CBCT Tumor Changes During-RT
1st Week of RT
INDIANA UNIVERSITY
SCHOOL OF MEDICINE

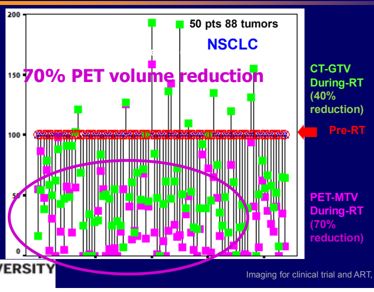

CBCT Tumor Changes During-RT
2nd Week of RT
INDIANA UNIVERSITY
SCHOOL OF MEDICINE


CBCT Tumor Changes During-RT
4th Week of RT
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
g AAPM 2017


CBCT Tumor Changes During-RT
6th Week of RT
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
g AAPM 2017


Tumor Shrinks During RT Measured by CBCT
40-50% volume reduction
NSCLC
During RT
Ramsey et al, 2006
Imaging for clinical trial and ART, Kong AAPM 2017
INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Metabolic Tumor Volume Shrinks More



INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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.

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

What is (ART)? Role of Advanced Imaging.

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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.

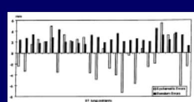
INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

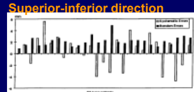
ART Original Concept (2D)

- 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.

Systemic and random errors



Superior-inferior direction



Lateral direction Yan et al, 1997 &1998

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Advanced Image Guided ART: Evolving ART Concept

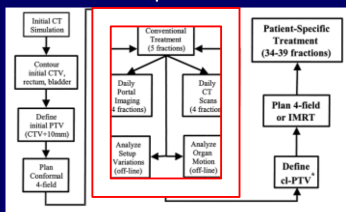
- 2D-EPID guided ART to individually adapt the PTV margin
- 3D-CBCT, CT-on-rail, MVCT guided ART for offline, online replanning
- 3D, 4D online MRI guided ART for online/realtime adoption
- 5D: Biological, functional imaging guided ART~ BigART

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Earlier Process of Adaptive RT

Set-up Errors



Brabbins et al, Red Journal, 2005

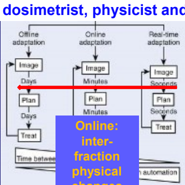
INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Current ART Process

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

Offline: Suitable for progressive change such as tumor response to RT



intra-fraction physical changes

Online: inter-fraction physical changes

Keall, Shu and Xing: http://clinicalgate.com/image-guided-adaptive-radiotherapy/, 2015

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Essential Components for Modern ART

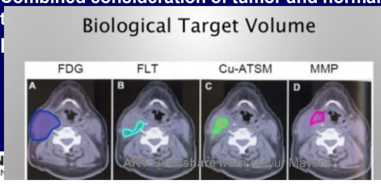
- Modern pretreatment imaging
- Real time imaging to detect the changes
- Evaluation the changes in tumor and OARs
- Precise image registration (deformable)
- Model based segmentation, automatic re-contouring (ideally)
- Accurate dose computation (deformable)
- Rapid automatic treatment planning (ideally)

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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



INDIANA UN
SCHOOL OF MEDICIN

…, Kong AAPM 2017

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

Kong et al, JAMA Oncology, 2017

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

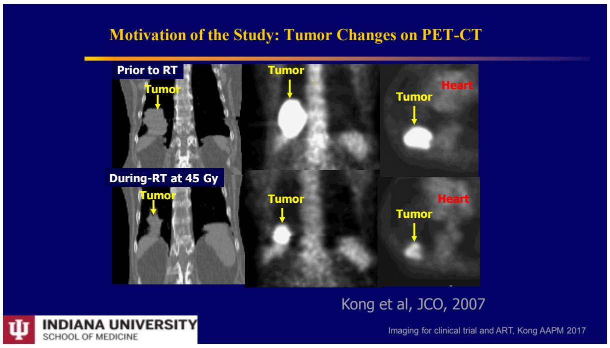
Imaging for clinical trial and ART, Kong AAPM 2017

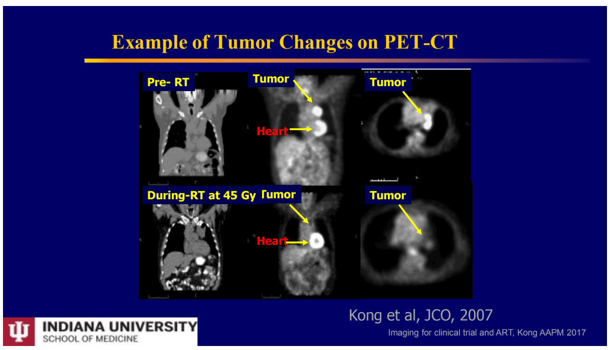
An ART Clinical Trial in NSCLC: BigART

Leaning from RTOG1106

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017





Advantages of during-PET ART

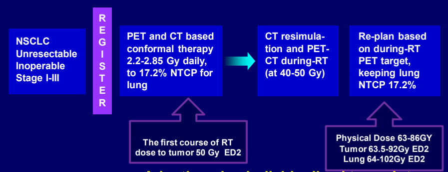
- **Tumor dose can be escalated by 19% more if the lung normal tissue complication probability (NTCP) is kept same**
- **Lung NTCP could be decreased by 18% if the tumor dose is unchanged**
- **Example:**
  - **Pt # Mr. B, keep lung NTCP unchanged (this case was 9%)**
    - Re-simulation at 40 Gy, start boost RT at 50 Gy
    - GTV reduced by 50%
    - Total dose escalated by 11 Gy
    - Code dose decreased by 12 Gy

Feng (Kong), Red Journal, 2009

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

UMCC 2007-123

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



Adaptive plan individualized to each tumor

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Original Dose In ART Arm

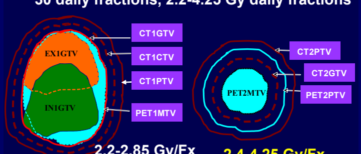
Mean Lung	Initial	# Fractions	Physical	Adaptive Phase	Adaptive Phase	# Fraction	Total
Dose for	Dose	for ~50 Gy	Dose	Max Dose	Physical	for ART	Physical
74 Gy	per fx	EQD2	at this point	per fx	Max Dose		Max Dose
PTV dose	(Gy)	Tumor Dose	(Gy)	(Gy)	(Gy)	(Gy)	(Gy)
<13.5	2.85	17	48.45	2.85	37.05	13	85.5
13.5	2.85	17	48.45	2.85	37.05	13	85.5
13.9	2.80	17	47.6	2.9	37.7	13	85.3
14.3	2.75	18	49.5	3	36	12	85.5
14.7	2.70	18	48.6	3.05	36.6	12	85.2
15.1	2.65	18	47.7	3.15	37.8	12	85.5
15.5	2.60	19	49.4	3.25	35.75	11	85.2
16.0	2.55	19	48.45	3.3	36.3	11	84.8
16.5	2.50	19	47.5	3.4	37.4	11	84.9
17.0	2.45	20	49	3.55	35.5	10	84.5
17.6	2.40	20	48	3.65	36.5	10	84.5
18.1	2.35	21	49.35	3.85	34.65	9	84.0
18.7	2.30	21	48.3	3.9	35.1	9	83.4
19.3	2.25	22	49.5	4.15	33.2	8	82.7
20.0	2.20	22	48.4	4.25	34	8	82.4
>20	2.20	22	48.4	4.25	34	8	82.4

INDIANA UN
SCHOOL OF MEDICINE

and ART, Kong AAPM 2017

Treatment Targets

30 daily fractions, 2.2-4.25 Gy daily fractions

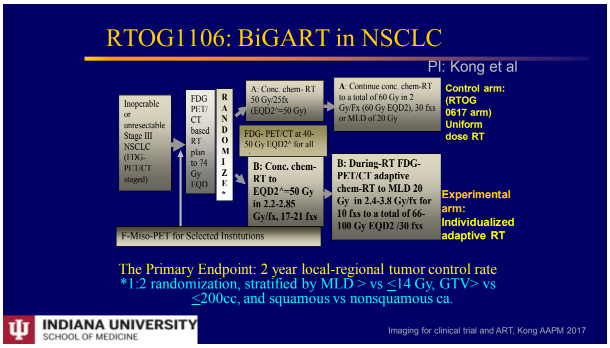


Targets for the 1st plan
CT1GTV = EX1GTV + IN1GTV + PET1MTV
CT1CTV = CT1GTV + 0.5 cm
CT1CTV = CT1GTV + at least 0.5 cm

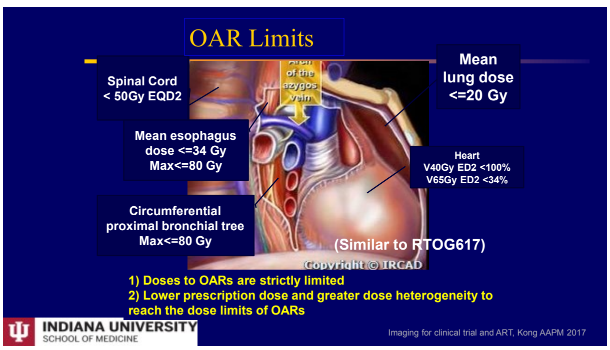
Targets for adaptive plan
PET2PTV = PET2MTV + 0.5 cm

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

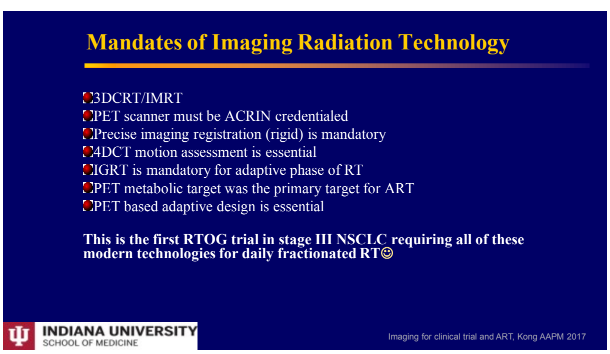
Imaging for clinical trial and ART, Kong AAPM 2017



RTOG1106: BiGART in NSCLC
PI: Kong et al
Inoperable or unresectable Stage III NSCLC (FDG-PET/CT staged)
FDG PET/CT based RT plan to 74 Gy EQD
RANDOMIZE*
A: Conc. chem- RT 50 Gy/25fx (EQD2^=50 Gy)
A: Continue conc. chem-RT to a total of 60 Gy in 2 Gy/Fx (60 Gy EQD2), 30 fxs or MLD of 20 Gy
Control arm: (RTOG 0617 arm) Uniform dose RT
FDG- PET/CT at 40-50 Gy EQD2^ for all
B: Conc. chem-RT to EQD2^=50 Gy in 2.2-2.85 Gy/fx, 17-21 fxs
B: During-RT FDG-PET/CT adaptive chem-RT to MLD 20 Gy in 2.4-3.8 Gy/fx for 10 fxs to a total of 66-100 Gy EQD2 /30 fxs
Experimental arm: Individualized adaptive RT
F-Miso-PET for Selected Institutions
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.
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017



OAR Limits
Spinal Cord < 50Gy EQD2
Mean esophagus dose <=34 Gy Max<=80 Gy
Circumferential proximal bronchial tree Max<=80 Gy
Mean lung dose <=20 Gy
Heart V40Gy ED2 <100% V65Gy ED2 <34%
of the azygos vein
(Similar to RTOG617)
Copyright © IRCAD
1) Doses to OARs are strictly limited
2) Lower prescription dose and greater dose heterogeneity to reach the dose limits of OARs
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017



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☺
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

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?

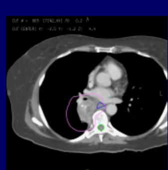
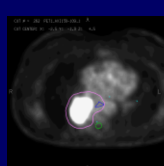
Preparation of RTOG1106 ART Trial

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

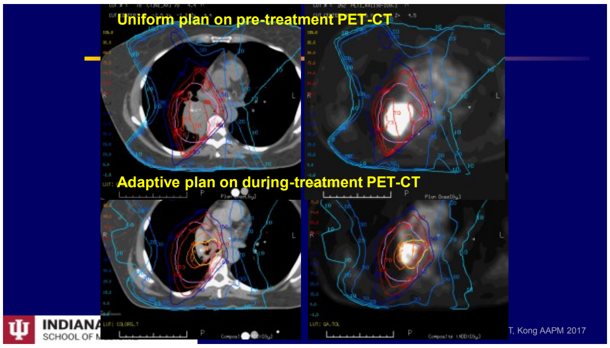
INDIANA UNIVERSITY SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

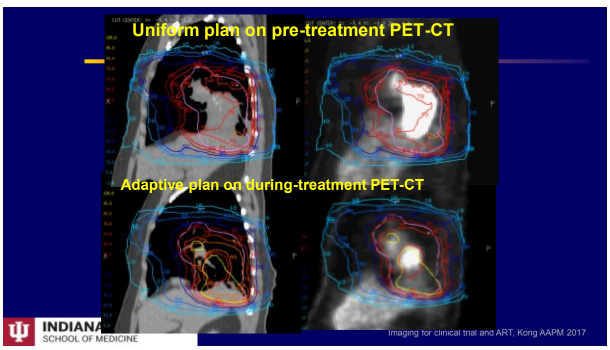
RTOG1106 Dry-Run Case #1

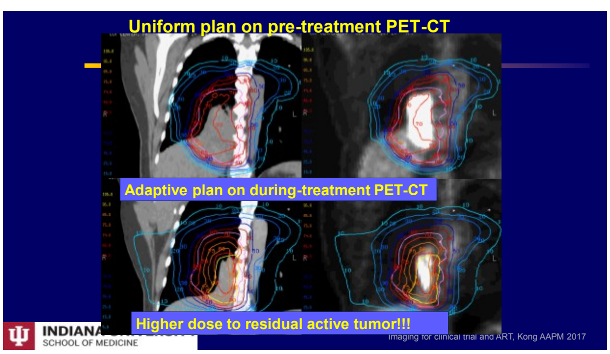
60 years old female with T4 N2 M0 stage IIIB NSCLC of the right lower/middle lobe, a patient treated at UMCC2007123

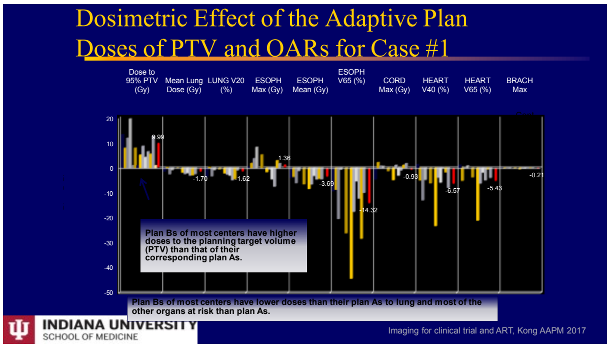



INDIANA UNIVERSITY SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017


Uniform plan on pre-treatment PET-CT
Adaptive plan on during-treatment PET-CT
INDIANA
T, Kong AAPM 2017


Uniform plan on pre-treatment PET-CT
Adaptive plan on during-treatment PET-CT
INDIANA
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

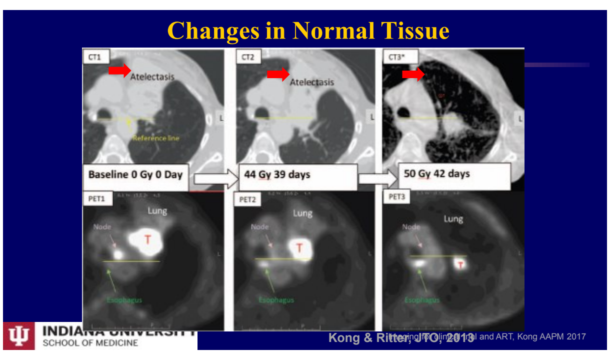

Uniform plan on pre-treatment PET-CT
Adaptive plan on during-treatment PET-CT
Higher dose to residual active tumor!!!
INDIANA
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

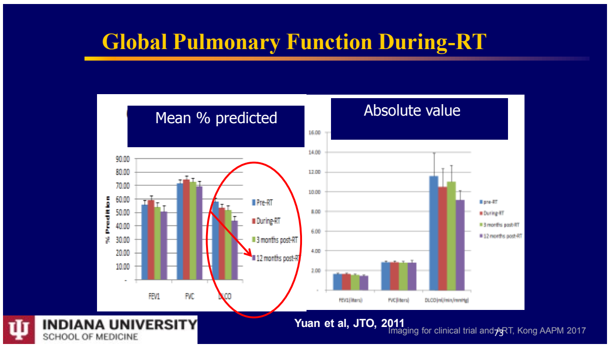


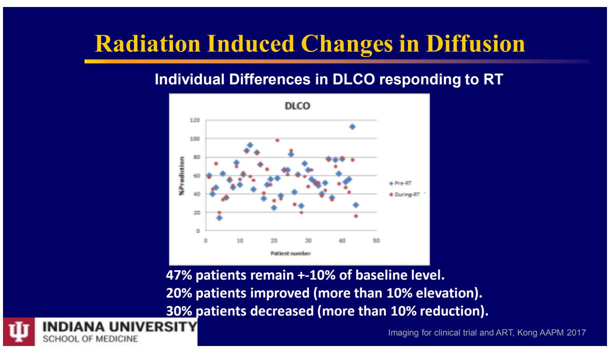
Members Participated 1st Case

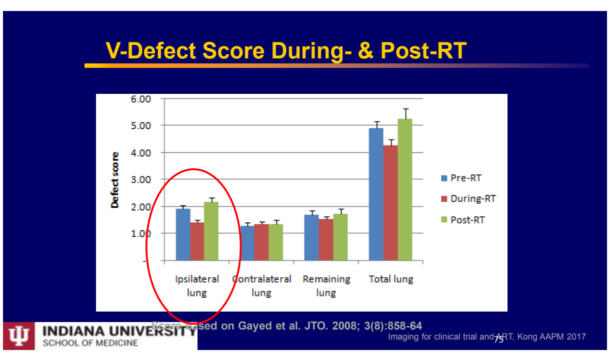
- **University of Michigan/AAVA:** Feng-Ming Kong MD PhD, Cassandra Brooks CMD, Tim Ritter PhD
- **Case Western University Hospital:** Mitchell Machtay MD, Jason Sohn PhD
- **Thomas Jefferson Hospital:** Maria Werner-Wasik MD, Ying Xiao PhD, Joyce Keil RTT, Nitin Ohri MD
- **Cleveland Clinic:** Gregory Videtic MD, Nicole Vassil CMD, Diana Mattson, CMD
- **Stanford University:** Billy Loo MD, Peter Maxim PhD
- **Medical College of Wisconsin:** Elizabeth Gore MD, An Tai PhD, Dan Grimm MS
- **Penn State Hershey Cancer Center:** John Varlotto MD, Jamie Knipple CMD
- **McGill Hospital:** Sergio Faria, MD, Emily Moon PhD
- **Moffitt Cancer Center:** Thomas Dilling MD, Mark Russell CMD, MaryLou DeMarco CMD
- **Princess Margaret Hospital:** Alexander Sun MD, Jane Higgins CMD
- **University of Texas Medical Branch:** Todd Swanson MD, E.J. Endres CMD
- **Peking Union Medical College:** Luhua Wang MD, Bo Chen MD
- **MD Anderson Cancer Center:** Ritsuko Komaki MD, Steph Bilton CMD
- **Washington University at St Louis:** Jeffrey Bradley MD, Lindsey Appenzoller, MS

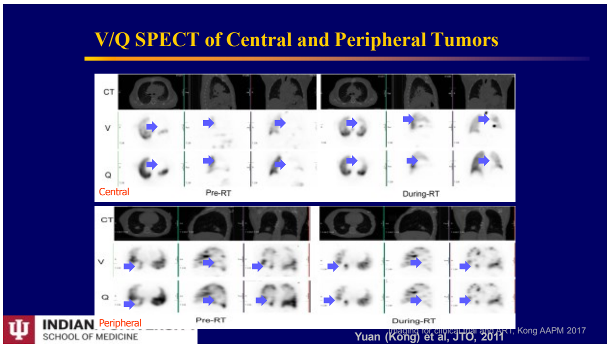
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

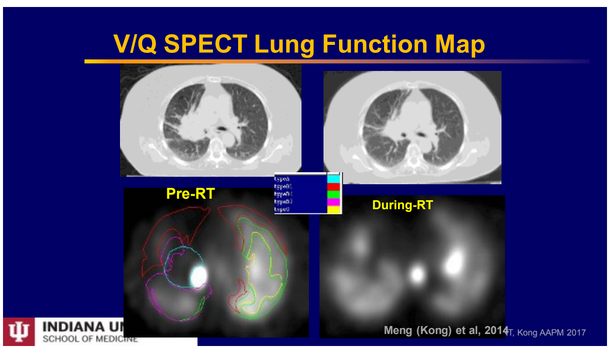


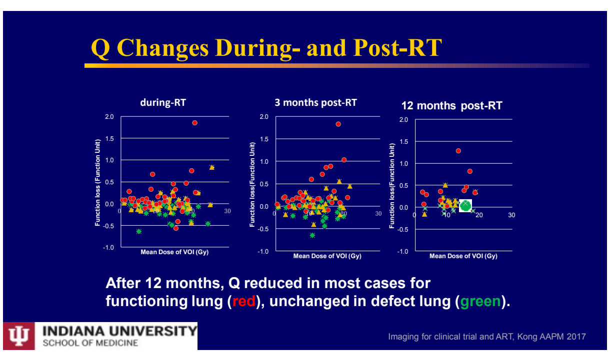

Global Pulmonary Function During-RT
Mean % predicted
Absolute value
Pre-RT
During-RT
3 months post-RT
12 months post-RT
FEV1
FVC
DLCO
Yuan et al, JTO, 2011
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

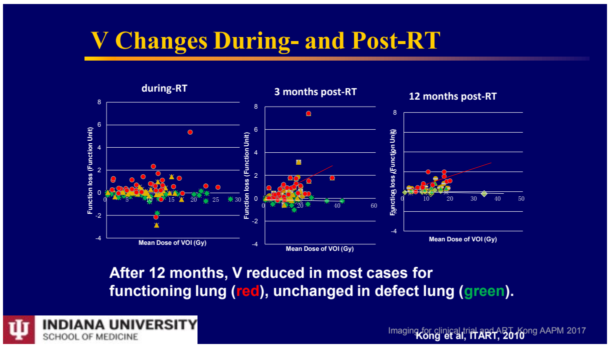

Radiation Induced Changes in Diffusion
Individual Differences in DLCO responding to RT
DLCO
Patient number
Pre-RT
During-RT
47% patients remain +-10% of baseline level.
20% patients improved (more than 10% elevation).
30% patients decreased (more than 10% reduction).
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

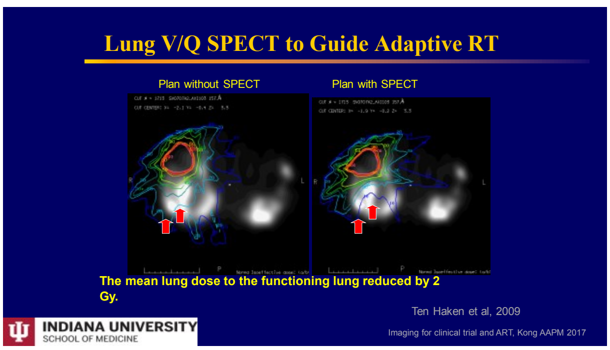

V-Defect Score During- & Post-RT
Defect score
6.00
5.00
4.00
3.00
2.00
1.00
Ipsilateral lung
Contralateral lung
Remaining lung
Total lung
Pre-RT
During-RT
Post-RT
based on Gayed et al. JTO. 2008; 3(8):858-64
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

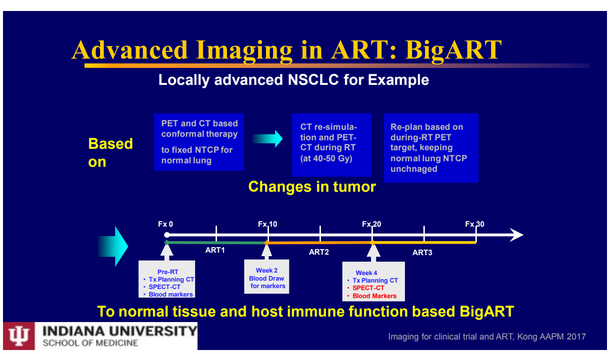

V/Q SPECT of Central and Peripheral Tumors
CT
V
Q
Central
Pre-RT
During-RT
CT
V
Q
Peripheral
Pre-RT
During-RT
INDIANA
SCHOOL OF MEDICINE
Yuan (Kong) et al, JTO, 2011
Kong AAPM 2017


V/Q SPECT Lung Function Map
Pre-RT
During-RT
INDIANA U
SCHOOL OF MEDICINE
Meng (Kong) et al, 2014
Kong AAPM 2017


Q Changes During- and Post-RT
during-RT
3 months post-RT
12 months post-RT
Mean Dose of VOI (Gy)
After 12 months, Q reduced in most cases for functioning lung (red), unchanged in defect lung (green).
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017


V Changes During- and Post-RT
during-RT
3 months post-RT
12 months post-RT
Function loss (Function Unit)
Mean Dose of VOI (Gy)
After 12 months, V reduced in most cases for functioning lung (red), unchanged in defect lung (green).
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Kong et al, ITART, 2010
Imaging for clinical trial and ART, Kong AAPM 2017


Lung V/Q SPECT to Guide Adaptive RT
Plan without SPECT
Plan with SPECT
The mean lung dose to the functioning lung reduced by 2 Gy.
Ten Haken et al, 2009
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017


Advanced Imaging in ART: BigART
Locally advanced NSCLC for Example
Based on
PET and CT based conformal therapy to fixed NTCP for normal lung
CT re-simulation and PET-CT during RT (at 40-50 Gy)
Re-plan based on during-RT PET target, keeping normal lung NTCP unchnaged
Changes in tumor
Fx 0
Fx 10
Fx 20
Fx 30
ART1
ART2
ART3
Pre-RT
• Tx Planning CT
• SPECT-CT
• Blood markers
Week 2
Blood Draw
for markers
Week 4
• Tx Planning CT
• SPECT-CT
• Blood Markers
To normal tissue and host immune function based BigART
INDIANA UNIVERSITY
SCHOOL OF MEDICINE
Imaging for clinical trial and ART, Kong AAPM 2017

Acknowledgement-1

- Medical physicists:
  - Randall Ten Haken
  - Martha Matusek
  - Timothy Ritter
  - Yue Cao
  - Scott Hadley
  - Jean Moran
  - Dick Fraass
- Medical dosimetrists:
  - Daniel Tatro
  - David Jerama
  - Cassie Brooks
  - Lon Marsh
- Physicians:
  - James Hayman
  - Avahram Eisbruch
  - Howard Sandler
  - Theodore Lawrence
- Statisticians:
  - Kerby Shedden
  - Daniel Normolle
  - Schipper
- Fellows/postdocs/residents:
  - Shuanghu Yuan
  - Xuwei Cai
  - Jingbo Wang
  - Weili Wang
  - Pawinee Mahasittiwat
  - Xue Meng
  - Libin Sun
  - Bing Xia
  - Jun Liu
  - Congying Xie
  - Luying Xu
  - Xiangpeng Zheng
  - Yaping Xu
  - Chenbo Han
  - Jianxin Xue
  - Nan Bi
  - Jian Qin
  - Ling Li
  - Matthew Stenmark
  - Klaudia Hunter
  - Paul Stanton

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Acknowledgement-2

- Medical Oncologists
  - Gregory Kalemkerian
  - Nithya Ramnath
  - Khaled Hassan
  - Dean Brenner
  - Kemp Cease
- Pulmonologists:
  - Douglas Arenberg
  - Kevin Flaherty
  - Jeffrey Curtis
- Pathologists:
  - Jeffery Myers
  - Lindsay Schmidt
- Lab Scientists:
  - David Lubman
  - David Beers
  - Yi Sun
  - Zhang
- Radiologists:
  - Kirk Frey
  - Leslie Quint
  - Moran Piert
  - Milton Gross
  - Kakit Wong
  - Richard Brown
- Surgeons:
  - Mark Orringer
  - Andrew Chang
  - Rishi Reddy
  - Jules Lin
- Data management:
  - Jody Sharp
  - Debra Arnoldi
  - Michele Castle
  - Kathy Blanchard
  - Kate Ersting
  - Kate Hurffman

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

Thank you!!!

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017

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

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 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

Meng (Kong) et al, Int J RadiatOncol Biol Phys. 2014
Yuan (Kong) et al.. Int J Radiat Oncol Biol Phys. 2012

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Imaging for clinical trial and ART, Kong AAPM 2017