INDIANA UNIVERSITY
SCHOOL OF MEDICINE

PET-CT for Adaptive Radiation Therapy

Feng-Ming (Spring) Kong, M.D., Ph.D., F.A.C.R.

Professor of Radiation Oncology and Medical & Molecular Genetics
Director of Clinical Research/Clinical Trial
IU Simon Cancer Center
Indiana University School of Medicine

AAPM ART, August 2, 2017

Disclosure

- Works presented were supported in parts by RSNA, ASCO, and NIH grants.
- Speaker's honorarium from Varian Medical Inc.

Outline

- Overall role of PET in oncology: lung cancer example
  - Diagnosis/staging
  - Target delineation
  - Treatment response assessment
    - Post-treatment imaging
    - During-treatment imaging
- FDG-PET guided adaptive therapy
  - Hodgkin's lymphoma: chemotherapy response based
  - Esophageal cancer: chemotherapy response based
  - Non-small cell lung cancer: mid-radiation response based

Outline

- Overall role of PET in oncology: lung cancer example
  - Diagnosis/staging
  - Target delineation
  - Treatment response assessment
    - Post-treatment imaging
    - During-treatment imaging
- FDG-PET guided adaptive therapy
    - Hodgkin's lymphoma: chemotherapy response based
    - Esophageal cancer: chemotherapy response based
    - Non-small cell lung cancer: mid-radiation response based

We Are Not Talk About This Pet.

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

PET: Positron Emission Tomography

PET scan is a nuclear medicine, functional imaging technique that is used to observe metabolic processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radioactive tracer, which is introduced into the body on a biologically active molecule.

- PET is an important research tool to map normal human brain and heart function, and support drug development.
- PET, both a medical and research tool, plays an important role in clinical oncology: diagnosis, staging, treatment decision, treatment response assessment.

History of PET Quantitative Imaging

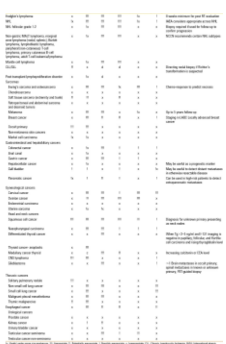
- Positron-emitting radioisotopes were first discovered in the 1930's
- Concept of tomography: David Kuhl Luke Chapman and Roy Edwards, U Penn, in late 1950s
- First scanner: James Robertson et al at Brookhaven National Laboratory, the first single-plane PET scan, nicknamed the "head-shrinker in 1961
- Further technique development: Michel Ter-Pogossian, Michael E. Phelps, Edward J Hoffman from Wash U, 1970-1975
- 2-fluoro-2-deoxy-D-glucose (FDG) was radiolabelled with ^{18}F-FDG by Louis Sokoloff along with Dr. Alfred Wolf and Joanna Fowler in 1976
- The first FDG Quantitative imaging of a human reported in 1978
- FDG-PET was first covered by Medicare for NSCLC staging in Jan, 1998 (then rising CEA colon cancer and lymphoma 1999)

PET Modality

- Hypoxia PET: ^{18}F-FMISO, ^{18}F-FAZA, ^{64}Cu-ATSM
- DNA PET: [^{18}F]3'-deoxy-3'-fluorothymidine (FLT)-PET
- Protein PET:
  - [^{11}C]-methionine PET
  - O-[^{11}C]methyl-l-tyrosine PET
- Neuroreceptor ligand PET:
  - [^{11}C] raclopride, [^{18}F] fallypride and [^{18}F] desmethoxyfallypride for dopamine D2/D3 receptors
  - [^{11}C] McN 5652 and [^{11}C] DASB for serotonin transporters
  - [^{18}F] Mefway for serotonin 5HT1A receptors
  - [^{18}F] Nifene for nicotinic acetylcholine receptors or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme).
- EGFR or other critical molecular targeted PET
- **Glucose PET: [^{18}F]-fluoro-2-deoxyd-glucose PET (FDG-PET), the one in daily clinical practice.**

Current Role of FDG-PET

Diagnosis
Staging
Response Evaluation
Restaging
Suspected Recurrence
Follow-up or Surveillance
Target Delineation for Radiotherapy Planning
Adaptive treatment



FDG-PET/CT Current Role-1

ACR Practice Appropriateness

- **Diagnosis**
  - To characterize a lesion to suggest whether it is benign or malignant
  - For the detection of a possible primary when the patient presents with metastases
  - To identify an appropriate site from which a biopsy would yield adequate representative tissue for diagnosis
  - Detection of malignancy when tumor markers are abnormal
- **Staging**
  - After the histological diagnosis, to assess the extent of disease before the start of treatment
- **Restaging**
  - Assessment of the extent of the disease after treatment or after confirmed recurrence

Argrawal and Rangarajan, 2015

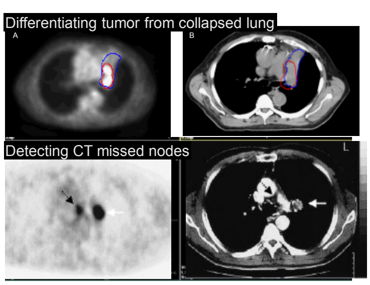
FDG-PET/CT Current Role-2

ACR Practice Appropriateness

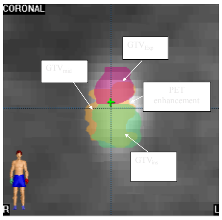
- **Suspected Recurrence**
  - Assessment of disease following clinical or biochemical suspicion of recurrence
- **Follow-up or Surveillance**
  - Assessment of disease in the absence of critical evidence of recurrence
- **Radiotherapy Planning (RT)** → **Target Delineation**
  - When the study is used for contouring and planning the radiation fields
- **Response Evaluation** → **Adaptive treatment**
  - Assessment of response to treatment

Argrawal and Rangarajan, 2015

FDG-PET Improves Target Accuracy



Using PET Volume for ITV



- PET image is usually obtained in about 30 minutes. The PET volume should include all the target excursion due to internal motion, and correlates with the ITV obtained from 4D-CT (3 phases –CT).

Jin JY et al. Green Journal, 2006

PET Target Can Include Motion

- 15 patients with NSCLC, tumor 233±237cc (ranged 30-876cc)
- Three phase scan CT simulation: inhale, exhale, and free breathing
  - Composite GTV of both inhale and exhale
- FDG-PET on treatment position
  - PET volume: multiple threshold PET volume
- Comparison of CT GTV vs PET volume
  - 19±5 % PET GTV matched best with CT composite GTV

Fernando (Kong) et al, 2005

PET Target May Include CT-CTV

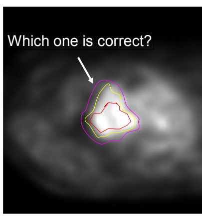
- 15 patients with NSCLC, tumor 233±237cc (ranged 30-876cc)
- Three phase scan CT simulation: inhale, exhale, and free breathing
  - Composite GTV of both inhale and exhale
  - ITV (Internal target volume)=composite GTV + 8mm expansion
- FDG-PET on treatment position
  - PET volume, multiple threshold PET volume,
- Comparison of CT GTV vs PET volume
  - 14±4% PET GTV matched best with ITV

Fernando (Kong) et al, 2005

Methods Used for PET-MTV Delineation

- 1. Visual inspection: Nuclear medicine physician set windows and levels, target delineated manually by radiation oncologists
  - Pro: Expert's hands; Con: subjective, difficult to reproduce
- 2. Absolute SUV cut-off (2.5)
  - Pro: Easy, objectively follow the number
  - Con: SUV varies with scanners, injection amount, time between injection and many other factors; RT plan systems do not have SUV
- 3. Tumor background/mediastinum ratio
  - Pro: Objective; Con: What is the right threshold? What do you do with the adjacent normal tissues
- 4. Relative threshold method (% maximum)
  - Pro: Objective; Con: can not find a fixed threshold for every tumor; the most commonly used 40% is wrong in 80% cases.
- 5. "Gradient method"
  - Pro: Objective; Con: Requiring specific program software? What do you do with the adjacent normal tissues

Contouring Tumor Target on PET

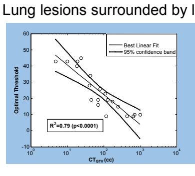


Threshold Method

Study	Method of Delineation
Erdi et al, 1997 & 2002	40% threshold
Kiffer et al, 1998	Visual interpretation
Mah et al, 2002	50% threshold
Vanuytsel et al, 2000	Identification only
Nestle et al, 2005	50% threshold
Bradley et al, 2004	40% threshold
Deniaud-Alexandre et al, 2005	50% threshold
Giraud et al, 2001	40% threshold
Brianzoni et al, 2001	40% threshold
Ashamalla et al, 2005	Visual interpretation

The 40% Threshold Is Not Correct for Majority Patients

Lung lesions surrounded by lung parenchyma



Tumor Size	# of Lesions	%Threshold Yielding Best PET-CT Match	Max SUV
>5cm	9	12 ± 4	18 ± 9
3-5 cm	8	26 ± 10	10 ± 4
< 3 cm	3	42 ± 1	2.9 ± 0.3
All	20	22 ± 12	12 ± 8

The 40% PET threshold underestimated CT tumor volume in 17/20 (85%) lesions. The mean threshold was 24% for CT sized tumor.

The threshold to generate best CT-PET match correlated with the tumor size and maximum SUV. 40% threshold (smart segmentation) works for T1 tumors, the SBRT tumors.

Biehl (Kong) et al, 2006

RTOG1106 Recommendation PETMTV

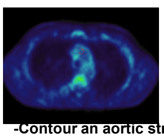
- Metabolic tumor volume (MTV) should be generated using a fixed tumor background ratio
  - 1.5 times of the mean activity of aorta.
- This can be done through various systems, such as MIM PET edge.
- The key issue is consistency between scans and patients.

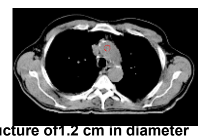
- Example steps from University of Michigan functional image analysis tools (FIAT) can be found:

Mahasittiwat (Kong) et al, J Radiat Oncol. 2013 Jun;2(2):191-202.

https://www.ncbi.nlm.nih.gov/pubmed/23795245

Delineation of PETMTV Step-1

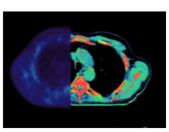


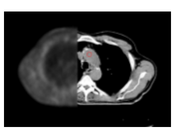


-Contour an aortic structure of1.2 cm in diameter (1 cc. in volume, about 3 slices) in the middle of ascending aorta in CT scan
-Transfer aortic structure to PET scan which is already registered with CT scan.

Mahasittiwat (Kong) et al, J Radiat Oncol. 2013 Jun;2(2):191-202.

Delineation of PETMTV Step-2

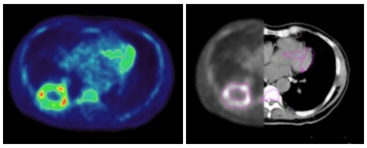




- **Check aorta volume on PET and fused PET-CT image**
- **Calculate the mean intensity of 1cc aortic structure in PET image**
- **Autotrack the tumor volumes by thresholding at 1.5*mean intensity of the aortic structure**

Mahasittiwat (Kong) et al, J Radiat Oncol. 2013 Jun;2(2):191-202.

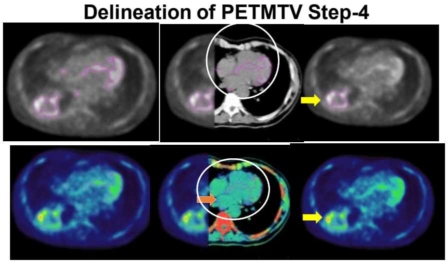
Delineation of PETMTV Step-3



-MTV can be done in one click depending on the contouring tool
-Check the MTV slice by slice in fused PET-CT image
-Identify normal structure incidentally included in the MTV

Mahasittiwat (Kong) et al, J Radiat Oncol. 2013 Jun;2(2):191-202.

Delineation of PETMTV Step-4



- Manually remove normal structures such as heart and esophagus (dark in the white circle) incidentally included in MTV
-PETMTV (yellow arrows) delineation is now complete.

Mahasittiwat (Kong) et al, J Radiat Oncol. 2013 Jun;2(2):191-202.

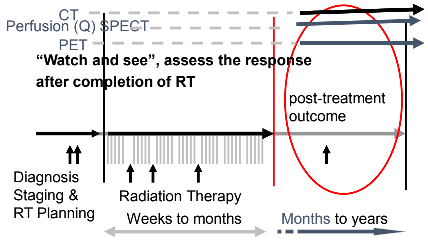
Sam#1 RTOG1106 uses which of following methods to define FDG-PET scan to guide adaptive treatment in non-small cell lung cancer:

- 1) threshold SUVmax at 2.5
- 2) threshold at 40% of SUVmax
- 3) manual drawing per treating physician
- *4) tumor backgound ratio

Biehl KJ, Kong FM, Dehdashti F, Jin JY, Mutic S, El Naqa I, Siegel BA, Bradley JD. 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? J Nucl Med. 2006 Nov;47(11):1808-12. PubMed PMID: 17079814.

Mahasittiwat P, Yuan S, Xie C, Ritter T, Cao Y, Ten Haken RK, Kong FM. Metabolic Tumor Volume on PET Reduced More than Gross Tumor Volume on CT during Radiotherapy in Patients with Non-Small Cell Lung Cancer Treated with 3DCRT or SBRT. J Radiat Oncol. 2013 Jun;2(2):191-202. PubMed PMID: 23795245; PubMed Central PMCID: PMC3686305

The Traditional Approach of Treatment Response Assessment



Post-Tx CT-PET Imaging for Tumor Control

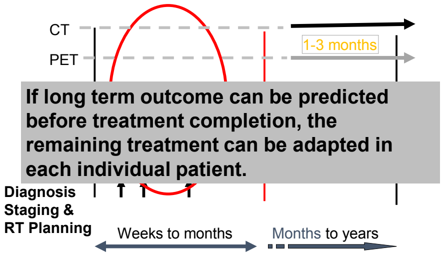
- Post-Tx CT response is the standard practice in most disease
- Post-Tx PET is better than CT as it can tell scars from active tumor
- Post-Tx PET is highly correlated with pathologic response.
- Post-Tx PET may be predictive of pattern of failure
- Post-Tx PET, as a biomarker, is predictive of long term survival,
  - post-Tx metabolic response is the most significant factor in predicting long-term survival.

But, post-Tx PET tumor response does not provide an opportunity to change the treatment plan. NO use for ART.

Outline

- Overall role of PET in oncology: lung cancer example
  - Diagnosis/staging
  - Target delineation
  - Treatment response assessment
    - Post-treatment imaging
- **FDG-PET guided adaptive therapy**
    - **Hodgkin's lymphoma: chemotherapy response based**
    - **Esophageal cancer: chemotherapy response based**
    - **Non-small cell lung cancer: mid-radiation response based**

MidTx PET-CT to Assess Individual Response



FDG-PET in Hodgkin's Lymphoma-1

- Prognostic value of early interim PET response after chemotherapyx2 cycles, No treatment modification was made based on PET response.
- A danish prospective analysis, 77 patients
  - 11 out of 16 (69%) PET-2-positive patients relapsing or progressing
  - 3 out of 61 (5%) PET-2-negative patients
  - PET-2 response was a significant predictor for both PFS and OS ($P < .01$).

  Hutchings et al, 2005 and 2006
- An Italian prospective trial, 108 patients (mostly advanced stage) treated with ABVD with 54% receiving IFRT.
  - PET-2 response correctly predicted treatment outcome in 95% of patients, with a positive predictive value of 90% and a negative predictive value of 97%.

  Gallamini et al, 2006
- A combined analysis of the above two prospective trials
  - the 2-year PFS was 12.8% for PET-2-positive patients compared to 95.0% if PET-2 negative ($P < .001$). PET-2 response was the only significant predictor of outcome on multivariate analysis ($P < .0001$).
  - Both the negative predictive value (NPV) and positive predictive value (PPV) of PET-2 response were excellent (92% and 93%, resp.)

  Gallamini et al, 2007
- A systematic review involving 360 patients with advanced-stage HL, interim PET/CT had an overall sensitivity of 81% and specificity of 97%

  Terasawa et al, 2009

FDG-PET in Hodgkin's Lymphoma-2

- Chemotherapy modification based on PET response, chemo based on PET-2 response
  - A study from Haifa/Israel, 108 patients
    - PET-2-negative patients receiving standard BEACOPPx2
    - PET-2-positive patients receiving BEACOPPesc (both 4 cycles). Radiation therapy, given to 36% of patients, included initial bulky disease (>10 cm) and a single PET-positive site after completing chemotherapy.
    - Interim PET-based treatment was effective and feasible, with 5-year event-free survival (EFS) and OS of 85% and 90%, respectively.

    Dann et al, blood, 2007
  - A phase II study from Hadassah University Hospital, Jerusalem
    - 43 advanced stage HL, a favorable PET response after 2 cycles of BEACOP received an additional 4 cycles of ABVD. Results comparable to similar patients (high-risk, advanced HL) treated in the German HD9 trial with 8 cycles BEACOPPesc. Avigdor et al, Annal of Oncology, 2010

FDG-PET in Hodgkin's Lymphoma-3

- Consolidative radiation therapy based on PET response
  - HD15 trial of the German Hodgkin Study Group (GHSG) 817 patients (stage IIB bulky/extranodal, III, IV) were randomized to three variations of BEACOPP chemotherapy and assessed for response by PET-CT at completion (6 to 8 cycles).
    - Patients with PET-positive residual disease (>2.5 cm in size) received 30 Gy IFRT. The PFS for patients with PET-negative residues (treated with chemotherapy alone) was 96% compared to 86% for PET-positive patients treated with chemotherapy and IFRT (P = .011). Kobe et al, 2008
  - One published randomization from Italy, 260 patients with bulky HL (>5 cm, all stages) with VE-BEP (vinblastine, etoposide, bleomycin, epirubicin, prednisone) chemotherapy for 6 cycles, randomized to versus no IFRT
    - PET CR: EFS 86% compared to 96% with IFRT, P = .03
    - PET residual disease: treated with high-dose chemotherapy and stem cell transplant), 50% EFS

Picardi et al, 2007

- Judge is still out for the role of FDG-PET on RT decision for Hodgkin's lymphoma.

FDG-PET in Hodgkin's Lymphoma-4

- Ongoing clinical trials
  - CALGB trials 50604 and 50801 (non bulky and bulky Stage I/II, resp.) assess for PET response after an initial 2 cycles of ABVD (clinicaltrials.gov ID NCT01132807 and NCT01118026, resp.).
  - The German HD16 comparing 2 cycles of ABVD and 30 Gy IFRT compared to the same regimen with PET response-guided radiotherapy
  - The H10 EORTC/GELA study is recruiting patients with stage I/II disease
  - Trials from Cancer Research UK (stage IIB-IV) and Southwest Oncology Group (SWOG, stage III/IV) treat PET-2-positive patients after ABVD with BEACOPP-based regimens (NCT00678327 and NCT00822120, resp.).

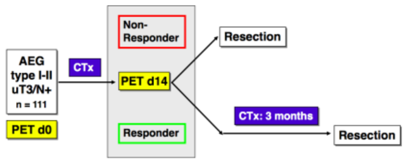
Sam#2: Which of the following is correct regarding PET-guided adaptive treatment in Hodgkins' lymphoma?

- 1) Current standard RT in lymphoma is tailored treatment based upon PET assessment.
- 2) There is consensus regarding the appropriate treatment of PET-avid disease (interim or after completion of therapy): i.e. more intensive treatment for poor responders.
- *3) PET response is strongly prognostic for treatment outcome
- 4) PET guided adaptive trial has demonstrated superiority of such treatment in lymphoma.

Aridgides P, Bogart J, Shapiro A, Gajra A. PET Response-Guided Treatment of Hodgkin's Lymphoma: A Review of the Evidence and Active Clinical Trials. Adv Hematol. 2011;2011:309237. doi: 10.1155/2011/309237. Epub 2010 Dec 27. PubMed PMID: 21234382; PubMed Central PMCID: PMC3017897.

FDG-PET in Esophageal Cancer

119 patients **MUNICON trial**



Response definition: Decrease of the SUV_{mean} PET_{d14} / $PET_{baseline} \geq 35\%$

Weber et al. *J Clin Oncol* 2001;19:3058-65 Ott et al. *J Clin Oncol* 2006;24:4692-8

FDG-PET in Esophageal Cancer

MUNICON trial

	PET-Responder (n = 50)	PET-Non-Responder (n = 54)
Complete remission (1a) 0% residual tumor	16.0% (n=8)	0% (n=0)
Subtotal remission (1b) < 10% residual tumor	42.0% (n=21)	0% (n=0)
Moderate remission (2) 10-50% residual tumor	20.0% (n=10)	3.7% (n=2)
No remission (3) > 50% residual tumor	22.0% (n=11)	96.3% (n=52)
Major remission (1a + 1b) 0 - 10% residual tumor	**58.0% (n=29)**	**0% (n=0)**

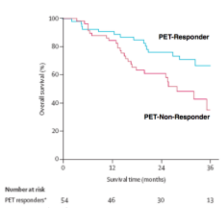
Remissions scored according to Becker et al. *Cancer* 2003; 98: 1521-30

χ^2-test: **p<0.001**

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

FDG-PET in Esophageal Cancer

MUNICON trial



Median survival [95% CI] in months:

Metabolic Responder: Not reached

Metabolic Non-Responder: 25.8 [19.4; 32.3]

Hazard ratio **2.13** [1.14-3.99]
Log-rank p-value: **p=0.015**

Median follow-up: 28.0 months

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

FDG-PET on Esophageal Cancer

MUNICON trial

	PET-Responder (n = 50)	PET-Non-Responder (n = 54)
R0 (tumor free resection margins)	**96%** (n=48)	**74%** (n=40)
R1 (microscopically affected resection margin)	4% (n=2)	26% (n=14)

χ^2-test: **p=0.002**

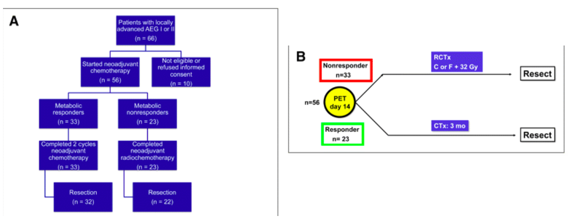
Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

Sam#3: Regarding the PET adapted MUNICON I trial in esophageal cancer:

- 1) This phase II trial is an PET adaptive study that involved adaptive radiation therapy
- 2) Of 110 patients enrolled, 54 patients had more than 35% reduction in SUV after 2 weeks of chemotherapy
- 3) Due to the use of PET adapted treatment, the metabolic non-responders had achieved similar survival than that of responders
- *4) The non-metabolic responders on PET showed no histological response

- Ref: Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007 Sep;8(9):797-805. PubMed PMID: 17693134.

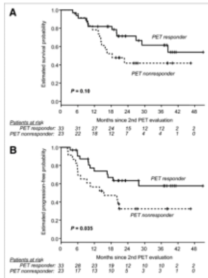
MUNICON II Trial in Esophageal Cancer



FDG-PET in Esophageal Cancer MUNICON II Trial

Relapse After Neoadjuvant Chemotherapy (Responders) and Neoadjuvant Radiochemotherapy (Nonresponders)

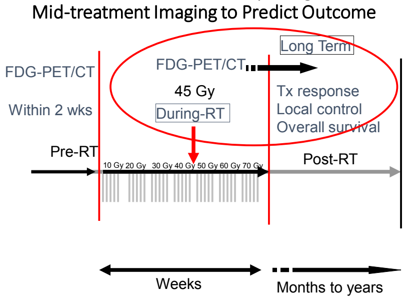
Regimen	Responder (n = 33)	Nonresponder (n = 23)
Relapse	39% (n = 13)	65% (n = 15)
Local	9% (n = 3)	17% (n = 4)
Distant	30% (n = 10)	48% (n = 11)



Comparison of Major Findings of MUNICON I and MUNICON II Trials

	MUNICON I		MUNICON II	
Parameter	Responder	Nonresponder	Responder	Nonresponder
PET	49%	51%	59%	41%
Histopathologic*				
1	58%	0%	36%	26%
2	20%	4%	21%	30%
3	22%	96%	39%	39%
Surgery				
R0	96%	74%	82%	70%
R1	4%	26%	6%	13%
RX			12%	17%
Survival				
Median TTP	32.9 mo	14.3 mo	Not reached	15.4 mo
Median OS	Not reached	25.8 mo	Not reached	18.3 mo

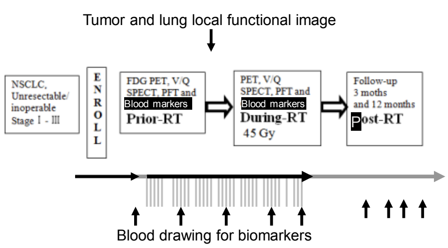
UMCC 2006040: Study Design
Mid-treatment Imaging to Predict Outcome



Hypothesis-1
Tumor Functional Imaging to Guide Individualized Adaptive RT

- The tumor response on FDG-PET during-RT is correlated with post-treatment response, and predictive of progression free, local progression free and overall survivals.
- PET during-RT response can guide individualized adaptive RT.

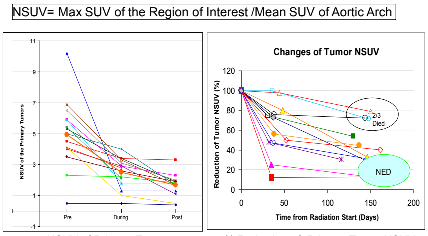
General Study Design



44

Primary Tumor FDG-Activity During & Post RT

NSUV= Max SUV of the Region of Interest /Mean SUV of Aortic Arch

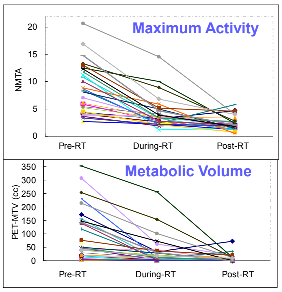


NSUV of Primary Tumor

% Reduction of Primary Tumor NSUV

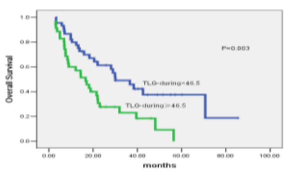
Kong et al, JCO, 2007

PET-Activity and Volume During-RT



J Wang (Kong) et al, 2012

During-RT PET and Overall Survival



TLG=total lesion glycolysis=MTV*MeanSUV

Li et al (Kong), ASTRO, 2013

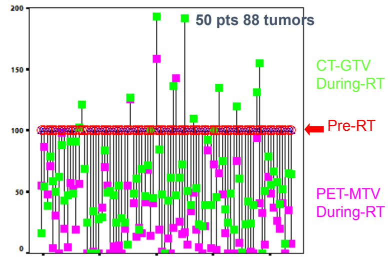
PET Variables for Survival Patients Treated with 60-70 Gy RT

Variable	HR	95% CI	P value
Pre SUVmean (per unit)	1.14	(0.85,1.54)	0.375
During SUVmean (per unit)	1.12	(0.694,1.8)	0.645
During-Pre SUVmean (per unit)	0.934	(0.637,1.37)	0.727
Pre SUVmax (per unit)	1.06	(0.993,1.13)	0.0793
During SUVmax (per unit)	1.11	(0.974,1.26)	0.121
During-Pre SUVMax (per unit)	0.939	(0.857,1.03)	0.17
Pre TLG (per 10 units)	1.01	(1,1.01)	0.00708
During TLG (per 10 units)	**1.03**	**(1,1.06)**	**0.0315**
During-Pre TLG (per 10 units)	**0.992**	**(0.986,0.998)**	**0.00993**
Pre MTV (per 10 units)	1.02	(1,1.04)	0.021
During MTV (per 10 units)	**1.08**	**(1.01,1.15)**	**0.0185**
During-Pre MTV (per 10 units)	**0.971**	**(0.947,0.995)**	**0.0187**
Pre CTGTV (per 10 units)	1	(1,1)	0.0563
During CTGTV (per 10 units)	1	(1,1)	0.0409
During-Pre CTGTV(per 10 units)	0.976	(0.946,1.01)	0.143

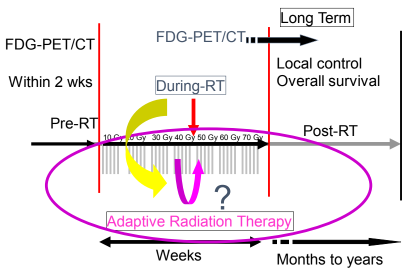
During-treatment volumetric factors are most significant for survival while FDG activity alone were not.

Kong et al, 16th World Lung Congress, 2015

Tumor Reduced More on PET During-RT



During-RT PET to Guide Adaptive RT



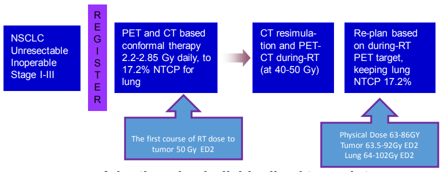
Advantages of during-PET ART

- 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

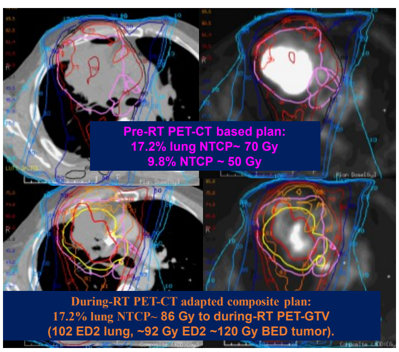
Feng (Kong), Red Journal, 2009

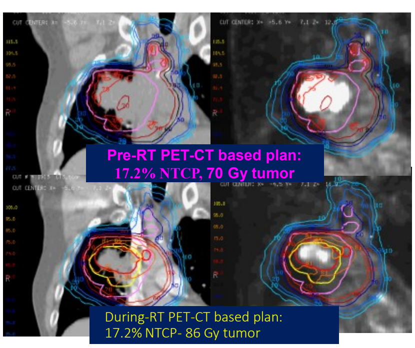
UMCC 2007-123

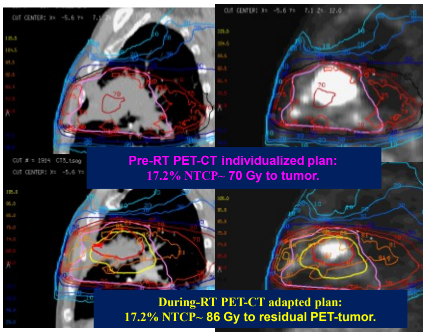
Using FDG-PET Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with NSCLC



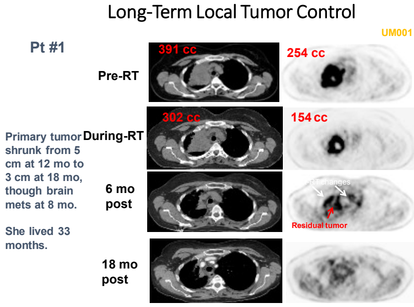
Adaptive plan individualized to each tumor



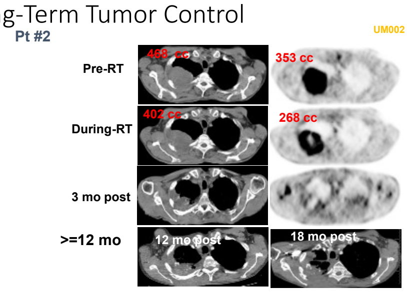




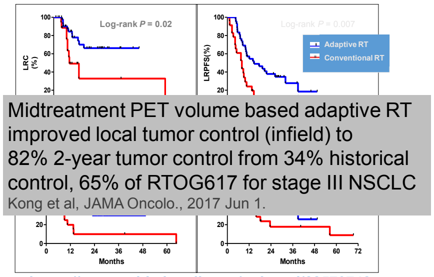
Long-Term Local Tumor Control



Long-Term Tumor Control



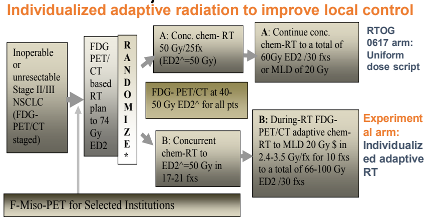
UMCC 2007123: Adaptive Treatment and Outcome



https://www.ncbi.nlm.nih.gov/pubmed/28570742

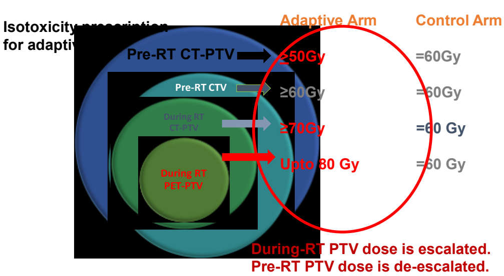
RTOG 1106 /ACRIN 9967 Schema

Individualized adaptive radiation to improve local control



The Primary Endpoint: 2 year local regional tumor control
Randomization stratified by primary tumor, nodal disease, and histology.

RTOG1106 Dose Prescription



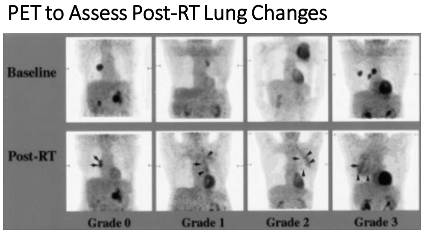
RTOG1106 Technology

- Must use PET for RT planning:
  - Use tumor background ratio of 1.5, using mediastinum blood pool as background, plus manual edits
- Demands 4D motion assessment for every patient:
  - Use average scan for lung dosimetry
  - IGTV for GTV
- Must use imaging guidance for daily treatment, CBCT recommended
- **The trial reached accrual goal of 138 patients in Spring of 2017**

Hypothesis-2 Changes in Normal Tissue on PET to Guide Adaptive RT

- The activity of FDG-PET during-RT is predictive of treatment toxicity
- PET during-RT response can guide adaptive RT to spare organs at risk and decrease treatment toxicity

Background: PET to Assess Post-RT Lung Changes

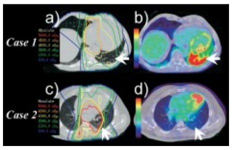


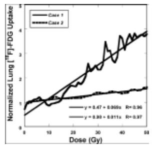
Post-RT lung changes associated with survival

Hicks et al, 2004

Post-RT Lung Changes and Dose Response

36 esophageal patients, 4-12 wks s/p RT+-chemo

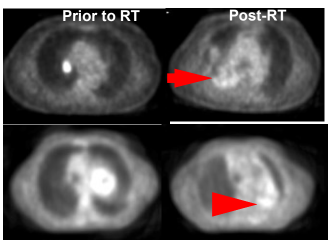




There is a remarkable individual difference in dose response relationships

Guerrero et al, Red Journal, 2007

Post-RT Changes Can Be Remarkable on PET

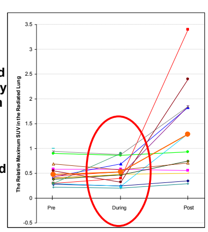


Grade 2 Hick's Changes

Grade 3 Hick's Changes

Changes on During-RT PET?

- **Feb 2004 to June 2005, a pilot study from University of Michigan (UMCC-200376)**
- **FDG-PET scans were performed within 2 weeks prior to, at 45 Gy during and 3 months after RT in 15 patients (14 pts with FDG-Avid tumors) with NSCLC**
- **2/15 patients had mild increased FDG-Activity During-RT, 7/15 had remarkable increase post-RT.**



Kong et al, JCO, 2007

Lung FDG Activity During-RT

Radiation Pneumonitis (Grade)	Changes on during-RT PET (grade)				Total
	0	1	2	3	
0	51	1	1	0	53
1	18	2	0	0	20
2	6	1	1	0	8
3	0	1	1	0	2
4	0	0	1	0	1
Total	75	5	4	0	84

***Fisher's exact P value*=0.001**

3/4 patients had changes during-RT developed clinical pneumonitis.

During-RT PET may predict post-RT pneumonitis.

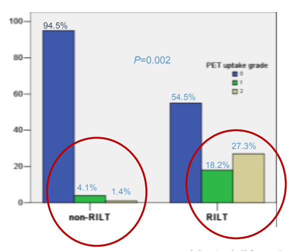
Li et al (Kong), ASTRO, 2013

During-RT Changes in FDG Uptake and RILT

- 84 patients with pre- and during-RT PET-CT, and RILT
- Of 9 patients with increased FDG uptake during-RT, 5 (55.6 %) developed RILT
- Of 11 patients developed clinical RILT, 88% had FDG uptake on the post-RT PET images.
- 89% RILT patients had notable changes of FDG uptake on post-RT PET images.
- There was a significant correlation between the incidence of RILT and FDG uptake changes on during-RT (*P*=0.002) and post-RT (p<0.001) PET images.

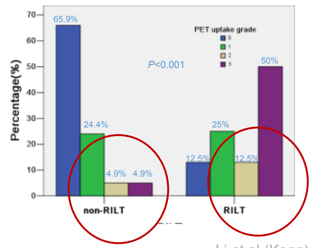
Li et al (Kong), ASTRO, 2013

During-RT FDG Uptake and Clinical RILT



Li et al (Kong), ASTRO, 2013

Post-RT FDG Uptake and Post-RT RILT



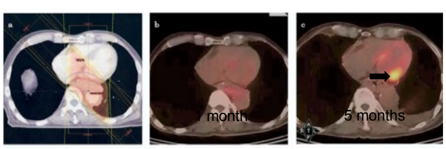
Li et al (Kong), ASTRO, 2013

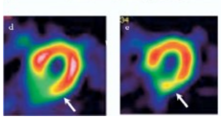
Sensitivity and Specificity of Hick's Grading Scale for Esophagitis

- FDG uptake during-RT to predict post-RT RILT
  - Sensitivity=45.5%, Specificity=94.5%
  - Positive predictive value=55.6%
  - **Negative predictive value=92.0%**
- FDG uptake post-RT and RILT post-RT
  - Sensitivity=87.5%, Specificity=65.9%
  - Positive predictive value=33.3%
  - **Negative predictive value=96.4%**

A patient with negative findings on during-RT PET is most likely at low risk for RILT, during-RT PET may thus guide adaptive planning to decrease clinical RILT.

PET for Heart Function

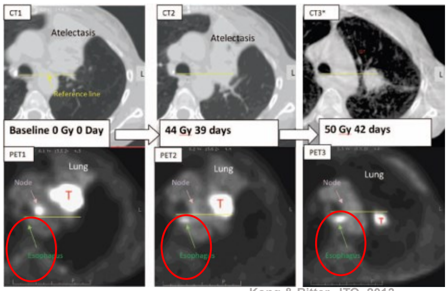




High FDG accumulation in the high-dose irradiated myocardium at five months after chemoradiotherapy are decreased markedly of heart function in the region (arrows)

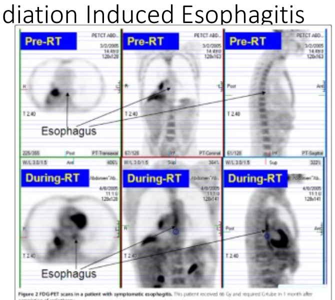
Jingu et al, 2006

Esophagus Also Changes During-RT



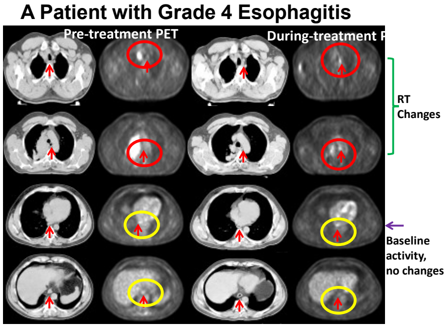
Kong & Ritter, JTO, 2013

Radiation Induced Esophagitis

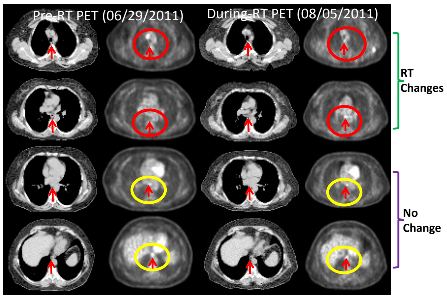


Yuan (Kong), 2014

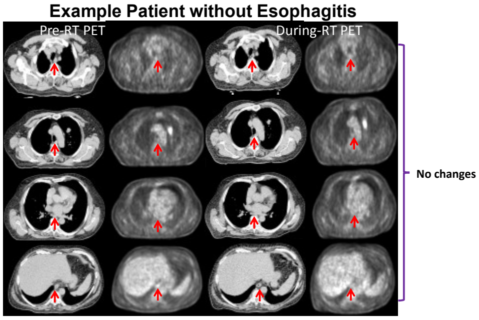
A Patient with Grade 4 Esophagitis



Another Patient with Grade 4 Esophagitis

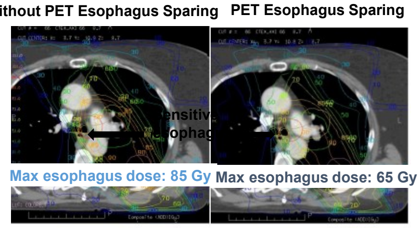


Example Patient without Esophagitis



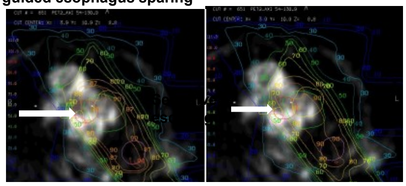
PET Guide Esophagus Sparing RT

Without PET Esophagus Sparing PET Esophagus Sparing



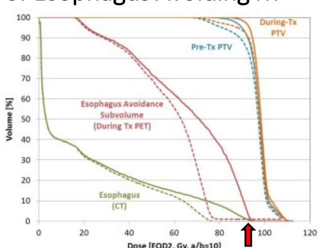
During-RT PET Guided Esophagus Sparing

Without during-RT PET guided esophagus sparing | **With PET esophagus sparing**



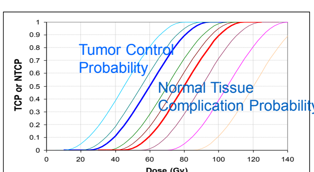
Max esophagus dose: 85 Gy | **Max esophagus dose: 65 Gy**

Effect of Esophagus Avoiding RT



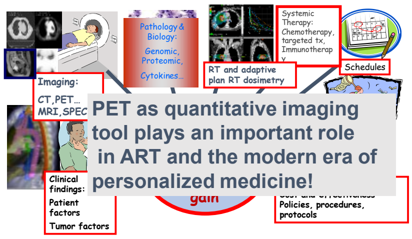
maximum and mean doses to esophagus
Without compromise of PTV coverage

PET guided ART to Improve Outcome



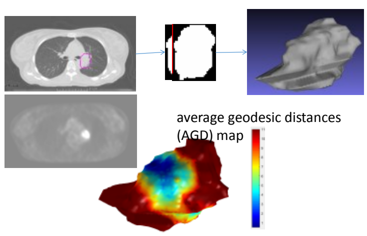
PET-CT may predict each individual's RT response, the dose prescription can be individualized for a maximized therapeutic gain.

Future: PET in Personalized Medicine



PET as quantitative imaging tool plays an important role in ART and the modern era of personalized medicine!

Future: PET Radiomics Feature Guided ART



Standardized moment= 0.58
OS is 67.23 months volume is 24323mm^3

Zhang/Jin/Kong

Acknowledgement

- Medical physicists:
  - Randall Ten Haken
  - Timothy Ritter
  - Jean Moran
  - Marc Kessler
  - James Balter
  - Daniel Mcshan
  - Dick Fraass
- Medical dosimetrists:
  - Daniel Tatro
  - Cassie Brooks
  - Lon Marsh
- Statisticians:
  - Daniel Normolle
  - Matt Schipper
  - Kent Griffith
  - Brady West
- Data management:
  - Kathy Blanchard
  - Kristin Brierley
  - Jody Sharp
- Research fellows and residents:
  - Shanghu Yuan
  - Congying Xie
  - Xuwei Cai
  - Lujun Zhao
  - Li Wang
  - Jun Liu
  - Mary Feng
  - Candace Correa
  - Mattew Stenmark
  - Pawinee Mahashiwitta
- Physicians:
  - James Hayman
  - Avahram Eisbruch
  - Theodore Lawrence
- Medical Oncologists
  - Gregory Kalemkerian
  - Dean Brenner
  - Susan Lyons
  - Kemp Cease
- Pulmonologists:
  - Douglas Arenberg
  - Kevin Flaherty
  - Jeffrey Curtis
- Radiologists:
  - Kirk Frey
  - Milton Gross
  - Richard Brown
  - Moran Piert
  - Leslie Quint
  - Paul Cronin